
Team LiB

Jay Schulkin

Rethinking Homeostasis

Allostatic Regulation in Physiology and Pathophysiology

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Allostatic Regulation in Physiology and Pathophysiology

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Dedicated to Kent Berridge, Bruce McEwen, and Peter Sterling; thank you for the friendship.

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Contents

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Preface

My scientific activities within biological inquiry have focused on the concept of homeostatic systems—specifically the craving for sodium and calcium. But early on it became apparent that the concept of homeostasis, rich as it is, was not sufficient to account for the diverse behavioral and physiological adaptations that are observed. That is, even within the study of homeostatic systems such as sodium, when one starts to think about its regulation in terms of neural integration, it becomes clear that animals are anticipatory, make adjustments, and have seasonal variation in response to metabolic and other bodily requirements. The brain is vitally involved in the regulatory responses to systemic physiological requirements.

When my research moved from bodily tissue needs to avoidance of fearful events, the concept of homeostasis was less appropriate. In what way is fear linked to homeostatic regulation? This was not obvious. However, evaluating the physical limits of a system's functioning is quite different from evaluating the specific point of regulation that a system is trying to maintain. But in both cases hormonal mechanisms are critical to behavioral and physiological regulation.

The concept of allostasis, for me, is a heuristic for generating research. I offer the concept as a humble suggestion. As in previous books, I apologize in advance to those investigators and their research that I may have omitted from this book. And I thank my family, friends, and colleagues. In particular, I thank Barbara Bettes, George Chrousos, Kristine Erickson, Phil Gold, David Goldstein, Lauren Hill, George Koob, E. E. Krieckhaus, Joe Majzoub, Jamie McGregor, Mike Power, Jeff Rosen, Louis Schmidt, Pathik Wadhwa, Alan Watts, and John Wingfield for their encouragement and help.

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Introduction

Evolution provided a rich set of mechanisms to maintain internal stability, which includes both local (e.g., kidney, heart) and broadly coordinated (e.g., brain) functions (Boyd and Noble, 1993). One essential concept to account for physiological stability is that of *homeostasis* (Cannon, 1932). *Homeostasis* is a common term within the biological sciences. A variety of well-known examples of behavioral and biological regulation to maintain homeostasis have been characterized. The maintenance of the internal environment by both physiological and behavioral means is a fundamental component in the well-being of complex animals like ourselves (both short- and long-term prospects). The concept of homeostasis is linked to mechanisms for maintaining internal viability and the defense of physiological events essential for bodily well-being. Some of the more obvious examples are: temperature, pH, glucose, protein, oxygen, sodium, and calcium.

But within considerations of homeostatic regulation, certain limitations of the concept have emerged (see Toates, 1979; Stricker, 1990). While homeostasis is the regulation of a set point in the body (e.g., glucose or oxygen in the blood or pH—as noted above), even that characterization is too rigid and perhaps misleading. For example, body temperature can vary to a certain degree (seasonal differences) and can be both reactive and predictive (Moore-Ede, 1986; Mrosovsky, 1990; Wingfield and Ramenofsky, 1999). There are both anticipatory responses to possible predictable events and reactive responses to unpredictable changes. These events are expressed both in terms of behavior and of physiology. There thus emerged implicit in the

homeostatic literature a conceptual expansion that required something more than simply a set point regulatory system (Nelson and Drazen, 2000).

Evolution favored a number of selected behavioral (Barkow et al., 1992) and physiological mechanisms designed to maintain internal viability. It is also apparent that the central nervous system plays an important role by superceding local physiological function in the maintenance of bodily tissue. In other words, the central nervous system is helping to orchestrate bodily stability (e.g., ingestion of sodium, water, etc.; Denton et al., 1996; Fitzsimons, 1999). This has added a new level of complexity to regulatory events. The central state reflects the balancing of a number of factors essential for maintaining physiological and behavioral viability. Within this context, in part, a new concept emerged.

Less well known is a recently coined term, *allostasis* (Sterling and Eyer, 1988). The term was introduced to take account of regulatory systems in which (1) there is no clear set point, (2) there are individual differences in expression (McEwen and Stellar, 1993), (3) the behavioral and physiological responses are anticipatory (Sterling and Eyer, 1988; Schulkin et al., 1994), and (4) there was a vulnerability to physiological overload and the breakdown of regulatory capacities (bone demineralization, brain deterioration, etc. from, for example, high levels of cortisol for long, unrestrained periods; McEwen, 1998a, b).

Allostasis is essential in maintaining internal viability amid changing conditions (Sterling and Eyer, 1988; McEwen and Stellar, 1993; Schulkin et al., 1994). What is similar about both concepts (homeostasis and allostasis) is the coordinated response to maintain internal stability (Langley, 1973).

The contents of the book are as follows:

The first chapter suggests that, from within considerations of homeostatic regulation, there was a search for a broader term (or a better definition of homeostasis) that could account for variation in response during the defense of the internal milieu, and also for the variation in response to the breakdown of bodily defenses when under chronic duress (figure I.1; Selye, 1982; Goldstein, 1995a, b; Chrousos, 1998).

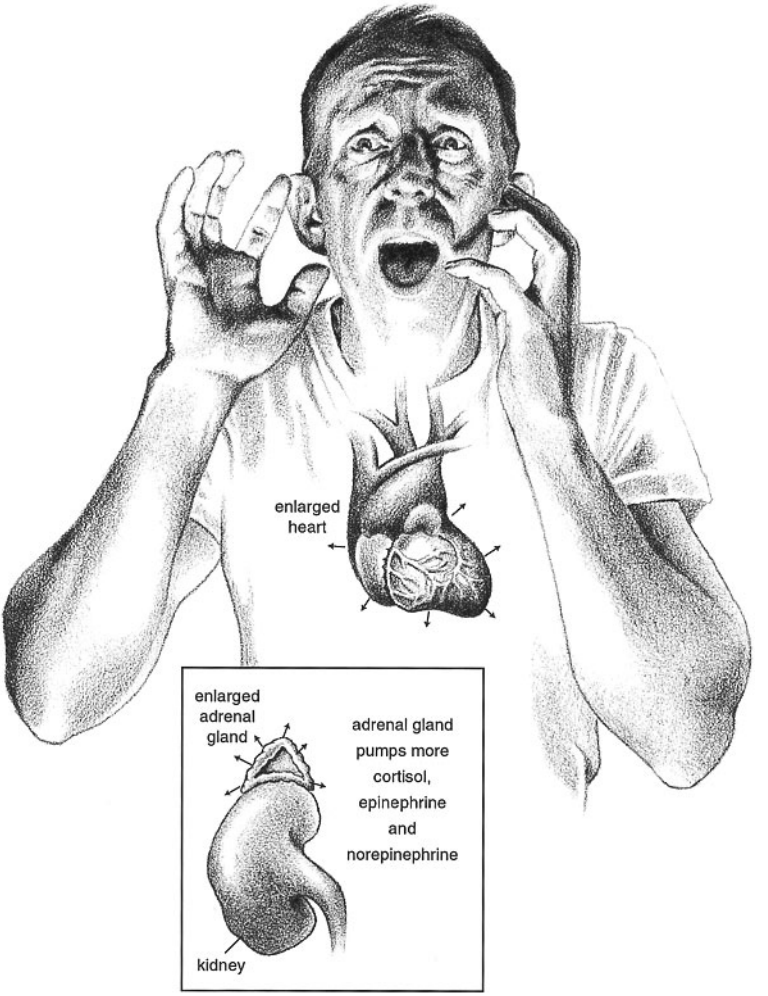

Figure I.1
Neuroendocrine alarm response (Yansen and Schulkin, unpublished).

The concept of allostasis is tied to the fact that one primary role for the central nervous system is to coordinate some of the regulator responses. Therefore in chapter 2, I discuss the hormonal/allostatic regulation of central motive states and the anticipatory nature of them in the organization of behavior. Specifically, I provide a neuroendocrine perspective in which central motive states (e.g., craving water, sodium, food, sex, cocaine, etc.) can be understood. A wide range of instances in which feedforward neuroendocrine mechanisms have functional consequences for behavior and physiological regulation is described. Central motive states (in suitable environments), in part, are sustained and generated by the actions of steroids and the positive induction they have on neuropeptides/neurotransmitters (Pfaff, 1999; Schulkin, 1999a).

One example can do: The secretion of adrenal steroids has diverse effects on neuropeptide systems, depending upon the ecological context and biological needs of the animal. When animals are in need of water or sodium (following blood loss, water deprivation, excessive heat), the adrenal steroid hormone facilitates water and sodium ingestion via the effects on angiotensinergic pathways in the brain (Sumners et al., 1991; chapter 2 of this book).

It is important to note, even in what appears to be a paradigmatic homeostatic system—maintaining body fluid and sodium balance through physiological and behavioral means—a variety of animals that have been tested to date, particularly the omnivorous rat, ingest more sodium than they need (e.g., Denton, 1982; Schulkin, 1991). Moreover, animals are opportunistic in that they ingest what they can when they find it. Nonetheless, sodium ingestion remains one among many outstanding examples of a behavioral and physiological regulatory system.

Chapter 3 describes the behavioral and neuroendocrine regulation of fear and adversity and the consequences that they have on the body. The chapter builds on chapter 2 with regard to the positive induction (or feedforward mechanism) of a neuropeptide corticotropin releasing hormone (CRH) playing a functional role for a motivational state (Swanson and Simmons, 1989;

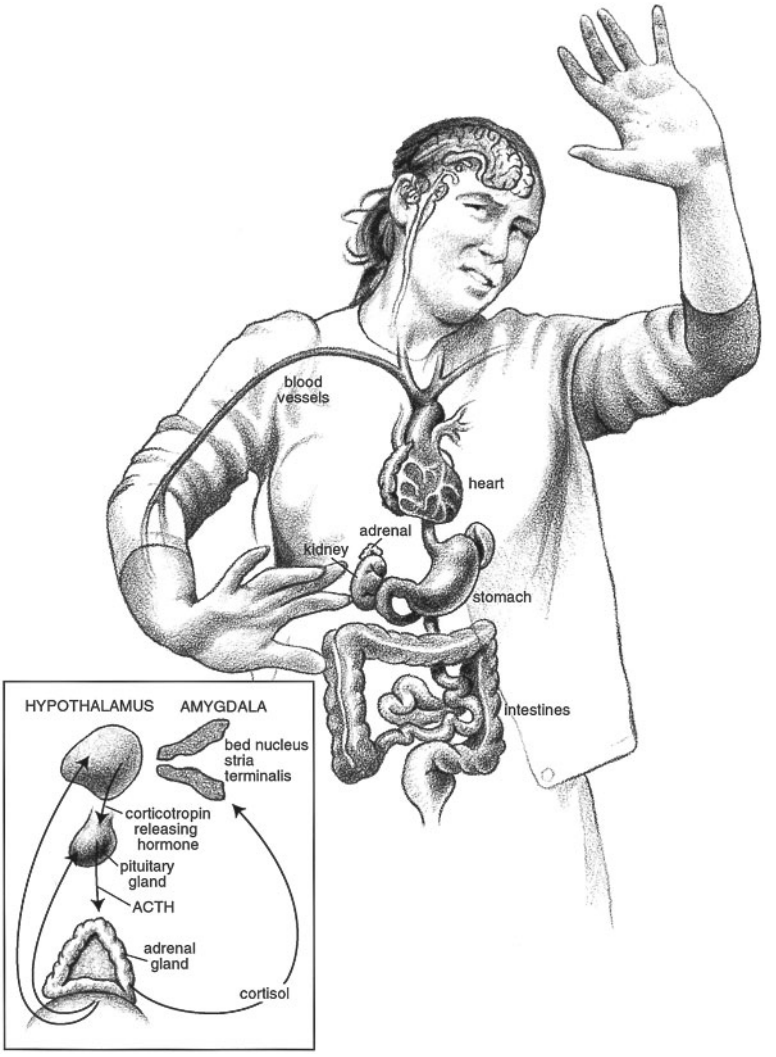

Figure I.2
Neuroendocrine fear response (Yansen and Schulkin, unpublished).

Watts and Sanchez-Watts, 1995). This chapter provides a neuroendocrine perspective on the mechanisms that underlie fear and adversity in terms of both homeostatic and allostatic regulation, and allostatic overload (figure I.2; Schulkin et al., 1994, 1998).

Evolution has selected mechanisms that are not only reflected in neural function but also in the placenta. The placenta is not different from the central nervous system with regard to feedforward endocrine regulatory mechanisms. In chapter 4, I discuss the endocrine regulation of normal birth and birth that is preterm as a result of maternal stress, the breakdown of normal regulatory processes, and the production of preterm babies. The normal example is another instance in which steroids facilitate the expression of peptides to promote a functional relationship—parturition (Majzoub et al., 1999; Challis et al., 2000; King et al., 2001). But under duress (psychosocial stress, risk behaviors) or adversity (bacterial infections), the facilitation may represent an emergency situation and a pathological state (allostatic overload by the overexpression of peptides—e.g., CRH) by steroids and the onset of early parturition (Petraglia et al., 1995a,b; Challis et al., 2000; Wadhwa et al., 2001). Moreover, these endocrine events during pregnancy can have long-term effects on physiological and behavioral expression in the infant (Welberg and Seckl, 2001).

Last, a chronic overextension of the stress system in the brain can characterize the street addict (Koob and Le Moal, 2001). For addicted people, the range of their focus narrows, while the potential events that the drugs are associated with increases. A state of chronic "wanting" pervades the addicted state (Berridge and Robinson, 1998). In chapter 5, I discuss the neuroendocrine and behavioral mechanisms that underlie drug cravings and the compromise it has on bodily functions. A neuroendocrine/behavioral perspective that is outlined in detail in chapters 2 and 3 is extended into chapter 5.

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Chapter 1

Allostasis: The Emergence of a Concept

The logic of this chapter is to begin with a brief discussion of the evolution of thinking about homeostatic systems; that is, historical and contemporary perspectives on maintaining internal physiological stability, and its breakdown during duress. One outcome of thinking about homeostatic systems has been the recognition that a concept was needed to explain how the animal *anticipates* and/or reacts to unpredictable change as a function of internal regulation of physiological events. Finally, I introduce the concept of allostasis and present its use in explaining regulatory physiological and pathological events. Thus this chapter should provide first an orientation to how we arrived at perhaps the need to develop a concept in addition to that of homeostasis in accounting for regulatory physiology and, second, to a consideration of allostasis, a concept to account for central nervous system influences on systemic physiological regulation.

The Defense of the Internal Milieu: Homeostasis

Two key concepts have been in our scientific lexicon for some time. Both have to do with bodily regulation: the defense of the internal milieu (Bernard, 1852, 1859) and homeostatic regulation (Cannon, 1915, 1929a).

Bernard offered two clear ideas in his studies on the regulation of the internal milieu. One is the whole-body physiological regulation of internal stasis, and that states can change if the animal is to be evolutionarily viable. The other is breakdown of tissue under duress—the failure of short-term physiological

solutions to resolve the "problem." These two themes would then resonate for those that came after (Goldstein, 1995a, b; Chrousos and Gold, 1998).

Consider the process of digestion. Bernard (1856, 1878) understood that the salivary glands and pancreas worked in unison in the process of digestion. Both served to incorporate needed nutrients into working physiological systems to maintain those systems. He observed the function of this system and searched for "juices" that are secreted. One of his interests was the digestion of fat. He inserted a fistula into the pancreas to determine what was secreted in the process of digestion. Bernard believed that the salivary gland, pancreas, brain, and other organs were in the service of maintaining the internal milieu.

Bernard also studied the breakdown of normal pancreatic function and morphological expression with metabolic stress (see 1856). Interested in understanding glucose homeostasis, he investigated the physiological mechanisms that render internal constancy possible, and then the breakdown of physiology under duress (e.g., extreme hunger, figure 1.1).[1]

Now consider the other key idea of homeostatic regulation. Cannon is associated with the concept of "the wisdom of the body," but the phrase was actually coined by the British physiologist Ernest Starling in 1923. In his paper, Starling referred to hormones as chemical messengers, to their overproduction in pathology (as in Graves' disease and thyroid dysfunction), and to "harmonic relationships" in maintaining bodily health. These physiological events represented "reservoirs of power" (Cannon, 1915, 1929b, p. 22).

Physiological analysis and better understanding of the maintenance of the internal system were coming into their own by the time Cannon arrived (Pfluger, 1877; Fredericq, 1885), and there was the perspective that "living entities seek equilibrium" (Richet, 1900; see Langley, 1973).

1. Nonetheless, he overstated the absolute separation of the internal milieu from the wider environmental contexts of the external world (Holmes, 1986; Sullivan, 1990).

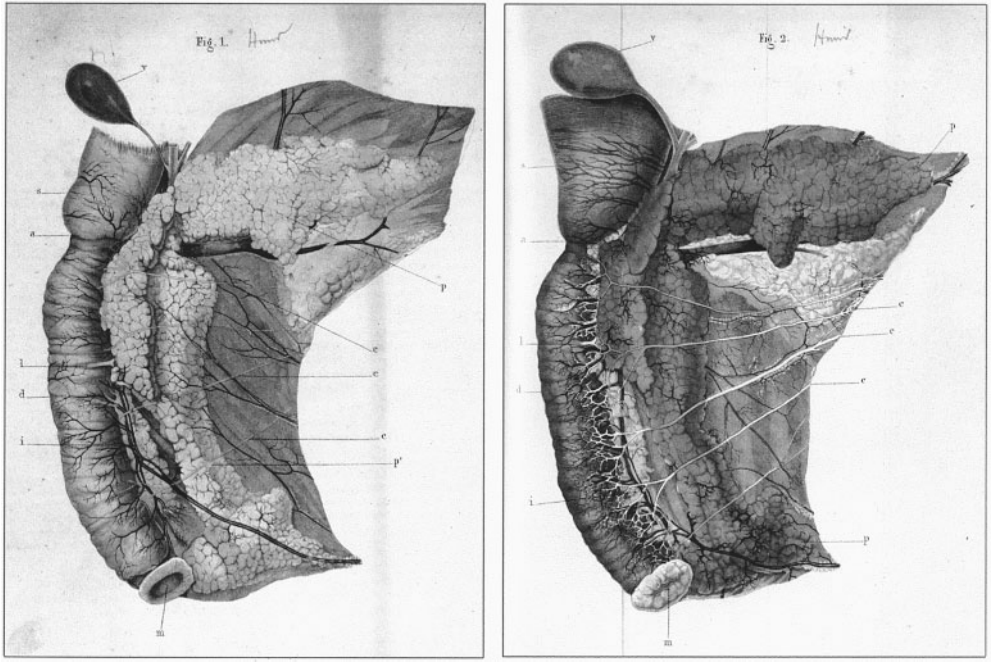

Figure 1.1
Pancreatic morphology of a dog that has not eaten for 36 hours (*left*) and a dog that has eaten (*right*) (Bernard 1856/1985).

Walter Cannon (1915, 1929a, b) placed an emphasis on the interaction of the emotions and regulatory physiology. Specifically, Cannon and his colleagues studied the digestive tract and the secretion of adrenal hormone during a number of conditions having to do with the maintenance and utilization of energy balance (figure 1.2). Conditions of normal adaptation, adversity, and excited extended activity result in increased energy use. Increased blood sugar was seen as essential for short-term energy regulation (Sapolsky, 1992; Dallman et al., 1995).[2]

Cannon's early work focused on adrenal secretion during conditions of duress. He suggested that there were limits to the system. Soldiers during the Great War, he noted, were being beaten down by nervous exhaustion (see Flemming, 1984; see also Haldane, 1929).

In summary, Bernard and Cannon were prescient in understanding the physiology of homeostatic regulation under both normal and pathological conditions. They focused, in part, on blood sugar, its storage by end-organ systems, and its use during need—both excess and normal. Both understood that stability is the key, in both the short and long term, in terms of both low and high taxation of the body's resources. The body's main defense is through physiological mechanisms, and the breakdown of regulatory mechanisms emerges when the organism is pushed beyond regulatory and compensatory capacities.

2. The chemicals secreted in the alimentary system, Cannon suggested (1927, 1931), would provide evidence for the theory that James and Lange suggested for the emotions. Cannon was looking largely at the sympathetic innervation of the adrenal gland and alimentary organs (i.e., perfusion of sugar into the liver) under a variety of conditions. Cannon's theory of the emotions was set in the context of emergency conditions. We recognize now that it is too limited a conception of the emotions to continue to entertain seriously (e.g., LeDoux, 1996; Berridge, 1996; Rosen and Schulkin, 1998; Panksepp, 1998; Lane and Nadel, 1999; Davidson et al., 2000), but what Cannon did capture was an understanding that fatigue, exhaustion, and going beyond what the body could sustain posed a danger to homeostatic regulatory balance (see also Goldstein, 2000).

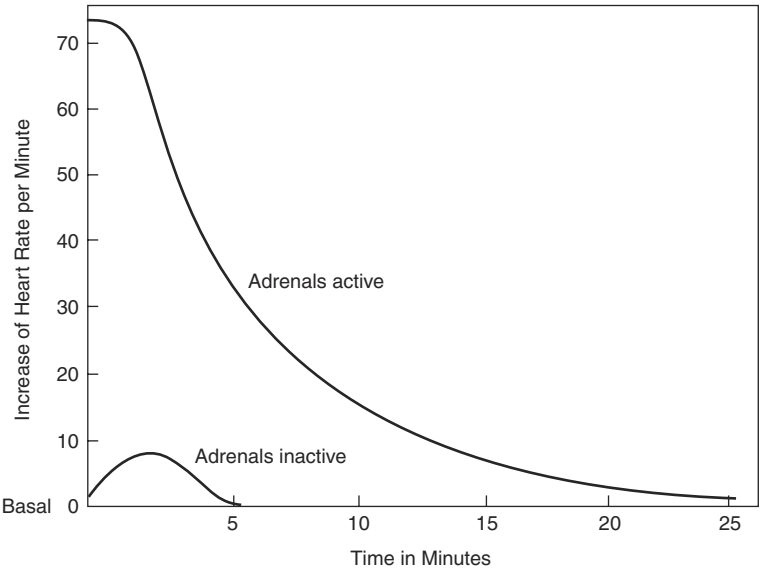

Figure 1.2
Adrenal activation and heart rate: greater response and longer persistence of heart rate in cats whose adrenals were active (Cannon, 1932, 1967).

Stress as a Deviation from Homeostatic Balance: Attempts to Expand the Concept of Homeostasis

Hans Selye of Montreal (1956, 1974, 1982), as is well known, helped establish the scientific study of stress and biological adaptation to everyday adversity. He set out to study the normal "wear and tear" on the body to determine when this stress becomes pathological. Stress turns to distress when the body is no longer able to tolerate the events to which it is subjected and begins to recede into compromised and deteriorating function.

Selye (1956, 1974) integrated his theory of stress with the findings of Bernard and Cannon and the concept of homeostasis, which he called normal adaptation or "general adaptation syndrome." He called it a general syndrome because many parts of

the body were involved and affected. The body's reactions were all in the service of maintaining equilibrium. Viability is endangered when, as Selye understood, one "subtracts" stabilization from the reaction response to the specific event. This can be seen, for example, in "the increased production of adrenocortical hormones, the involution of the lymphatic organs or the loss of weight" (figure 1.3; 1956, 1976, p. 17). Regarding stress, the adaptation syndrome ranges from alertness to fatigue (Goldstein, 2000). The alarm response has endocrine and other bodily consequences. Selye went to great lengths to identify these responses. He argued that stress is a basic physiological event.[3]

Selye, like Cannon, focused on the hypothalamic-pituitary-adrenal (HPA) axis, which, in addition to the immune physiology, is an important regulator in coping with adverse events (Richter, 1942; Mason, 1975a, b). Selye understood that inflammation and the immunological response were essential for adaptation. He postulated that they have long-term costs for bodily health. However, they remain important for short-term viability; evolution does not design immortal organisms (at least not many). He cataloged the range of disease states that can occur from exhaustion and stress (e.g., from nervous tics, sleep disturbances, feeding abnormalities, gastrointestinal disturbances, and migraine headaches to disturbances of the heart and hypertension). He speculated that chronic psychologic worry might be important for the etiology of physiological pathology.

Selye was searching for a concept beyond homeostasis and its link to stress and described what he called *heterostasis* (1956, 1976, p. 85). He stated, "When faced with unusually heavy demands, however, ordinary homeostasis is not enough" (p. 85), because the "homeostat" has been raised to a level beyond its capacity, perhaps to a higher level (e.g., increased production)

3. Many investigators have pointed out the limitations of Selye's view (e.g., Mason, 1971a,b, 1975; McCarty and Pacak, 2000; Goldstein, 2000; McEwen, 2001) with regard to the fact that a variety of neuronal and hormonal responses participate in the response to stress, and the responses are not always nonspecific in the context of the general adaptation syndrome.

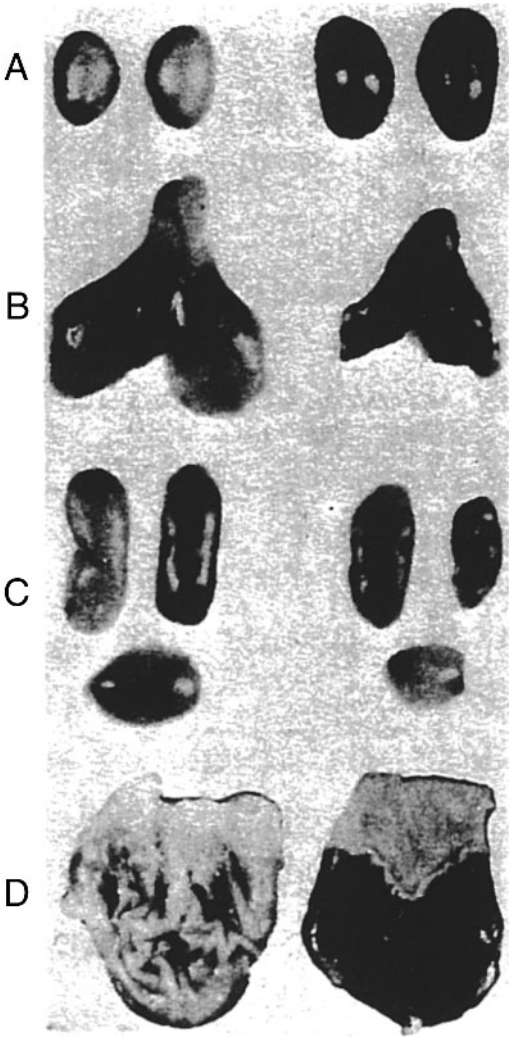

Figure 1.3
The biological alarm reaction. (*A*) Adrenals. (*B*) Thymus. (*C*) A group of the three lymph nodes. (*D*) Inner surface of the stomach. Organs in the left column are from unstressed rats; organs in the right column are from stressed rats (Seyle, 1956, 1976).

of function (see also Goldstein, 1995a, b, 2000). The major difference between the two states of bodily regulation is that one relates to maintaining normal balance, while the other relates to heightened activity with an accelerated rate of defense of bodily viability.

Many investigators have expanded on the insights of Bernard, Cannon, and Selye (e.g., Mason, 1975a, b; Goldstein, 1995a, b, 2000; Chrousos, 1996, 1998; McCarty and Pacak, 2000). One just has to look at the *Encyclopedia of Stress* (Fink, 2000) and the rich assortment of bodily events that are characterized to understand the impact of Selye. Often a critical feature of stress is that it is a threat to homeostasis and that discrepancies of expected outcome result in adaptive physiological responses (Goldstein, 1995a, b). Real stress occurs when expected measures far exceed what the physiological systems can tolerate (Goldstein, 1995a, b, 2000). Complex physiological systems designed to maintain internal stability use common effector systems; when there is a breakdown in one system, there are compensatory responses in others. Moreover, nature has insured safety valves in common effector systems (Goldstein, 1995a, b; Fink, 2000).

"Resetting" of homeostatic systems is an essential function for long-term survival (Goldstein, 1995a, b, 2000; Bauman, 2000). Selye argued that prediction and action in the face of discrepancy were indicative of both physiological and behavioral responses. Distress and defensive behaviors, used to accommodate the stress, have fundamental links to homeostatic regulation (table 1.1).

Of course, the continued elevation of the HPA axis will eventually compromise a number of normal functions (Chrousos, 1996, 1998). Not only are the classical stress systems (including the immune system) of concern to Selye (1982), but so are the profound changes in reproductive hormones. Table 1.1 should be read in context; the table represents chronic duress. This is not a pervasive biological phenomenon (Wingfield and Romero, 2001). In a variety of species, social stress in subordinates decreases levels of reproductive hormones and increases cortisol levels (Sapolsky, 1992, 1995, 1996; Herbert, 1996a). These events

Table 1.1
Behavioral and physical adaptations during acute stress

Behavioral Adaptation	Physical Adaptation
Increased arousal and alertness	Oxygen and nutrients directed to the CNS and stressed body site(s)
Increased cognition, vigilance, and focused attention	Altered cardiovascular tone, increased blood pressure and heart rate
Euphoria or dysphoria	Increased respiratory rate
Suppression of appetite and feeding behavior	Increased gluconeogenesis and lipolysis
Suppression of reproductive behavior	Detoxification from endogenous or exogenous toxic products
Containment of the stress response	Inhibition of growth and reproductive systems
	Inhibition of digestion-stimulation of colonic motility
	Containment of the inflammatory / immune response
	Containment of the stress response

Adapted from Chrousos, 1998

in turn decrease levels of oxytocin and prolactin as neuropeptides and increase corticotropin-releasing hormone (CRH) in extrahypothalamic sites (see chapters 3–5). This results in decreased reproductive fitness and may represent a short-term phenomenon, as the animal utilizes strategies to increase its likelihood of reproductive success by removing itself from the environment and placing itself in a more habitable one.

Homeostatic systems are typically couched, from an endocrine point of view, in terms of negative feedback (Goldstein, 1995a, b, 2000). The classic example is the restraint of the HPA axis and its attendant long-term effects on bodily tissue (see, e.g., Chrousos, 1997, 1998). Most regulatory systems have a way to decrease or inhibit the activation of physiological and

behavioral systems (see Le Magnen, 1984; Smith, 1997a). It is a mistake, however, to assert that one should be suspicious of "any hypothesis that includes a positive feedback loop" (Goldstein, 1995a, p. 28) or to suggest that positive feedback loops are "inherently unstable and rare" (Wingfield and Ramenofsky, 1999). In fact, both negative and positive feedback loops interact in the regulation of the internal milieu. Positive feedback loops or feed forward mechanisms are an important part of allostatic regulation (chapters 2–5) but they are nested within restraining physiological systems.[4]

Perhaps it is more correct to suggest that, in the context of homeostatic systems, positive feedback is less common than negative feedback (Fink, 1997, 2000; but see Kalra, 1993 for a discussion of both positive and negative feedback). One might want to distinguish, as I would (see also Pfaff, 1980, 1999; Herbert, 1993; Schulkin, 1999a) between systemic physiological regulation and the induction of neuropeptides (positive induction by steroid hormones) and the expression of central states that serve regulatory needs. Indeed, many of the regulatory events that underlie behavior, such as water and sodium ingestion, food ingestion, sex, and other appetitive behaviors, all have positive feedback loops (see chapters 2–5). The animal is changing state in order to change its behavior. If the change in behavior satisfies the "need," then the animal will change the state again.

It is important to note that prediction and anticipation of adverse events and behavioral adaptation by external cues (Miller, 1957, 1959; Weiss, 1970, 1971; Weiss et al., 1981) avert physiological pathology. For example, gastric ulceration can be prevented by the prediction of aversive events, which also reduces the elevation of the hormones of stress (Mason, 1971, 1975a, b). In other words, when uncertainty is pervasive, predictability has real consequences for both physiological regulation and behavioral expression (Miller, 1957, 1959; Weiss, 1970, 1971). Mason and his colleagues (1957, 1975a, b), for example, provided contexts

4. I appreciate very much the conversations I have had with Dave Goldstein on this issue.

in which predictability had real consequences on the activation of the HPA axis. Let's turn to Pavlov to consider anticipatory, prediction, and cephalic response to maintain homeostatic balance.

Cephalic Regulatory Responses: Expanding Homeostasis to the Anticipatory

The brain is intimately involved in regulatory events. Pavlov (1927) and many other investigators (see Stellar, 1954, 1960; Kuenzel et al., 1999) have expanded the notion of homeostasis toward the neural/behavioral regulation of local physiological regulation (see Smith's 1995, 1997a, b, 2000 informative depiction of Pavlov's work). The digestive reflexes are biological events through which to understand the relationship between an animal and its external environment. Pavlov noted (1894, 1895, p. 82), "the digestive canal, in respect to its chief function in the organisms" is like "a chemical factory where the raw material—food—undergoes a predominantly chemical treatment; this makes possible its absorption by the juices of the organism and its utilization by the organism for the maintenance of the vital processes." Pavlov, like Bernard, believed salivary secretion to be continuous with gastric secretion. Both serve the same end—namely, the utilization of food sources for bodily needs. Pavlov went on to demonstrate differential salivary secretion to different food sources. Dry food, for example, evokes greater salivary secretion than wet food.

Pavlov realized that a reflex could be associated not only with the sight and sound of food, but with other stimuli, and those other stimuli can elicit food-related physiological responses. A conditioned response to an arbitrary buzzer, for instance, prompted a salivary secretion of 16.5 ml (Pavlov, 1927, 1960). In other words, an arbitrary stimulus could elicit the "conditional" salivary reflex (Todes, 1997a, b; Rescorla, 1988).

Also of importance, Pavlov introduced the concept of *cephalic phase* in the process of digestion (see Powley, 1977, 2000; Mattes, 2000). The cephalic phase is an *anticipatory* response that

prepares the digestive tract to absorb and utilize nutrients essential for bodily maintenance and function (Grill and Berridge, 1985; Powley and Berthoud, 1985). The cephalic response has been demonstrated in several species, including humans, and in various hormonal systems (Teff, 2000; Mattes, 2000; Nederkoorn et al., 2000). The secretion of insulin, for example, to utilize nutrients also plays a functional role to minimize perturbations in homeostatic imbalance by the ingestion of the meal (Woods, 1991)—eating, digestion, and absorption provide the necessary nutrients to keep the organism viable; homeostatic mechanisms operate to keep tissue and fluid balance within viable limits. These events are mediated by vagal and brainstem function (figure 1.4; Powley, 1977). In other words, anticipatory and physiological homeostatic responses are invoked to minimize internal disruption, in terms of both low sources and excess sources (Solomon, 1980; Siegal and Allan, 1998). Compensatory responses are elicited in both contexts to minimize internal disruption. Exaggerated cephalic phase insulin secretory responses have been linked to obesity and conditioned hypoglycemia in animal models (Woods, 1991). It is important to note that a wide range of hormonal secretions that play a role in the regulation of the internal milieu can be elicited not only by stimuli that are inherently linked to what needs to be regulated, but also by arbitrary stimuli associated with them (Konturek and Konturek, 2000; Katschinski, 2000)—part of the evidence for the central nervous system involvement in the regulation of the internal milieu.

Neural/Behavioral Influences on Homeostasis

States of the brain profoundly influence regulatory physiology and behavior. The interactions between behavioral and physiological mechanisms in the maintenance of the internal milieu are widely accepted in many other domains—for example, thermal regulation. Temperature regulation has been under investigation for several hundred years (Blagden, 1775; Hunter, 1778; Langley, 1973), ever since the discovery of the means to mea-

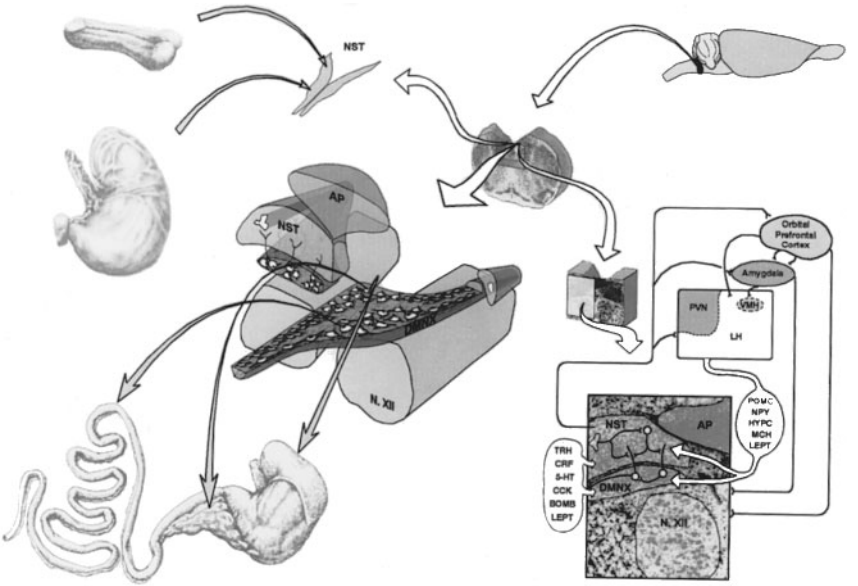

Figure 1.4
The organization of the dorsal vagal complex. The dorsal vagal complex (*center of figure*) is located in medulla oblongata (*upper right*). The complex consists of the dorsal motor nucleus (DMNX), nucleus of the solitary tract (NST), and area postrema (AP). Primary afferents from the different organs of the gastrointestinal tract, e.g., the tongue and stomach, project topographically to different regions of the NST (*upper left*). Preganglionic motor neurons of the DMNX project topographically to the organs of the gastrointestinal tract, e.g., the stomach, pancreas, and intestines (*lower left*). The neurons of the NST and DMNX are distributed in an organization that provides the architecture of the cephalic and other vagal reflexes (*lower right*). This circuitry of the dorsal vagal complex receives projections from more rostral limbic sites and contains dense concentrations of binding sites for different metabolic peptides and hormones (*lower right*). LH, lateral hypothalamus; N. XII, nucleus of 12 or the hypoglossal nucleus; PVN, paraventricular nucleus; VMH, ventromedial hypothalamus (Powley, 2000).

sure temperature (Galileo). Most mammals maintain internal or core temperature at a steady state internally; birds achieve thermal regulation by both physiological and behavioral means (Schmidt-Nielson, 1975). There is some variability in temperature regulation. Mammals also maintain thermal homeostasis by regulating body temperature using both external and internal means (Schmidt-Nielson, 1975; Gisolfi and Mora, 2000).

A variety of animals make nests for safety, reproduction, and warmth (figure 1.5). Curt Richter (1942–43) demonstrated in the laboratory what had been noted in the field—the behavioral regulation of thermal physiology by showing that rats will build nests under cold conditions. He later showed that these regulatory behaviors depend upon an intact hypothalamic pituitary adrenal axis.

Various investigators have demonstrated that a number of species (e.g., rats, goldfish, humans) will perform operant-conditioned behaviors such as bar pressing to gain access to something that would help them return their temperature to

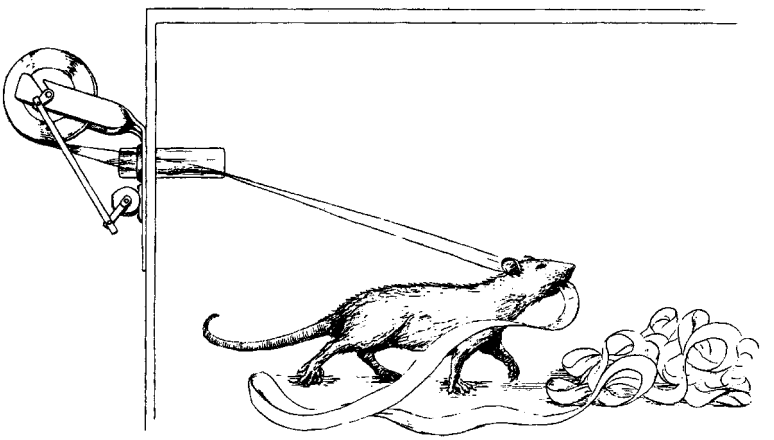

Figure 1.5
Behavioral regulation of temperature—building a nest (Richter, 1942, 1976).

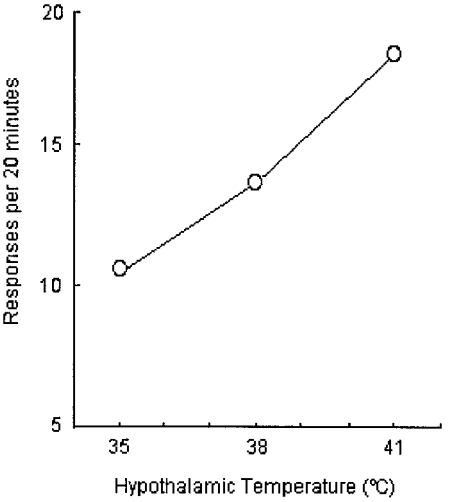

Figure 1.6
Bar pressing to regulate the temperature of hypothalamic neurons (adapted from Corbit, 1973).

within a tolerable range (Rozin, 1961, 1965, 1968; Stellar and Corbit, 1973). Of importance, regions of the hypothalamus respond to changes in thermal temperature, which results in behavioral changes (Satinoff, 1964, 1978). Rats, for example, under excess heat can perform operants to cool the hypothalamus directly (figure 1.6; Corbit, 1973; Cabanac and Dib, 1983). In humans, this regulatory behavioral response is associated with pleasure and / or the easing of discomfort (Cabanac, 1971, 1973, 1979; Stellar and Corbit, 1973).

Circadian Rhythms: Reactive and Predictive Homeostasis

Circadian or other rhythmic pattern regulation of bodily needs reveals diverse regulation of the internal milieu (see Richter, 1922, 1957a, 1965; Moore-Ede et al., 1982; Moore-Ede, 1986;

Wingfield and Romero, 2001). Adaptation is pervasive. Great variation in, for example, cortisol secretion reflects seasonal breeding, hibernation, and the ability to alter metabolic rates.

Thus a term called *predictive homeostasis* was coined by Moore-Ede (1986; Moore-Ede et al., 1982). Predictive homeostasis is an anticipatory adaptation and is to be distinguished from what he called *reactive homeostasis*. This distinction arose in the context of considerations of circadian timing systems in the brain and their role in behavioral and physiological regulation in the anticipation of future needs when they appear (Rosenwasser et al., 1988; Mistlberger, 1994).

Of importance in ethological and laboratory contexts, the circadian clock has been shown to play a role in helping the animal predict what time objects such as food, water, and sodium may appear. This is what Moore-Ede (1986) linked to predictive homeostasis (see also Henen, 1997). In other words, to be able to predict, one has to have a sense of time and be able to detect rhythmic events (Gallistel, 1992).

But the capacity to anticipate events is not just related to a circadian clock; the anticipatory secretion of insulin to food sources is not time-locked to a twenty-four-hour period (Woods, 1970). Behavioral and physiological anticipation in the service of maintaining internal stability is an evolutionary advance in the regulation of the internal milieu (see also Nicolaidis, 1977; Fitzsimons, 1979; Bauman and Currie, 1980; Mrosovsky, 1990).

Rheostasis was a term coined by Mrosovsky (1990) to account for the wide range of biological systems that are regulated differentially depending upon the context, the season, and the external competition. Set-point parameters in a number of systems demonstrate wide variation depending upon the context. Rheostasis was invented as a concept to account for the "physiology of change" (Mrosovsky, 1990).

Both reactive and predictive homeostasis underlie the behavioral and physiological regulation of the internal milieu. It is clear in the literature of appetite regulation, fear, delivery of babies, and even addictions that both are operative. Allostasis brings a whole new dimension, perhaps, to predictive homeo-

stasis in terms of emphasizing the extensive nature in which the central nervous system is involved in behavioral and physiological regulation.

We now turn to consider allostasis.

Origins of the Concept of Allostasis

Allostasis (Sterling and Eyer, 1981, 1988) was introduced to refer to the process of insuring viability in the face of challenge and change. Allostasis means achieving viability through change of state (bodily variation). It refers in part to the process of increasing sympathetic and HPA activity to promote adaptation and to reestablish internal stability (Sterling and Eyer, 1981; McEwen and Stellar, 1993). At the heart of the concept is the depiction of change in order to maintain (or achieve) a state appropriate to the circumstances. Allostasis also highlights our ability to anticipate, adapt to, or cope with impending future events (Schulkin et al., 1994).

For Sterling and Eyer (1988), "allostasis . . . involves whole brain and body rather than simply local feedback," and this is "a far more complex form of regulation than homeostasis" (p. 637). Sterling and Eyer focused on several systems, principally cardiovascular and immunological regulation. In their view, normal regulation for viability is one thing, long term overuse is another. For example, chronic arousal has potential long-term effects on normal renal/cardiovascular function (figure 1.7). These physiological changes are cephalic in nature; they are driven by the brain's attempt to maintain internal viability amid changing circumstances in diverse environments. But they can also reflect the failure of short-term solutions to solve a continuing problem. Allostatic overload (see below) is expressed when the renin-angiotensin-corticosteroids are elevated for long periods of time, during which sodium is ingested (chapter 2) but perhaps not sufficiently excreted. At these times, hypertension may emerge and compromise bodily health (Denton, 1982; Denton et al., 1996).

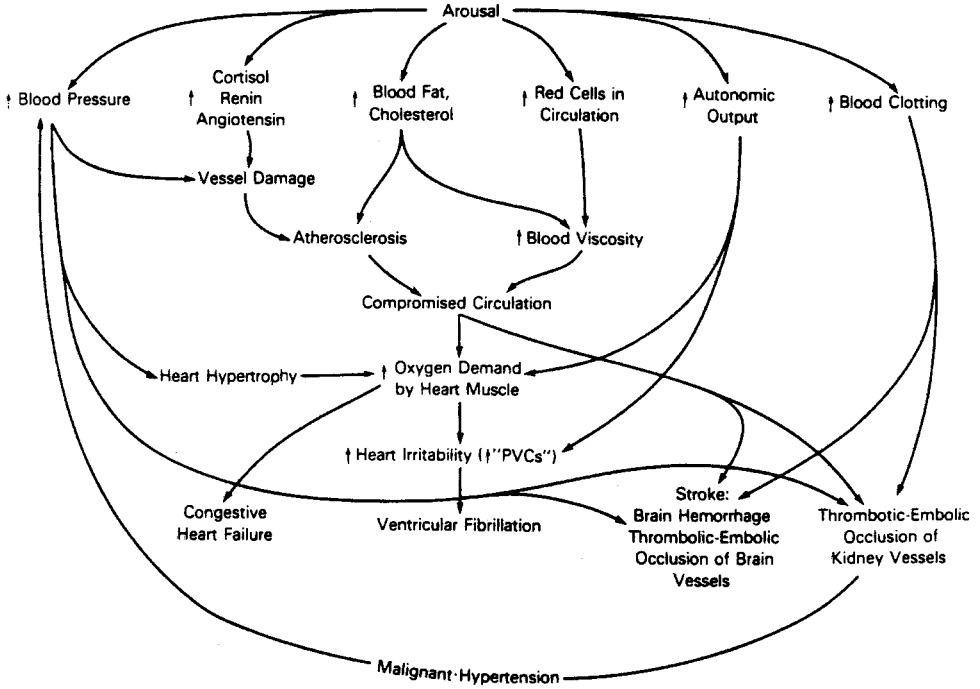

Figure 1.7
Renal-cardiovascular pathology from chronic arousal (Sterling and Eyer, 1981).

Consider another example, that of phosphate regulation of cephalic influence on physiological regulation. The kidney increases phosphate absorption when the animal is deprived of phosphate; the effects are seen within twenty-four hours. A behavior, increased phosphate ingestion, emerges to complement the actions of the kidney in the conservation and maintenance of phosphate levels in the body (Sweeny et al., 1998; Mulroney et al., 2000). It is important to note that the brain itself, in addition to affecting behavior, influences the phosphate regulatory function of the kidney. In phosphate-deprived rats, infusions of phosphate into the third ventricle reduced the expression of

phosphate transporter at the level of the kidney and the brain (figure 1.8), despite the fact that the plasma phosphate remained low (Mulroney et al., 2000).[5] The brain, in other words, has a profound (anticipatory) effect on systemic (kidney) physiological regulation (e.g., Matsui et al., 1995). In fact, the brain receives and sends neural projections directly to most peripheral organs (Powley, 2000) and therefore is involved in most local homeostatic functions.

Chronic arousal, or what Sterling and Eyer referred to as "arousal pathology," is one of the primary features of the modern age. In a carefully presented argument, Eyer and Sterling (1977) reviewed the comparative cultural literature and found dramatic differences in blood pressure that reflected the extent to which chronic arousal was a real everyday factor. This reflects diet, level of exercise, and biological vulnerability. But let us not mythologize the past as peaceful and the present as contaminated by overstimulation. There was overstimulation in the past; nonetheless, examples of physiological responses related to chronic arousal are elevated use of energy; cardiovascular activity; decreases in reproductive function, growth, and appetite; and strain on the immune responses and the aging process (Sapolsky, 1992, 1995; Seeman et al., 1997; Johnston-Brooks et al., 1998).

Sterling and Eyer (1981, 1988) thought major causes of death were linked to arousal pathology: Too much excitement, too much light, too much salt and consumption led to premature death. Fluctuations dominate in systemic physiological stability, and it is the organismic response by the brain that they (Sterling and Eyer, 1988) thought necessitated the invention of the term *allostasis.* "Feedforward" mechanisms induced in the brain by steroid activation of neuropeptides—or neurotransmitter systems, for example—may have an impact on the cardiovascular system, where blood pressure rises in the context of chronic arousal (see Goldstein, 1995a, b, 2000).

5. See Mrosovsky's (1990) discussion on calcium regulation.

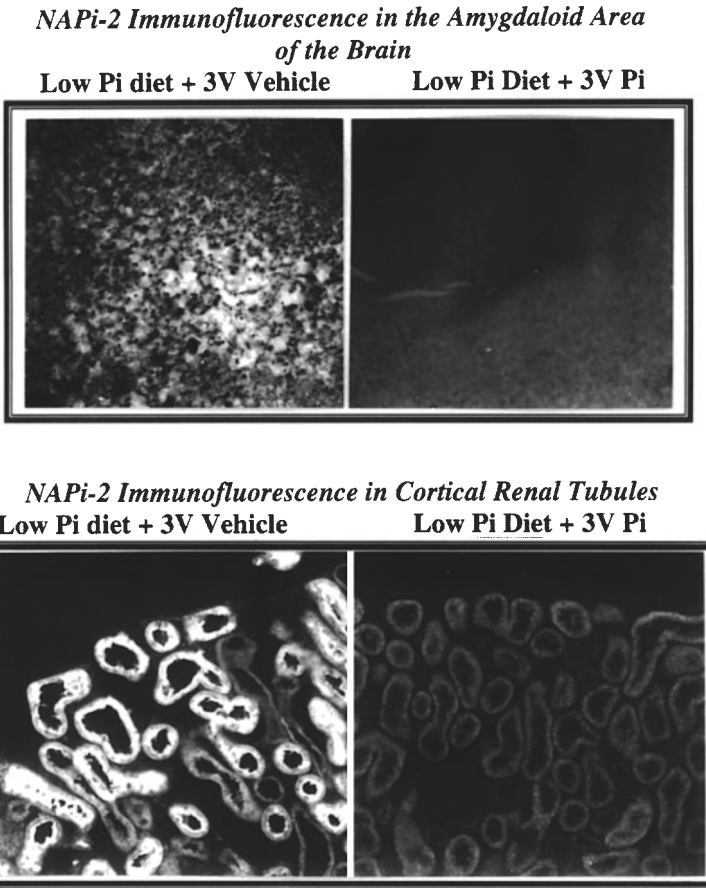

Figure 1.8
Renal and central nucleus phosphate transporter changes in response to central infusions of phosphate in phosphate deficient rats (Mulroney et al., 2000).

Consider several meanings associated with the concept of allostasis (see Sterling and Eyer, 1988; McEwen, 1999; Koob and LeMoal, 2001).

1. *Allostasis:* The process by which an organism achieves internal viability through bodily change of state. Allostasis comprises both behavioral and physiological processes that maintain internal parameters within the limits essential for life.
2. *Allostatic State:* Chronic overactivation of regulatory systems and the alterations of body set points.
3. *Allostatic Overload:* The expression of pathophysiology by the chronic overactivation of regulating systems.

Common physiological mediators include glucocorticoids, DHEA, catecholamines, pituitary hormones, neuropeptides, and cytokines (McEwen, 1998a, b, 2001). In the short term, these mediators serve as beneficial. The immune mediators, in the short term, are boosted in defense of bodily viability, but in the long term, they tend to be compromised in function, both in the periphery and the central nervous system (Sapolsky et al., 2000; Dorries, 2001). The same holds for cardiovascular and metabolic function (Sapolsky et al., 2000), which is why it is important to consider both short-term adaptations and long-term allostatic overload.

Sapolsky and colleagues (2000), in a nice review of the literature on glucocorticoid hormones and stress, suggested that we try to understand the glucocorticoid actions in the following four contexts:

1. Their permissive actions
2. Their suppressive actions
3. Their stimulating actions
4. Their preparative actions

This is a useful way in which to envision glucocorticoid hormones in regulatory physiology. I am mainly focused on their stimulating and preparative actions, of the cephalic role in

regulatory physiology. In part, this occurs through a feedforward mechanism (one form of allostatic regulation), which I assume would be glucocorticoids stimulating and inducing preparative actions (see chapters 2 and 3).

What we can say is that when the physiological mediators, such as cortisol, are overexpressed for long periods of time, pathology can emerge. Examples of allostatic overload include loss of bone mass in people with depression, which is associated with moderately elevated levels of glucocorticoids (Michelson et al., 1996; chapter 4 of this book), and atrophy of neurons in the hippocampus as a result of recurrent depression (Sheline et al., 1996; Bremner et al., 2000). By compromising hippocampal function, allostatic overload impairs normal HPA function as well as memory processes (Axelson et al., 1993; Starkman et al., 1993; Sheline et al., 1996; McEwen, 1997, 1998a, b). Prolonged exposure to glucocorticoids can result in deterioration of the hippocampus in several species (Sapolsky, 1992, 1995; McEwen and Sapolsky, 1995). Prolonged glucocorticoid secretion can compromise glucose transport and utilization, energy store, and use; it can potentiate neuronal toxicity via excitatory amino acids, atrophy of dendrites, reduce neurogenesis (Sapolsky, 1992, 2000). That is, high levels of glucocorticoids (from Cushing's syndrome, from depression, from initial trauma in posttraumatic stress disorder) can have potentially damaging effects on hippocampal tissue and on cognitive functions (figure 1.9; McEwen and Sapolsky, 1995; Bremner et al., 1995, 2000; Sapolsky, 2000).

There are three types of allostatic overload: (1) overstimulation by frequent stress, resulting in excessive stress hormone exposure; (2) failure to inhibit allostatic responses when they are not needed or an inability to habituate to the same stressor, both of which result in overexposure to stress hormones; and (3) inability to stimulate allostatic responses when needed, in which case other systems (e.g., inflammatory cytokines) become hyperactive and produce other types of wear and tear (figure 1.10; McEwen, 1998a, b, 2001).

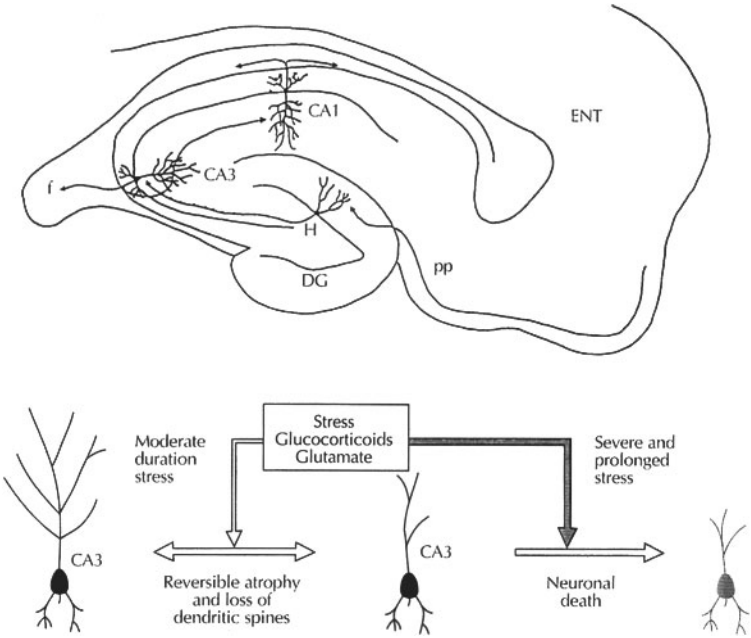

Figure 1.9
Hippocampal neuronal changes in stressed animals (McEwen, 1999).

Indicators of allostatic overload include the following (adapted from McEwen, 1998):

- Cardiovascular pathology
- Metabolic deterioration
- Brain atrophy
- Immune dysfunction and vulnerability to viral impact
- Bone demineralization
- Vulnerability to preterm delivery
- Changes in the sensitization processes

Thus susceptibility to disease is a feature of allostatic overload. The cumulative effect of allostatic overload may be subtle and

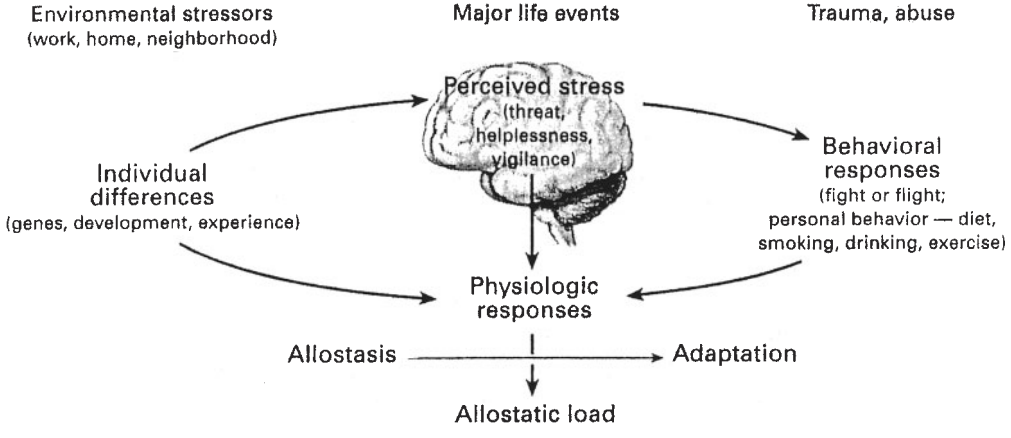

Figure 1.10
The stress response and development of allostatic load as depicted by McEwen (1998).

gradual (e.g., accumulation of body fat and atherosclerotic plaques; McEwen, 2001) or not subtle, as in obesity and change in fat deposition.

Levels of cortisol that are higher during the evening than in the morning, when the hormone is usually elevated, produce greater metabolic costs on the body (e.g., glucose tolerance and insulin regulation; see Plat et al., 1999). Failure to decrease levels of cortisol during the dark phase of circadian rhythm, for example, may reflect both an allostatic state and a vulnerability to physiological deterioration (McEwen, 1999; Van Cauter et al., 2000).

Consider the expression of corticotropin-releasing hormone (CRH) in the brain, something that will be discussed in more detail in later chapters. The overactivation of CRH expression may be one example of allostatic overload (chapters 3–5). What does this mean? Under extremely adverse conditions, such as during chronic anticipatory angst, CRH, the major molecule of duress (Nemeroff et al., 1984; Gold et al. 1988a, b), is overexpressed in regions of the brain linked to fear and anxiety (Koob et al., 1993; Kalin et al., 1994; Makino et al., 1994a, b). When this occurs under extreme conditions, both autonomic and behavioral functions related to fear and anxiety are exacerbated. If these conditions persist over long periods of time (i.e., chronic stress), decay of bodily organs emerges (McEwen and Stellar, 1993; McEwen, 1997, 1998a, b).

Along with compromised HPA function, possibly mediated in part by a damaged hippocampus, there is heightened vigilance incurred by amygdala stimulation to perceive fearful events (Schulkin et al., 1994). This heightened and perhaps chronic vigilance is sustained by high glucocorticoid levels and by the induction of elevated CRH production in the central nucleus of the amygdala and the bed nucleus of the stria terminalis (Swanson and Simmons, 1989; Makino et al., 1994a, b; Watts and Sanchez-Watts, 1995; see chapter 3 of this book). This is not necessarily a pathological state, but an adaptation. An adaptation turns into a pathology, however, when it continues for too long (Rosen and Schulkin, 1998).

Conclusion

Homeostasis is a familiar term in our scientific lexicon; *allostasis* is not. However, there do seem to be physiological and behavioral events that fall outside of a single concept of homeostasis. One can understand that the concept of homeostasis, when expanded from a rather rigid fixed beginning, could perhaps account for allostasis. I would suggest that the concept of allostasis is useful in reorganizing our thinking and facilitating research into understanding regulatory physiology. Part of what allostasis adds is that regulatory events are both behavioral and physiological, and furthermore, that such events are reactive and anticipatory (Moore-Ede, 1986; see Sterling and Eyer, 1988; Schulkin et al., 1994) and that a brain with feedforward mechanisms is one mechanism toward this end.

Allostatic regulation in part reflects cephalic (anticipatory to systemic physiological regulation) involvement in primary regulatory events (Sterling and Eyer, 1988). Evolution selected an important adaptive feature in animals: the anticipation of events. In emergency situations (Wingfield and Ramenofsky, 1999; Wingfield and Romero, 2001), for example, animals with great diversity can increase or decrease, in anticipation of metabolic requirements, the rate of their own regulatory events. Animals anticipate events and modify their physiology accordingly, both daily and seasonally (Nelson and Drazen, 2000). The strategy in environmental contexts for regulation depends on the hormonal and physiological mechanisms that maintain stability and underlie energy expenditure. For example, glucocorticoid hormones are secreted to maintain internal stability in changing environments with regard to nutrient availability and energy homeostasis (Dallman et al., 2000).

Multiple mechanisms are at play at both behavioral and physiological levels of analysis. This all leads to the animal maintaining bodily viability. The route from Bernard to Richter bridges physiological and behavioral mechanisms serving to maintain internal viability. There is no one path to survival, because the world is complex and changing.

The concept of allostasis figures prominently in the recognition of the changing world in which animals like ourselves are constantly adapting, or trying to adapt. With this, the central nervous system involvement with systemic physiological regulation has evolved. Animals need to change state and coordinate a number of competing drives to remain viable. Homeostatic mechanisms tend to resist change of state; allostatic mechanisms were designed to adapt to change. Allostatic mechanisms—both behavioral and physiological—are responsive to anticipatory needs within changing contexts. Like homeostasis, allostasis serves to maintain internal stability.

Allostasis works well when the systems are turned on only when needed and turned off again when no longer in use. However, when allostatic systems remain active, they can cause wear and tear on tissues and accelerate pathophysiology—a phenomenon called *allostatic overload* (McEwen and Stellar, 1993; Schulkin et al., 1994; McEwen, 1997, 1998a, b; Schulkin et al., 1998).

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Chapter 2

Central Motive States: Feedforward Neuroendocrine Systems in the Brain

Motivational states are generated by the brain. As my deceased colleague Alan Epstein would say when discussing central motive states and drinking behavior, "Thirst is a state of the brain" (Epstein et al., 1973). However, the acceptance of concepts such as motivation has declined in some intellectual traditions. They warrant resurrection, particularly in the context of the hormonal regulation of behavior, and in the context of allostatic regulation of behavioral and physiological events.

This chapter begins with a discussion of the concept of motivation—its relationship to the central nervous system function and specific hormonal systems. I give some of the logical reasons why the concept of motivation is required in our explanation of behavior. I suggest that the behavioral expression of central motive states (e.g., craving sodium, cocaine, etc.) is coded by neuropeptide expression in the brain and regulated by steroids, that is, positive regulation of neuropeptide expression typically, but not exclusively, by steroids (see Herbert, 1993; Schulkin, 1999a; Pfaff, 1999). Recall that allostatic regulation is anticipatory-cephalic (Sterling and Eyer, 1988; Schulkin et al., 1994). Although homeostatic explanations tend to emphasize negative restraint (Goldstein, 1995a, b; Fink, 1997, 2000), central motive states of the brain are, in part, regulated by steroids in a feedforward fashion, nested within restraining systems.

The concept of allostasis is particularly germane in the analysis of regulatory systems. Many kinds of adaptive responses are not strictly linked to homeostatic regulation. Animals are optimizing their regulatory requirements relative to the season and

Table 2.1
Effects of glucocorticoid hormones

Short-Term Adaptation	Long-Term Disruption
Inhibition of sexual motivation	Inhibition of reproduction
Regulate immune system	Suppress immune system
Increase glucogenesis	Promote protein loss
Increase foraging behavior	Suppress growth

Adapted from Wingfield and Romero, 2001.

the context in which they find themselves (Bauman and Currie, 1980; Wingfield and Romero, 2001). Glucocorticoids are elevated under diverse conditions and are not strictly relegated to the management of stress (table 2.1). But, consider the diverse roles they play in what Wingfield and Romero (see also Sapolsky et al., 2000) termed "contexts of duress."

These effects have relevance for our consideration of motivational systems. Cortisol can facilitate motivational behaviors essential to maintain water and sodium balance and energy balance (for the preparatory role of glucocorticoids, see Sapolsky et al., 2000). These are two systems in which feedforward mechanisms are known to play somewhat of a role in the regulation of appetitive motivational systems. Allostasis is perhaps a more useful concept than traditional homeostatic concepts (which were good for the kidney) but not for the role of motivated behaviors and functional roles in maintaining physiological viability.

Let us turn first to a consideration of the concept of motivation and then to feedforward systems (one kind of allostatic regulation). Thus I begin with a general discussion of the concept of motivation and central motive states of the brain, general features in the brain that underlie central motive states, and then a description of allostatic regulation via feedforward neuroendocrine mechanisms that underlie several central motive states.

The Concept of Motivation

The concept of motivation has figured in the explanation of human behavior throughout recorded history. It may have, in part, evolved as a cognitive ability that was selected to facilitate the prediction and explanation of goal-directed behavior.

Freud (1924), for example, understood that the concept of drive, or libido, generated by the brain was fundamental to explain behavior. But both his drive-reduction model and his singular focus on sexual behavior limited his vision. Although he started out studying the brain to help explain motivated behavior, he abandoned that approach by the turn of the century.

The concepts of motivation and drive were also fundamental in the scientific lexicon of psychology and ethology (Lashley, 1938; Hebb, 1949; Tinbergen, 1951). Unfortunately, however, motivational systems have always had a tendency to multiply like instincts. Of course, that is no different from the unrestrained multiplication of the newest peptide receptor sites (note the proliferation of serotonin, angiotensin, and CRH receptor sites).

Here are some questions to consider:

1. The concept of motivation is bedeviled by questions such as: How many kinds of motivational explanations are there? There are several, and they are not necessarily mutually exclusive. They include drive reduction or homeostatic theories, incentive theories, hedonic theories. For example, when food is attractive, it can be attractive because the animal is hungry (internally pushed); the food is interesting and salient (externally pulled toward an object); or the food is pleasing and hedonistically satisfying (see Toates, 1986; Berridge, 1996), or some combination of all three.
2. Is there a family of core motivational states? Yes. There are core motivational states that subserve the health and reproductive fitness of the animal (Pfaff, 1999; Schulkin, 1999a).

3. What constraints are there in the legitimate use of the term? The constraints come from both psychobiological and neuroscientific levels of analysis (Nader et al., 1997; Swanson, 2000).
4. When is it legitimate to invoke a motivational explanation? It emerges when the concept of motivation provides a definite context and legitimate scientific function in the explanation of animal and human behavior (Hinde, 1968; Toates, 1986).

Motivational systems have long been understood in the context of anticipatory systems generated in the brain (Stellar and Corbit, 1973; Epstein, 1982) that function along with local physiological systems to maintain bodily viability. Perhaps this is why the concept of allostasis may be particularly important to motivational systems that have relevance to bodily viability.

Eliot Stellar (1954) formulated a view held by a generation of investigators about the general mechanism that underlies motivational states. In his classic paper, "The Physiology of Motivation," Stellar suggested that the hypothalamus played a fundamental role in the regulation of excitatory and inhibitory central states (figure 2.1; Stellar, 1954; see also Hebb, 1949). The framework was one in which both internal physiological changes and sensory detection mediated by central hypothalamic sites resulted in behavioral adaptation. Although often construed as merely under hypothalamic control, other regions of the brain are obviously involved in the expression of motivated behaviors, including the cortex and brainstem.

Experiments using electrical (Olds, 1958) and chemical self-stimulation of the hypothalamus and other forebrain sites (Miller, 1957; Grossman, 1968) suggested that stimulation of specific systems in the brain could result in the expression of specific behavior. This result was subsequently challenged by findings that the same site in the hypothalamus, when stimulated, could elicit a range of behaviors such as thirst, hunger, or sex drive, depending upon the context (Valenstein et al., 1970; Valenstein, 1973; see also Wise, 1971). One reasonable explana-

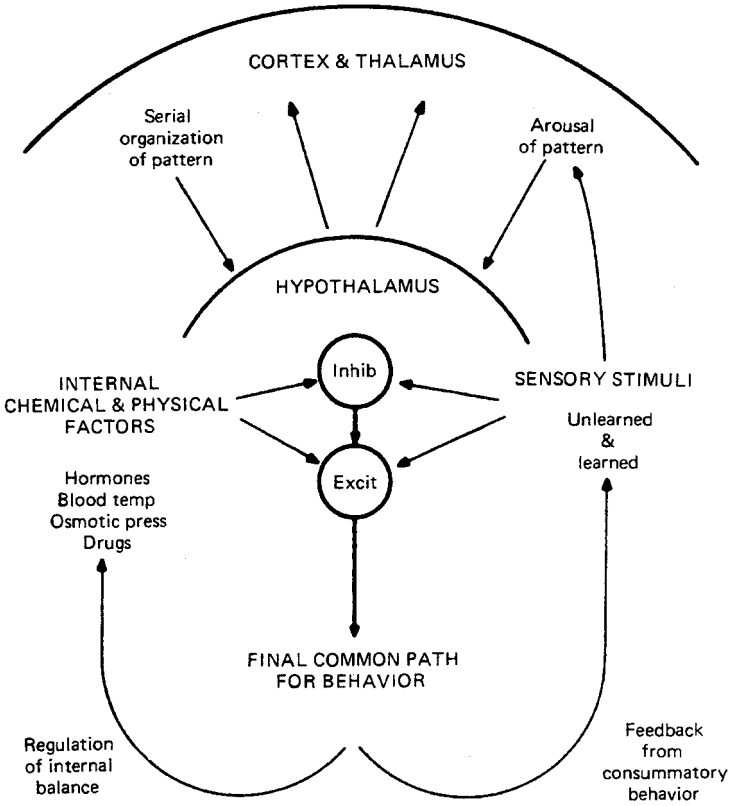


Figure 2.1
The physiological control of motivated behavior (Stellar, 1954).

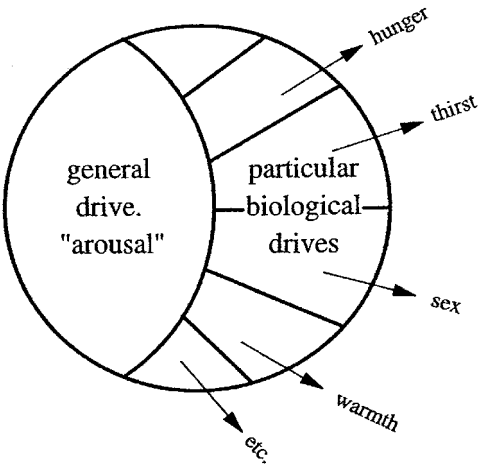


Figure 2.2
The concept of drive or motivation has at least two types of components. There is a component necessary for the *energization* of behavior—arousal—that is general across motivational states. There are also mechanisms that respond to humoral and other particular physiological signals arising from specific biological needs, such as hunger, thirst, sex hormones, temperature changes, and the like. This type of component gives *direction* to motivated behavior (Pfaff, 1999).

tion for the effects of electrical self-stimulation on behavior is that the stimulation increases the salience of environmental stimuli (Berridge and Valenstein, 1991). In retrospect, the expression of behavior by the activation of neural circuits depends upon context or ecological conditions. Behavior does not occur in a vacuum.

This idea that there are no specific signals for the elicitation of behavior also does not always hold. There are both general and specific mechanisms that underlie motivated behaviors (Pfaff, 1999; figure 2.2). Neuropeptides, for example, play specific roles in the expression of motivated behaviors (see Pfaff, 1999; Schulkin, 1999a), in which there are a number of examples of feedforward allostatic regulation. But neuropeptides may also play diverse roles in both physiological and behavioral

regulation, where they have specific physiological functions (e.g., angiotensin, oxytocin, vasopressin; see Herbert, 1993; see below).

Thus motivational states should be characterized as the readiness to behave adaptively in suitable environments (Hinde, 1968, 1970). Motivational behaviors are best understood in the context of being directed toward a certain goal or set of goals in a certain trajectory (Tinbergen, 1951). Neural systems potentiate or depotentiate the readiness for behavioral expression (von Holst and St. Paul, 1963; Gallistel, 1980). Also note, however, that the thirst the animal is trying to quench at the water hole occurs in the context of the fear of possible predation and the need to detect danger signals. The hunger may be related to a specific nutrient or mineral. Motivational systems compete for expression (see McFarland, 1991).

Figure 2.3 depicts one of the ways in which Neil Miller and his colleagues and students understood motivation (Miller, 1957, 1959). For Miller, motivation was an essential category in experimental design; the physiological and neural levels of analysis were linked to the behavioral level of analysis. The behav-

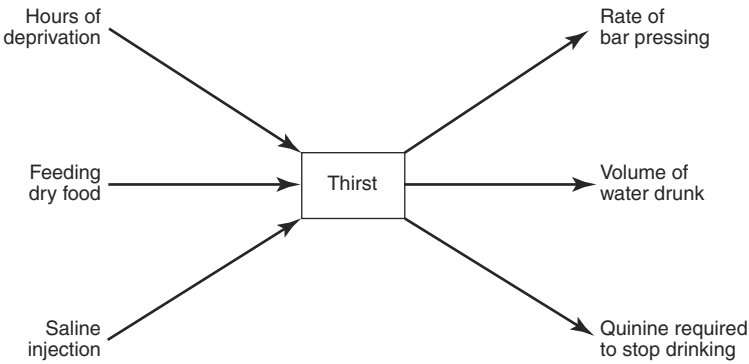


Figure 2.3
The instrumental way in which Neil Miller characterized drive states and in this case the state of thirst (Miller, 1959; Toates, 1986).

iors in the laboratory often reflected the degree of deprivation (water), the ability to undergo travail to approach or avoid a set of environmental conditions, and attractiveness of the water source. I would also add some additional factors to the figure: incentives, genetic and temperamental features, competition with other drives.

At a psychological level, motivational states were analyzed in the context of behavioral flexibility to attain a goal—the range of behavioral options that could be employed toward an end and reflected in a motivated animal (e.g., Tinbergen, 1951; Teitelbaum, 1967, 1977; Epstein, 1982). The concepts of goal and behavioral flexibility figured as criteria for motivation, and a range of physiological responses is essential to *allostatic regulation,* which is why the concept of allostasis may be of importance in the consideration of motivational systems that subserve regulatory physiology.

Limitations of the Homeostatic View of Central States

The concept of motivation is linked to those of drive, energy (e.g., Freud, 1924; Hull, 1943; Lorenz, 1981). The metaphor of motivation is hydraulic in nature. No doubt, the degree of food deprivation and the degree of decrease in glucose levels result in the search for food and instrumental behaviors to procure the required nutrients. The homeostasis model, linked to depletion and repletion of energy and the use of energy, is part of the consideration of a motivational state. But it is neither a necessary nor a sufficient condition (Toates, 1986; Stricker, 1990). The ingestion of food depends upon a number of factors, including the palatability of the food (Young, 1941, 1966) and the assessment of danger in the environment in which the food is located.

The drive-reduction model of learning was impoverished. Many animals can learn about where sources of food or water or salt are at a time when they may not be in any of these central motivation states (Tolman, 1932). One example will suffice. Rats can learn where salt is and how to acquire it even when they are not hungry for sodium (Krieckhaus and Wolf, 1968; Schul-

kin, 1991). Information processing about objects at locations, how to acquire a substance, and even what time of day a particular nutrient might appear (Rosenwasser et al., 1988) occurs with or without sodium hunger at a particular time. Two points stand out from these observations: central motivation states are a larger class than simple drive-reinforcement categorization (see also Tolman, 1932). The simple drive-reduction models of learning (in which there is no clear set point) (see also Hull, 1943; Miller, 1959) were placed in a larger behavioral context in which learning about objects was much broader (Shettleworth, 1998).

In fact, Miller (1959) helped introduce an information-processing model to the study of animal learning, broadening the narrow behavioristic conception that had limited the study of animal behavior. Some years later, behavioristic studies would themselves become part of the cognitive revolution that eventually swept through psychology, including behaviorism (see Rescorla and Wagner, 1972; Dickinson, 1980).

Information-processing systems that represent objects are integral to motivational systems, complex or simple. The brain is an information-processing organ; motivation represented in neural circuits is coded by neuropeptides or neurotransmitters (Herbert, 1993; Pfaff, 1999; Schulkin, 1999a). Thus the concept of motivation is tied to function and evolution and needs a regulatory construct, such as allostasis, which emphasizes anticipatory, reactive, and feedforward regulatory systems in the brain that underlie behavior. It plays an important epistemological role in the explanation of behavior; that is, the logical status of motivation in our scientific lexicon. Motivation predisposes animals to behave "predictably" within an internal and external context and under conditions within the evolutionary context of the organism.

Central Motive States

The concept of a central state is relatively modern and more linked to allostatic regulation (central nervous system involvement in systemic physiological regulation rather than

homeostasis). It is clearly stated in the works of Lashley (1938), Tinbergen (1951), Hinde (1970), Hebb (1949), Morgan (1966), Beach (1942) and Stellar (1954). A central motive state is a state of the brain (Lashley, 1938; Beach, 1942) that is often expressed in terms of two central tendencies toward objects that are either attractive and approached or aversive and avoided (table 2.2; Konorski, 1967; Lang et al., 1998).

For example, there are two prominent features of the central motive state of hunger. The first is the appetitive phase—the search for the desired entity—and the second is the consummatory phase—actually ingesting the desired item or otherwise fulfilling a need. This distinction was expressed early on by the American naturalist Wallace Craig (1918) and later by the pragmatist philosopher John Dewey (1925). Within a short period of time, it was incorporated within ethology (Tinbergen, 1951; Marler and Hamilton, 1966; Hinde, 1970), psychobiology (Beach, 1942), and physiological psychology (Hebb, 1949; Stellar, 1954).

Sodium appetite, as I previously mentioned, is a good model of a motivational system (see Wolf, 1969; Denton, 1982; Schulkin, 1991). On the appetitive side, salt-hungry rats or sheep will press a bar for salt in relation to the degree of sodium they need (Quartermain and Wolf, 1967; Denton, 1982). Salt-hungry rats are also willing to run down an alley for very small quantities of salt (about 0.1 ml for each run; Zhang et al., 1984; Schulkin et al., 1985). Moreover, the intensity of running is related to the strength of the sodium hunger induced by mineralocorticoids alone or by the combination of angiotensin and mineralocorticoid hormones (figure 2.4).

Next, consider the consummatory phase. Infusions into the oral cavity reveal a pattern of facial responses linked to ingestion or rejection (Grill and Norgren, 1978a) that are in fact governed by the caudal brainstem (Steiner, 1973; Grill and Norgren, 1978b). A sweet taste usually, though not always, elicits an ingestive sequence, a bitter taste, a rejection sequence. Hypertonic sodium chloride elicits a mixed ingestive-rejection sequence in a rat that is in sodium balance. But when rats are salt-hungry, the oral-facial response to sodium chloride changes. The re-

Table 2.2
The essential phases of central motive states

Initiation Phase
Deficit signals
Incentive and exteroceptive sensory information
Cognitive information (conditioning, anticipatory)
Circadian influences
Long-term memory
Procurement Phase
Arousal (general)
Foraging behavior
Locomotion
Sensory integration
Previous experience
Short-term or long-term memory
Incentives
Visceral integration
External cues
Consummatory Phase
Programmed motor responses
Discriminatory factors
Satiety mechanisms
Reinforcement
Hedonic motivation
Competition for Behavioral Expression
Multiple motivational states
Environmental factors
Assessment of success/failure

Adapted from Swanson, 1988.

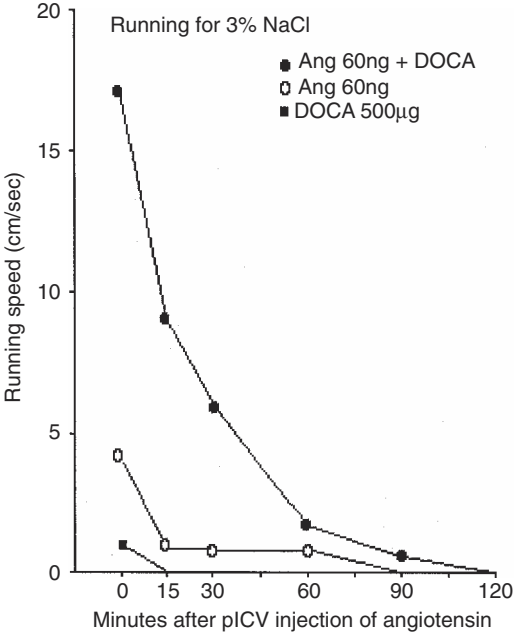


Figure 2.4
Running speed for 3% NaCl of rats that were treated with only DOCA (deoxycorticosterone), only angiotensin, or with both DOCA and angiotensin (adapted from Zhang et al., 1984).

sponse is now largely ingestive; the rejection response decreases (Berridge et al., 1984; Berridge and Schulkin, 1989). This effect, at least in rats, is specific. Other tastants (e.g., hydrogen chloride) elicit equally mixed ingestive-aversive responses that are not changed when the rat is salt hungry (Berridge et al., 1984). Moreover, the oral-facial change to intraoral infusion of hypertonic sodium chloride is not dependent upon experience. The phenomenon is demonstrated the first time rats are sodium depleted (Berridge et al., 1984), and this hedonic shift can be associated with arbitrary gustatory stimuli that have been associated with sodium (Berridge and Schulkin, 1989) (figure 2.5).

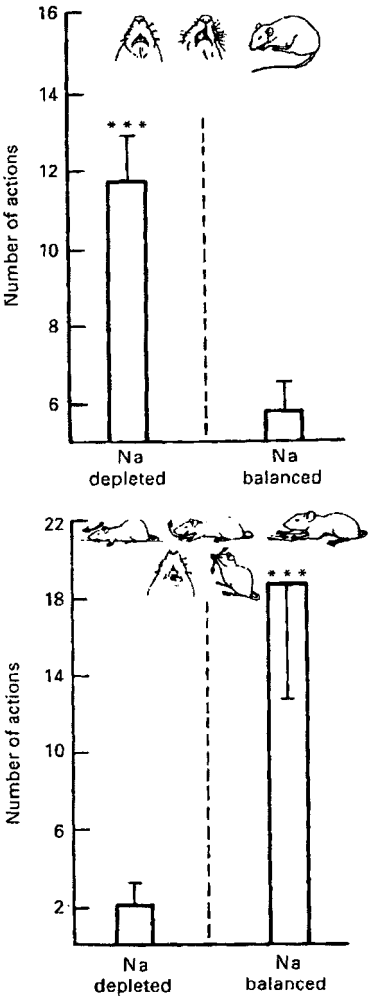


Figure 2.5
Taste reactivity profiles of rats to intraoral infusions of hypertonic NaCl (sea water) when sodium hungry (Na depleted) and when not hungry for sodium (Na balanced). The top panel represents positive facial responses to the intraoral infusions, and the bottom panel represents negative or rejection responses to the infusions (Berridge et al., 1984; Berridge and Schulkin, 1989).

Palatability Judgments

Palatability information processing, in this case of hypertonic sodium (sea water), underlies central motive states such as the tendency to ingest sodium (Berridge et al., 1984; Berridge and Schulkin, 1989). The behavioral and neural mechanisms that underlie palatability are unconscious, and the overuse of these reward mechanisms (e.g., during addictions) have been linked to a form of *allostatic dysregulation* (Koob and LeMoal, 2001).

The facial patterns depicted in figure 2.6 are widespread in a number of primates to sweet stimuli and acceptance, to aversions and rejection to bitter substances (Steiner et al., 2001). Palatability judgments are not the same as the acceptance of a

Figure 2.6
Facial expressions to infusions of bitter and sweet tasting substances (from Berridge, 2000; Steiner et al., 2001).

substance or the sensory characteristics (Berridge and Grill, 1983; Berridge and Schulkin, 1989).

Allesthesia is a more physiological term that has been used (Cabanac, 1971, 1979) to depict the regulatory role of hedonics in behavior. Like the example above with regard to sodium hunger, shifts in everything from temperature to sexual attraction underlie hedonic judgments. In fact, one of the more interesting examples is the motivational behaviors that are revealed with regard to cooling the brain: Rats will press a bar to alter their brain temperature (Corbit, 1973; Stellar and Corbit, 1973). Key features of central states are the appetitive behaviors and their diverse expression and consummatory behaviors.

Central states are again wider than this class. Central states can also be depicted as remaining in states of ease and comfort (e.g., the cat's seductive peering behavior and grooming behaviors of social animals).

The ingestion of sodium, like the attraction to a number of appetitive and subsequent consummatory objects, is determined by salience, interests (Bindra, 1969, 1978; Berridge, 1996; 2000), hedonic attractiveness (Young, 1949), and sensory stimulation (Beebe-Center, 1932; Schneirla, 1959, 1965). The influence through hedonic stimuli is an ancient theme in what renders animals attracted to and repelled from objects.

In the literature of ingestion, one distinguishes preference from appetite (Young, 1959) and liking from wanting (Berridge, 1996). The concept of central motive state serves as an umbrella term in accounting for a number of different functions. In other words, central motive states reflect the interactions between the state of the animal, its prior associations, drive state, hedonic judgments about events, and the incentives that are evaluated in suitable environmental contexts (Bindra, 1969; Bolles, 1975; Toates, 1986; Mook, 1987). To the sodium-hungry animal, the hypertonic salt stands out, is hedonic, and is positive. Sources where sodium was located are recalled in memory, objects associated with sodium are salient, (Krieckhaus and Wolf, 1968; Schulkin, 1991). Central motive states reflect the

activation of brain function and the orientation to objects in one's environment.

Similar scenarios hold for most hormonally induced central motive states. Such motivational states result in behaviors that include the craving for and ingestion of food and water, sex behavior as well as social attachments (including parental behavior), fear, and addictive drug use (see Koob et al., 1989; see chapter 5 on addiction). And in each of these examples, feedforward *allostatic* regulatory mechanisms are at play.

The idea of the simple motivational system is that it is tractable at many levels of analysis (Wolf, 1969). This is part of the excitement in studying phenomena such as sodium hunger or thirst, which are less sexy examples when compared with sex behavior, parental behavior, and drug cravings. All these behaviors result from central motive states induced and sustained by hormonal mechanisms. They all feature appetitive as well as consummatory phases of motivation and include salience or interest in various objects. The behaviors linked to hormonal effects on neuropeptides or neurotransmitters are particularly amenable in the analysis of the central mechanisms underlying motivated behavior (Schulkin, 1999a; Pfaff, 1999).

The roots of motivational systems are found within a biological perspective (Sober and Wilson, 1998); behavior evolved to serve animal reproductive ability and fitness (figure 2.7). Motivational states often cause a state change, but are also designed to maintain internal viability and to navigate external circumstances (see Gallistel, 1975, 1980).

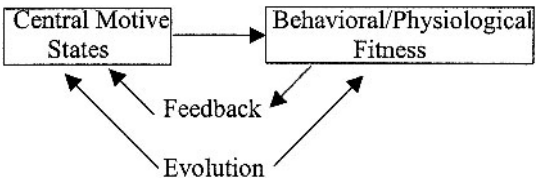


Figure 2.7
Evolution, central states and behavioral adaptation.

The issue of flexibility as the cardinal feature of a motivational system may not be correct (James, 1890; Epstein, 1982). That is, I suspect the contrast between motivation and instinct (Epstein, 1982) is somewhat misleading. In this view, instinct is blind and dumb. Motivation, by contrast, is replete with representations of objects and their importance and behavioral options to attain the goal. Surely the concept of representation figures significantly in understanding the brain as an information-processing system independent of whether the animal is limited in its behavioral options. Something can be instinctual and be fixed, and something can be motivated and be fixed. They are not exclusive. But the intuition that Alan Epstein adumbrated was that motivational systems are flexible and opportunistic, resourceful in the achievement of the goal. This no doubt captures an important element of central motive states.

In debates about the usefulness of the concept of motivation, it has been noted that representations of goal objects are neither necessary nor sufficient for motivated behavior (see also Dethier, 1966; Stellar and Stellar, 1985). The hungry fly may be a machine, narrow in purpose, with few behavioral options and still have representations of goal objects.

Neural Circuits and Motivational States

General Neural Circuits Underlying Motivational States

The reticular formation was envisioned to underlie arousal, as was later the activation of catecholamines (Palkovits, 1981; Stricker and Zigmond, 1986). We now know that a number of neurotransmitter systems (e.g., serotonin, dopamine) that project widely throughout the brain serve to arouse and placate neuronal systems that underlie central motive states (Hoebel, 1988). These systems play an important role in motivated behaviors. For example, ascending noradrenergic pathways from the brainstem to the forebrain are essential for alertness and attention, and serotonergic pathways are essential for mood states (Stellar and Stellar, 1985; Hoebel, 1988).

Consider the central gustatory/visceral system in the brain. At the turn of the century, C. Judson Herrick (1905) described a pathway in the catfish from the solitary nucleus to the amygdala, which later Carl Pfaffmann and his colleagues (Pfaffmann et al., 1977) and others (see Spector, 1995) thought might underlie motivated behavior. The seventh, ninth, and tenth cranial nerves transmit visceral information to the central nervous system and terminate in the rostral portion of the solitary nucleus. Gustatory and other visceral information are then transmitted to the medial region of the parabrachial nucleus (Norgren, 1984, 1995). From this region, there are two main projection systems: a dorsal projection to the ventral basal thalamus and insular cortex and a ventral projection, which crosses through the lateral hypothalamus into the central nucleus of the amygdala, in addition to the bed nucleus of the stria terminalis (Norgren, 1984). It was suggested (Pfaffmann et al., 1977; Spector, 2000) that the sensory evaluation of a food or fluids—whether sweet or salty—is made by the dorsal projection and that the organization of the drive, and the hedonic value of the stimulation, are made by the ventral projection. Interestingly, many of the neuropeptides, or their receptor sites and steroid receptor sites that are linked to central states, are localized within these regions (figure 2.8).

Angiotensin is one peptide that is localized in many of the regions of this visceral pathway in the brain (see Lind et al., 1984). A number of neuropeptides are also distributed along the central visceral axis (e.g., Swanson et al., 1983; Swanson, 2000). This axis includes the central nucleus of the amygdala, the bed nucleus of the stria terminalis, the paraventricular nucleus (PVN) of the hypothalamus, and brainstem sites such as the parabrachial and solitary nuclei (Gray, 1990). This is the same pathway that organizes motivated behaviors in general (Pfaffmann et al., 1977; Stellar and Stellar, 1985). It is part of the neural system—described by Herrick (1905) and expanded upon by Walle Nauta (1961)—that underlies central excitatory states.

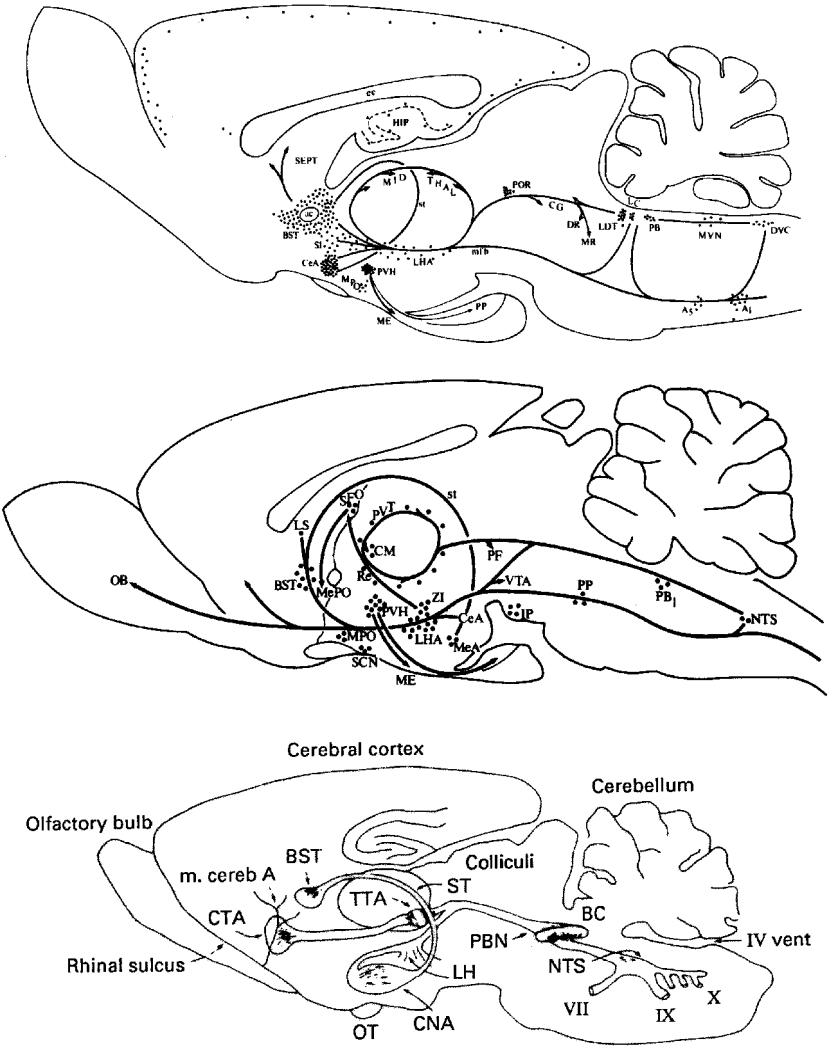


Figure 2.8
From top to bottom the figures depict corticotropin releasing hormone in the brain (Swanson et al., 1983), angiotensin sites in the brain (Lind et al., 1985) and the central gustatory neural axis (Norgren, 1995). One should note that many of the peptide sites overlap with gustatory sites in the brain.

Walle Nauta noted that the concept of the limbic system should include motor regions of the basal ganglia (see Mogenson and Huang, 1973; Mogenson and Yang, 1991; Alheid et al., 1996, 1998). The basal ganglia form an essential link in translating motivational signals from the amygdala and hypothalamus into the organization of action (Swanson and Mogenson, 1981; Kelley, 1999a, b) via the activation of brainstem sites (e.g., Pfaff, 1999). Specialized motor pathways emerged to translate motivational desires into organized goal-directed action (Swanson, 2000).

Since Nauta's original suggestion, research has substantiated that regions of the basal ganglia do in fact seem to underlie a variety of motivated behaviors, including addiction (Koob and LeMoal, 2001). For example, damage to the ventral palladium interferes with the "liking" system underlying the palatability processing of food sources (Berridge, 1996, 2000).

The nucleus accumbens, via glutamate receptors within the accumbens, may underlie appetitive instrumental learning and may be an important link in translating limbic functions into functional action (Kelley, 1999a, b). The range of action or motivational signals is quite diverse and will figure prominently for the rest of this chapter and in subsequent chapters. Let us now turn specifically to the hormonal regulation of motivational states, in which there are a variety of examples of feedforward neuroendocrine systems.

Positive Induction of Neuropeptide Gene Expression by Steroids and the Expression of Central States: An Example of Allostatic Regulation

Steroids, by facilitating neuropeptide expression and regulation in the brain, increase the likelihood of motivational states, both sustaining them and decreasing their expression (e.g., Herbert, 1993; Pfaff, 1999; Schulkin, 1999a). By influencing central states, hormones and their actions in the brain prepare an animal to perceive stimuli and behave in certain characteristic ways; they

increase the likelihood of responding "appropriately" to environmental signals (e.g., Gallistel, 1980; Mook, 1987).

There are a variety of contexts in which steroids and peptides interact to regulate behavior (e.g., Hoebel, 1988; Herbert, 1993). They range from ingesting food, water, and sodium to maternal behavior, fear, and aggression. Nature uses the same hormones to generate a variety of different central states. These, in turn, generate behaviors that, through both anticipatory and reactive mechanisms, help the organism maintain internal stability and external coherence to internal demands (McEwen and Stellar, 1993; Schulkin et al., 1994, 1998; McEwen, 1998a, b). This represents a form of allostatic regulation. Steroids and peptides or neuropeptides interact to influence behavior by their actions in the brain. There are many examples in which hormones that regulate physiology also affect behaviors that serve the same goal.

Steroid hormones such as estrogen, progesterone, aldosterone, corticosterone, testosterone, and vitamin 1,25D3 are widely distributed in the brain (e.g., Pfaff, 1980; Stumpf and O'Brien, 1987; McEwen and Alves, 1999). They have profound effects, for example, on the induction or inhibition of neuropeptide gene expression and subsequent central states and behavioral output (Herbert, 1993; Herbert and Schulkin, 2002).

Consider another fact about peptides and neuropeptides; consider oxytocin. Oxytocin plays multiple roles in facilitating physiological regulation of milk production during lactation and water homeostasis (Kaufman, 1981). But oxytocin expression in the brain underlies behavioral functions such as maternal attachment (see, e.g., Insel, 1992; Carter et al., 1999; Kendrick, 2000), and perhaps more generally for social recognition that underlies attachment behaviors (Ferguson et al., 2001). Oxytocin is both a pituitary peptide linked to milk production and a neuropeptide linked to a variety of central states in which behavior serves physiological regulation and reproductive fitness. The central motivational state that underlies parental behavior is rich and behaviorally diverse (Marler and Hamilton, 1966; Hinde, 1970), and goes beyond anything homeostatic.

Or consider angiotensin, a peptide produced in both the brain and the periphery that has a major impact on the cravings for both water and sodium. Injected centrally, angiotensin-II increases both water intake and sodium intake, independent of sodium loss (see Fitzsimons, 1979, 1999). The behavior of water and sodium ingestion complements the regulatory effects of angiotensin at the level of the kidney and other systemic organ systems (e.g., the heart) linked to body fluid homeostasis. The central motive state of thirst, a state in which feedforward allostatic mechanisms are operative in the brain, is one of several phenomena to which we now turn.

Mineralocorticoids, Glucocorticoids, and Angiotensin: Cravings for Water and Sodium

The adrenal steroid hormones play a profound role in the regulation of body fluid balance. At the level of systemic physiology, both steroids facilitate sodium reabsorption and distribution in the maintenance of sodium and body fluid balance. Of course, aldosterone is a dominant hormone for the regulation of fluid balance (Fitzsimons, 1979, 1999; Denton, 1982; Schulkin, 1991).

Mineralocorticoid hormones increase sodium ingestion (Richter, 1942–43; Wolf, 1964). In part, they do so via changes in angiotensin expression in the brain. For example, mineralocorticoids increase angiotensin-II receptors in the brain and in cell-line cultures. The same treatment is known to increase angiotensin messenger RNA (mRNA) in cell-line cultures in addition to mobilizing intracellular calcium and second-messenger systems (S. J. Fluharty, unpublished observations). Mineralocorticoids also potentiate angiotensin-II-induced sodium intake (Fluharty and Epstein, 1983; Sakai, 1986). This is a feedforward regulatory system that subserves adequate sodium ingestion, but is nested in a larger physiological system that then constrains the levels of natriorexegenic hormones, once sodium and water are ingested and balance is achieved.

It is possible that the overexaggeration activation of this neuroendocrine system underlies some forms of hypertension (Denton, 1982; Watt et al., 1992). In fact, we know that in various

animal models in which angiotensin or mineralocorticoids are overexpressed, there is both an exaggerated sodium consumption and a vulnerability to hypertension (Denton, 1982). The normal regulatory systems to maintain water and sodium balance, when coupled with vulnerable genetic susceptibility and sodium ingestion, can result in allostatic overload.

Interestingly, a key example emphasized by Sterling and Eyer (1981, 1988; Eyer and Sterling, 1977) in one of their original papers was the exaggerated sodium consumption, vulnerability to hypertension, and chronic elevation of the renin-angiotensin-adrenal steroid systems. In cultures in which there was low sodium consumption and less chronic worry, there was little incidence of hypertension and increased mortality (see also Denton, 1982). Chronic stress (allostatic overload) creates a context of reduced life span. By their actions in the brain, the hormones of sodium homeostasis create an environment that results in enhanced sodium consumption—and along with the sodium retention, it results in a greater vulnerability to life-threatening situations.

Consider glucocorticoids, and recall that they, either through their permissive, stimulatory, or preparative functions, play a fundamental role in blood pressure regulation (Sapolsky et al., 2000). And, of importance, elevated glucocorticoids potentiate angiotensin-II-induced drinking. The background of glucocorticoids that are normally elevated following depletion of the body's fluids induces angiotensin-II cells, thereby potentiating the hormone's dipsogenic (Ganesan and Sumners, 1989; Sumners et al., 1991) and natriorexegenic actions. This interaction generates the central states of thirst and sodium hunger, in which both appetitive and consummatory behaviors are expressed. Both behaviors serve the same end point as the renin-angiotensin-aldosterone system—namely, the body's fluid homeostasis (figure 2.9).

More generally, one should note that while sodium depletion (or fluid volume depletion) may be the initial trigger for the hormones linked to sodium and water appetite (Fitzsimons, 1979, 1999; Denton, 1982; Denton et al., 1996), the appetitive and con-

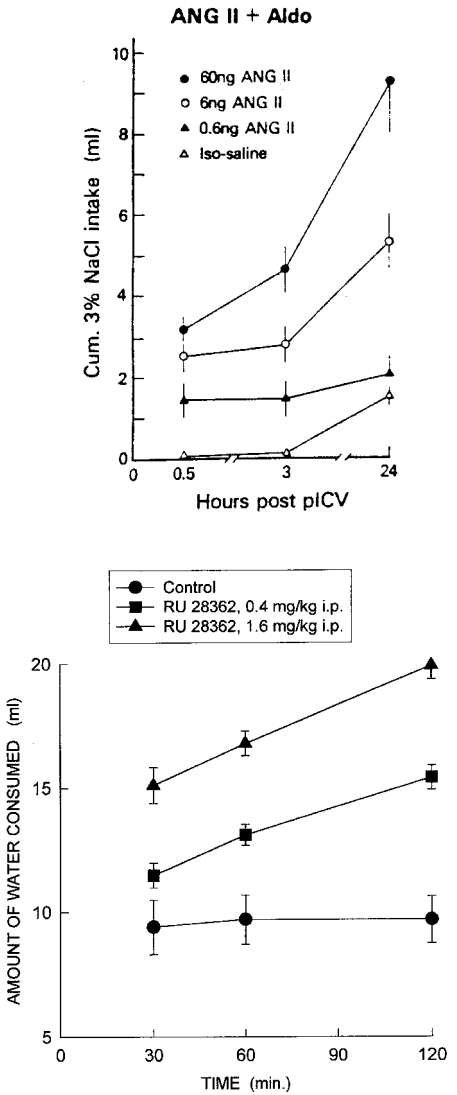


Figure 2.9
(*Top*) Sodium ingestion in rats following daily injections of aldosterone (40 μg) followed by central injection of angiotensin (Sakai, 1986). (*Bottom*) Water ingestion following systemic daily injections of the glucocorticoid agonist followed by a central injection of angiotensin II (10n) (Sumners et al., 1991).

summatory behaviors reflect the expression of the hormonal activation, the effects of aldosterone and corticosterone on central angiotensin (Fluharty and Epstein, 1983; Epstein, 1991; Sumners et al., 1991; Fluharty and Sakai, 1995), and perhaps the decreases in oxytocin expression (see Stricker, 1990; Verbalis et al., 1993).

Homeostatic mechanisms mediated by negative restraint (volume and osmotic receptors) exist alongside allostatic mechanisms (the positive induction of the neuropeptides) and the expression of central motive states of the brain and resultant behavior. The allostatic state can lead, however, to allostatic overload (e.g., chronic activation of the renin-angiotensin-aldosterone system) and vulnerability to excessive sodium consumption, hypertension, and congestive heart failure (Weaber, 2001).

Glucocorticoids and Neuropeptide Y: Food Intake

In the mobilization to procure adequate food sources, glucocorticoids are elevated under conditions in which hunger is a central state of the brain (Dallman et al., 2000). The glucocorticoids have wide and diverse effects on many regulatory systems in the brain and in peripheral end-organ systems that subserve bodily viability. Here again it is useful to break glucocorticoid function down in terms of long- and short-term effects, and whether the actions are permissive, suppressive, stimulatory, or preparative (Sapolsky et al., 2000). One also has to ask what the environmental contexts are in which a wide variety of needs are appraised for bodily viability, including seasonal variations (Wingfield and Romero, 2001).

The context that I want to draw the reader's attention to is one in which low but nonetheless elevated levels of corticosterone can stimulate food intake (Leibowitz, 1995; Bell et al., 2000; Dallman et al., 2000). This situation appears to do so, in part, through activation of neuropeptide Y in the brain, in addition to a variety of other known effects (Dallman et al., 2000). Produced in gastrointestinal sites as well as the central nervous system, neuropeptide Y is activated functionally in the arcuate nucleus and the PVN by food deprivation and corticosterone

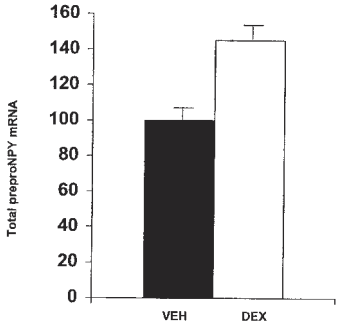
(Brady et al., 1990; Dallman et al., 1994, 1995). This increase in food intake depends on an intact adrenal gland and an activation of type-2-corticosteroid receptors (Lebowitz, 1995). Long-term activation of the glucocorticoids (allostatic overload) has significant implications for body fat distribution (Dallman et al., 2000).

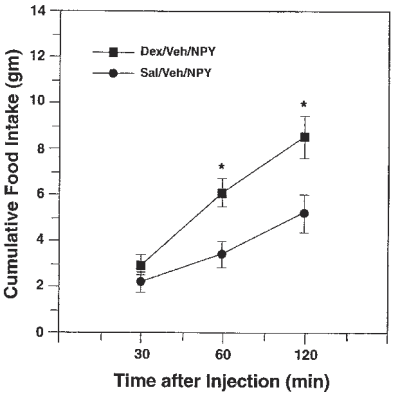
Importantly, low doses of glucocorticoids or food deprivation can potentiate neuropeptide-Y-induced food ingestion (Heinrichs et al., 1992); specifically, corticosterone and neuropeptide Y generate carbohydrate ingestion, or fast energy pickups (Leibowitz, 1995). This steroid and neuropeptide hormone facilitates the central motive state of craving carbohydrates (figure 2.10). (Of course, these findings apply to rats; in species that are indifferent to sweet tastes, this phenomenon might not occur.) Adrenalectomy abolishes these effects, and corticosterone will restore them. But without a suitable context in which other concerns are made prevalent in the information-processing systems in the brain (predator detection, conflict with conspecifics, etc.), eating may or may not take place.

Food intake is mediated by mechanisms for short- and long-term regulation that utilize diverse mechanisms (e.g., insulin, leptin; see Dallman et al., 2000). I have focused on a putative feedforward mechanism that may underlie the motivation to search and ingest food sources. This, of course, is but one mechanism at play in food procurement, a positive feedforward system (allostatic)—glucocorticoid potentiation of neuropeptide Y. The overexaggeration of this system, allostatic overload, perhaps could lead to a wide variety of metabolic disturbances (obesity, heart disease, etc.).

Estrogen, Oxytocin, and Prolactin: Sex and Attachment

An example of steroids and peptides acting together to generate central motive states that underlie successful reproduction is that of estrogen-primed rats given progesterone and oxytocin to induce sexual receptivity (Pfaff, 1980, 1999). These events do not occur in a vacuum, despite our laboratory attempts to sim-





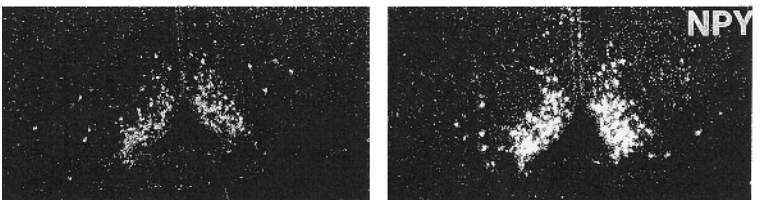


Figure 2.10
(*Top*) Total hybridization pre-pro-neuropeptide Y (preproNPY) mRNA in the arcuate nucleus in vehicle-injected controls (VEH) and hamsters injected daily for 28 days with dexamethasone (DEX) (adapted from Mercer et al., 1996). (*Middle*) Cumulative food intake following pretreatment with dexamethasone (100 µg/kg) or vehicle following 6 hours later by central injection of a vehicle or neuropeptide Y (500 ng Heinrichs et al., 1992). (*Bottom*) Darkfield photomicrographs of neuropeptide-Y mRNA in the arcuate nucleus in sated (A) and food-deprived (B) rats (from L. S. Brady et al., 1990).

plify the context in order to understand the mechanisms. Sex and attachment in a wide variety of animals takes place amid competing interests, competing hormonal influences, and numerous other factors (Wingfield and Romero, 2001).

For example, many of the events during reproduction are demanding on energy resources. Anticipatory mechanisms for predictable events predominate, particularly for seasonal breeding animals (Bauman and Currie, 1980; Wingfield and Romero, 2001). Under duress by what Wingfield and Romero have characterized as a context of emergency life situation, the mechanisms that underlie reproduction can be altered. Reactive mechanisms are operative in these emergency situations, where, for example, reproduction might not be possible (too cold, not enough food, no outlet for reproductive expression, etc.).

In the laboratory a variety of animals treated with systemic estrogen and then with progesterone demonstrate similar sexual receptivity (Wade and Crews, 1991; Pfaff, 1999). Estrogen increases oxytocin expression in cells in the ventral medial hypothalamus. Without sufficient estrogen, oxytocin levels decline and are restored only when estrogen is again elevated (e.g., Schumacher et al., 1990). Oxytocin infused within this region of the brain elicits sexual receptivity, and in estrogen- and progesterone-primed rats, the dose of oxytocin needed to elicit the behavior is decreased. Thus, by increasing oxytocin expression in the brain's ventral medial hypothalamus, estrogen facilitates the likelihood of sexual motivation and receptivity.

In other words, by facilitating the expression of neuropeptides (e.g., oxytocin) and/or receptor sites (e.g., progestin), the gonadal steroid hormones lower the threshold at which a sexual response to environmental stimuli will be elicited by inducing central states in the brain (e.g., Pfaff, 1999). But one should note and consider the multiple effects of estrogen on neuropeptides and neurotransmitters in the brain (figure 2.11; Pfaff, 1999). Within this context, well-known appetitive and consummatory expressions of central states are seen (see Beach, 1942, 1947; Everitt, 1990). But the behavioral expression is not axiomatic and varies with the environmental circumstances and the competi-

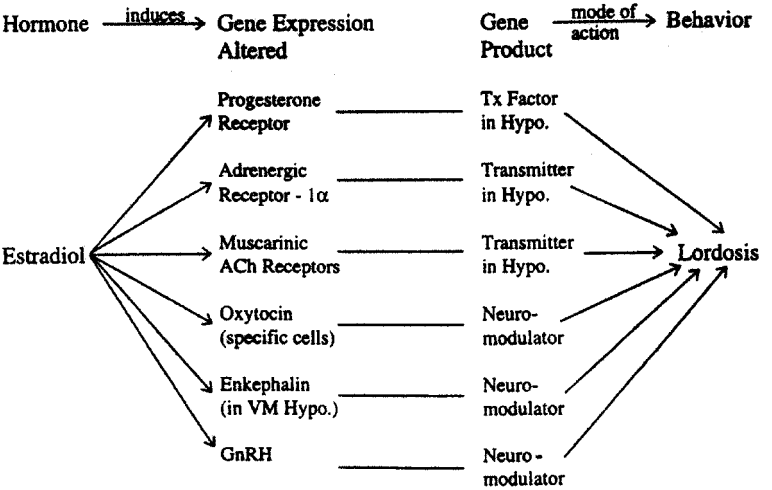
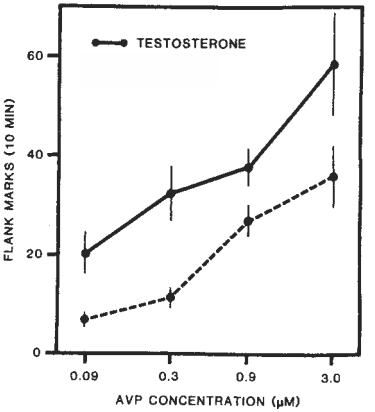


Figure 2.11
Diverse effects of estrogen on the brain essential for reproductive behavior (Pfaff, 1999).

tion with other internal needs or competing motivations (Hinde, 1968, 1970). Motivation figures in determining the direction that behavior will take. An allostatic mechanism is in the induction and sustaining the neuropeptide and neurotransmitters in functional circuits in the brain that underlies the behavior.

Now consider the relationship between estrogen, prolactin, and maternal behavior. Like oxytocin and a number of other peptides, prolactin is both a pituitary hormone and a neuropeptide with a diversity of functions. Central infusions of prolactin facilitate maternal behavior (Bridges and Freemark, 1995)—but only if there is a sufficient level of background estrogen. In other words, as is the case with oxytocin, estrogen facilitates the likelihood of maternal behavior by increasing prolactin expression in the brain (Bridges et al., 2001). The potentiation of the prolactin effects is another example of a feedforward, or allostatic, neuroendocrine system that underlies behavior. Prolactin stimulates maternal central states through both physiological and behavioral mechanisms.


TESTOSTERONE
FLANK MARKS (10 MIN)
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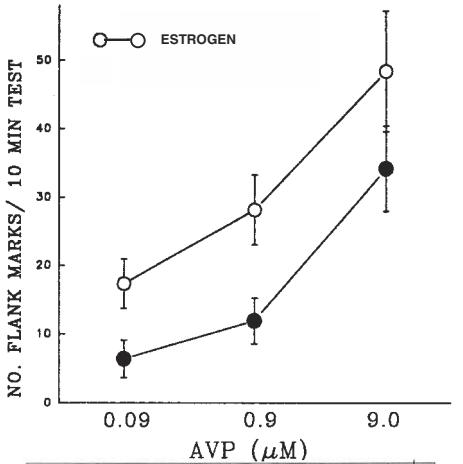
0.09
0.3
0.9
3.0
AVP CONCENTRATION (μM)


ESTROGEN
NO. FLANK MARKS/ 10 MIN TEST
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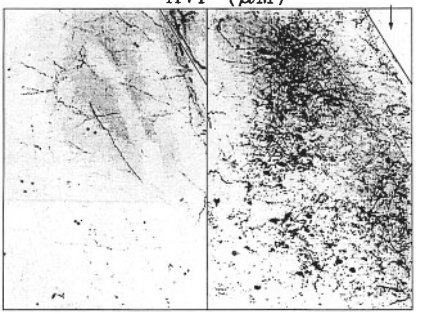
9.0
AVP (μM)



Gonadal Steroids and Vasopressin or Vasotocin: Territory and Kin Relations

In many animals, testosterone concentrations vary with the seasons (e.g., Wingfield et al., 1999). One testosterone-mediated behavior linked to territorial behavior that is well known in a wide variety of mammals is scent marking. It occurs via the gonadal steroid's activation of vasopressin in the brain, particularly in the bed nucleus of the stria terminalis. Infused into this region, vasopressin facilitates the expression of scent marking. A background treatment of testosterone, providing a sustaining mechanism for vasopressin regulation in the brain, enhances this response (figure 2.12; Albers et al., 1988). The same holds for male parental behavior among prairie voles. Presumably, testosterone facilitates this behavior by sustaining and increasing central vasopressin or vasotocin synthesis (DeVries et al., 1995; see also Moore et al., 1992; Goodson and Bass, 2001). This central state does not occur in a vacuum and competes internally for expression.

The vasopressin gene appears to be significantly involved in affiliation (Pitkow et al., 2001). Without testosterone, for example, vasopressinergic neurons are severely depleted in specific regions of the brain that underlie parental behavioral and territorial aggression (DeVries et al., 1995; Albers et al., 1988; Albers and Cooper, 1995). For example, regions of the medial amygdala are significantly involved in flank-marking behavior. Testosterone facilitates flank marking via the induction of vasopressin expression in the medial amygdala (DeVries et al., 1995). The removal of testosterone reduces vasopressin gene expression in this region of the brain and reduces flank-marking behavioral expressions.

Figure 2.12
Flank-marking reaction to central administration of AVP in testosterone-treated or estrogen-treated and control hamsters (Albers et al., 1988; Huhman and Albers, 1993) and vasopressin-immunoreactive cells and fibers in the medial nucleus of the amygdala in castrated (*left*) and control (*right*) rats (courtesy of G. J. DeVries, 1995).

Conclusion: Allostatic Feedforward Mechanisms and Central Motive States

Steroids, by facilitating neuropeptides or neurotransmitters or receptor sites, can influence central states that are typically, though not exclusively, linked to functional requirements. Feedforward systems that underlie central states are nested in negative restraint of those systems; the animals ingest sodium and the natriorexegenic hormones are decreased. Furthermore, central motive states do not exist in a vacuum; they depend upon the environment and other cognitive (including other central motive states) and physiological events. Adaptation reflects an environment in which an animal is trying to cope and provide frameworks of coherence. Central motive states serve bodily viability both in the short and the long term through feedforward allostatic regulation. The state of craving sodium reflects the positive relationship between the activation of adrenal steroids and the induction of central angiotensin (Epstein, 1991).

In fact, what has been emphasized in this chapter is the steroid facilitation of neuropeptide expression and regulation. This is one central feature in the regulation of central motive states. Each of the examples serve important roles in the maintenance of the internal milieu. The events are anticipatory, reflecting the brain's influence over behavioral and physiological events. They reflect cephalic regulation of the internal milieu. These events are linked to adaptive events, including the pleasure of remaining in a state of ease, the satiety sequence associated with satiety (Smith, 1997a), and the states that animals are contented to stay in.

The more general question about the concept of motivation and drive is trying to use the terms in nonviciously circular senses and where it is not clear that it serves a scientific role (Wise, 1987). I would suggest that motivation is both a biological function and a core concept in our sense of ourselves and our representational abilities. It is a piece of cognitive adaptation that is fundamental to a theory of the direction of behav-

ior (Hebb, 1949; Lakoff and Johnson, 1999). Models of motivation include specific behavioral profiles (Oatley, 1970) and reflect both specific motivation and nonspecific mechanisms (Grossman, 1968, 1979). I suggest that we not look for one definition but rather to instrumental use and characterization of the information-processing systems in the brain. Putting the concept of motivation in the context of the circuitry and problem solving that the brain generates in suitable environmental climates renders the concept meaningful in a neuroscience context.

Core motivational states are biological functions that serve the animal in the organization of behavior and the adaptation to changing environmental demands. Functional circuits in the brain underlie both specific and nonspecific aspects of motivational states. Steroids, by the positive induction and regulation of neuropeptides, play an essential role in the expression of motivational states and provide one mechanism in the cephalic involvement in the regulation of the internal milieu and to long-term reproductive success. Thus these feedforward *allostatic* regulatory systems are an essential expression of the nervous system.

Central motive states serve to keep the organism viable by regulating homeostatic mechanisms that try to keep an organism within a state. Allostatic mechanisms drive the animal into a state appropriate (at best) to the challenge and to the environmental context. These states can be high energy, short term, and not desirable to stay in, but they are necessary for viability.

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Chapter 3

Anticipation, Angst, Allostatic Regulation: Adrenal Steroid Regulation of Corticotropin-Releasing Hormone

The emotion of fear is regulated by neuroendocrine events in neural circuits that underlie fear-related behavioral and autonomic responses. One brain region critical in the regulation of fear is the amygdala. I suggest that one function of glucocorticoid hormones is to facilitate the synthesis of the neuropeptide CRH in this nucleus (along with the lateral bed nucleus of the stria terminalis). CRH aids in maintaining and coping with events that are perceived as frightening. Elevated levels of glucocorticoids, secreted by the adrenal gland, act on the amygdala and bed nucleus of the stria terminalis to facilitate CRH gene expression (feedforward allostatic mechanisms) and to sustain the central motive state of fear. In this model, long-term fear (chronic angst) is an allostatic state.

This chapter extends (more detail about the behavior and the neuroendocrine regulation of the central state) the feedforward allostatic framework discussed in chapter 2. I begin with an overview of the central motive state of fear and its biological basis. I then discuss the neural circuitry that underlies the perception of fearful events. Next, I describe the neuroendocrine basis of fear and discuss the role of glucocorticoids and CRH in sustaining fear-related behaviors. In each section, I indicate that the same neural and endocrine system underlies pathological states associated with excessive fear that perhaps underlie allostasis and allostatic overload. Certainly fear is the sort of central state in which no constant set point is regulated. I end with a brief discussion of the logical status of the concept of fear in our scientific lexicon.[1]

1. Fear, one should note at the onset, is not synonymous with freezing or startle behaviors. They are, however, useful behavioral measures in the context of

Central Motive State of Fear

Fear is a prototypical exemplar of a central state—a state of the brain. Although systemic physiological changes influence the state of fear (James, 1884, 1890), peripheral changes are not sufficient for the emotional expression of motivated behaviors such as fear (Cannon, 1915, 1929a; Bard, 1939). It is the physiological change in the brain that is linked to the state of fear. We are afraid when we perceive danger, but bodily events influence and reinforce this state (James, 1890; Damasio, 1994). For example, changes in heart rate, blood pressure, respiration, facial muscles, and catecholamines, both peripheral and central (e.g., Yank et al., 1990), influence the state of fear (see LeDoux, 1996, 2000; Rosen and Schulkin, 1998).

The central state of fear is tied to attention and learning as well as to the assessment of relevant information (Dickinson, 1980), which is important in predicting future outcomes (Miller, 1959; Rescorla and Wagner, 1972). The central state of fear is linked to action tendencies (Frijda, 1986), attention (Lang et al., 1998), and appraisals more generally of environmental stimuli (Lazarus, 1984, 1991; Rosen and Schulkin, 1998; Lane and Nadel, 1999).

Fear is also linked to an appetitive system (which includes consummatory behaviors) and an aversive system, such as withdrawal and protectiveness (Konorski, 1967; Davidson et al., 2000). In Konorski's terms (1967), the former is preservative and the latter is protective. Fear maps onto approach/appetitive and avoidance/withdrawal mechanisms influenced by sensory stimulation (Schneirla, 1959; Konorski, 1967).

Fear is an adaptive response to the perception of danger, and it is fundamental in problem solving and survival. In fact, fear as an emotion evolved as a part of problem solving (Darwin, 1872). Fear prepares an animal to respond to danger by height-

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studying fear-related behavioral responses, just as one should note that the amygdala is not just involved in the regulation of negative events (e.g., Gallaverna et al., 1993; Gallagher and Holland, 1994; Baron-Cohen et al., 1999; Davis and Whalen, 2001).

ening vigilant attention (Gallagher and Holland, 1994) and motivating behavior (Bindra, 1978), such as defensive behaviors (Bolles and Fanselow, 1980). The state of fear is one in which there is a readiness to perceive events as dangerous or alarming (LeDoux, 1995, 1996; Rosen et al., 1996). The state is knotted to learning about what is safe and what is not (Miller, 1959), as well as the informational value of stimuli that has predictive value to the animal (Rescorla and Wagner, 1972; Dickinson, 1980).

The physiological and behavioral responses aroused by fear are rooted in our evolutionary past. Fear is an adaptation (Lazarus, 1991), but fear certainly is not always part of our everyday life. Moreover, there are no clear set points in known physiological parameters that underlie the central state of fear, and therefore it is easily understood in the context of allostasis, allostatic state, and allostatic overload.

Emotions like fear are linked to action tendencies (Frijda, 1986) and motivate behavior in response to danger (Rosen and Schulkin, 1998). Behaviors such as startle and freezing are expressions of fear across many species; fear is linked to defensive behavior, but they are not the same. Fear functions to alert the animal to danger, preparing the animal to freeze or flee (Bolles and Fanselow, 1980). The motivated animal seeks relief from this allostatic state, and, with the elimination of fear, there is the sense of relief (Miller, 1959). In other words, fear functions as a central motive state in threatening contexts, resulting in behaviors that serve to alleviate the state, resulting in reducing or warding off harm. Put another way, from an "internal" perspective, fear is typically an aversive state of the mind—the animal acts in ways to reduce this aversive state of mind. Externally, those behaviors serve to reduce or eliminate threats to the animal. The perception of fearful events may be constrained by neuronal processing of information. The vigilance that is required during fear limits the attentional mechanisms that might normally be used elsewhere (Davis et al., 1993; Rosen and Schulkin, 1998). The central state of fear, and there is more than one kind (Hebb, 1946; Kagan and Schulkin, 1995), embodies an

elaborate and complex organization of behavior that includes social signals that reduce fighting and maintain alliances (Marler and Hamilton, 1966; Hauser, 1996).

Neural Circuits Mediating Fear

Amygdala

The amygdala found in vertebrates is centered in the temporal region of mammals (Herrick, 1905). It is almond-shaped and was originally called the *smell brain.* It has long been considered part of the limbic system in the organization of emotional responses (e.g., Papez, 1937; Bard, 1939; MacLean, 1955; LeDoux, 1995; Swanson, 2000).

Regions of the amygdala have been characterized as a *sensory gateway* (Aggleton and Mishkin, 1986; LeDoux et al., 1990) because the amygdala receives information from both cortical and subcortical regions (Krettek and Price, 1978). Specifically, the lateral and basal lateral regions are richly innervated by neocortical and subcortical sites, which relay information to the central nucleus (e.g., Krettek and Price, 1978; Swanson and Petrovich, 1998; Stefanacci and Amaral, 2000). The central nucleus also receives visceral information from brainstem sites that include the solitary and parabrachial nuclei (Norgren and Leonard, 1973) and reciprocally project to these brainstem regions (e.g., Schwaber et al., 1982). The amygdala's direct link to the nucleus accumbens led Nauta (1961, 1972) to suggest an anatomical route by which motivation and motor control action are linked in the organization of behavior (see also Mogenson, 1987; Swanson and Petrovich, 1998; Kelley, 1999a, b; Gray, 1999; Swanson, 2000).

Damage to the amygdala interferes with fear-related behavioral responses. In the past 10 years, evidence has converged to show particularly that the central nucleus within the amygdala orchestrates the behavioral responses related to fear (LeDoux, 1995, 1996, 2000). Lesions or stimulation of the central and lateral nuclei are known to influence behaviors associated with fear (Kapp et al., 1979; LeDoux et al., 1990; Roozendaal and

McGaugh, 1997a, b). Stimulation of the central nucleus of the amygdala, for example, activates the neural circuitry underlying the startle response and amplifies this reaction (Rosen and Davis, 1988). Stimulation of the amygdala heightens attention toward events that are perceived as fearful (Gallagher and Holland, 1994; Rosen et al., 1996). In other words, amygdala activation increases the likelihood that an event will be perceived as threatening, uncertain, or unusual (Gallagher and Holland, 1994; Rosen and Schulkin, 1998; LeDoux, 2000; Dolan et al., 2000) and can lead to anticipatory angst (Schulkin et al., 1994). Infusions of *N*-methyl-D-aspartate (NMDA) antagonists into the central or lateral nuclei interfere with fear-related conditioning (Davis et al., 1993). Neurons within the amygdala are activated by fearful signals (LeDoux, 2000) and are influenced by prefrontal cortex activity (Davidson et al., 2000; figure 3.1).

In elegant detail, LeDoux and his colleagues (e.g., LeDoux et al., 1990; LeDoux, 1995, 1996, 2000) have outlined an anatomical circuit in rats underlying conditioned freezing to an auditory cue. It consists, in part, of pathways from the medial geniculate nucleus en route to the lateral and central nuclei of the amygdala. In addition, projections from the auditory and perirhinal regions of the neocortex, through the lateral nucleus en route to the central nucleus of the amygdala, convey information about acoustic conditioning. Interruption to this input, to the lateral and central nucleus of the amygdala, impairs the fear conditioning. The central nucleus, through its projections to the central gray, regulates freezing and escape behaviors (LeDoux, 1996).

The neural circuitry for conditioned freezing, for conditioned startle (Rosen et al., 1991), and for unconditioned fear require the lateral region of the amygdala to receive information and the central region to orchestrate the behavioral and autonomic responses. Other regions in the forebrain that organize fear include the prefrontal cortex (Morgan and LeDoux, 1995), the perirhinal cortex, and the bed nucleus of the stria terminalis, which, as I will describe, may be linked to the neuroendocrine regulation of anxiety (see Davis et al., 1997; Rosen and Schulkin, 1998).

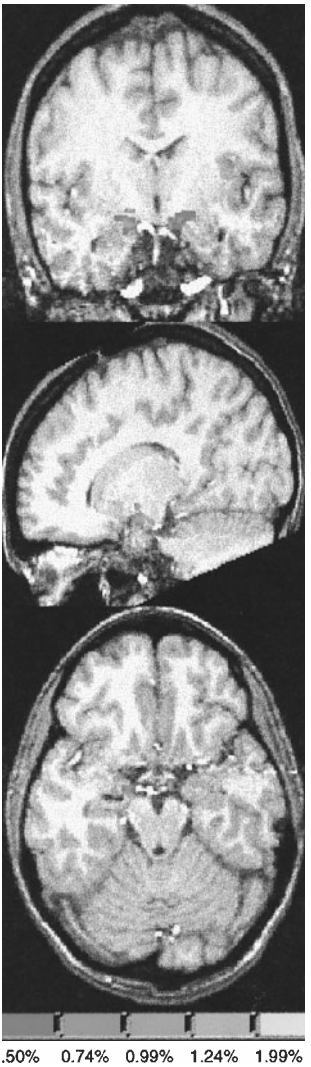
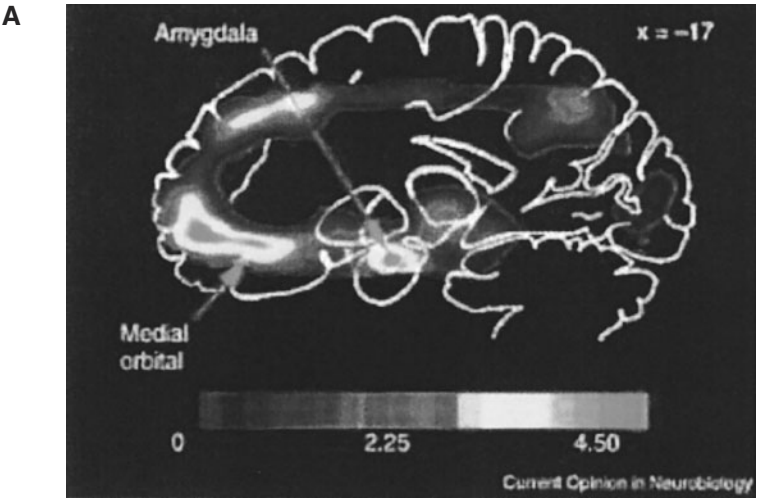


Figure 3.1
Activation of the amygdala in normal subjects to fear-eliciting stimuli (Irwin et al., 1996).

There is also a good deal of evidence in humans that the amygdala is linked to fear (e.g., Aggleton, 1992, 1995, 2000; LeDoux, 1996; Morris et al., 1996; Calder et al., 2001). For example, recently it has been observed that lesions of the amygdala impair fear-related behavior and autonomic responses to conditioned stimuli (e.g., LeDoux, 2000). Several studies have found that lesions of the amygdala interfere with the recognition of fearful facial expression (Adolphs et al., 1995). Also, positron emission tomography (PET) imaging studies have shown greater activation of the amygdala during fear and anxiety-provoking stimuli (Ketter et al., 1996). Such PET studies have also revealed that the amygdala is activated when presented with fearful versus happy faces (Morris et al., 1996; Dolan et al., 2000; Wright et al., 2001). With the use of functional magnetic resonance imaging (MRI), it has further been shown that the amygdala is activated and then habituates when shown fearful in contrast to neutral or happy faces (Breiter et al., 1996), but the amygdala is also responsive to a variety of facial responses (Lane et al., 1999; Dolan et al., 2000; Wright et al., 2001).

Clinically, some forms of depression (anxious) are associated with fear (Gold et al., 1988a, b). Elevated blood flow to the amygdala has been observed using PET in patients who are both fearful and depressed. Many of these patients tend to have higher levels of cortisol than normal controls (Drevets et al., 1992; Drevets, 2001). The metabolic rate of the human amygdala (and neocortical areas) has also been used to predict both depression and negative affect (figure 3.2; Ketter et al., 1996; Davidson et al., 1999).

A hyperexcitable state of the amygdala has been suggested by a number of authors that may underlie excessive fear, chronic arousal, and chronic angst (Kagan et al., 1988; LeDoux, 1996; Rosen and Schulkin, 1998). In animal models, kindling is a way to excite the brain via electrodes targeted to an anatomical site using electrical current delivered to the targeted brain region (see, e.g., Adamec, 1997). In other words, the result of this experimental manipulation is a putative hyperexcitable state in the brain that creates an experimental form of chronic arousal



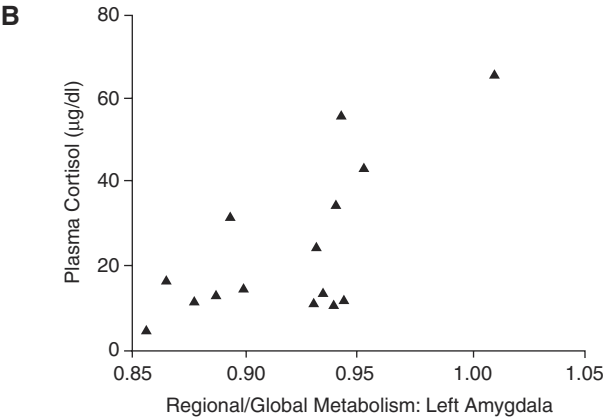


Figure 3.2
(*A*) Activation of the amygdala and medial frontal/orbital cortex in depressed subjects (Drevets, 1999). (*B*) Relationship between plasma cortisol concentrations measured immediately prior to the PET radiotracer injection and normalized glucose metabolism in the left amygdala for the depressed subject (Drevets et al., 2002).

(allostatic). In that study, the idea was that partial amygdala kindling would potentiate fear-related behavioral responses but that dorsal hippocampal kindling would not. Rats were conditioned to be fearful to a light paired with a foot shock. During the next several days, they received partial kindling of the amygdala or of the dorsal hippocampus. Rats were then presented with an auditory startle stimulus with or without light. Fear-potentiated startle was tested one week later (Rosen et al., 1996). The group that underwent amygdala kindling displayed elevated startle amplitude; they were more readily prepared to startle, to perhaps perceive an event as fearful.

Frontal Cortex

One interesting set of observations is that while the amygdala tends to have higher metabolic activity associated with depression and fear (Morris et al., 1996; Drevets, 2001; Drevets et al., 2002), the subgenual prefrontal cortex tends to have decreased metabolic activity (Drevets et al., 1999). Regions of the frontal cortex are fundamental for the emotions, including fear (e.g., Davidson et al., 1990, 1999, 2000; Quirk et al., 2000; Posner and Rothbart, 2000).

Building on the work of Schneirla (1959, 1965), a number of investigators have shown that the representation of emotional events is differentially expressed within this large region of the brain. Right neocortical activation is linked to more negative emotions and withdrawal, whereas the left side of the frontal region is linked to more positive emotions (Davidson et al., 1999, 2000). For example, lesions of the left region are more closely associated with states of depression; the converse holds with damage to the right region (Davidson et al., 1990, 2000). In functional brain-imaging studies, the elicitation of positive emotions is closely linked to left frontal neocortical activation (central states that we prefer to stay in) and negative emotions are closely linked to right neocortical activation (states that we want to remove; Schmidt et al., 1999a; Davidson et al., 2000). In a number of contexts, activation of the left frontal cortex is tied to positive representations, experiences, and contexts; the converse

holds true for negative representations (Davidson and Sutton, 1995; Davidson, 1998). Moreover, this cortical activation is associated with affective states; patients who are depressed have greater relative activation of right frontal cortex than those who are not (Davidson et al., 1999).

The frontal neocortical activation is stable and appears in ontogeny. Young children who are fearful have greater relative activation of the right frontal cortex (Schmidt et al., 1999a). This event is linked to elevated levels of cortisol (Kagan et al., 1988; Gunnar et al., 1989; see Gunnar and Davis, 2001 for a full discussion of cortisol under a variety of central states). In monkeys, this differential representation of cortical function is linked to CRH expression (see below). Some of the key areas linked to the expression of fear and CRH are depicted in figure 3.3.

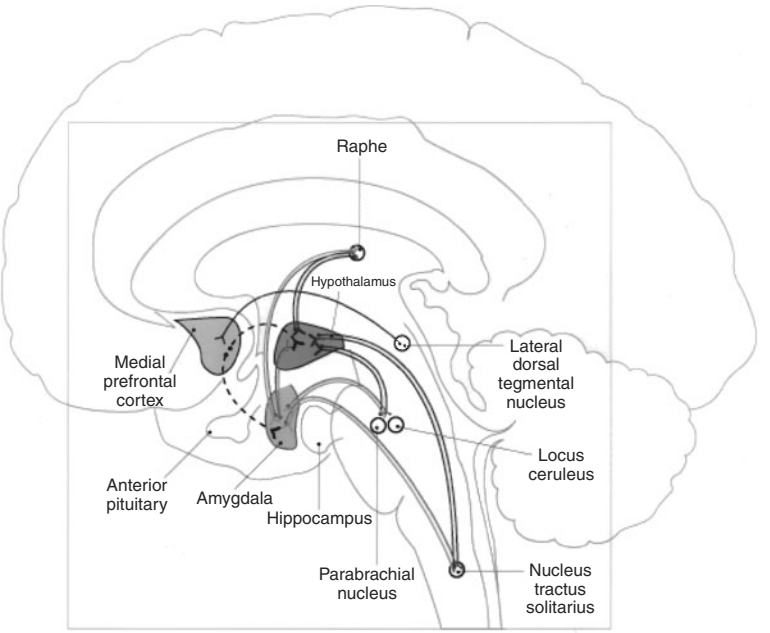


Figure 3.3
Some of the key areas in the brain that underlie fear.

From Normal Fear to Anticipatory Angst and Allostasis

Understanding human anxiety disorders lies in the study of normal fear and its associated behaviors. This includes not only the fear-related autonomic and behavioral responses that are activated during pathological anxiety but, also important, the perceptual fear response of greater vigilance. Unraveling the mechanisms of the perceptual fear response may lead researchers to a greater understanding of pathological anxiety because dysfunction or overactivation of the perception of fear can lead to anxious thought and maladaptive behavior (e.g., Rosen and Schulkin, 1998; Davis and Whalen, 2001).

Animals are ready to respond to external stimuli and, in many cases, in a prepotent or fixed manner (Tinbergen, 1951; Lorenz, 1981). This seems to be particularly true of fear responses (Bolles, 1962). If the perceptual-response system is primed and more sensitive or excitable, then there is a greater tendency for action. Increases in the readiness to respond would produce greater or exaggerated responses to stimulation and would allow for these responses to be elicited with lower intensity stimulation (Arnold, 1969; Frijda, 1986). The various cognitive biases (e.g., interpretive, attention, or memorial) and increased startle responses (Morgan et al., 1995; Grillon et al., 1996) demonstrated by anxiety disorder patients in response to threatening stimuli indicate that neural fear systems are hyperexcitable in anxiety disorders. Neurologically, this can be conceptualized as hyperexcitability of brain structures that evaluate (exteroceptive, interoceptive, and proprioceptive) stimuli as dangerous. Thus external as well as internal autonomic and muscular events are evaluated more readily as signaling danger in a hyperexcitable fear evaluation system.

Trauma at an early age, particularly infant-mother separations, has a detrimental effect on emotional development (Bowlby, 1977). Numerous animal studies have demonstrated that maternal separation or deprivation can have prolonged effects on the behavior and on the physiology of the offspring. Brief, repeated separations may actually immunize for later stress, whereas longer periods of maternal deprivation can

increase later responses to stress (e.g., Levine, 1975, 2000; Meaney et al., 1993). Interestingly, studies throughout several decades demonstrate that maternal behavior can ameliorate the effects of early stress on later behavioral and physiological responses to stress (Levine, 1975; Liu et al., 1997; Van Oers et al., 1998; Caldji et al., 1998). Lack of such ameliorative maternal behavior may sensitize the offspring to stressors.

Glucocorticoids, CRH, and the Allostatic Regulation of Fear

Fear is sustained by neuroendocrine events in most vertebrates that have been studied (Jones et al., 1988; Sapolsky, 1992; Jones and Satterlee, 1996), and there is no clear physiological set point that underlies the states of fear. Under threat, the HPA axis is activated (e.g., Cannon, 1915, 1929a; Selye, 1956; Dallman et al., 2000), as are sites in the brain that participate in the regulation of fear. Let us consider the glucocorticoids first. The secretion of glucocorticoids helps to sustain a number of behavioral responses including fear-related behaviors (Richter, 1949; see review by Korte, 2001). Without glucocorticoids, as Richter (1949) noted, animals die under (conditions of extreme) duress (see also Ingle, 1954; Selye, 1956). Adrenalectomized animals are unable to tolerate fear, duress, or chronic stress and suffer fatally. Glucocorticoids prepare the animal to cope with emergency and taxing environmental contexts (Cannon, 1915, 1929a; Richter, 1949).

Glucocorticoids are also essential in the development of fear (Takahashi, 1995). Removal of corticosterone in rats before (but not after) 14 days of age impairs fear of unfamiliar objects. In other words, there is a critical period in neonatal development in which glucocorticoids facilitate the normal expression of fear of unfamiliar objects (Takahashi, 1995). These events are centrally mediated (Takahashi and Kim, 1994). There are also periods in development that have been characterized as the "stress-hyporesponsive period" (Levine et al., 2000).

Glucocorticoids are secreted under a number of experimental conditions in which fear, anxiety, novelty, and uncertainty are

experimental manipulations (Mason et al., 1957; Mason, 1975a, b; Breier et al., 1988). In contexts in which there is loss of control, or the perception of control (worry is associated with the loss of control), glucocorticoids are secreted. This fact holds across a number of species, including humans (e.g., Breier et al., 1988). Perceived control reduces the levels of glucocorticoids that circulate. In rats, for example, predicting the onset of an aversive signal reduces the level of circulating glucocorticoids (Kant et al., 1992). Within the clinical sphere, one of the most consistent findings in fearful, depressed patients is elevated levels of cortisol and an enlarged adrenal cortex (Sachar et al., 1970; Carroll et al., 1976; Nemeroff et al., 1992). These findings are congruent with those of Richter (1949), who observed an enlarged adrenal gland in stressed, fearful wild rats when compared to unstressed laboratory analogs (figure 3.4).

From a biological view, the chronic activation of glucocorticoid hormones is costly. The subordinate male macaque has elevated cortisol levels but lower levels of testosterone than the dominant one (Sapolsky, 1992, 2000). The lower level of testosterone decreases its reproductive fitness in the short term. The cost of chronic subordination is perhaps more fearfulness and uncertainty of attack as well as a further decrease in the likelihood of successful reproduction. This phenomenon of high corticosterone and low testosterone has been demonstrated in a number of species (see, e.g., Lance and Elsey, 1986).

Sustained fear is also metabolically costly. Although glucocorticoids are essential in the development of neuronal tissue and in adapting to duress, if the elevation of glucocorticoids is sustained over time, tissue (e.g., brain and bone) will begin to deteriorate (Sapolsky, 1992; McEwen, 1997). Chronic glucocorticoid activation, for example, increases the likelihood of neurotoxicity and neural endangerment through the loss of glucocorticoid receptors.

Perhaps to avoid this deterioration, negative regulation of the HPA axis evolved to restrain the stress response. In other words, glucocorticoids restrain the output of the PVN of the hypothalamus and pituitary gland, decreasing CRH and

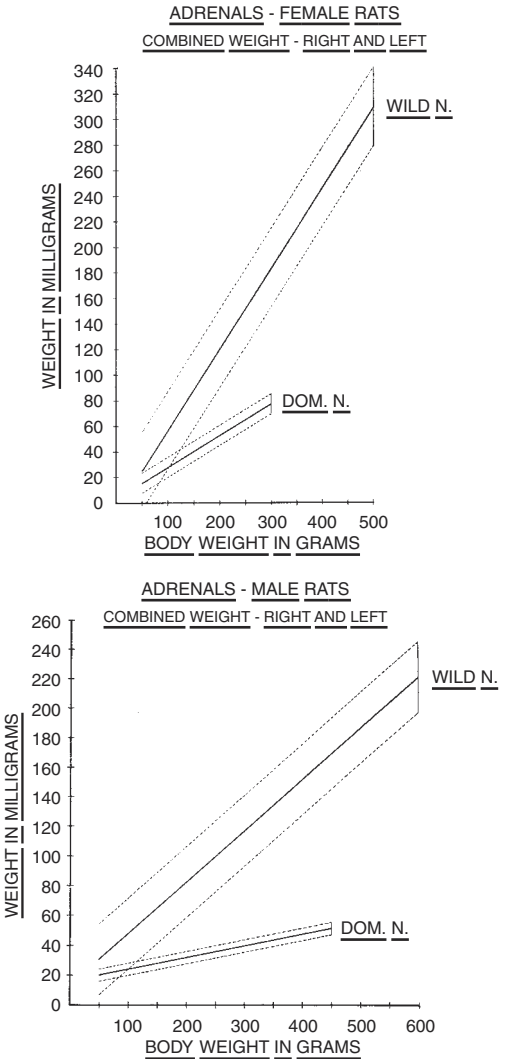


Figure 3.4
Weight of adrenal glands of wild and domestic (DOM) rats (Richter, 1949).

adrenocorticotropic hormone (ACTH) and thereby limiting their own production (Munck et al., 1984; Sawchenko, 1987; Dallman et al., 1987, 1992, 2000). This is classic negative feedback, one mechanism to restrain the activation of the HPA (Munck et al., 1984; Kovacs and Sawchenko, 1996; Dallman et al., 2000). The restraint of CRH, at the level of the PVN, is profound and sustained over time. The restraint of HPA function appears to be regulated in part through glucocorticoid activation of the hippocampus and bed nucleus of the stria terminalis (Beaulieu et al., 1987; Sapolsky et al., 1991; Cullinan et al., 1993). This occurs through efferent control of the PVN by gamma-aminobutyric acid (GABA)-mediated inhibitory neurons (Herman and Cullinan, 1997).

Glucocorticoids play a fundamental role in energy balance (hence their name). They are secreted in young children that are energetic (Gunnar, 1998), they can play a role in attachment behaviors in humans and other animals (DeVries et al., 1995; Fleming et al., 1997; Carter et al., 1999), and they facilitate a number of behavioral events (e.g., Denton, 1982; Schulkin, 1991; Sumners et al., 1991; Wingfield and Ramenofsky, 1997; Dallman et al., 2000) by their actions in the brain and the induction of neuropeptides and neurotransmitters (Herbert and Schulkin, 2002). Glucocorticoids are also important in sustaining a fear response. Fear is a state that is energy expensive (Sapolsky, 1992) and can go on for long periods of time in anticipation of events that may or may not occur. In order to understand the impact of fear on the body and brain, a new conceptual framework that involves two concepts, allostasis and allostatic overload, can serve a conceptual role in our understanding the state of fear, a chronic state, and the eventual breakdown of biological tissue and function.

Corticotropin-Releasing Systems in the Brain

Corticotropin-releasing hormone is now well known to be both a peptide that regulates pituitary and adrenal function and an extrahypothalamic peptide hormone linked to a number of

behaviors, including behavioral expressions of fear (Tarjan et al., 1992; Koob et al., 1993; Kalin et al., 1994).

Corticotropin-releasing hormone is a 41 amino acid peptide hormone initially isolated from the PVN of the hypothalamus that facilitates ACTH secretion from the anterior pituitary (Saffran et al., 1955; Guillemin and Rosenberg, 1955; Vale et al., 1981). In addition, CRH is linked to immune, sleep, and appetitive functions (Owens and Nemeroff, 1991).

Corticotropin-releasing hormone cell bodies are widely distributed in the brain (Swanson et al., 1983; Palkovits et al., 1983; Gray, 1990). The majority of CRH neurons within the PVN are clustered in the parvicellular division. Other regions with predominant CRH-containing neurons are the lateral bed nucleus of the stria terminalis and the central region of the central nucleus of the amygdala. To a lesser degree, there are CRH cells in the lateral hypothalamus, prefrontal, and cingulate cortex. In brainstem regions, CRH cells are clustered near the locus coeruleus (Barrington's nucleus) (Valentino et al., 1994, 1995), parabrachial region, and regions of the solitary nucleus (see figure 2.8).

The CRH receptor has been cloned and contains a 451 amino acid protein (Chen et al., 1993; Perrin et al., 1993; Lovenberg et al., 1995). Activation of the CRH receptor is linked to a G protein and activates adenylate cyclase cascade and an increase in intracellular cyclic adenosine monophosphate (cAMP) and calcium levels (Perrin and Vale, 1999). The distribution of CRH receptor sites includes regions of the hippocampus, septum, and amygdala (medial and lateral region), and neocortex, ventral thalamic, and medial hypothalamic sites, and sparse receptors are located in the PVN and the pituitary gland. The distribution is widespread in cerebellum in addition to brainstem sites such as major sensory nerves and the solitary nucleus (Potter et al., 1994).

In both rodents and primates, further studies have revealed that there are at least two distinct CRH receptor subtypes (Lovenberg et al., 1995; Aguilera et al., 2001; Dautzenberg et al., 2001). The CRH 1 subtype is prominent in limbic regions such

as the amygdala, and the CRH 2 subtype is more widely distributed throughout the brain (Potter et al., 1994). It is the CRH 1 receptor subtype that has been linked to both the regulation of the HPA axis and in extrahypothalamic sites to the reduction of fear and the sense of adversity (Smith et al., 1998; Arborelius et al., 2001; Bale et al., 2001a), and perhaps even a reduction of depression (see below). The regulation of both types of receptors has been linked to allostatic regulation (Coste et al., 2001).

Negative Restraint of PVN CRH Gene Expression by Glucocorticoids: Homeostatic Regulation

Glucocorticoid hormones have one well-known function—namely, to restrain the HPA axis by negative feedback mechanisms (Munck et al., 1984). This negative feedback is a fundamental way in which the HPA axis is restrained during stress and activity (Munck et al., 1984) and is understood in the context of negative feedback regulation (e.g., Goldstein, 1995a, b, 2000). One should also note that recent evidence suggests that negative restraint of CRH may not be confined solely to the PVN; it may also appear in the locus coeruleus (Pavcovich and Valentino, 1997).

The restraint of HPA activation by glucocorticoids is rapid and profound (Dallman et al., 1987). It is also specific; mineralocorticoids do not produce these effects (Sawchenko, 1987; Watts and Sanchez-Watts, 1995). Moreover, glucocorticoids directly control neuronal excitability (Joels and DeKloet, 1994). Given that some of the glucocorticoid effects on the brain are quite rapid, it is possible that corticosterone has nongenomic membrane effects via GABAergic mechanisms (Orchinik et al., 1994), in addition to its genomic effects.

The degree of the HPA activation is coordinated by both humoral and neural mechanisms. Efferent pathways from the hippocampus and amygdala regulate the expression of CRH in the PVN (Sapolsky et al., 1991; Herman and Cullinan, 1997). For example, lesions or stimulation of the central nucleus of the amygdala either decrease or increase HPA activation,

respectively (Beaulieu et al., 1987). Furthermore, neurons within the lateral bed nucleus of the stria terminalis may activate or inhibit PVN function via GABAergic mechanisms (Cullinan et al., 1993; Herman and Cullinan, 1997).

While the profound effect of inhibition is indisputable, there are neuronal populations within the PVN that project to the brainstem that are not decreased by glucocorticoids and some of which are actually enhanced (Swanson and Simmons, 1989; Tanimura and Watts, 1998). That is, CRH neurons en route to the pituitary are restrained by glucocorticoids, but CRH en route to other regions of the brain appears not to be restrained (Swanson and Simmons, 1989; Watts and Sanchez-Watts, 1995; Watts, 1996; Palkovits et al., 1998b).

Positive Induction of CRH Gene Expression in the Central Nucleus of the Amygdala and Bed Nucleus of the Stria Terminalis by Corticosterone: Allostatic Regulation

Several colleagues and I (Schulkin et al., 1994) suggested that corticosterone could restrain one set of CRH-producing cells, namely, that system linked to HPA function, while initiating amygdala production of CRH for fear-related behaviors (Schulkin, 1994; Schulkin et al., 1994). We suggested that there might be this disassociation within the endocrine literature on glucocorticoid regulation of CRH expression on these two different sites. There were intimations of this in the literature (Young and Akil, 1988; Bagdy et al., 1990; Frim et al., 1990; Owens et al., 1990; Imaki et al., 1991). These results have direct relevance for the concept of allostasis and feedforward neuroendocrine systems.

Swanson and Simmons (1989) demonstrated that replacement of corticosterone in adrenalectomized rats would decrease hypothalamic CRH in the parvicellular PVN while it restored and even increased CRH in the central nucleus of the amygdala. This differential regulation of PVN CRH neurons, from central nucleus CRH neurons, in adrenalectomized rats was then extended explicitly and more broadly tested by others (Watts and Sanchez-Watts, 1995; Palkovits, et al., 1998b). It was also noted that within magnicellular neurons within the PVN that pro-

jected to the brainstem there was an actual increase in CRH, and no change in CRH neurons in the lateral hypothalamus (Swanson and Simmons, 1989; Imaki et al., 1991; Watts and Sanchez-Watts, 1995; Tanimura and Watts, 1998). Watts and Sanchez-Watts (1995) also reported that in adrenalectomized rats, aldosterone can increase CRH gene expression in the central nucleus of the amygdala in the absence (but not the presence) of corticosterone, and mineralocorticoid receptor levels are increased by CRH infusions in the brain (Gesing et al., 2001) and thus important interactions exist between both adrenal steroid hormones and CRH. Interestingly, while adrenalectomy results in increases in CRH expression in the paraventricular nucleus, it reduces CRH expression in the central nucleus of the amygdala (Palkovits et al., 1998b).

Makino and colleagues (1994a, b) demonstrated that when adrenally intact rats were treated with high levels of corticosterone for extended periods of time (4 days–2 weeks), there was a decrease of CRH mRNA from the PVN, but an increase in CRH mRNA, or protein, from the central nucleus of the amygdala. In other words, corticosterone could decrease the expression of CRH in the PVN (restraint of HPA axis) while it simultaneously increased CRH gene expression in the central nucleus of the amygdala (Thompson et al., 2000). However, in cell culture CRH neurons of the amygdala, dexamethasone had no effect (Kasckow et al., 1997).

When we (Makino et al., 1995) looked at changes in CRH receptor levels following corticosterone treatment in regions of the amygdala where they are located (basal lateral region), we found at best a modest change in receptor distribution. We found a slight decrease of CRH receptor levels in the basal lateral region of the amygdala following high levels of corticosterone treatment. Dexamethasone pretreatment produced no such effect in extrahypothalamic sites such as the amygdala (Zhou et al., 1996a, b). There are few, if any, CRH receptor sites in the central nucleus of the amygdala (Makino et al., 1995), although CRH receptors have been reported to be altered by high levels of glucocorticoids in tree shrews under chronic psychosocial stress (Fuchs and Flugge, 1995).

Turn now to the bed nucleus of the stria terminalis. The bed nucleus of the stria terminalis plays a fundamental role in the regulation of the HPA axis during stress, and it is the major relay to the PVN from the amygdala and the hippocampus (Herman and Cullinan, 1997; Gray, 1999). Both the central nucleus of the amygdala and ventral subiculum influence HPA function (Beaulieu et al., 1987; Cullinan et al., 1993; Herman et al., 1998) and perhaps do so via the bed nucleus of the stria terminalis.

During fear/anxiety states, the bed nucleus of the stria terminalis may regulate systemic physiological responses. Thus one way in which to envision the hippocampus and the amygdala is through their influence on the bed nucleus of the stria terminalis function and subsequently upon the PVN. The bed nucleus of the stria terminalis may act as the *head ganglia* of the HPA axis in the regulation of systemic physiology as it transduces information from both the hippocampus and the amygdala. The bed nucleus of the stria terminalis is therefore positioned to exert control over output measures from both the hippocampus and the amygdala in the regulation of fear/anxiety-related responses.

The lateral region of the bed nucleus of the stria terminalis contains CRH-producing neurons (Ju et al., 1989; Gray, 1990; Makino et al., 1994b; Watts and Sanchez-Watts, 1995). Corticotropin-releasing hormone gene expression within this region of the bed nucleus of the stria terminalis is increased following corticosterone treatment. In the laboratory, this held for both adrenalectomized rats treated with corticosterone (Watts and Sanchez-Watts, 1995) and adrenally intact rats also treated with corticosterone (Makino et al., 1994b; see chapter 5).

Taken together, these results are examples of allostatic regulation. Now let's see how they underlie a fearful state.

Central CRH, Angst, Allostasis, and the Amygdala

Central CRH and central amygdala activation are linked to the induction of fear in animal studies (Kalin and Takahashi, 1990; Koob et al., 1993). Central infusions of CRH potentiate a number

of fear-related behavioral responses (Takahashi et al., 1989), and infusion of CRH antagonists both within the amygdala and outside of it reduce fear-related responses (Swiergel et al., 1992; Koob et al., 1993). Of importance, infusions of CRH into the ventricles are known to access to CRH receptor sites (Bittencourt and Sawchenko, 2000).

Startle responses are enhanced by CRH infusions (Swerdlow et al., 1989). It is important to note that lesions of the central nucleus of the amygdala, and not the PVN, disrupt CRH-potentiated conditioned fear responses (Liang et al., 1992). That is, only lesions of the amygdala and not the hypothalamus disrupt the behavioral response. Moreover, peripheral blockade of ACTH/glucocorticoids does not disrupt central CRH-related fear responses (Pich et al., 1993a). It is central CRH that is the critical neuroendocrine factor.

Corticosterone Facilitation of CRH and Behavioral Activation of Fear

As I have indicated, high levels of systemic glucocorticoids are associated with fear (or the perception of adverse events) in a number of species (Mason et al., 1957; Jones et al., 1988; Breier, 1989; Takahashi and Kim, 1994; Kalin et al., 1998a, b; Buchanan et al., 1999; see review by Korte, 2001). In one set of experiments, in collaboration with Keith Coordimas and Joe LeDoux (Coordimas et al., 1994), rats (adrenally intact) were pretreated with corticosterone to investigate whether it facilitated conditioned fear-induced freezing. All rats received conditioning trials in which the unconditioned stimulus (foot shock) was presented concurrently with the conditioned stimulus (auditory tone). Several days after the trials, the rats were treated with corticosterone (Coordimas et al., 1994). We found that the same treatment of corticosterone that increased CRH gene expression in the central nucleus of the amygdala and bed nucleus of the stria terminalis also facilitated conditioned fear-induced freezing in rats (Coordimas et al., 1994).

As noted above, CRH facilitates startle responses. This response does not depend on the adrenal glands, because centrally delivered CRH facilitates startle responses in the absence of the adrenal glands (Lee et al., 1994). In their study, Lee and colleagues demonstrated that high chronic plasma levels of corticosterone in adrenally intact rats facilitated CRH-induced startle responses (Lee et al., 1994). Perhaps what occurs normally is that the glucocorticoids, by increasing CRH gene expression, increase the likelihood that something will be perceived as a threat, which results in a startle response. Thus a dose of CRH, given intraventricularly, did not produce a startle response, but when the adrenally intact rats were maintained at high levels of corticosterone for several days prior to the CRH injection, the same dose did produce a startle response.

Corticotropin-releasing hormone centrally infused at high doses into the lateral ventricle facilitates seizures linked to amygdala function (Weiss et al., 1986). In a collaboration with Rosen and his colleagues, we found that a dose of CRH by itself does not induce kindling but does so with a background of high glucocorticoid levels. That is, instead of reducing seizures as was predicted by corticosterone's restraint on the HPA axis, it actually potentiated the seizures in adrenally intact rats (Rosen et al., 1994). One way to understand these findings is that by increasing CRH expression in the brain, the glucocorticoids lower the threshold for the induced seizure. It is now known that long-term effects on CRH gene expression result from adverse experiences (Bruihnzeel et al., 2001) creating perhaps a long-term allostatic state.

In a later study, we looked at contextual fear conditioning in groups of rats that were treated with corticosterone as above and given a vehicle treatment. We replicated our original finding that CRH expression was differentially regulated in the central nucleus of the amygdala and the parvicellular region of the PVN (Thompson et al., 2000; figure 3.5, below). One week after the completion of the conditioning and the last corticosterone injection, the rats were tested for the retention of conditioned

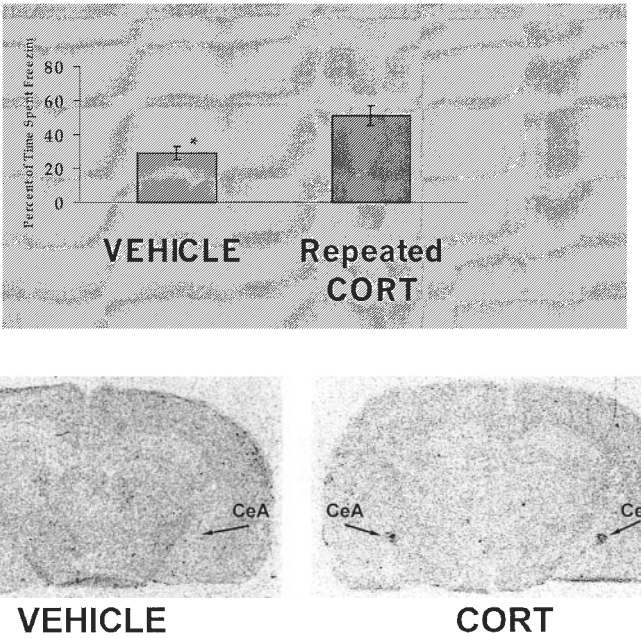


Figure 3.5
Digitized images of CRH mRNA in the central nucleus of the amygdala (CeA) in corticosterone (CORT) (4 mg) or vehicle treated rats (after Thompson et al., 2001). Freezing responses of rats in the retention test in corticosterone treated (5 mg per day for 4 days) or vehicle treated (adapted from Thompson et al., 2000).

fear. The corticosterone-treated rats displayed more fear conditioning than the vehicle-treated rats. The data suggest that repeated high levels of corticosterone can facilitate the retention of contextual fear conditioning, perhaps by the induction of CRH gene expression in critical regions of the brain such as the amygdala.

In an important experiment, Shepard et al. (2000) demonstrated that implants of corticosterone directly into the amygdala resulted in an increase in CRH expression in the central

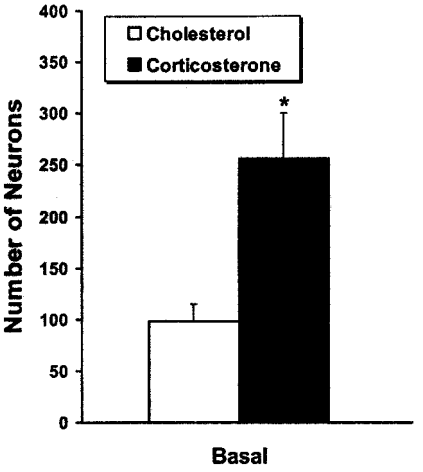


Figure 3.6
Increases in CRH mRNA to injections of corticosterone directly to the central nucleus of the amygdala (Shepard et al., 2000).

nucleus of the amygdala and a reduction in open-field exploratory behavior (figure 3.6). Rats are typically hesitant at first to explore new environments, and this was exacerbated with the induction of CRH in the central nucleus when corticosterone was directly delivered into the amygdala (rats remained in the open chamber for 22.6 sec vs. 67.3 sec for controls). In addition, corticosterone implants directly into the central nucleus increased levels of CRH expression, without affecting AVP levels, in the parvicellular region of the paraventricular nucleus of the hypothalamus (Shepard et al., 2003). Moreover, gastric pathology, one consequence of allostatic overload (colon distension), was apparent as a result of the corticosterone. In further tests, pretreatment with the type-1 receptor CRH antagonist abolished these effects (see also for the role of the CRH type-1 receptor, Smith et al., 1998; Arborelius et al., 2000; and the role for the type-II receptor, Bale et al., 2000; Bakshi et al., 2002).

A Possible Role for Glucocorticoids and CRH within the Bed Nucleus of the Stria Terminalis for Fear-Related Context Learning and Anxiety

Context learning (no one specific cue associated with an event) and uncertainty are known to elevate glucocorticoid levels in a number of species (Mason et al., 1957; Mason, 1975a, b). Uncertainty that stems from environmental context influences CRH expression. For example, in macaques, uncertainty of food availability during development results in elevated levels of cortisol, in addition to increases in the expression of CRH in the cerebrospinal fluid when they are adults (Coplan et al., 1996, 2001).

Corticosterone is also essential in the normal development of fear (Takahashi, 1995) and for context-related fear learning. For example, blocking corticosterone secretion impairs long-term consolidation of context-dependent fear conditioning. Replacement of corticosterone in adrenalectomized rats returns this function to normal (Fleshner et al., 1997; Pugh et al., 1997). These effects are specific for context-dependent fear, as there were no decrements in conditioned fear to a specific stimulus.

The above effects on fear may be mediated by central CRH. In fact, CRH is known to facilitate nonspecific fear conditioning (Davis et al., 1997). Perhaps corticosterone acts to increase CRH gene expression in certain regions of the brain and thereby increases the likelihood of context-dependent fear conditioning.

The bed nucleus of the stria terminalis has been linked to context-dependent learning (Lee and Davis, 1997b), to general anxiety associated with drug abuse (Erb and Stewart, 1999; Koob and LeMoal, 2001; see chapter 5 of this book), and to symptoms associated with generalized anxiety (Stout et al., 2000). Perhaps some of the effects on context-related fear conditioning seen in hippocampal lesions studies (Phillips and LeDoux, 1992; Kim et al., 1993) may be mediated by regions of the bed nucleus of the stria terminalis (Davis et al., 1997; Lee and Davis, 1997a), while the specific conditioned fear state depends upon the amygdala (LeDoux, 1996; Rosen and Schulkin, 1998; Davis and Whalen, 2001).

Lesions of the bed nucleus of the stria terminalis do not interfere with conditioned fear-related responses, unlike lesions of regions of the amygdala, which interfere with fear-potentiated startle or freezing (Hitchcock and Davis, 1991; LeDoux, 1995; Lee and Davis, 1997a, b). Nor does stimulation of this region facilitate fear-potentiated startle responses, whereas stimulation of the central nucleus of the amygdala does (Rosen et al., unpublished observations; Davis et al., 1993). However, lesions of the bed nucleus of the stria terminalis can interfere with basic unconditioned startle responses (Gray et al., 1993; Gray and Bingaman, 1996) and with long-term CRH effects on behavior (Davis et al., 1997).

Of importance, infusions of CRH directly into the bed nucleus of the stria terminalis facilitate fear/anxiety-related behavioral responses; antagonists of CRH into this region do the converse (Davis et al., 1997; Lee and Davis, 1997a; see chapter 5 for a discussion of the effects of drug addiction). This theory of the role of glucocorticoids in facilitating CRH gene expression in several sites in the brain would suggest that pretreatment with glucocorticoids should further potentiate this effect, but this is not known. This again suggests an allostatic mechanism of regulation.

Experiment of Nature: Elevated Cortisol and Central CRH—Inhibited Children and Macaques and Their Fear of the Unfamiliar

A subset of excessively shy and/or fearful children are known to have had, at some point in their developmental history, higher levels of cortisol in several contexts than normal controls (Kagan et al., 1988; Gunnar et al., 1989; Schmidt et al., 1997; Dettling et al., 2000). Interestingly, young children who demonstrate high motor and negative emotional responses at 9 months of age tend to be behaviorally inhibited at 4 and 7 years old. They also tend to have higher cortisol levels. The amount of time that shy and fearful children spend cowering and worrying suggests that the behavioral inhibition is an active process, a metabolically expensive event (figure 3.7).

Figure 3.7
Shy fearful child (Schmidt and Schulkin, 1999).

Although cortisol is certainly not the molecule of fear and anxiety, it is the molecule of energy metabolism; fear, anxiety, and trauma are metabolic events. With this caveat, extremely shy, socially withdrawn children may be vulnerable to anxiety disorders and perhaps depression throughout their lives (Hirshfield et al., 1992; Kagan and Snidman, 1999). They should be vulnerable to allostatic load—for example, vulnerability to allergic symptoms (Kagan et al., 1991) and vascular disease (Bell et al., 1993) perhaps because of the chronic worry that they experience in social contexts or in unfamiliar environments. Interestingly, high cortisol levels have been linked not only to fearfulness in childhood but to repression in adulthood (Brown et al., 1996).

An analogous phenomenon to that of shyness and fearful behavior in children has been observed in a subset of young, fearful rhesus monkeys that have high levels of cortisol. This subset also freezes for longer periods of time than other rhesus monkeys (Champoux et al., 1989). In adult rhesus monkeys, high levels of cortisol, in addition to high levels of CRH from the cerebrospinal fluid, is associated with behavioral inhibition (Kalin et al., 2000; Habib et al., 2000). In addition, when faced with an unknown intruder in an adjacent cage, macaques increase their CRH expression (figure 3.8; Habib et al., 2000). Increases (or sensitization) of CRH in the brain occurs after stress, abuse, and maternal deprivation in macaques (Habib et al., 1999, 2000). Interestingly, the converse holds for neuropeptide Y, a neuropeptide linked to reward, food intake, and positive emotions (e.g., Heinrichs et al., 1992; Wahlestedt et al., 1993).

A subset of these macaques not only have higher levels of CRH and cortisol than normals, but also demonstrate greater fearful temperament and greater activation of right-hemispheric activation which has been linked to withdrawal and negative perception of events (figure 3.9; Davidson et al., 1990, 1999; Habib et al., 1999, 2000; Kalin et al., 2000). Differences in temperamental expression to a number of unconditioned fear-related stimuli may reflect frontal neocortical activation (Kalin et al.,

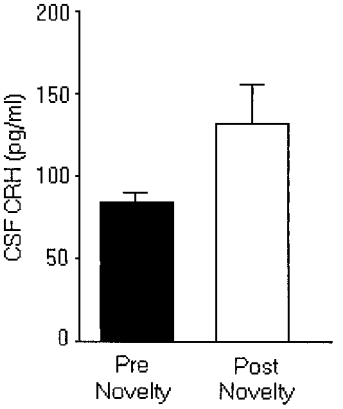


Figure 3.8
Levels of corticotropin releasing hormone in the cerebrospinal fluid of macaques in response to a familiar (prenovelty) and unfamiliar (postnovelty) object (adapted from Habib et al., 1999, 2000).

2001), because ibitenic acid lesions (cell body destroyed and fibers left intact) of the macaque amygdala left a number of unconditioned behavioral traitlike responses intact (Kalin et al., 2001), in addition to the normal asymmetry associated with traitlike dispositions.

Perhaps these excessively shy, fearful children and monkeys reflect differences in endogenous production of CRH. For example, rats that tend to have higher levels of CRH expression in the central nucleus of the amygdala may be more vulnerable to exaggerated fear responses (Altemus et al., 1994). Transgenic mice that overproduce CRH have greater fear-related responses in unfamiliar environments (Stenzel-Poore et al., 1994) in addition to other behavioral abnormalities such as sexual inhibition (Heinrichs et al., 1997; but see also Weninger et al., 1999, or Bakshi and Kalin, 2000, for discussions of the role of the CRH receptor subtypes and the behavioral responses associated with CRH). These same animals also have high levels of corticosterone.

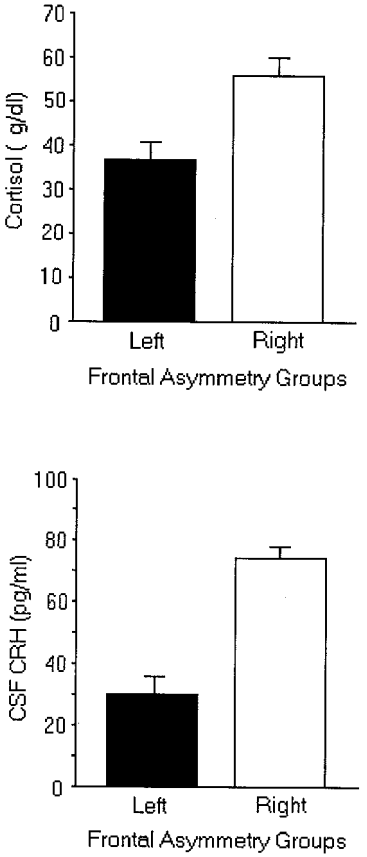


Figure 3.9
Levels of CSF CRH and systemic cortisol in left and right frontal brain activation in macaques (adapted from Kalin et al., 1998a, b, 2000).

Anxious or Melancholic Depression: CRH and Cortisol and Allostatic Overload

Unipolar depression is a major health concern that can affect up to 10–15 percent of the population at any point in time. It is generally held that there is a greater incidence of depression in women than men. There are several types of depression (e.g., seasonal, postpartum, anxious, or melancholic; Nemeroff, 1992, 1999; Gold and Chrousos, 1998). For example, melancholic depression reflects a hyperaroused state—a state of vigilance. This state is marked by a profound sense of chronic angst, decreased pleasure, sleep abnormalities, and alterations of appetite, sense of pleasure, and libido (Nemeroff et al., 1992, 1999; Gold and Chrousos, 1998). Decreased libido and lethargy can be pervasive, with clear decreases in reproductive functions (Chrousos et al., 1998). A number of neurotransmitters and neuropeptides are altered during episodes of melancholic depression, including altered levels of adrenergic and serotinergic functions (e.g., Bunney and Davis, 1965; Gold et al., 1988a, b; Drevets et al., 1999; Lambert et al., 2000; Wong et al., 2000; Caberlotto and Hurd, 2001).

Interestingly, both atypical and seasonal depression are characterized by decreases in arousal, lethargy, a tendency to eat and sleep more, and decreased hypothalamic function (e.g., reduced levels of CRH; Vanderpool et al., 1991; Gold and Chrousos, 1998). As we will see below, anxious depression reflects a tendency for altered levels of both CRH and cortisol (cf. Gold et al., 1984; Nemeroff et al., 1984; Roy et al., 1987, 1988; Geracioti et al., 1997).

A significant subset of patients with agitated depression have elevated levels of cortisol (Sachar et al., 1970; Carroll et al., 1976; Roy et al., 1988; Kling et al., 1991; Nemeroff et al., 1992; Gold and Chrousos, 1998; see also Young et al., 2001). Yet levels of CRH are also elevated in the cerebrospinal fluid of such individuals (Nemeroff et al., 1984; Nemeroff, 1992, 1999, but see review by Kasckow et al., 2001 for the range of studies on levels of CRH

in the cerebrospinal fluid). Interference with the type-1 CRH receptor may reduce some of the symptoms associated with clinical depression (Zobel et al., 2000). This clinical finding forms a basis in which to envision that cortisol might increase extrahypothalamic CRH gene expression when pushed to extreme adverse conditions, such as that of depression. In other words, elevated levels of systemic cortisol in addition to altered levels of central CRH are a feature of melancholic depression (Gold et al., 1984, 1988a, b; Holsboer et al., 1984; Nemeroff et al., 1984, 1992; Holsboer, 2000). Moreover, levels of cortisol in depressed patients are correlated with enhanced amygdala activation (Drevets et al., 2002; see bottom of figure 3.2).

In addition to the overactivation of CRH and cortisol, there is the overactivation of the amygdala and the right frontal cortex in depressed and anxious people (Drevets et al., 1992). Moreover, we know that chronic anxious depression takes its toll on the body. Three examples I mentioned earlier are the demineralization of bone (Michelson et al., 1996), the reduction of hippocampal size and function (Sheline et al., 1996), and prefrontal cell pathology (Rajkowska et al., 1999). In fact, a number of pathophysiological events can occur that are associated with anxious depression. Coronary heart disease and regional fat content have also been linked to anxious depression (Negro et al., 2003). Of importance, CRH and its analogs, in addition to other adrenal hormones (Goldstein, 1995a, b; 2000), are linked to cardiovascular regulation and pathology (Parkes et al., 2001).

Consider another physiological event: bone density changes in depression (Michelson et al., 1996; Robbins et al., 2001; Negro et al., 2003). In one study, for example, people with current major depression, compared to nondepressed controls, had bone mineral density decreases at a number of sites including the hip, spine, and neck (figure 3.10; table 3.1). Cortisol was elevated in the depressed group. When compared with matched controls, for example, the bone density was between 7 and 14 percent lower at various places. Interestingly, vitamin D and parathy-

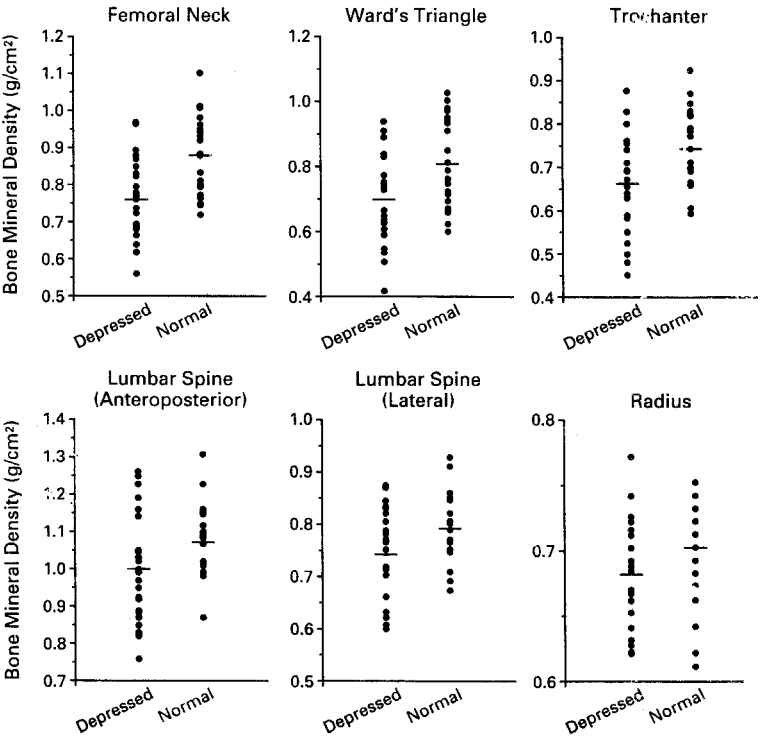


Figure 3.10
Bone mineral density in depressed and normal subjects (Michelson et al., 1996).

roid levels were equivalent in the two groups. Hypercortisol secretion is known to have consequences on bone metabolism and to facilitate bone loss over time (Canalis and Giustina, 2001). In addition to creating a vulnerability to other central and systemic disorders (e.g., cardiovascular pathology; Aromaa et al., 1994; Roy et al., 2001), it increases the likelihood of premature cardiovascular disease. These are examples of the manifestation of physiological/allostatic overload (Cizza et al., 2001).

Table 3.1
Bone mineral density in 24 depressed and 24 normal women

Bone Measurement	Depressed Women	Normal Women	Mean Difference (95% CI)
Lumbar spine (anteroposterior)			
Density (g/cm)	1.00 ± 0.15	1.07 ± 0.09	0.08 (0.02–0.14)
SD from expected peak	−0.42 ± 1.28	0.26 ± 0.82	0.68 (0.13–1.23)
Lumbar spine (lateral)			
Density (g/cm)	0.74 ± 0.09	0.79 ± 0.07	0.05 (0.00–0.09)
SD from expected peak	−0.88 ± 1.07	−0.36 ± 0.80	0.50 (0.04–1.30)
Femoral neck			
Density (g/cm)	0.76 ± 0.11	0.88 ± 0.11	0.11 (0.06–0.17)
SD from expected peak	−1.30 ± 1.07	−0.22 ± 0.99	1.08 (0.55–1.61)
Ward's triangle			
Density (g/cm)	0.70 ± 0.14	0.81 ± 0.13	0.11 (0.06–0.17)
SD from expected peak	−0.93 ± 1.24	0.18 ± 1.22	1.11 (0.60–1.62)
Trochanter			
Density (g/cm)	0.66 ± 0.11	0.74 ± 0.08	0.08 (0.04–0.13)
SD from expected peak	−0.70 ± 1.22	0.26 ± 0.91	0.97 (0.46–1.47)
Radius			
Density (g/cm)	0.68 ± 0.04	0.70 ± 0.04	0.01 (−0.01–0.04)
SD from expected peak	−0.19 ± 0.67	0.03 ± 0.67	0.21 (−0.21–0.64)

Michelson et al., 1996

Post-Traumatic Stress Disorder and Allostatic Overload

Post-traumatic stress disorder (PTSD) is associated with anxiety, memory impairment, and alterations in the HPA axis (Smith et al., 1989; Yehuda et al., 1995a, 1996; Kanter et al., 2001). PTSD is characterized by a state of hypervigilance, chronic arousal, diminished concentration, and altered sleep patterns. Individuals with PTSD often look "shell shocked." The phenomenon has been studied in veterans, in individuals who have been sexually abused, and in a number of other groups.

Patients with PTSD have been found to demonstrate alterations in fear-related responses (Morgan et al., 1995; Grillon et al., 1996). The syndrome is often (Mason et al., 1988; Yehuda et al., 1995a, b) but not always associated with low basal cortisol (Yehuda, 1997; Carrion et al., 2002). For example, low levels of cortisol have been reported in Vietnam veterans who suffered from

PTSD, but not Vietnam veterans who were traumatized but did not suffer from PTSD (Yehuda, 1997; Carrion et al., 2002). Interestingly, in those subjects who did not suffer from PTSD, there was no difference in cortisol levels when compared to normal controls.

More generally, women who have been raped and holocaust survivors who suffer from PTSD have lowered levels of basal cortisol than controls (Yehuda, et al., 1995a; Yehuda, 1997; Steiger et al., 2001). This phenomenon of low basal cortisol is noted in individuals with PTSD but not in individuals who underwent the same traumatic event but do not have PTSD (Yehuda, 1997, 2002).

Interestingly, these same PTSD patients have heightened reactivity or enhanced negative feedback regulation of the HPA axis (Yehuda et al., 1995b). For example, metyrapone, which reversibly inhibits cortisol synthesis, results in greater ACTH secretion in PTSD patients; this may reflect greater activation of CRH (Yehuda, 1997). In other words, while PTSD patients may have lower basal levels than normal subjects, they actually may be more responsive to the activation of the stress hormones (Mason, 1975a, b).

Glucocorticoids modulate memory, in part, via changes in noradrenergic transmission (McGaugh, 2000). These events are mediated in part by the basal lateral region of the amygdala (Roozendaal, 2000). Glucocorticoids can enhance or degrade long-term memory functions (de Quervain et al., 1998). The memory impairments identified among PTSD patients point to a role of the hippocampus that perhaps depends on transmission from the basal lateral region, in addition to the receptor deterioration that can result from excessive levels of glucocorticoids (Roozendaal, 2000; McGaugh, 2000). Short-term memory deficits in soldiers suffering from PTSD are not uncommon, and MRI studies have shown decreased hippocampal volume in patients who suffer PTSD (Bremner et al., 1995). This latter finding is consistent with animal studies that have demonstrated that chronic stress, or allostatic overload, can have long-term consequences such as memory impairment (McEwen and Sapolsky, 1995; McGaugh, 2000).

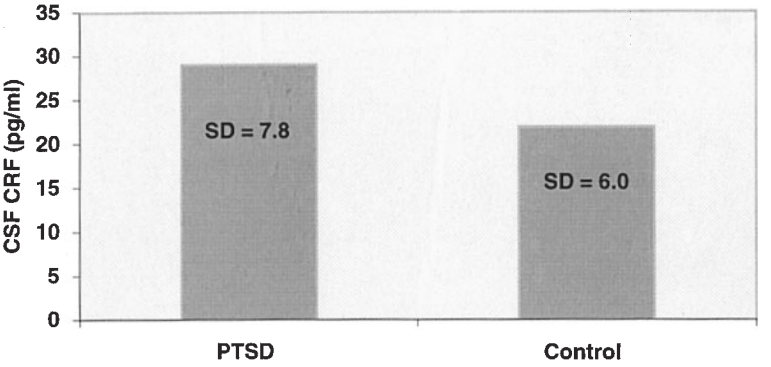


Figure 3.11
Cerebrospinal fluid (CSF) corticotropin releasing hormone levels in post-traumatic stress disorder (PTSD) patients and control subjects (adapted from Bremner et al., 1997).

This finding of low basal cortisol in PTSD patients stands out in contrast to the cortisol levels of people with melancholic depression or excessively shy children. It is important to note that there is some evidence that patients with PTSD have elevated levels of CRH in their cerebrospinal fluid (figure 3.11; Darnell et al., 1994; Bremner et al., 1997; Baker et al., 1999), despite the fact that they have normal levels of cortisol (see also Smith et al., 1989). In other words, patients who suffer from PTSD have elevated CRH levels in the brain under the basal condition, despite the low levels of cortisol that circulate systemically.

One way to understand this phenomenon is that experience with traumatic events induces long-term elevated levels of CRH. As in other contexts in which systemic hormones can have long-term consequences in influencing neuropeptide levels and central states, what matters is not the level of peripheral cortisol or corticosterone, but the induction of a hyperactive CRH system. But the chronic alterations of central CRH and the chronic arousal that is associated with it suggests allostatic dysregulation.

Conclusion: Allostasis and Allostatic Overload

Fear is an adaptation; chronic angst is not. Underlying both, however, is the positive induction of CRH by glucocorticoids in extrahypothalamic sites. I have summarized the evidence that glucocorticoids have differential effects on CRH gene expression in the forebrain. In the parvicellular region of PVN, CRH gene expression is inhibited under some experimental circumstances. In these same contexts, in the central nucleus of the amygdala and the lateral bed nucleus of the stria terminalis, CRH is elevated (Swanson and Simmons, 1989; Makino et al., 1994a, b; Watts and Sanchez-Watts, 1995; Watts, 1996). The elevation of CRH gene expression by glucocorticoids in the central nucleus of the amygdala and lateral bed nucleus of the stria terminalis may underlie a number of fear/anxiety functions as well as pathological states (see Cook, 2002).

I suggested that allostatic regulation is anticipatory and lacks clear set point boundaries—and therefore is not simply reactive to homeostatic imbalances (e.g., restoring plasma levels of sodium in response to alterations of extracellular fluid volume). States of fear and anxiety (or calmness) do not have a simple set point that is maintained and regulated. When elevated in the short term, they may represent an allostatic state (see Koob and LeMoal, 2001 for a discussion of an allostatic state; see chapter 5). Also, I suggested that chronic elevation of corticosterone and central CRH may represent a condition of allostatic overload (Schulkin et al., 1994). Normal fear, unbridled by constraints, can turn into chronic anticipatory angst. In this context, the mechanisms of normal fear are overexpressed, resulting in pathological anxiety (Rosen and Schulkin, 1998; Davis and Whalen, 2001). All of this takes a toll on normal systemic bodily and neural function.

Allostatic overload, as I intimated in the introduction, may reflect the chronic elevation of CRH gene expression in the central nucleus of the amygdala and lateral bed nucleus of the stria terminalis, as well as the concurrent loss of inhibitory CRH gene expression in the PVN by glucocorticoids. In this regard, there

are several experimental contexts in which the effects of restraint stress result in both concurrent elevated levels of corticosterone and CRH gene expression in the central nucleus of the amygdala and the PVN of the hypothalamus. In other words, high levels of corticosterone circulating under restraint stress result in increased levels of CRH release in the central nucleus of the amygdala in addition to the medial basal hypothalamus as measured by microdialysis (Pich et al., 1993b), or increased levels of CRH mRNA in the central nucleus of the amygdala in addition to the PVN measured by in situ hybridization histochemistry (Kalin et al., 1994).

Consider another example: neonatal rats who were stressed during postnatal development are more vulnerable to behavioral expression of helplessness later in life. In this instance, all three classes of CRH mRNA in the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and the PVN of the hypothalamus are elevated when compared to control rats (Plotsky and Meaney, 1996; Caldji et al., 1998; Levine, 2000). These events reflect a compromised inhibitory control over the HPA axis, resulting in greater CRH gene expression at the level of the PVN and concurrent activation of CRH in the central nucleus of the amygdala and lateral bed nucleus of the stria terminalis (Meaney et al., 1993).

In addition, rats injected during this postnatal development with CRH (to create early life adversity) into the third ventricle also resulted in hippocampal cell loss and perhaps dysfunction (Brunson et al., 2001a). The authors suggest that the glucocorticoids are not necessary for this effect, because adrenalectomy did not prevent the neuronal loss. However, by injecting CRH directly into the brain, the authors bypass one normal role of glucocorticoid, namely, regulation of CRH gene expression.

Interestingly, CRH gene expression is elevated in the central nucleus of the amygdala in subordinate adult rats that undergo chronic social stress. There is, however, a concomitant and more varied CRH gene expression in the PVN under these conditions that may reflect the heightened responsiveness to novel stres-

sors and corticosterone secretion in subsets of these subordinate rats (Albeck et al., 1997).

For the depressed person, allostatic overload manifests itself in compromised prefrontal cortex and hippocampal function and chronic amygdala activation (Drevets et al., 1992, 1999, 2002; Davidson, 1998). A depressed person is in a state that he or she has difficulty escaping. Episodic and declarative memory can be impaired, and the individual's perception of the world is colored by the bias of enhanced amygdala activity. For the person suffering from PTSD, there may be highly compromised hippocampal function and deficits of declarative and episodic memory, which may reflect the result of exaggerated levels of glucocorticoids on human performance (e.g., Newcomer et al., 1994, 1999). There may also be hyperactivity of the amygdala (Racuh et al., 2000). For the shy, fearful child or young adult, we do not know definitively about changes in the activation of brain systems, but one hypothesis is a hyperactive amygdala (Kagan et al., 1988) and perhaps some compromised hippocampal function over the long term (McEwen, 2001). There may also be a greater tendency for right frontal activation (Schmidt et al., 1999a).

On the endocrine side, for both the depressed patient and PTSD patient, central CRH is elevated. For the depressed patient and the excessively fearful shy child, cortisol levels are elevated, and for the patient with PTSD, the HPA axis is highly reactive. Each of these situations may reflect allostatic overload. Long-term elevation of central CRH and glucocorticoids can compromise reproductive health, immune function, sleep patterns, feeding, and the general sense of well-being. Chronic worry can compromise metabolic function, rendering one vulnerable to a number of physiological disturbances (McEwen, 1998a, b). Chronic inability to restrain central CRH and systemic glucocorticoids may be an example of allostatic overload.

Richter (1957b) speculated that "voodoo death," being frightened to death, was a state of hopelessness characterized by acute parasympathetic blockage that stops the heart (Goldstein,

1995a, b, 2000). No set point can be found for the chronic fear associated with voodoo death (Schulkin et al., 1994). Chronic fear is a metabolically expensive event; over time, an animal's bodily organs are compromised as the attempt to sustain stability recedes into decreased functional capacity. The body turns frail, stability is compromised, and allostasis, the attempt to maintain stability in diverse circumstances, reaches its limits.

Chapter 4

Normal and Pathological Facilitation of Parturition by a Feedforward Endocrine Mechanism

The emergence of mammals is tied to evolved brains, evolving placental function, and lactation (Easteal, 1999). The placenta is unique in its vast storehouse of biochemical information molecules that are vital to the developing fetus. Nature conserved, extended, and utilized the diverse myriad of information molecules that are well represented in the brain and the placenta and that are fundamental for normal development (Petraglia et al., 1990). Moreover, nature selected a number of endocrine mechanisms to facilitate the viability of fetal development and the progression of a healthy baby; one is an endocrine mechanism that is feedforward. It also provided mechanisms to insure reproductive fitness; for example, extreme nausea during pregnancy may, under some conditions, be a reaction to teratogens (Profet, 1991).

Let me begin with a question: Why the study of preterm delivery of babies in a book on allostatic regulation? There are several reasons. First, placental CRH is elevated during adverse events in pregnancy. It may be a predictor of preterm labor when there are conditions of adversity (see, e.g., Wolfe et al., 1988; Goland et al., 1993; Wadhwa et al., 2001). Second, a positive feedback loop underlies parturition, providing an allostatic mechanism; namely, cortisol increases CRH gene expression in the placenta under normal conditions. And third, this feedback loop may be exaggerated during adverse conditions (*allostatic overload*). In the case of adverse events in pregnancy such as infections, metabolic stress, and social stress, CRH may be overexpressed in the placenta. Similarly, in the case of fear and anxiety, CRH may be altered in the brain (Gold et al., 1984; Nemeroff et al., 1984; Nemeroff, 1992) or with a sense of potential harm (Kalin et al.,

1989; Koob, 1993a; Schulkin et al., 1994). In other words, similar mechanisms that are feedforward (allostatic) endocrine systems underlie the expression of CRH in the brain and CRH in the placenta. This chapter is therefore consistent with the preceding chapters—particularly chapter 3 on fear—with regard to positive feedback endocrine systems. Moreover, these events in utero are known to have long-term physiological and behavioral consequences, including changes in the central nucleus of the amygdala and vulnerability to perceive events as fearful in the infant (Welberg and Seckl, 2001).

Preterm Low-Birth-Weight Babies

Consider the real-world consequences of preterm delivery of babies. Preterm delivery accounts for up to 10 percent of all births and is a leading factor in neonatal morbidity. Consequences of preterm birth include low birth weight and decreased respiratory function (Center for Disease Control, 1997). It accounts for up to 70 percent of newborn deaths (Goldenberg et al., 2000). The rate of preterm delivery has not declined in this country over the past 20 years, but survival of preterm infants has increased.

There are a number of biological and demographic predictors of risk for preterm birth. For example, there are significant differences in the rate of preterm and low-birth-weight infants born to African American women when compared to other racial/ethnic groups. Babies born to African American women are nearly twice as likely as those of any other group to be preterm and have a low birth weight (National Vital Statistics Report, 2000). This difference tends to hold even when one controls for demographic characteristics and the link between infectious diseases and preterm delivery. More generally, a number of infectious diseases (e.g., bacterial vaginosis) increase a woman's vulnerability to preterm delivery (Goldenberg et al., 2000). Levels of CRH, as we will see below, are significantly linked to preterm delivery (Holzman et al., 2001; Wadhwa et al., 2001; figure 4.1).

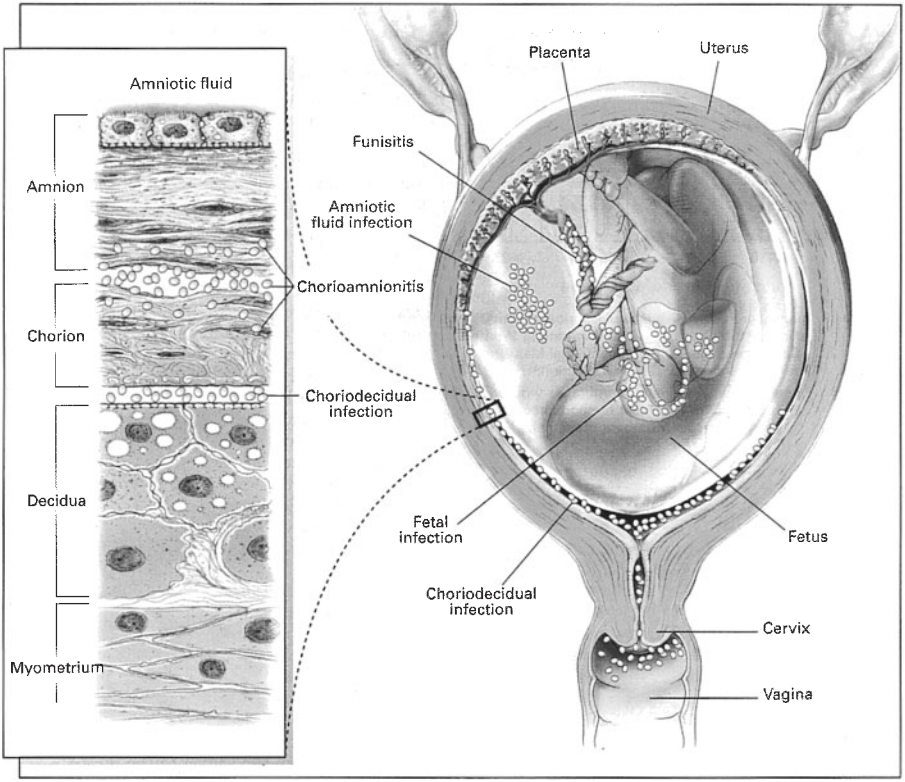


Figure 4.1
Potential sites of bacterial infection within the uterus (Goldenberg et al., 2000).

Placenta and Chemical Messages

Several physiological systems linked to the placenta may play a role in preterm delivery (see, e.g., Goland et al., 1988, 1992a, b, 1995; MacGregor et al., 1994, 1995; Pepe and Albrecht, 1995; Goldenberg et al., 1998). A large number of hormones are produced in the placenta (see, e.g., Ahmed et al., 1992; Lefebvre et al., 1992; Bramley et al., 1994; Petraglia et al., 1990, 1995a, b):

ACTH
Angiotensin
Atrial natriuretic factor
Corticotropin-releasing hormone
Cytokines
Follicle-stimulating hormone
Gonadotropin-releasing hormone
Growth hormone
Growth hormone-releasing hormone
Opioids
Oxytocin
Parathyroid hormone
Parathyroid hormone-related peptide
Prolactin
Prostaglandin
Somatostatin
Thyrotropin-releasing hormone

These placental peptides are homologous in structure to those in the fetal and the mature brain (Challis et al., 1995).

A growing amount of attention in studies of preterm births has focused recently on CRH. Recall that it is a 41-amino acid peptide hormone and a component of the hormonal pathway that regulates the stress response in human beings. Placental CRH is suspected of playing a role in both normal parturition and in preterm birth (Wolfe et al., 1988; Goland et al., 1988). Corticotropin-releasing hormone's role in parturition is therefore especially attractive as a focus of interdisciplinary research for investigators who are working toward an

inclusive central theory of preterm and term labor in human beings.

Discovery of CRH in Human Placenta

Corticotropin-releasing hormone was first isolated from sheep hypothalamus by Vale and colleagues in 1981. A major regulator of the HPA axis, it was named for its ability to stimulate the release of ACTH by the pituitary gland. Corticotropin-releasing hormone was subsequently discovered in extrahypothalamic sites—including the human placenta (figure 4.2), where it was found to have the same structure and bioactivity as hypothalamic CRH (e.g., Sasaki et al., 1987; Robinson et al., 1988).

In the human placenta, CRH is produced exclusively in syncytiotrophoblasts. It is only after cytotrophoblasts fuse into syn-

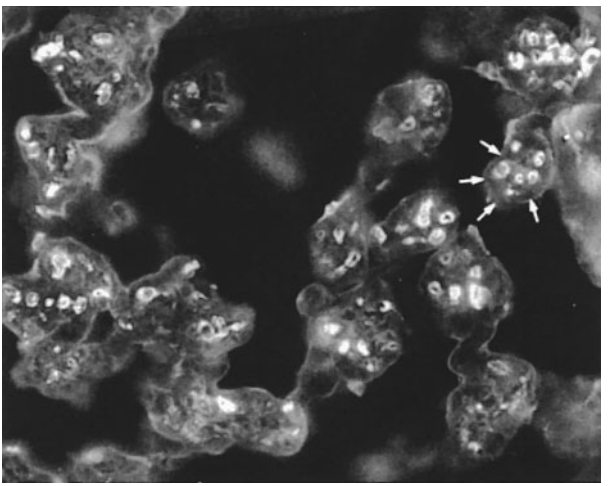


Figure 4.2
Corticotropin-releasing hormone immunostaining in the human placenta (arrows) (courtesy of F. Petraglia and P. Sawchenko).

cytiotrophoblasts that CRH is expressed and secreted into both maternal and fetal circulations (Challis et al., 1995). Levels climb much higher in the maternal than in the fetal circulation, where the upper limit of concentration is in the 300 pg/mL range (Majzoub et al., 1999; Erickson et al., 2001).

Corticotropin-releasing hormone in humans is not detectable in plasma except during pregnancy (Sasaki et al., 1987; Cambell et al., 1987; Goland et al., 1988; Wolfe et al., 1988). During the second and third trimesters of normal pregnancy, CRH (derived from the placenta) is elevated in maternal plasma (figure 4.3). At the same time, both fetal and maternal ACTH and cortisol levels are elevated (Challis et al., 1995; Goland et al., 1995; Erickson et al., 2001). Following parturition, CRH levels in the plasma rapidly decrease to nadir levels. In other words, CRH gene expression in placental trophoblast cells rises during pregnancy in

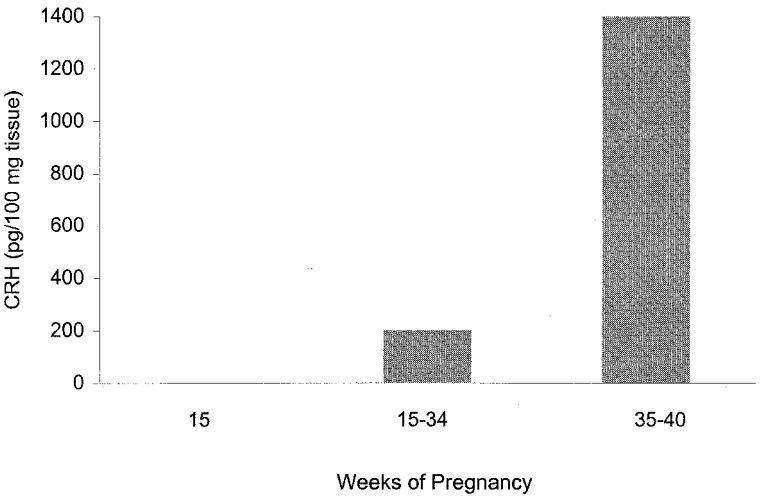


Figure 4.3
Concentrations of immunoreactive corticotropin-releasing hormone (CRH) in placental tissue at various stages of human gestation (adapted from Frim et al., 1988).

several species, including humans (Frim et al., 1988; Riley et al., 1991), gorillas (Robinson et al., 1989), chimpanzees (Smith et al., 1999), and rhesus monkeys (Wu et al., 1995), although there appear to be primate species (Goland et al., 1992a, b; Smith et al., 1993).

It is possible that CRH levels, although low in early gestation, increase at an exponential rate throughout gestation and are detected as rapidly rising only near the end of pregnancy. However, other data suggest that CRH levels are low until the beginning of the third trimester, and only after that do they begin to rise at an accelerated rate. There is large variation, as much as fiftyfold, in maternal CRH concentrations at term among normal pregnancies (Goland et al., 1988; Wolfe et al., 1988; Majzoub et al., 1999; Erickson et al., 2001). The elevation in placental CRH secretion is associated with a surge of fetal glucocorticoids and the production of estriol during the several weeks before normal parturition. This observation, as well as the wide variability in the level of CRH expression seen in different women, has led investigators to speculate that CRH may not be playing an important role in the mother throughout most of gestation but may play a role in initiating parturition (see Wolfe et al., 1988; Goland et al., 1988; Challis et al., 1995).

A parallel rise in fetal cortisol production occurs during the same period, as measured by fetal cortisol sulfated metabolites in maternal blood and urine. The human fetal pituitary system develops early in gestation and responds to low cortisol levels by secreting ACTH. This is best demonstrated in fetuses with enzymatic blocks in cortisol synthesis, resulting in congenital adrenal hyperplasia (Challis et al., 2000). Their systems compensate by increasing the synthesis of all steroids proximal to the enzymatic block, resulting in the virilization of female fetuses by 8 to 10 weeks gestation. Corticotropin-releasing hormone mRNA is also present in placental trophoblast cells by 8 weeks gestation, and CRH levels rise exponentially (as much as 20 times) during the last 6–8 weeks of gestation. Similarly, CRH

peptide levels in maternal blood are quite low until the final 8–10 weeks of gestation (Robinson et al., 1988; Challis et al., 2000).

Role of CRH in Normal Gestation

Feedforward Induction of CRH Gene Expression in the Placenta by Glucocorticoids: Normal Allostatic Regulation

Glucocorticoids are known to restrain CRH production by negative feedback (Munck et al., 1984; Dallman et al., 2000) but, of importance, in one early study it was reported that dexamethasone treatment did not suppress levels of CRH in the plasma of pregnant women (Tropper et al., 1987). It was then demonstrated that glucocorticoids do not inhibit the production of CRH in the placenta as expected; rather, they increase CRH gene expression in the placenta (Robinson et al., 1988; Jones et al., 1989; see also Chan et al., 1988). Glucocorticoids increase CRH gene expression in primary cultures of human placental trophoblasts. These effects are dose related and may be greater in response to dexamethasone than cortisol, suggesting that these effects are dependent upon type-II glucocorticoid receptor sites (Jones et al., 1989; Challis et al., 1995).

Another study demonstrated that pregnant women treated with betamethasone after 30 weeks of gestation had increased CRH levels in both plasma and placental tissue (Marinoni et al., 1998) . An additional study also revealed that pregnant patients at 24 weeks of gestation also have increased levels of plasma CRH following betamethasone treatment (Korebrits et al., 1998). Thus, in marked contrast to glucocorticoids' well-known inhibition of CRH via type-II glucocorticoid receptor sites at the level of the parvicellular region of the PVN of the hypothalamus and the well-known negative restraints (Munck et al., 1984; Sawchenko, 1987; Swanson and Simmons, 1989), glucocorticoids increase CRH gene expression in the placenta (figure 4.4).

This feedforward allostatic regulatory effect on placental expression of CRH represents a mechanism to facilitate normal fetal maturation and eventual parturition. The stimulation of CRH expression by glucocorticoids in placental tissue is via cy-

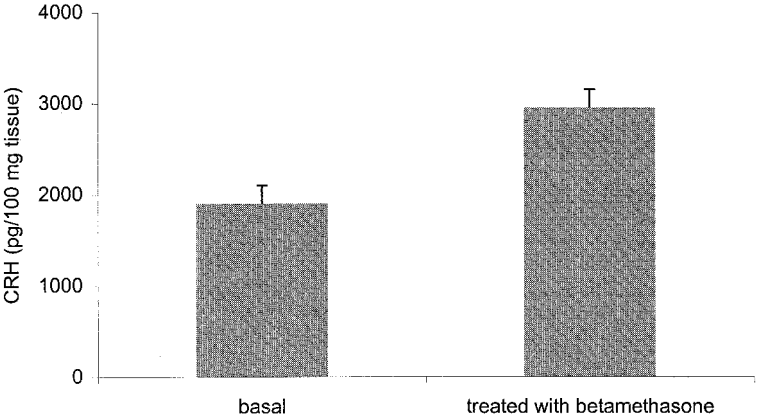


Figure 4.4
Maternal plasma levels of corticotropin-releasing hormone in pregnant women at 35 weeks gestation receiving betamethasone and in control patients (basal) (adapted from Marinoni et al., 1998).

clic adenosine 3,5 monophosphate (Cheng et al., 2000). Primary cultures of human cytotrophoblasts demonstrate increased CRH expression following dexamethasone treatment (figure 4.5). This upregulation of CRH reflects cAMP-mediated CRH promoter activity (Cheng et al., 2000).

One model that seeks to explain the simultaneous rise in CRH and cortisol suggests that, within the placenta, the exponential rate of increase in CRH is positively related to the concentration of cortisol (Majzoub et al., 1999; Challis et al., 2000). Placental CRH, transported through the umbilical vein to the fetus, could stimulate the fetal pituitary-adrenal axis to produce cortisol and cortisol sulfate, which would then be capable of further stimulating placental CRH production, creating a positive feedback loop (figure 4.6). Moreover, the placental production of CRH may in part function for the fetus, reminiscent of neural function, as both a sensory and effector system in providing important sources of adaptation to environmental demands (Wadhwa et al., 2001).

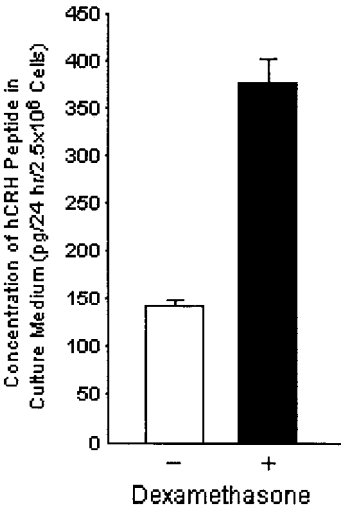


Figure 4.5
Dexamethasone stimulates cAMP-mediated hCRH promoter activity in placental tissue (Cheng et al., 2000).

Again, this model is supported by both in vitro and in vivo data—betamethasone administration to pregnant women results in either no fall in CRH or clear stimulation of placental CRH secretion into the maternal circulation (Majzoub et al., 1999). This placental model is quite different from the regulation of CRH expression in the parvicellular regulation of the PVN of the hypothalamus, which responds to cortisol with downward regulation or negative restraint (Sawchenko, 1987; Swanson and Simmons, 1989; Watts and Sanchez-Watts, 1995).

The Timing of Parturition

The primate placenta is, by its lack of 17-hydroxylase/17–20 lyase, unable to directly synthesize estradiol from progesterone, the only steroid hormone that the primate placenta can synthesize de novo (Pepe and Albrecht, 1995). The fetal adrenal zone therefore serves instead as the predominant source of that

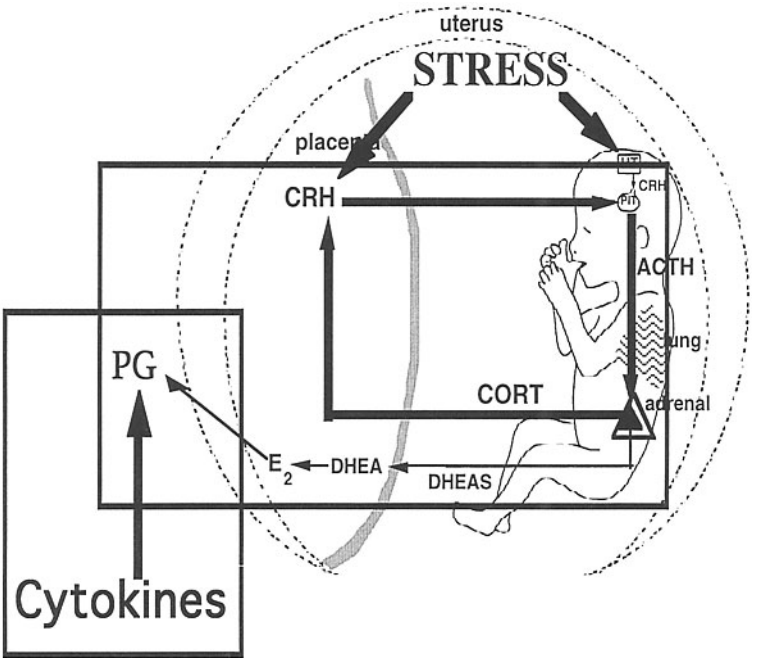


Figure 4.6
The fetopolacental corticotropin-releasing hormone and glucocorticoid positive feedback hypothesis. Corticotropin-releasing hormone, secreted by the placental trophoblasts (T), enters the fetal circulation via the umbilical cord vein and stimulates (+) fetal ACTH release from the fetal pituitary (PIT). Fetal ACTH stimulates secretion of fetal adrenal cortisol sulfate, which enters the placental sulfatase, and cortisol stimulates further placental corticotropin-releasing hormone secretion, thereby completing the positive feedback loop. Fetal corticotropin-releasing hormone, secreted from the fetal hypothalamus (HT), may independently stimulate fetal ACTH release, and placental and fetal hypothalamic corticotropin-releasing hormone may be directly stimulated by environmental stresses (Majzoub et al., 1999).

steroid's precursor, dehydroepiandrosterone (DHEA). Thus placental production of CRH, with its ability to stimulate the fetal adrenal system, may have evolved in primates to stimulate fetal ACTH and ultimately to satisfy the high demand for DHEA synthesis in the fetal adrenal system. This proposed feedback mechanism would function to stimulate a fetal adrenal "factory," contributing to placental estradiol production and to the endocrine sequelae necessary for parturition (Majzoub et al., 1999; Challis et al., 2000). This includes the stimulation of prostaglandin synthesis, oxytocin receptors, and gap junctions. Consistent with this hypothesis are these findings: circulating levels of CRH in fetal blood are similar to those measured in the hypothalamic-pituitary portal circulation; CRH infusion into midgestational fetal baboons activates the fetal HPA axis; and androstenedione infusion into pregnant rhesus females results in preterm delivery. It has also been found that fetal cortisol secretion is tied to maturation of fetal lungs and other systems before birth (Pepe and Albrecht, 1995). Thus, the concomitant stimulation of fetal cortisol and DHEA by placental CRH is of obvious benefit for postnatal survival in that it synchronizes the glucocorticoid effects on fetal organ maturation with the DHEA effects on the timing of parturition.

Moreover, there is some evidence that progesterone may play a role in this differential regulation of CRH in the hypothalamus and placenta—in essence, acting as a brake on the latter system of positive regulation. In vitro studies have shown that when progesterone is added back to placental trophoblast cultures during cortisol stimulation, there is an inhibition of the increases in CRH mRNA and peptide. Furthermore, mifepristone (RU-486), a progesterone/glucocorticoid antagonist, stimulates CRH mRNA. This suggests that a withdrawal of progesterone stimulates CRH effects in the placenta (Karalis et al., 1996; Majzoub and Karalis, 1999).

No progesterone receptors are present in trophoblast cells. Therefore, it is speculated that high levels of placental progesterone early in gestation could compete with cortisol for the glucocorticoid receptors (Falguni and Challis, 2002) inhibiting cortisol

and its effects on CRH synthesis (Majzoub et al., 1999). Because progesterone appears to bind to glucocorticoid receptors about 25–50 percent (as does cortisol), only when levels of cortisol become high enough to effectively block progesterone's inhibitory effect would the CRH elevation occur (Majzoub and Karalis, 1999). Thus progesterone might inhibit the effects of cortisol on placental CRH in a dose-dependent fashion. Inhibition of CRH would be reversed only if the rise in fetal adrenal cortisol secretion in late gestation were late enough to compete with progesterone at the level of the glucocorticoid receptors, essentially causing a functional withdrawal of progesterone at the level of the glucocorticoid receptors. In this way, progesterone might serve as an early brake on the system—a brake that is overridden only after cortisol rises to an appropriately high level (Challis et al., 1995, 2000; Majzoub and Karalis, 1999).

Figure 4.6 shows a schematic representation of leading theories on human parturition. The figure depicts the proposed positive feedback loop responsible for differential regulation of CRH in the fetoplacental axis. In this model, CRH produced in the placenta is secreted into the fetal circulation at a concentration of about 200–300 pg/mL. This is consistent with CRH levels found in the hypothalamic-pituitary portal circulation and sufficient to stimulate corticotropin secretion from the anterior pituitary. Placental CRH, through fetal ACTH or possibly through direct interaction with fetal adrenal CRH receptors, is proposed to stimulate the fetal adrenal system to produce cortisol. Cortisol binds to placental glucocorticoid receptors to block the inhibitory effect of progesterone, which further stimulates CRH production in a positive fashion.

The progressive rise in placental CRH, and concomitant decrease in CRH-binding protein, would stimulate not only fetal cortisol but also the secretion of fetal adrenal DHEA sulfate. This leads to an increase in synthesis of placental estradiol and subsequent factors (prostaglandins, oxytocin, oxytocin receptors, gap junctions) that cause the onset of labor. In this fashion, fetal maturation stimulated by the rise in fetal cortisol secretion, and parturition, stimulated by the rise in fetal DHEA secretion, would

be intimately linked, an obvious benefit for postnatal survival (Nathanielsz, 1998; Challis et al., 2000).

An alternative hypothesis to explain the activation of the fetal HPA axis before primate labor was proposed by Pepe and Albrecht (1995). According to their model, the fetal HPA axis is quiescent during the first half of gestation because of its suppression by the maternal influx of cortisol. During the second half of gestation, the rise in estrogen is hypothesized to stimulate placental 11B-hydroxysteroid dehydrogenase, and this causes cortisol to be converted to its inactive metabolite cortisone. Thus, less cortisol would pass from mother to fetus and negative glucocorticoid feedback on the fetal pituitary gland would be released. As previously mentioned, this would result in an increase in fetal secretion of ACTH, cortisol, and DHEA sulfate, resulting in both fetal maturation and stimulation of parturition.

Allostatic Overload and the Role of CRH in Preterm Labor

From this hypothetical framework of CRH's role in normal parturition, it is relatively easy to make a conjecture regarding its involvement in preterm delivery. The normal feedforward regulatory mechanism is exaggerated under duress (see below) creating an allostatic state and increasing the likelihood of preterm delivery. Much of the groundwork has already been done by several clinical researchers who have demonstrated an association between abnormal, or early elevation in, CRH levels and preterm labor. This is one plausible mechanism, but it is not the only one (see Majzoub et al., 1999; Challis et al., 2000).

Maternal plasma CRH concentrations are also elevated in pregnancy-induced hypertension and intrauterine growth restriction (Wolfe et al., 1988; Goland et al., 1993). In addition, elevation in hypothalamic CRH levels has been demonstrated in response to infection, inflammation, hemorrhage, and stress (Chrousos, 1996, 1998). However, whether the CRH gene in the placenta is similarly regulated is not known. Higher levels of CRH may be associated with intrauterine growth restriction, low birth weight, and preterm birth in the third trimester. In

other words, the most consistent fact about CRH detected in the plasma of pregnant women is its link to both potential maternal-fetal distress and to greater metabolic and physiological demands in women who go on to experience preterm labor (Wolfe et al., 1988; Warren et al., 1990; but see also Berkowitz et al., 1996).

In one early study, diabetics, twin pregnancies, and pregnancy-related hypertension were all associated with CRH levels that were elevated throughout most of the pregnancy (Wolfe et al., 1988). More generally, CRH and glucocorticoid levels are increased following bacterial infectious diseases (Petraglia et al., 1995a, b), preeclampsia (Goland et al., 1995; Leung et al., 2000), diabetes (Wolfe et al., 1988), growth retarded fetal development (Goland et al., 1993), and multiple gestation (Wolfe et al., 1988; Warren et al., 1990; figure 4.7). These events in utero can have long-term impacts on basic physiological functions (Barker, 1997; Seckl, 1997; Martyn et al., 1998; Phillips et al., 1998; Forsen et al., 1999) and perhaps behavioral functions of the neonates (Welberg and Seckl, 2001).

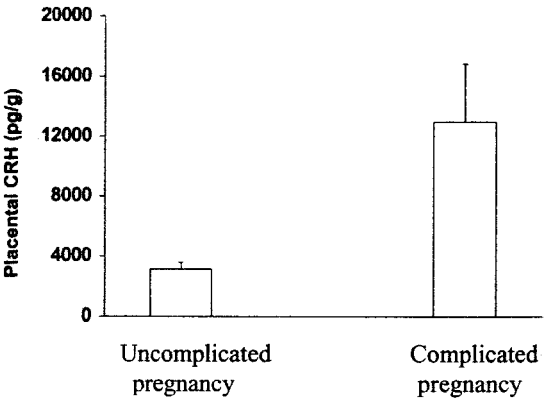


Figure 4.7
Human placental corticotropin-releasing hormone peptide content in pregnancies complicated by pre-eclampsia and uncomplicated pregnancies (adapted from Goland et al., 1995).

It is important to note that at 18–20 weeks of gestation, a subset of women who went into preterm labor, and who reported higher psychosocial stress than controls, also demonstrated higher levels of CRH circulating in the plasma (Hobel et al., 1999b). This was demonstrated in a prospective study of women that controlled for age, previous birth outcome, smoking status, and race. The stress tests were two tests used to assess perceived anxiety about their life and a list of adjectives that depict their situation. Interestingly, while CRH was higher throughout pregnancy for those who went on to deliver preterm, it was only in this first 18–20 weeks that perceived anxiety was correlated with higher CRH levels. But in another study in which CRH and catecholamines were collected at 28 weeks, there was no relationship between psychosocial stress and altered levels of either molecule (Petraglia et al., 2001). The authors suggest that, at this point in the pregnancy, levels of CRH are too high to determine an effect coupled with protective mechanisms to preserve the viability of the healthy fetus.

In this context, the normal feedforward allostatic mechanism is now amplified by the adverse condition. This results in what has been called an "allostatic state" (Koob and LeMoal, 2001), the overactivation of the normal feedforward system. The end point is a baby that is viable, but when the mother is also compromised because of adverse conditions, the fetus perhaps is unloaded.

In another study, preterm birth was associated not only with elevated levels of CRH by 7–23 weeks, but elevated CRH levels were found in women who reported greater risk-related behavior. In this study, this group of risk takers was defined in terms of not buckling their seatbelts while driving (Erickson et al., 2001). A common theme for the exaggerated level of CRH is its link to risk-related events, whether in the brain or in the placenta (figure 4.8).

Pregnancy, however, may also be protective for the mother and the fetus against some of the effects of stress (Wadhwa, 2001). In one study (Glynn et al., 2001), the perceived stress effects from an earthquake were significantly greater in the first

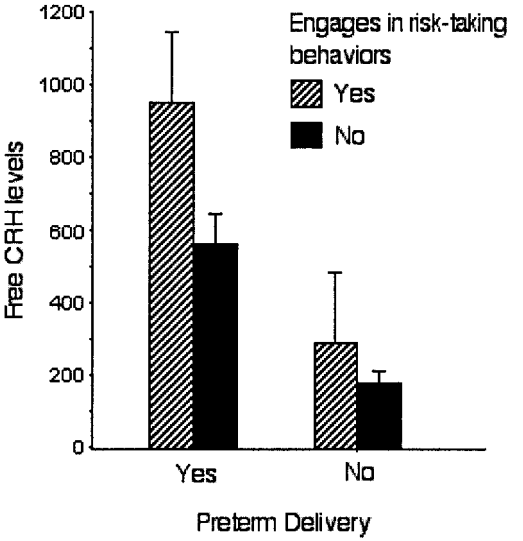


Figure 4.8
Levels of CRH in women who were risk and non-risk takers in midpregnancy and who had or did not have a preterm delivery (adapted from Erickson et al., 2001).

trimester of pregnancy than it was in the second trimester; postpartum women looked like the first trimester women.

Interestingly, in rats, CRH levels in the brain may be reduced by estrogen. The overexpression of central CRH is known to interfere with reproductive function (e.g., Heinrichs et al., 1997). But estrogen does not necessarily reduce fear; mice given estrogen have demonstrated enhanced fear-related behavioral responses (e.g., Morgan and Pfaff, 2001).

Multiple Endocrine Pathways and Parturition

Evolution favored multiple mechanisms underlying parturition, and there appears to be no single path leading to preterm delivery (figure 4.9). Cervical, decidual, and fetal membrane cells

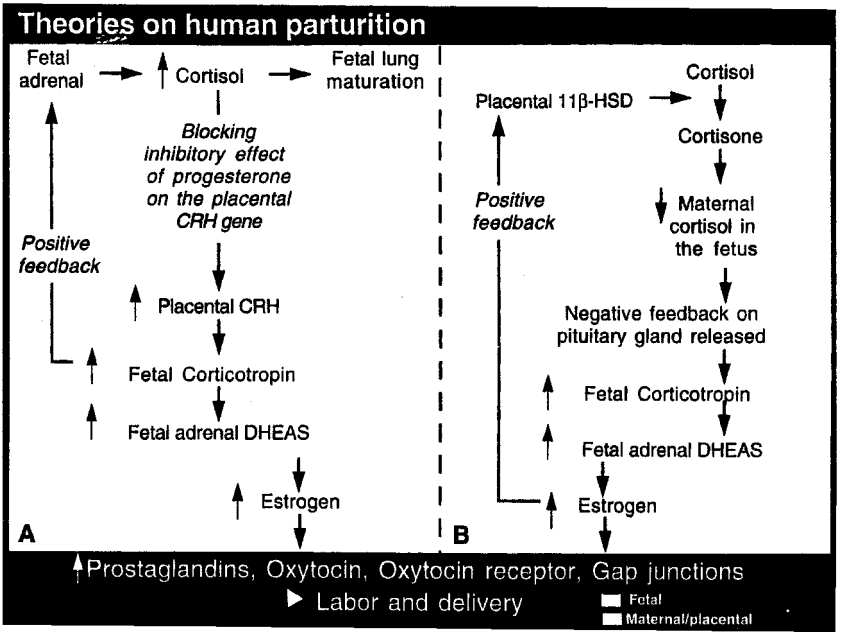


Figure 4.9
Etiological factors promoting preterm delivery (Lockwood, 1994).

may act in concert to promote parturition. Amniochorionic and decidual cells of the placenta, located as they are between the myometrium and fetus, are strategically poised to respond to physiological, hormonal, paracrine, and autocrine regulation. Various influences include stress, infection, and hemorrhage, which trigger prostaglandin and oxytocin secretion and thereby initiate contractions (Lockwood, 1994; McGregor et al., 1995; Goldenberg et al., 1998, 2000; Romero et al., 2001). The same conditions may stimulate production of proteases that degrade the extracellular matrix of cervical and fetal membranes (Challis et al., 2000).

Placental secretion of CRH, possibly triggered further by infection-associated increases in production of inflammatory cy-

tokines (creating an allostatic state, and perhaps allostatic overload), would probably act as a paracrine effector, triggering prostaglandin and endothelin production as well as the production of collagenases that are capable of degrading placental and cervical tissue in preparation for birth (Nathanielsz, 1999a, b; Challis et al., 2000). Recently, decreased inactivation of prostaglandins, through a reduction in prostaglandin dehydrogenase activity, was implicated at the onset of preterm labor (Majzoub et al., 1999; Challis et al., 2000). It is possible that increased CRH, or the resulting rise in fetal cortisol secretion, could contribute to a downward regulation of this enzyme. Immunological and endocrine systems communicate extensively, and within the placenta this might be mediated by interactions between CRH and inflammatory cytokines. Alternatively, hypothalamic CRH might be released by the fetus in response to a physiological stressor, such as hypoxemia caused by uroplacental vascular insufficiency. Finally, maternal stress might activate placental secretion of CRH, leading to preterm delivery.

Corticotropin-releasing hormone is also expressed by amniocytes, cytotrophoblasts, and decidual cells in response to stress, which enhances prostaglandin production by isolated amnion, chorion, and decidual cells. Both prostanoids and oxytocin in turn stimulate CRH release in a cycle that could accelerate toward preterm delivery.

One should note that not all the studies are supportive: One study, although failing to demonstrate a correlation between abnormal CRH elevations and preterm delivery, did show a negative correlation between CRH-binding protein values and gestational age in patients who eventually delivered preterm (Berkowitz et al., 1996). These findings may be interpreted as evidence of the greater bioavailability of CRH-binding protein, which is produced in placental and intrauterine tissues, which may locally counteract the effects of CRH on prostaglandin release and myometrial contractility (Challis et al., 1995, 2000; Lockwood and Kuczynski, 2001). Corticotropin-releasing hormone's link to preterm delivery may not always be reflected by

changes in maternal blood levels (cf. McLean et al., 1995; Coleman et al., 2000; Challis et al., 2000; Erickson et al., 2001).

Placental Clock

A number of organs are organized by biological clocks; circadian, weekly, monthly, and so on. Both peripheral systemic sites and central nervous representations of those sites, and the behavioral and physiological organization reflect the profound effect on bodily regulation of endogenous clocks (Richter, 1965). A further example of a clock is the 9-month gestation. Levels of CRH may be linked to the onset of parturition tied to the placental clock.

A prospective longitudinal study involving nearly 500 women showed that CRH concentrations measured at 16–20 weeks' gestation could predict term, preterm, and postterm birth (Bocking et al., 1999; McLean et al., 1999; McGrath et al., 2002; but see also Coleman et al., 2000; Ellis et al., 2002). The idea that these events are self-contained and self-regulating has been expressed through the analogy of the placental clock, for which the timing is set early in the first trimester of pregnancy, yet remains predictive of later events, including both preterm delivery and postterm birth (McClean et al., 1995; Bocking et al., 1999; Challis et al., 2000). However, it is important to remember that the clock is not self-correcting, and its internal timing may go awry under physiological or psychological duress. At such times, placental CRH secretion may be stimulated by glucocorticoids, inflammatory cytokines, and anoxic conditions to such an extent that it triggers labor prematurely.

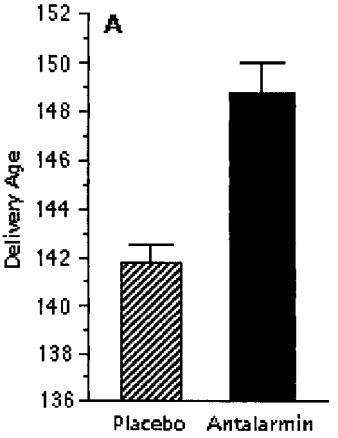
Under normal conditions, levels of CRH can be one predictive factor (McClean et al., 1995, 1999; Bocking et al., 1999; Leung et al., 2000), but not always (Berkowitz et al., 1996; Coleman et al., 2000), for women who are vulnerable to preterm delivery. Thus early or abnormal exposure to cortisol may upwardly regulate CRH gene expression in the placenta, prematurely rendering a woman more vulnerable to preterm labor. Abnormal CRH elevation may be a response to inflammatory stress from the decid-

ual or fetal membrane, or from placental infection, or it may be a response to episodic or chronic stressors of a physiological or psychosocial nature (e.g., hypoxia associated with placental insufficiency/allostatic overload). Alternatively, a fast-running placental clock associated with the body's response to a variety of stressors, occurring early in the first trimester, could result in abnormally elevated CRH levels later in pregnancy.

Interestingly, the type-I CRH receptor has been linked to parturition; blockade of this receptor inhibits parturition in sheep (Chan et al., 1998). The type-I receptor antagonist antalarmin was infused into pregnant sheep over a 10-day period, and parturition was delayed (figure 4.10A; Chan et al., 1998). While this same antagonist reduces fear in rats (Deak et al., 1999), a type-I receptor antagonist did not delay parturition in rats (Funai et al., 2000). In monkeys, the Type-I receptor antagonist reduces fear (figure 4.10B; Habib et al., 2000) and the Type-I receptor has also been linked to depression (Zobel et al., 2000).

Childhood Sexual Abuse and Pregnancy

Not to confuse the role of CRH in premature birth from that of its role in early trauma, note that there is some evidence that childhood sexual abuse may have long-term effects on pregnancy-related events. Childhood sexual abuse is defined as an activity that involves inappropriate sexual activities and does not always mean sexual intercourse or physical force (Horan et al., 2000). Childhood sexual abuse is often chronic. Some of the long-term consequences from childhood abuse include chronic pelvic pain; musculoskeletal complaints, gastrointestinal distress, chronic headache, sexual dysfunction; asthma, and other respiratory ailments; in addition to PTSD, depression, vulnerability and thoughts about suicide, drug and alcoholic abuse, and sexual abnormality (McCauley et al., 1997). Moreover, as we will see in the next chapter, drug-abuse-related behaviors are associated with elevated levels of CRH; consumption of high levels of drugs can also be associated with preterm delivery (Kendler et al., 2000). All of this may reflect a vulnerability to allostatic overload.



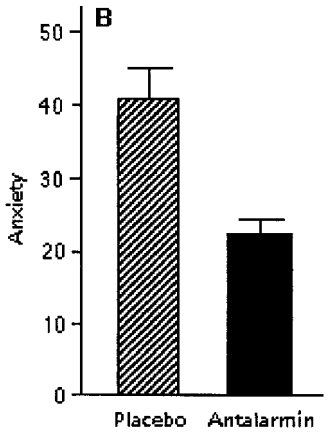


Figure 4.10
(*A*) CRH Receptor type-I antagonist, antalarmin, inhibits parturition in sheep. Six pregnant sheep per group received either an infusion of vehicle (1:1 ethanlo-Cremophor EL mix) or antalarmin (50 g/L in vehicle). The gestational age at delivery is calculated based on the last complete 24 h of gestation (Chan et al., 1998). (*B*) Effect of antalarmin treatment (20 mg/kg orally) on adult male macaques' anxious behaviors to the introduction of two unfamiliar subjects in adjacent cages separated by a transparent Plexiglas plate for 30 min starting 150 min after receiving the drug or placebo in a blind fashion. *, P = 0.04 (Habib et al., 2000).

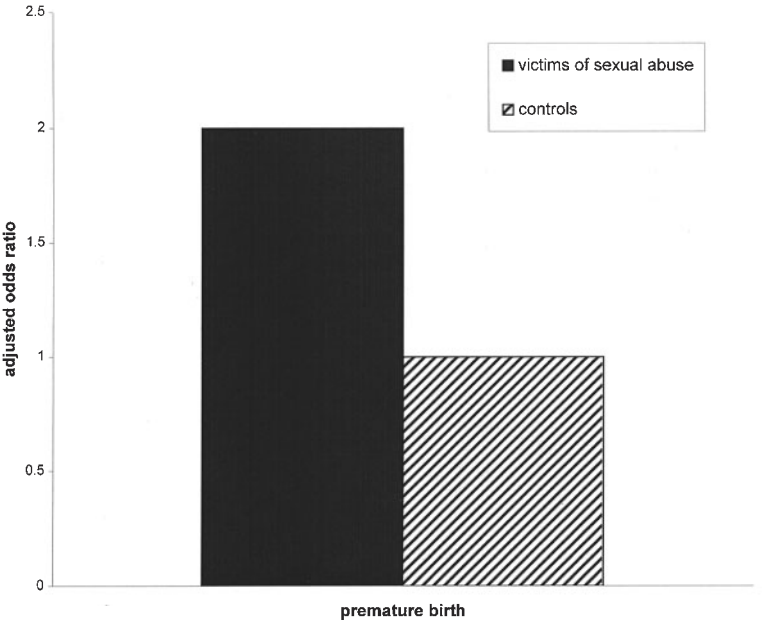


Figure 4.11
Women who were victims of childhood sexual abuse were twice as likely to have a premature infant than were controls. Adjusted odds ratio controlled for severity of abuse, maternal age, poverty, and maternal alcohol use (Evans, 1988).

Pregnancy and childbirth may be a particularly stressful time for survivors of sexual abuse. For example, women who were sexually abused in childhood demonstrate a greater degree of suicidal thoughts during pregnancy (Farber et al., 1996). Although there is a paucity of evidence, one doctoral dissertation by Evans (1988), which controlled for alcohol and tobacco use, demonstrated a relationship between childhood sexual abuse and preterm delivery (figure 4.11). They also had greater medical problems. In another study, survivors of sexual abuse were more likely to have have preterm deliveries and to deliver smaller babies even at full term (Stevens-Simon et al., 1993).

Perhaps—and this is speculative—early sexual abuse or trauma in the life of the mother kindles a vulnerability in the HPA axis to be overactive (Heim et al., 2000, 2001), with perhaps an overactive HPA axis in the fetus, and perhaps at the level of the placenta during pregnancy (Horan et al., 2000).

Conclusion: Allostasis and Allostatic Overload

Glucocorticoid regulation of CRH gene expression in the placenta, in the amygdala, and in the bed nucleus of the stria terminalis look remarkably similar. While glucocorticoids restrain CRH gene expression in the parvicellular region of the PVN of the hypothalamus, they magnify the effects of CRH in these other areas. The induction of CRH gene expression by feedforward mechanisms under certain conditions may contribute to regulatory or allostatic overload. These conditions are wide ranging, and all can compromise reproductive fitness. They include gestational diabetes, multiple births, preeclampsia, bacterial infections, sexually transmitted diseases, and psychosocial stress.

It should be noted that we do not know whether the mechanisms that underlie the placental increase of CRH by glucocorticoids are the same for both the brain and the placenta. Nor do we know whether the induction of CRH gene expression in the placenta originates with the mother, the fetus, or even the placenta itself. What is clear, however, is that, contrary to the belief that glucocorticoids always react to restrain the expression of CRH, glucocorticoids facilitate CRH expression in the placenta and in regions of the brain that underlie the experience of adversity. It is this CRH expression that may be significant in preterm labor (e.g., allostatic overload) at the level of the placenta and in the brain to sustain the experience of adversity. This regulatory response may figure in promoting successful reproductive outcomes, but also in aborting or shortening the gestational expense of ill-fated outcomes.

The concept of allostasis is again tied to systems in which there is no clear physiological set point. That is, the set point

during pregnancy is fluid and changing (Sterling and Eyer, 1988). Allostasis refers to the ability to achieve viability through change. Whereas homeostatic systems such as blood oxygen, blood pH, and body temperature must be maintained within a narrow range, allostatic systems are more labile, allowing them to adjust to external and internal circumstances (McEwen and Stellar, 1993). Both homeostatic (Bernard, 1865; Cannon, 1932; Richter, 1942–43) and allostatic regulation help to maintain the internal milieu (Sterling and Eyer 1988; Schulkin et al., 1994, 1998; McEwen, 1998a, b). It is this latter concept that I hypothesize has relevance to understanding the endocrine mechanisms that may underlie preterm labor induced by maternal-fetal distress.

There is much literature that looks at the effects of prenatal stress in animal models (see review by Takahashi et al., 1998). For example, unpredictable aversive events can result in elevated levels of corticosterone in the mother as well as in the fetus (Takahashi et al., 1998). Alterations of corticosterone in utero in rats have long-term effects on amygdala glucocorticoid mRNA expression in the amygdala and on anxiety-related behavior (Welberg et al., 2000). Prenatal stress can increase the vulnerability to anxiety in the offspring (Vallee et al., 1997). Elevated maternal levels of CRH are thought to affect the human fetus; habituation studies with the fetus provide some evidence (Sandman et al., 1999). Prenatal stress is known to alter levels of CRH expression in the amygdala of neonatal rat pups (Cratty et al., 1995) and to alter biogenic amine levels in primates (Schneider et al., 1998).

The CRH that is hypersecreted in pregnant women following situations of bacterial infectious diseases, preeclampsia or hypertension, multiple gestations, or psychosocial stress may be the result of allostatic overload. Under conditions of allostatic overload, premature parturition may be an adaptive mechanism for both mother and fetus by both reducing stress on the pregnant woman and removing the fetus from an overstressed environment—in other words, making the best of a bad situation (Nathanielsz, 1999a, b; Wadhwa et al., 2001).

One neuroendocrine model has been suggested linking elevated levels of glucocorticoids and amygdala programming in utero (Welberg and Seckl, 2001). Both adrenal steroids (glucocorticoids and mineralocorticoids) compete for access to the receptor sites (de Kloet, 1991); converting enzymes regulate access to the receptor sites (11b-hydroxysteroid dehydrogenase type 2; Seckl, 1997) and both hormones can influence CRH expression (Watts and Sanchez-Watts, 1995)—and perhaps a vulnerability for increased fear/anxiety and decreased reproductive fitness as adults (see review on the role by Korte, 2001; Brunson et al., 2001a, b).

In the species that have been studied, glucocorticoid and CRH elevation decrease reproductive fitness and decrease sexual behavior (e.g., Rivier and Rivest, 1991). When glucocorticoids are elevated under duress, testosterone or estrogen is reduced in most species that have been studied (Sapolsky, 1992; Herbert, 1993; Wingfield and Romero, 2001). But glucocorticoids are also known to be linked to attachment behaviors (Fleming et al., 1997; Carter et al., 1999), and facilitate sexual behavior in some species (e.g., the musk shrew; Schiml and Rissman, 1999). Clearly, one has to consider the degree to which the glucocorticoids are elevated, the functional context, and whether it is a short-term or long-term elevation.

The states of combating disease or experiencing fear (or psychological stress) are metabolically expensive events and thereby reduce the hormones of reproduction and the likelihood of successful reproduction (Sapolsky, 1992; Wingfield and Romero, 2001; see also Sapolsky, 2001). Interestingly, in experiments with subjects that have elevated levels of estrogen, there is a reduction in glucocorticoid receptor binding (Peifer and Barden, 1987; Carey et al., 1995). In addition, an estrogen response has been identified on the CRH gene (Vamvakopoulos and Chrousos, 1993).

Finally, the normal facilitation of parturition reflects in part a feedforward allostatic mechanism: namely, the induction of CRH gene expression by glucocorticoids. This normal mechanism is further augmented under conditions of adversity. For

example, anxiety and depression are linked to preterm labor (Dayan et al., 2002). The underlying hypothesis is that CRH is a signal of danger in both the placenta and in the brain. In the first context, the impact of elevated glucocorticoids on CRH gene expression may render women more vulnerable to preterm labor. In the second, glucocorticoids facilitate the perception of danger and act to magnify or sustain the CRH signal. The physiological events turn into allostatic overload when the normal mechanisms are compromised.

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Chapter 5

Addiction to Drugs: Allostatic Regulation under Duress

There are several features of addiction that are relevant to allostasis. The first is the simple elevation in use of a number of neural systems during addiction, both in the appetitive and in the consummatory phases of the central motive state. The second is the dysregulation of the reward system associated with the chronic use of drugs (Koob and Le Moal, 2001). There are indications (for example, in animal models) that drug consumption can have long-term potentiation in specific neurons from cocaine ingestion (e.g., Ungless et al., 2001) and perhaps relapse from association of the drug with environmental events that are linked to this hyperexcitable state of the brain (Stanislav et al., 2001). The third link to allostasis is the long-term consequences of the drug abuse, and the vulnerability to allostatic overload.

This chapter begins with a depiction of the central motive states (linking to chapters 2 and 3) of wanting drugs and some of the neural systems that underlie addictive behaviors. One system underlying drug addiction is extrahypothalamic CRH and HPA regulation. Allostatic feedforward regulation, particularly at the level of the bed nucleus of the stria terminalis, may underlie some of the increased vulnerability for drug consumption. In other words, vulnerability to relapse, in animal studies, is linked to the overexpression of CRH in critical regions of the brain (such as the bed nucleus of the stria terminalis (Shaham et al., 2000; Koob and Le Moal, 2001), in addition to the increase in incentives to an enlarged social context that is associated with a drug culture that reflects dopamine overactivation (Berridge and Robinson, 1998). The addict is trying to maintain internal stability and adapt to an adverse environment (allostasis,

allostatic state) and may eventually slip into allostatic overload (compromised immunological, neural, and bone tissue).

The hypothesis is that the overactivation of central CRH increases the vulnerability for drug use, relapse, and withdrawal. Corticosterone, perhaps by feedforward *allostatic* mechanisms, may facilitate these events. Chronic overactivation of this system can compromise negative inhibition at the level of the PVN, in addition to compromising a number of end-organ systems. The cycle of addiction is an essential obsessive focus on a particular substance, linked to withdrawal and binge-related behaviors (DSM-IV). My focus in this chapter is largely on only part of the neural and physiological systems that underlie addictive behaviors.

I begin with a preliminary discussion of addiction. Cigarettes, alcohol, and other addictive substances are associated with a quarter of all deaths in the United States (McGinnis and Foege, 1999). Substance use also accounts for a large amount of economic burden and social costs to families and communities, including crime, birth defects, family violence, and divorce. The answers to addictive behaviors are not simple. Addictive objects vary considerably; some have properties in common, others do not. Consider the range of objects to which one could become addicted or obsessed with:

Alcohol
Sedatives
Hypnotics
Anxiolytics
Amphetamines
Cocaine
Nicotine
Caffeine

Of course, the range of things for which one can form an obsession or addiction is endless: gambling, work, money, food (see Elster and Skog, 1999). With this great array of candidates, social context matters; addiction takes place in a social milieu

that has consequences for the whole life of the addict, including tolerance, vulnerability to relapse, and overdose (Siegel, 1972, 1975; Woods, 1991).

Central States of Wanting Drugs

An addicted state of mind is one in which the will is compromised. A rape of the will and loss of control are key experiential elements. The focus of the addicted person is narrow and shortsighted (Lowenstein, 1999). Most of the addict's ability to postpone gratification is short-circuited. The greater the addiction, the greater the takeover and loss of control. Addiction is a cycle of increased dysregulation of the reward systems (Koob et al., 1998), and some individuals are at increased risk for long-term substance use and abuse (Koob et al., 1998).

Several emotional states, such as grief and obsessive love, have some of the same properties as addiction (Sabini and Silver, 1998; Elster, 1999). They are conditions in which the individual is overcome with emotion. The root meaning of the passions or the emotions is being overcome, and these states are characterized by the experience of being rendered passive and unable to act effectively. This represents the addicted state but surely does not represent all emotional states (Sabini and Silver, 1998; Elster, 1999). Emotional adaptive behavioral responses evolved, in my view and that of others (e.g., Ekman, 1992; Panksepp, 1998; Lane and Nadel, 1999; Davidson et al., 2000), because they confer cognitive information processing and successful problem solving (Darwin, 1872; Marler and Hamilton, 1966; Schulkin, 2000). They are not just passive confused states that render action incoherent.

Central motive states are states of the brain, linked to a desire, that result in appetitive and consummatory behaviors (Lashley, 1938; chapter 2 of this book). Recall that there are two phases to a central motive state. One is appetitive—the search for the desired object or condition, and the other is the consummation of that desire. In the example of hunger, the state motivates a search for food and, upon finding the food, the state is satisfied

by eating. Addiction is a good example of central motive states (Koob, 1998). Motivational states modulate emotional responses and inherently involve information processing (Lang et al., 1998). Hence motivational states are cognitive. Central motive states underlie our behavioral responses (Lashley, 1938; Stellar, 1954). Furthermore, they are also states of the brain that are constrained by neurobiology (Nader et al., 1997; Swanson, 2000). Hormones associated with a particular central motive state prepare the individual to perceive relevant environmental stimuli necessary for obtaining the desired outcome (Schulkin, 1999a).

Once an individual is caught in the cycle of addiction, this central motive state can become all consuming. Craving motivates the appetitive phase, the search for the object (i.e., the drug), and this search supersedes all else in the addicted person's life. The consummation of this motive state is taking the drug, and the addict is then satisfied for a period of time. Those close to the addicted person are often forced to turn their backs to normalize their own lives, but this has no immediate effect on the addict's lifestyle. The appetitive phase in addiction becomes more important than social interaction, family, friends, personal needs, and obligations.

Many neurotransmitter systems and brain areas are engaged during drug use and abuse (Higley and Bennett, 1999; Koob and Le Moal, 2001). Each drug involves a different constellation of systems (table 5.1). For example, a history of chronic stress interacts with the dopaminergic systems in the brain. An increase in dopamine release occurs in the frontal cortex of rats exposed to chronic stress, while rats without a chronic stress history do not show as much frontal cortex dopamine release when put in the same stressful situation (Cuadra et al., 1999). Chronic stress can also lead to a decrease in dopamine in the nucleus accumbens (Gambarana et al., 1999), and a number of studies have shown that prenatal exposure to, for example, cocaine can have long-term consequences on dopaminergic pathways and the response to duress (e.g., Elsworth et al., 2001).

Conditioned positive and negative reinforcement are both relevant to continued drug abuse and to relapse after prolonged

Table 5.1
Neurobiological substrates for the acute reinforcing effects of drugs of abuse

Drugs of Abuse	Neurotransmitter	Sites
Cocaine and amphetamines	Dopamine Serotonin	Nucleus accumbens Amygdala
Opiates	Dopamine Opioid peptides	Ventral tegmental area Nucleus accumbens
Nicotine	Dopamine Opioid peptides?	Ventral tegmental area Nucleus accumbens Amygdala
Tetrahydro-cannabinol (marijuana)	Dopamine Opioid peptides?	Ventral tegmental area
Ethanol	Dopamine Opioid peptide Serotonin Gamma-aminobutyric acid (GABA) Glutamate	Ventral tegmental area Nucleus accumbens Amygdala

From Koob et al., 1998.

abstinence. If substance use is based purely on unconditioned positive and negative reinforcement (and their underlying neural substrates) then relapse after extended abstinence should not be the social problem that it is in our society. One habit-forming aspect of compulsive drug use is the result of the associated euphoria. Examples of conditioned positive reinforcement exist in the animal and human research literature. Animal research suggests that the amygdala, nucleus accumbens, and ventral striatum are important for associating, acquiring, and responding to the conditioned reinforcing effects of stimuli associated with addiction (Robbins et al., 1989; Altman et al., 1996; Robbins and Everitt, 1999; Ito et al., 2000; Carboni et al., 2000; Thomas and Everitt, 2001). Heroin addicts find injections of saline pleasurable because the conditioned positive reinforcement of the injection is associated with heroin injections. The motivation to continue drug use in order to avoid the negative affective and

physiological consequences of withdrawal is a negatively reinforcing aspect of dependence (Koob, 1998). And, of course, the chronic arousal, the fear, the uncertainty that pervades the heroin or cocaine addict creates a brain state that reflects allostatic overload. Not only are the normal feedforward systems active, but the circuits that underlie a reward, and probably fear, are vulnerable to allostatic overload (see Koob and Le Moal, 2001).

Vulnerability to Drug Abuse: Animal Studies

An individual's inborn characteristics can have mediating effects on both response to stress and reactions to drugs. Animals can be selectively bred to have higher basal levels of corticosterone, and in this context there can be a condition for higher levels of CRH gene expression. Similarly, strains of animals that prefer specific drugs and are more likely to respond to specific drugs can be bred in laboratories. Behavioral and physiological characteristics of selectively bred animals can give insights into characteristics of human vulnerability.

Many studies demonstrate that rats with higher glucocorticoid levels are more likely to self-administer a number of psychotropic agents (figure 5.1; Piazza et al., 1993). In different strains of rats that have different genetically based levels of corticosterone, the corticosterone levels are related to the likelihood of self-administration of psychotropic drugs. Rats with higher levels of corticosterone are more likely to self-administer cocaine, heroin, and amphetamines. In other words, the greater the level of corticosterone that activates the central nervous system, the greater the probability of rats self-administering these agents (Piazza et al., 1989, 1993; Erb et al., 1996). The vulnerability story is more complex than cortisol, corticosterone, or CRH levels, in addition to dopamine levels. Corticosterone also effects dopaminergic expression in several regions of the brain that probably contribute to increased motor behavior (Rouge-Pont et al., 1993, 1998; Lucas et al., 1998a, b), and increased tendency to impulsive choice (Cardinal et al., 2001).

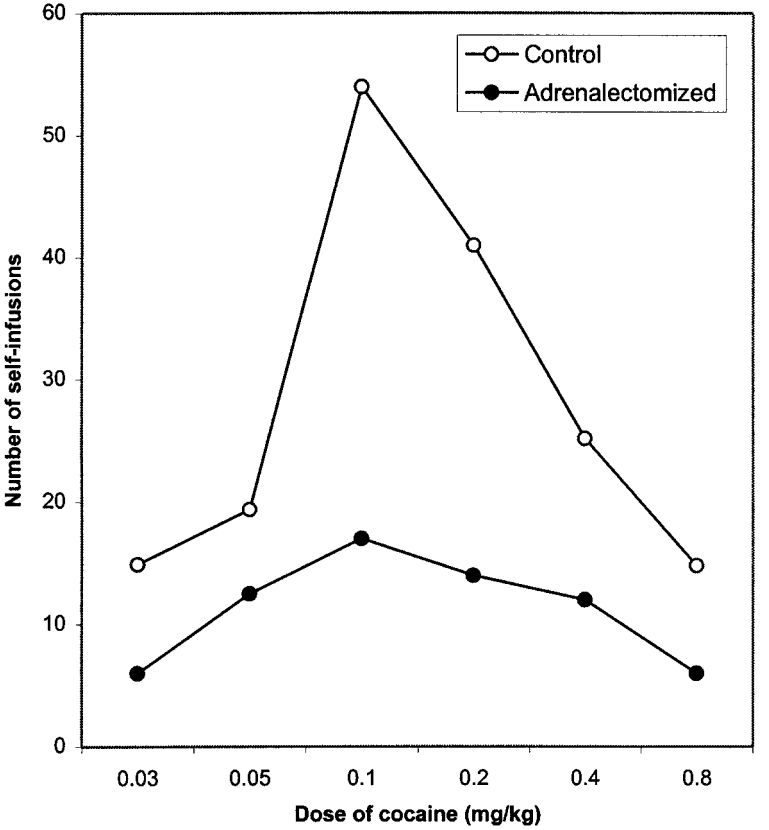


Figure 5.1
Effects of adrenalectomy on cocaine self-administration in rats (after Koob and Le Moal, 1997).

Research suggests that even prenatal stress can have lifelong effects (chapter 4). When cortisol is elevated in both mother and fetus, CRH levels in the amygdala are significantly higher in the offspring when they become young adults (Cratty et al., 1995; Welberg and Seckl, 2001). Additionally, CRH injections to the mother during pregnancy increase the fear responses of the offspring when they are provoked as adults. Prenatal stress can also impair future motor development in primates (Schneider et al., 1992, 1998), and vulnerability to high anxiety and drug use (Vallee et al., 1997).

Parental deprivation is an important variable for predicting later vulnerability to stress among nonhuman primates. Plasma cortisol levels quickly increase in rhesus monkey infants when they are separated from their mothers and peers (Higley et al., 1992). There is a tendency to have higher systemic levels of cortisol in rhesus monkeys maternally deprived during development than in mother-reared monkeys. Rhesus monkey infants subjected to short-term maternal separation and isolation exhibit higher cortisol levels, and perhaps higher levels of central CRH (Kalin et al., 2000). These events create a vulnerability to chronic arousal and a vulnerability to allostatic overload. Rhesus infants reared by surrogate mothers and with limited peer contact do not show as high a cortisol response to isolation (Shannon et al., 1998).

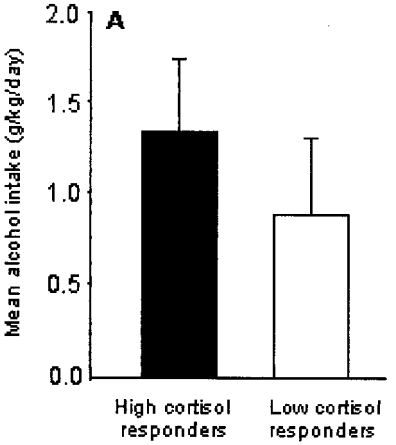
Early life experience with food availability is another stressor with long-lasting consequences. Studies using macaques show that experience of variable food availability during development results in greater CRH levels in the cerebrospinal fluid during adulthood and greater fear-related behavioral responses (Coplan et al., 2001). The changes in the stress system, as a result of early trauma, stems from a lack of predictability and the extreme demands upon the CRH system.

Stressful events, which lead to higher glucocorticoid levels, also induce an increased likelihood of self-administration of drugs at higher rates. When rats are exposed to noncontingent shock, they self-administer cocaine at much higher rates than rats who are exposed to contingent shock or no shock (Goeders,

1998). The noncontingent shock rats were more responsive to lower cocaine doses than the rats in the other shock groups, who required two times the dosage before engaging in significant amounts of cocaine self-administration. Levels of plasma corticosterone in the noncontingent shock rats were much higher than in the other rats.

Maternally deprived macaque monkeys have both higher plasma cortisol concentrations and higher central CRH in the cerebrospinal fluid as young mature adults (Higley et al., 1992, 1996; Habib et al., 1999, 2000). Behaviorally, macaques raised by their peers show higher baseline rates of alcohol consumption when compared with macaques raised by their mothers. However, when subjected to social separation, mother-reared monkeys increase their alcohol consumption during social separation until the consumption is equal to that of peer-reared macaques (Kraemer and McKinney, 1985; Higley et al., 1991). Mother-reared macaques also have larger increases of ACTH than peer-reared macaques during social separation (Clarke, 1993). Macaques separated from their mothers and raised by peers are more socially inept, more aggressive, engage in more deviant behaviors, and consume more alcohol than their mother-reared counterparts (figure 5.2; Higley et al., 1996). Interestingly, in both mother-reared and maternally separated conditions, those macaques that tend to have higher levels of cortisol (and probably higher levels of central CRH) tend to consume more alcohol (Fahlke et al., 2000).

Corticotropin-releasing hormone levels are elevated during both positive and negative experiences (Richter et al., 1995; Merali et al., 1998). Expression of CRH in the brain increases the salience of environmental stimuli (Rosen and Schulkin, 1998) and has implications for situational learning both in addiction and during a child's development. In the case of addiction, this is relevant in terms of the search for and acquisition of the desired object. The actions of glucocorticoids might also be adaptable mechanisms for reducing overactivity of physiological stress systems, allowing the animal to cope more effectively with a stressful situation (Piazza and Le Moal, 1997).



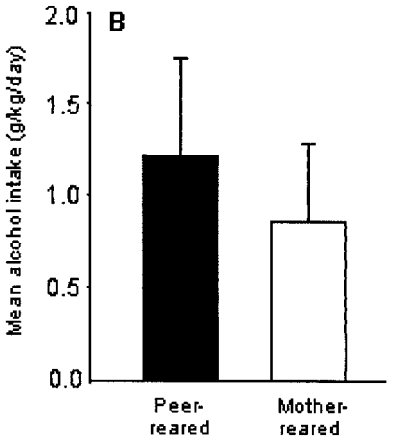


Figure 5.2
High cortisol respondents and low respondent (A) and peer-reared and mother-reared macaques (B) and their ingestion of alcohol. This is the average amount consumed over 10 days (adapted from Higley et al., 1991; Fahlke et al., 2000).

Both glucocorticoids and CRH have psychomotor effects, as does dopamine. Cocaine is considered a psychomotor stimulant. The psychomotor and euphoric effects resulting from cocaine consumption may reflect activation of the neuropeptide CRH and neurotransmitter dopamine as well as their regulation by glucocorticoids (Piazza et al., 1993; Schulkin et al., 1998; Koob, 1998). Cocaine activates the pituitary adrenal axis in both rats and nonhuman primates. Corticotropin-releasing hormone is activated in both hypothalamic and extrahypothalamic areas during cocaine consumption (Koob, 1998). After three weeks of binge cocaine administration, rats show higher basal corticosterone levels when compared with rats in a no-cocaine placebo group (Kreek, 1997; Sarnyai et al., 1998). Increases in CRH activity during cocaine consumption, along with mesolimbic dopaminergic activity, may increase the salience of cocaine and its associated stimuli.

The effects of drug consumption interact with individual stress responses and may be relevant to both the initiation and maintenance of drug abuse. Individual differences in biological responses to stress are measurable in the laboratory. Rats can be categorized as low responders or high responders to stress by measuring corticosterone release and locomotor reactivity in response to a stressful situation. Most animals avoid stressful situations because those situations are unpleasant. However, some animals—and some humans—can be described as stress seeking (Piazza et al., 1993). Animal research shows that these individuals are more likely to self-administer and are more sensitive to the effects of psychostimulants.

Once within the cycle of addiction, individual biology is not as relevant to the animal's interpretation of the environment. One result of cocaine binge administration in rats is the diminution of individual differences in corticosterone hormone response to stress (Sarnyai et al., 1998). Rats that showed high levels of corticosterone release in response to stress and those that showed low levels of release were put in either binge cocaine or saline/control conditions. The individual differences were maintained in animals injected with saline over 3- and

6-week periods. However, the differences in response to stress between low responders and high responders disappeared in the rats treated with cocaine during the same time periods (Sarnyai et al., 1998).

Withdrawal from drug abuse is another aversive condition characterized by elevated glucocorticoid and CRH levels (Koob and LeMoal, 2001). The drugs that produce a pattern of elevated glucocorticoids and CRH in the PVN of the hypothalamus and the central nucleus of the amygdala during withdrawal conditions include ethanol (Pich et al., 1995; Adinoff et al., 1996), cocaine (figure 5.3; Sarnyai et al., 1998; Richter and Weiss, 1999), morphine (Richter et al., 1999, unpublished), cannabis (Rodriguez deFonseca et al., 1997), and even nicotine (Rasmussen, 1998). In rats, alterations of the type-I CRH receptor reduces

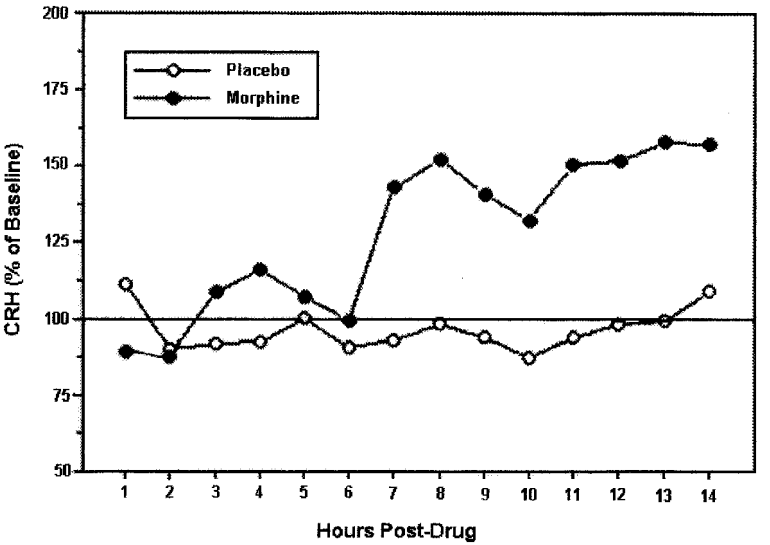


Figure 5.3
Levels of corticotropin releasing hormone (CRH) measured by dialysis following withdrawal from morphine (Richter, Schulkin, and Weiss, 1999, unpublished observations).

the behavioral and endocrine response to morphine and cocaine on alcohol (Skelton et al., 2000; Goeders and Guerin, 2000; Goeders, 2002; Sillaber et al., 2002).

Affectively, anxiety and depression characterize drug withdrawal in humans. In animals, increased reactivity to stress characterizes drug withdrawal. Cerebrospinal fluid concentrations of CRH are elevated during the first day of abstinence from alcohol and decrease over the next three weeks in humans (Adinoff et al., 1996). While CRH is elevated during withdrawal, several neurotransmitters or neuropeptides show decreased expression. Moreover, CRH expression in the brain affects a number of neurotransmitters and neuropeptides (e.g., Swanson, 1991; Watts, 1996; Price and Lucki, 2001).

Feedforward Allostatic Regulation: Vulnerability to Relapse and the Bed Nucleus of the Stria Terminalis

Vulnerability to relapse is a common occurrence for the formerly addicted individual. The best defense for the individual is to remove him or herself from the environment in which he or she might relapse. But that can be very difficult to accomplish. Avoidance behavior is a kind of adaptation, linked perhaps to ensuring internal stability to acquire what is needed and avoid what is not. In both cases, it is anticipatory. With relapse so prominent among those who have been addicted to a substance, what is known about some of the mechanisms of relapse?

Levels of corticosterone are linked to vulnerability to drug administration. This occurs in amphetamine and cocaine self-administration studies in rats, and high responders to amphetamine self-administration have higher levels of circulating corticosterone (Piazza et al., 1989). These levels of corticosterone may increase the salience of objects associated with the drug administration and the sensation of seeking aspects of drug reward (Piazza et al., 1993) by the increased dopamine synthesis facilitated by corticosterone in the nucleus accumbens and the change of state—allostasis.

Various models of stress-related relapse have been studied. Rats that were trained to self-administer cocaine for 12 days, for example, and then withdrawn from the drug use, quickly reinstated their self-administration when they were given a foot shock. This stress-inducing event was more potent than simply being exposed to the cocaine (Erb et al., 1996). This paradigm has been used to assess the relapse for a number of psychotropic drugs of abuse (Erb et al., 2000; Shaham et al., 2000).

While peripheral blockade of corticosterone does not interfere with this effect, interference with central CRH does (Erb et al., 1998). Indeed, CRH is linked to vulnerability to stress-related relapse for former users of heroin (Shaham et al., 1997) and cocaine (Erb et al., 1998). Foot shocking increased relapse, which went on, to some extent, despite the CRH antagonist that was administered (Erb et al., 1998) and was unaffected by dopamine receptor agonist or opioid receptor antagonist (Shaham et al., 2000).

One critical area for this vulnerability, mediated in part by central CRH, appears to be the bed nucleus of the stria terminalis (figures 5.4 and 5.5; Shaham et al., 2000). Recall that this region of the brain is linked to the amygdala (although this is disputed; see Swanson and Petrovich, 1998). Neurons within the lateral region, both dorsal and ventral, contain CRH (Swanson and Simmons, 1989; Makino et al., 1994a, b; Watts and Sanchez-Watts, 1995) and CRH changes within the bed nucleus reflect vagal activation under duress (Nigsen et al., 2001).

The bed nucleus of the stria terminalis, as I indicated in chapter 3, is linked to CRH-related effects on anxiety-like behavioral responses (Davis et al., 1997). Corticotropin-releasing hormone infused into the bed nucleus elicits anxious behavior and an increased tendency to self-administer medication; CRH antagonists in the bed nucleus interfere with foot-shock-related relapse, but this does not occur when the CRH antagonist is infused into the amygdala (Erb and Stewart, 1999). Conversely, when CRH is infused directly in the bed nucleus, cocaine self-administration increases, and this does not occur when CRH is directly infused into the amygdala (figure 5.6).

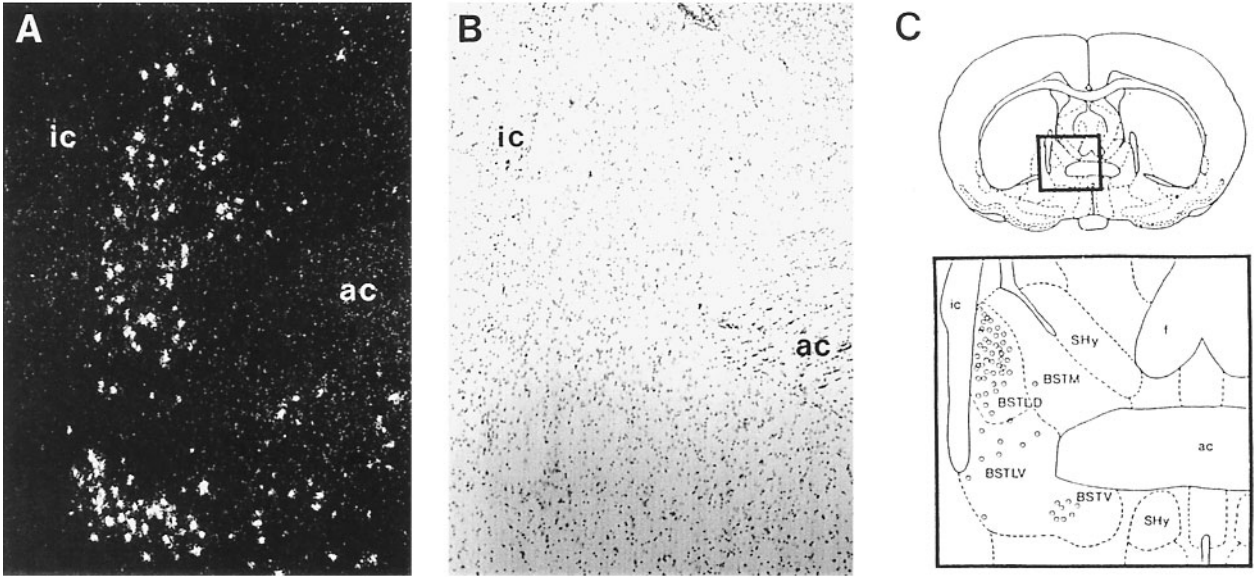


Figure 5.4
(*A*) Dark-field photomicrograph shows localization of CRH mRNA signals in the bed nucleus of the stria terminalis (BNST). Autoradiographic silver grains appear white. CRH mRNA is mainly accumulated in the dorsal part of lateral BNST, and signals are also observed in the ventral part of BNST. (*B*) Cresyl violet stained section corresponding to (*A*) shows cellular architecture of the region. (*C*) Open circles show the distribution of CRH immunoreactive cell bodies, (*A*,*B*, original magnification, x 50) BSTLD, dorsolateral BNST; BSTLV, ventrolateral BNST, BSTM, medial BNST, ventral BNST, ventral BNST; ac, anterior commisure; f, fornix, ic, internal capsule; SHy, septohypothalamic nucleus (Makino et al., 1994b).

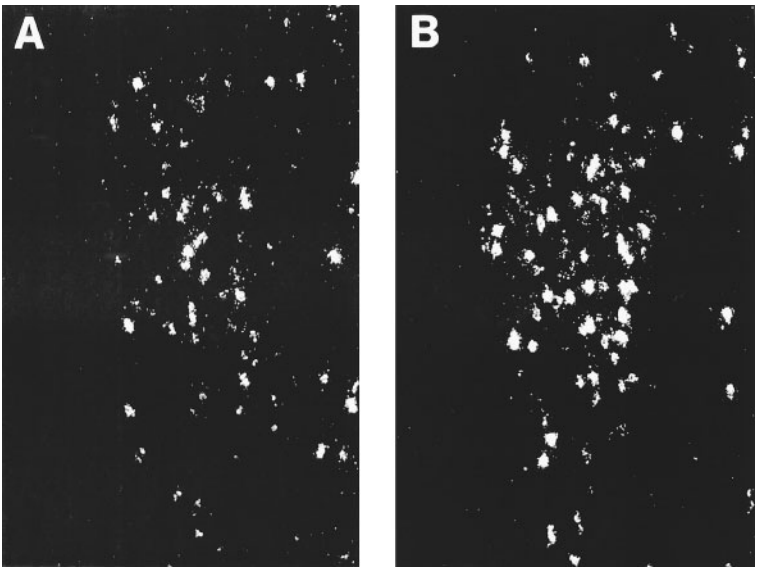


Figure 5.5
Effects of corticosterone (CORT) injection on CRH mRNA levels in the dorsal part of lateral bed nucleus of the stria terminalis (BSTLD). Dark field photomicrographs show the autoradiographic distribution of CRH mRNA in the BNST of control (*A*) and high CORT-treated (*B*, at 4 days) rats. Autoradiographic silver grains appear white. High (CORT) treatment increased CRH mRNA in the BSTLE (original magnification, ×100) (Makino et al., 1994b).

The bed nucleus of the stria terminalis also appears to be linked to some of the withdrawal symptoms experienced when individuals with a past history of drug abuse who are stressed for some reason start to crave the drug again. Thus CRH (in addition to other systems within the bed nucleus of the stria terminalis, e.g., Walker et al., 2000) may contribute to the withdrawal symptoms within the bed nucleus of the stria terminalis which has been linked to a number of biological factors underlying drug abuse (figure 5.7; Koob et al., 1998). But many neural systems are affected by withdrawal. Some of them are depicted in table 5.2.

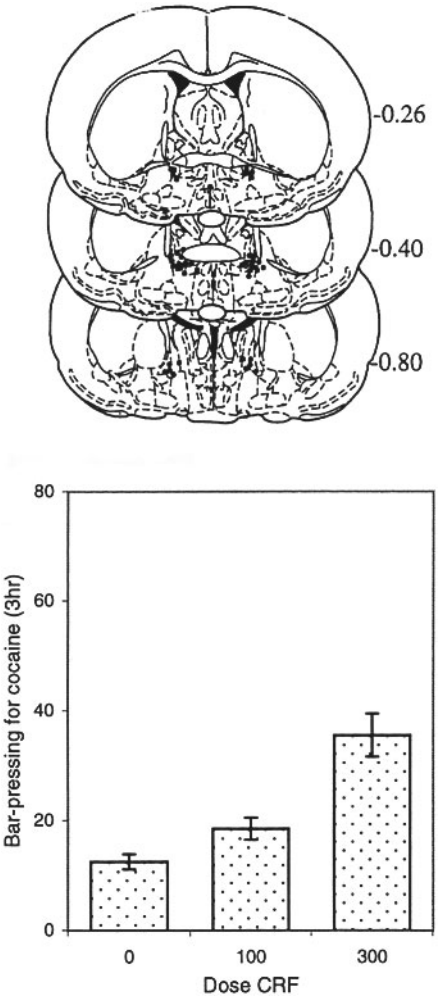


Figure 5.6
CRF injections in the bed nucleus of the stria terminalis and reinstatement of cocaine self-administration (adapted from Erb and Stewart, 1999).

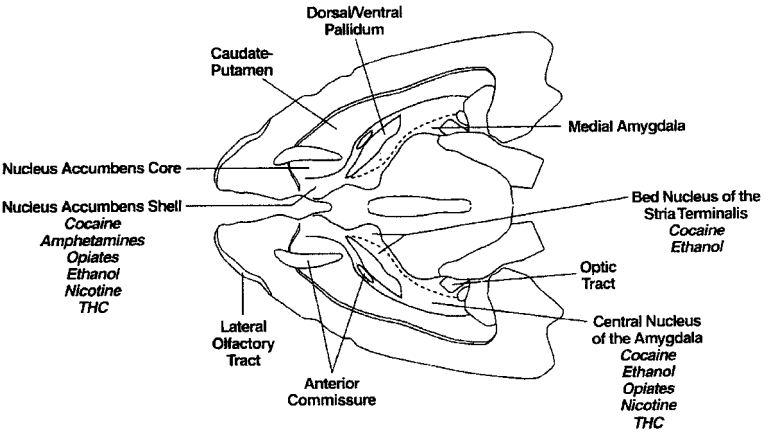


Figure 5.7
Horizontal section of a rat brain depicting some of the principal structures involved in drug use. These structures include the central nucleus of the amygdala, the shell part of the nucleus accumbens, and the bed nucleus of the stria terminalis. The drugs listed below each structure refer to potential sites of action of drug reinforcement during the addiction cycle, either positive or negative. (Koob et al., 1998; see also Alheid et al., 1988; but also Swanson and Petrovich, 1998).

Table 5.2
Some of the neurotransmitters/neuropeptides affected during withdrawal

↓ Dopamine
↓ Opioid peptides
↓ Serotonin
↓ GABA
↑ Corticotropin-releasing factor

Creating a Hyperexcitable State

Neural sensitization means the increased excitability of neurons. The ability of stress hormones and preexposure to psychosocial stressors in animals to precipitate greater stress responses indicates that sensitization processes play a major role in turning normal responses into exaggerated abnormal behavior (Marks and Tobena, 1990; Rosen and Schulkin, 1998). By definition, sensitization implies that the threshold for activation of the system is lower following the presentation of a stimulus. In other words, the system becomes hyperexcitable. The role of sensitization in the development of addiction is not well understood (Koob et al., 1989, 1998; Marks and Tobena, 1990; Robinson and Berridge, 2000). Theoretically, sensitization is an important factor in the etiology of hyperexcitability of the circuits underlying the addict's behavior. However, a number of researchers have linked the sensitization process underlying drug addiction to allostatic regulation (Koob and Le Moal, 2001; see also Rosen and Schulkin, 1998; Cook, 2002) and to CRH regulation (Richter et al., 1995).

Repeated cocaine self-administration in rats, for example, can result in the development of seizures linked to amygdala activation (Weiss et al., 1986), and both CRH and glucocorticoids facilitate cocaine-induced seizures (Weiss et al., 1992; Kling et al., 1993). In one experiment, repeated cocaine administration resulted in the development of seizures that were facilitated by both dexamethasone and, to a lesser extent, corticosterone (figure 5.8; Kling et al., 1993; Lee et al., 1989).

Chronic uncertainty (which can engender hyperexcitablility) can exacerbate the sensitization process. Experimental paradigms, in which an inescapable foot shock is delivered to rats, increase generalized anxiety and can increase the vulnerability of relapse to drug abuse (Erb and Stewart, 1999). The results of sensitization to stressors (i.e., hyperexcitability and pathological anxiety, vulnerability to relapse and allostatic overload) become long lasting and difficult to treat.

Sensitization may produce hyperexcitability by itself or in combination with various learning processes. Simple associative

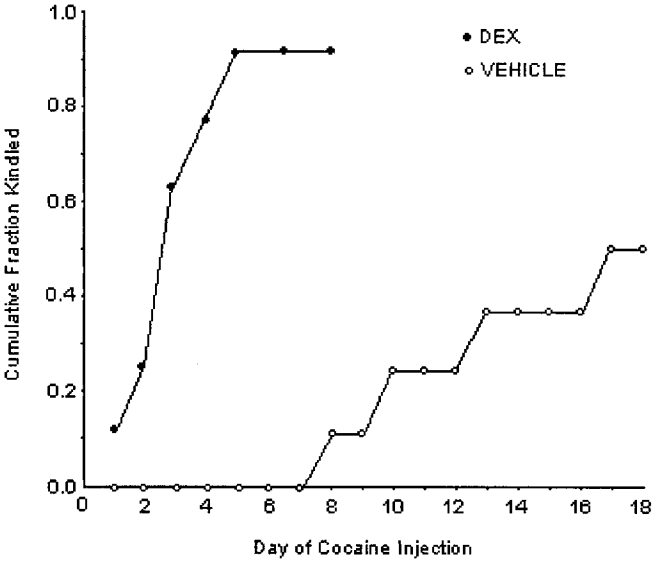


Figure 5.8
Effects of dexamethasone or vehicle administration on the development of kindled seizures to repeated cocaine administration. Rats were pretreated i.p. with dexamethasone (DEX, 250 μg/rat/day), or vehicle daily at 16.00 h beginning 3 days prior to initiating daily i.p. injections of cocaine HCL (40 mg/kg/day) at 09.00 h. Cumulative percentage of rats developing seizures is indicated as a function of days of study. Dexamethasone-treated rats had an increased frequency of kindling compared with controls (adapted from Kling et al., 1993).

conditioning does not explain the development of pathological anxiety. Several factors, including one's history of exposure to uncontrollable and unpredictable stressors, the nature of the stressors and conditioned stimuli (how conditionable they are), and one's temperament all influence learning processes (Rosen and Schulkin, 1998; Bouton et al., 2001). These factors may sensitize neural circuits to associative conditioning processes and thus facilitate responses now associated with the addiction.

Kindling (as in the cocaine example) produces a decrease in threshold and engages the same neural mechanisms in the first

few stimulations as LTP does, but it then recruits additional mechanisms as kindling proceeds further (Rosen and Schulkin, 1998). Thus both LTP and the early stages of kindling may induce similar molecular changes that are important for hyperexcitability. Induction of hyperexcitability from repeated exposure to activation may induce a cascade of biological events that includes the expression of immediate-early genes, such as peptides and structural proteins that render the tissue more sensitive to subsequent stimulation (Rosen and Schulkin, 1998).

Glutamate receptors, particularly the NMDA type, are important for the development of LTP and hyperexcitability in the hippocampus and the amygdala (LeDoux, 2000). Foot-shock-induced sensitization and facilitation of a fear-conditioned response require NMDA activation.

Glutamate, mediated through activation of various second messengers (e.g., calcium and cAMP), is also important for inducing a cascade of genetic transcriptional events. Kindling can also induce the expression of a number of neuropeptides, possibly through mechanisms involving the immediate-early genes. Finally, structural changes also occur in synapses following LTP and kindling (LeDoux 1996, 2000; Adamec, 1997; Rosen and Schulkin, 1998).

These immediate-early genes act as transcriptional factors to induce transcription of other genes, such as neuropeptides that affect behavior and modulate neurotransmission and other processes in the brain. A number of neuropeptides and their mRNA, which also are not normally expressed in fear-related limbic regions or have low levels in these areas, are transiently expressed following kindling (Rosen and Schulkin, 1998). These include peptides that are thought to play roles in pathological anxiety and affect (e.g., CRH, cholecystokinin, thyrotropin-releasing hormone, and neuropeptide Y) (Adamec, 1997). Changes in the expression of other molecules (e.g., growth and neurotrophin factors) that are important for growth and maintenance of neurons may also be affected by fear, stress, and sensitization. Both inescapable stress (restraint) and kindling alter the expression of mRNA for a number of growth factors, including nerve

growth factor, brain-derived neurotrophic factor and neurotrophin-3 (Smith et al., 1995a, b). These factors may be important as a vulnerability for neuronal death (allostatic overload) that may be caused by chronic stress of drug abuse (Sapolsky, 1992; McEwen, 2001).

Overactivity of the amygdala during seizure activity can be translated as a physical metaphor for drug addiction. Addiction is not a pleasurable state and is characterized by overactivity and obsession with the search for and consumption of psychotropic drugs. These are the negative consequences of allostasis. Corticotropin-releasing hormone concentrations are increased during aversive and uncertain events, and the state of addiction is riddled with uncertainty. As I suggested earlier, glucocorticoids are the molecules of energy metabolism, and the addicted person uses all energy to secure the craved substance, to the exclusion of everything else. The states of craving and withdrawal are often characterized by psychomotor overactivity, just as the amygdala becomes overactive when glucocorticoids and CRH levels are elevated—the positive induction of the neuropeptide by this steroid (Cook, 2002).

Corticosterone, CRH, Feedforward Mechanisms, and Self-Administration of Psychotropic Agents

The induction of CRH gene expression in the amygdala, and the bed nucleus of the stria terminalis, by glucocorticoid hormones may also underlie addictive behaviors; these effects appear to be manifested in the anxiety associated with withdrawal. Both high levels of corticosterone and central CRH have been linked to addictive behavior. For example, CRH infusions into the lateral ventricle facilitate amphetamine-induced self-administration (Sarnyai et al., 1993). Corticosterone levels are known to influence the expression of amphetamine self-administration (Piazza et al., 1991; Cador et al., 1993). Systemic injections of corticosterone increase the likelihood of amphetamine self-administration, as do stressful events (Maccari et al., 1991) via activation of glucocorticoid receptor sites (Steckler and Holsboer,

2001)—which increase both corticosterone and central CRH (Heinrichs et al., 1995). Individual differences in levels of corticosterone are correlated with amphetamine self-administration: the higher the level, the greater the self-administration (Piazza et al., 1991).

Corticosterone levels have also been shown to influence dopamine-dependent psychomotor effects of both morphine and cocaine self-administration (Deroche et al., 1994, 1995). Corticosterone is known to influence self-administration of cocaine; the greater the degree of corticosterone that circulates, the greater the probability of self-administration (Goeders and Guerin, 1996). Moreover, changes in dopamine levels in the nucleus accumbens is dependent upon adrenal steroid function (Barrot et al., 2000). The further activation of both CRH and dopaminergic neurons by glucocorticoids from feedforward allostatic mechanisms creates (when the glucocorticoids remain elevated) a vulnerability for drug abuse.

Corticotropin-releasing hormone in the brain has been linked to the anxiety associated with heroin and morphine withdrawal (Sarnyai et al., 1995; Zhou et al., 1996b), alcohol withdrawal (Pich et al., 1995), and cocaine withdrawal (Sarnyai et al., 1992a, b, 1993). In addition, a recent study has demonstrated that cannabinoid withdrawal also elevates CRH in the central nucleus of the amygdala (Rodriguez de Fonseca et al., 1997).

Reducing CRH expression in the amygdala reduces morphine withdrawal systems (Heinrichs et al., 1995). Inhibiting corticosterone synthesis by metyrapone decreases the vulnerability to relapse in cocaine self-administration (Piazza et al., 1994). Corticotropin-releasing hormone is linked to stress-facilitated vulnerability to relapse (Shaham et al., 2000). Perhaps by increasing or decreasing CRH gene expression by corticosterone, these rats are more vulnerable to self-administration of these psychotropic drugs. What this suggests is that the steroid may normally act to facilitate the level of neuropeptide in these extrahypothalamic sites that underlie the behavior. This is similar to the neuroendocrine mechanisms that facilitate and sustain other central motive states discussed in chapter 2.

Conclusion: Allostasis, Allostatic Overload, and Drug Use

The lifestyle of drug abuse, with its health-related consequences, is a run-down state. Addicts spend most of their time thinking of how to procure the next fix. The actual time of pleasure decreases as the addiction takes hold. It requires more drugs to produce the desired effect, the effect may not last very long, and the dominance of the obsession takes hold of the individual.

Homeostasis refers to stability through maintaining constant parameters. Negative feedback mechanisms exist throughout the brain and body in which a change in a system triggers an automatic response, bringing the system back to a basal level of functioning (Goldstein, 1995a, b; Fink, 2000). Allostasis refers to the principal of viability through change; there is no consistent set point (Sterling and Eyer, 1988). The organism responds to the demands of the external environment by changing its internal set points. This is evident in blood pressure changes during the course of an individual day; blood pressure rises in response to stressful, arousing situations that are psychologically experienced as pain, fear, or rage—or the craving for drugs. The chronic overuse of neurotransmitters linked to reward results in their biochemical depletion (Koob and Le Moal, 2001).

Allostasis reflects anticipatory factors (Schulkin et al., 1994), the growth of the associative processes linked to the drug (Berridge and Robinson, 1998; Everitt, 1999), and the long term changes that can occur in both systemic and central systems (Schluger et al., 2001) in biological regulation of the internal milieu. Addiction results in chronic arousal as the individual constantly seeks out the drug—the endless hypervigilant state (Koob and Le Moal, 2001). Brainstem sites such as the locus ceruleus are involved in the interaction of both molecules and interact with forebrain sites such as the amygdala, bed nucleus of the stria terminalis, and the PVN of the hypothalamus (Valentino et al., 1993, 1995). These sites underlie, perhaps, the chronic anxiety of the addict. The positive induction of CRH or dopamine by corticosterone (allostatic mechanism) in regions of the brain that underlie addiction may contribute to the addiction and physio-

logical overload over time along with the input from brainstem feedforward mechanisms of arousal from norepinephrine (Stricker and Zigmond, 1986; Koob and Le Moal, 2001). The changes in excitatory amino acids (e.g., McEwen, 1998a,b) may create a context for vulnerability to relapse and allostatic overload.

When an animal is in a state of relaxation, its body is able to repair damaged tissue and rebuild energy stores. However, when an animal is in a state of psychological arousal, its body begins breaking down metabolic compounds to produce energy. States of arousal are associated with a number of physiological responses, including increased blood pressure, increased breakdown of carbohydrates, fat, and protein, and decreased production of immune system cells. A number of hormone levels increase, including cortisol, vasopressin, angiotensin, and endogenous opiates.

An advantage of allostatic mechanisms is perhaps an increased efficiency in dealing physiologically with changing environmental demands. Moving from a state of complete relaxation to a state of complete alertness is difficult for a homeostatic system because of the great increase in energy demand. When an animal exists in an environment that frequently requires arousal states, allostatic mechanisms allow the body to physiologically change the basal set points of various systems to meet the arousal requirements. This allows the organism to maintain a constant state of alertness. However, there is a price to pay for this allostatic adjustment: increased energy demands on the body compromise other important functions, such as the immune system.

Physiological systems are designed in part to minimize the impact of drastic changes; this holds for situations ranging from the regulation of food to that of drug abuse (Solomon and Corbit, 1974; Woods, 1991; Koob, 1996; Koob and Le Moal, 1997; Siegal and Allan, 1998). Anticipatory responses that serve regulatory physiology can reduce the impact of overingesting as much as underingesting a desired substance—whether it be good or bad for the individual. Anticipatory responses that

serve to reduce the physiological impact of drug use may also hinder the individual.

When allostatic overload is introduced (for example, during the prenatal period or during childhood) by chronic socioeconomic stress or by traumatic experiences, the way in which physiological systems respond later in life can be affected. Multiple adverse events, which can manifest through unpredictable environmental situations, are one type of allostatic overload.

The state of allostasis is the shifting of physiological and behavioral resources in maintaining internal viability. For the addict, stuck in a massive web of salient cues reinforcing the chronic want of the drug, one outcome of allostasis is the possible depletion of a variety of neural systems (e.g., reward; Koob and Le Moal, 2001). A history of chronic drug abuse shifts the reward function (sensitization, tolerance, etc.) with the result of needing more of the drug and gaining less of a high.

Maintaining an addiction, in part, nonetheless, is like maintaining glucose levels or calcium levels. There is a homeostatic element involved in each of these situations (Koob, 1998). The body requires the drug in order to maintain equilibrium and to avoid getting sick, much as the body requires glucose or calcium. The negative reinforcement effects of drugs take hold. Central motive states are elicited, and both appetitive and consummatory behaviors are expressed. Further, as psychological and physical tolerance develops, the consummatory phase is less and less satisfying. When an individual becomes drug dependent, there are changes in the internal drug set points; there is an allostatic reaction to the constant presence of a drug such as cocaine, heroin, or alcohol. In rats, a limited period of daily access to a drug leads to maintaining the same levels of intake from one session to the next. An increased period of daily access (6 hours) leads to increased self-administration of the drug (Ahmed and Koob, 1998). A higher level of intake is required to gain the same hedonic effect from the drug (Koob, 1998).

Again, one way to understand these results is that they represent a shift in sensitivity of the reward function and a varied set point (allostasis) for the drug to have its effects. The drug is now

used more frequently, and physical health deteriorates in the addict because of extended wear and tear on the physical body. At one level, the event is homeostatic (Cannon, 1929a), and the behavior serves the physiology (Richter, 1942–43, 1956). At another level, the behavior is allostatic, a phenomenon that includes anticipatory responses and not just reactive responses (see also Sterling and Eyer, 1981).

It is clear that using drugs is not the same as maintaining sodium or water balance, in which there is a clear set point that has to be maintained. Again, there are physical limits, but that is different from a set point that is actively maintained. The negative aspects of the addiction grow and negative effects accrue while positive effects recede into the background. Yet the addict is enslaved by desire. Allostatic mechanisms, Koob and Le Moal (1997, 2001) suggested, have to do with the normal mechanisms of homeostasis insofar as it relates to reward. But when animals have reached states of dysregulation, the levels of intake are too high. Wanting of the drugs increases, and the addicted person becomes consumed by the desire. The addict's life is replete with endless consumption—and little satisfaction.

The addict's life, characterized by chronic worry, is replete with anticipatory angst, and both glucocorticoids and central CRH are elevated (Schulkin et al., 1998; Koob and Le Moal, 2001). Chronic allostatic overload exists when both glucocorticoids and central CRH are elevated and the body is unable to reduce the levels. There is a breakdown of normal inhibitory response. Maintaining high levels of glucocorticoids for long periods of time, which is the normal state of the addict, has many consequences. The breakdown of tissue, along with the associated addicted lifestyle, leads to an increased risk of many diseases, including human immunodeficiency virus and hepatitis. Compromised immune function, bone deterioration, and impaired memory functions (McEwen, 1998a, b) are a few of the results of maintaining high-energy arousal states over a long period of time.

The molecular substrates underlying craving, reinforcement, and withdrawal are being laid down. However, these

discoveries must be couched in terms of the social milieu in which addicts function. Methadone blocks both reward and withdrawal from opiates, but that is only part of the solution. Thus, CRH blockers will also not solve substance abuse problems. The human connectedness factor must be addressed (Jaspers, 1913). We are social animals, we need each other. Neuroendocrine evidence demonstrates that social adaptation, interacting, and communicating reduces, in suitable environmental conditions, stress hormones and increases the hormones linked to attachment behaviors (oxytocin, prolactin, vasopressin; see Insel, 1992; Bridges and Freemark, 1995; Carter et al., 1999; Bale et al., 2001).

Early life trauma and blunted cortisol response are associated with later substance use as well. However, these studies are necessarily based on clinical populations. Patients being treated for anxiety disorders and substance abuse might only be a subset of those who suffered early life trauma. Relatively large proportions of people who suffer early traumas maintain relatively normal lives, socially and biochemically.

Perhaps consistent and reliable positive human touch and contact can mediate the long-term effects of trauma, and perhaps the pathways influenced are directly related to CRH activity (Liu et al., 1997). It is known that rats who are handled, for example, have reduced levels of stress hormone activation at the level of the PVN production of CRH, pituitary ACTH, and adrenal corticosterone (Levine, 1975; Levine et al., 1989; Meaney et al., 1988, 1989, 1996). They show diminished responsiveness when challenged; it is as if the experience of being cared for or nurtured somewhat enhances the ability to cope with the impact of adversity. This is important for the recovering addict—or for any of us.

Successful drug rehabilitation programs often employ social contact as a vehicle toward mental health (Ouimette et al., 1998). The idea of reaching out to others to maintain abstinence is certainly not new. The effectiveness of this approach might be related to the reduced stress levels and, consequently, reduced CRH levels within the recovering individual. We know that so-

cial contact is an important adaptive behavior, and it is known to reduce stress hormones and to elevate hormones that can enhance well-being—that is, the central state associated with it (Carter et al., 1999). An important strategy, perhaps preferentially expressed as a tendency among the females of our species, and possibly others, is to make contact and sustain meaningful relationships when coping with duress (Taylor et al., 2000). Perhaps those who do not relapse into drug use are those who maintain and strengthen their social contacts, while those who experience relapse are those who refuse social support and are too impulsive to stay on the course of recovery.

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Conclusion: Adaptation, Allostasis, and Anticipation

Both homeostasis and allostasis, whole body regulatory concepts, function in our lexicon as integrative terms for understanding physiological/behavioral systems. They reflect our need to understand how internal viability is maintained in a changing environment (see also Mrosovsky, 1990; Bauman, 2000). Allostasis is tied to the central nervous system as it supervenes in the assessment and regulation of bodily states (Sterling and Eyer, 1988; Schulkin et al., 1994).

One impetus for the idea of allostasis was linked to concern about our social world. In a paper by Eyer and Sterling (1977) entitled "Stress-Related Mortality and Social Organization," a major portion was a critique of our society and the onset of a variety of disease states. Sterling and Eyer (1988) and others pointed to the detrimental sequelae of "chronic arousal" (Chrousos and Gold, 1992, 1998; McEwen and Stellar, 1993; Schulkin et al., 1994; Goldstein, 1995a, b). Sterling and Eyer were concerned about widespread chronic fatigue due to overstimulation. They endorsed practices that enhance calmness, such as transcendental meditation and community-based attachments.

One result of chronic arousal is the overactivation of allostatic anticipatory mechanisms, feedforward mechanisms, and eventual allostatic overload (McEwen, 1998a, b; Koob and Le Moal, 2001). The concept of allostasis emphasizes multiple systems in both the adaptive phase and the decline in pathology. The gradual decline of end-organ systems reflects allostatic overload, through their chronic overactivation and exaggerated expression. Moreover, long periods of physiological regulation are emphasized under allostatic regulation, in addition to cephalic

innervation of physiological functions (within the rubric of allostatic regulation). In addition, the concept of allostasis was invoked to account for the way in which one lives; whether one smokes, drinks, or uses psychotropic drugs; how one eats; whether one is defending against deadly viruses.

Allostasis and Cortisol—The Hormone of Energy Metabolism

Cortisol, as I have indicated, has permissive, stimulatory, suppressive, and preparative functions in orchestrating bodily viability to acute challenges (Ingle, 1952; Munck et al., 1984; McEwen, 1998a, b; Sapolsky et al., 2001). Glucocorticoids regulate cardiovascular, metabolic, and neural adaptive functions in the short-term context in a wide variety of ways (Sapolsky et al., 2000).

Social rank is one instance in which cortisol is clearly linked to behavioral expression. Social ranking and attachment have profound effects on internal physiology (Herbert, 1993; Gunnar, 1998; Sapolsky, 2000). In addition, cognitive factors, such as determining what is a real threat from what might not be, can determine cortisol levels; baboons who were less able to determine the real from the not real had higher levels of cortisol and perhaps chronic arousal (figure C.1; Sapolsky, 2000). But more generally, baboons with elevated levels of cortisol were linked to a number of appraisal responses to danger; those with higher cortisol tended to be less likely to differentiate threatening and neutral stimuli, initiate a fight that can be won, differentiating winning and losing a fight, and less likely to express displaced aggression after losing a fight (Sapolsky, 2001). In rats, chronic elevated levels of glucocorticoids along with elevated levels of central CRH are associated with lower social dominance and defeat (Albeck et al., 1997).

Socioeconomic status and a mother's vulnerability to depression affect the levels of cortisol in children (figure C.2; Lupien et al., 2000). For example, children in Montreal with the lowest socioeconomic status had the highest level of cortisol (Lupien et al., 2000). Some factors, however, are unknown, including:

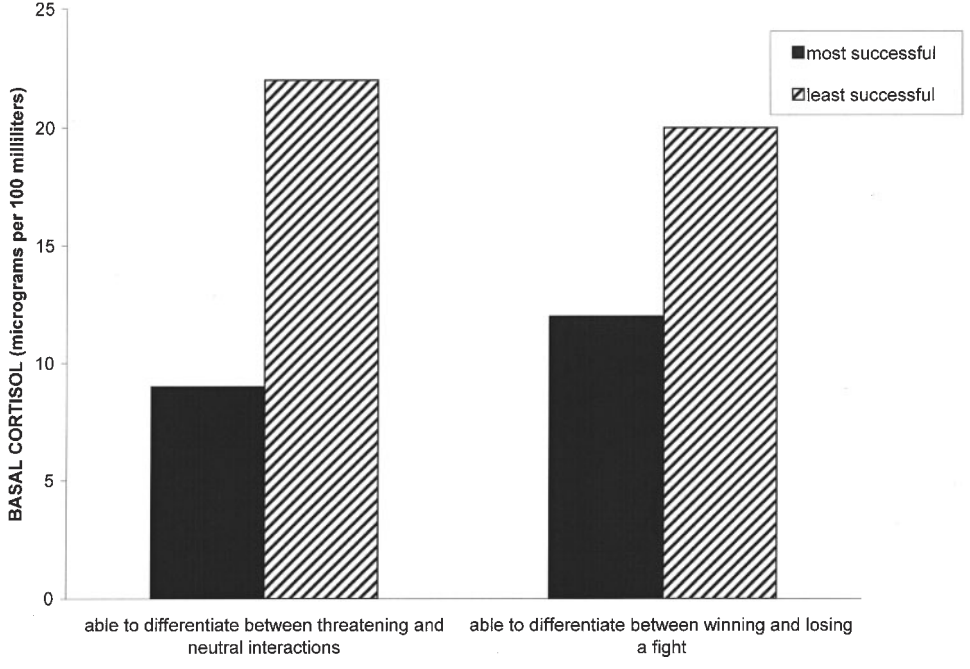

Figure C.1
Male baboons that are less able to determine the reality of a competitive situation have higher basal levels of cortisol (Sapolsky, 2000).

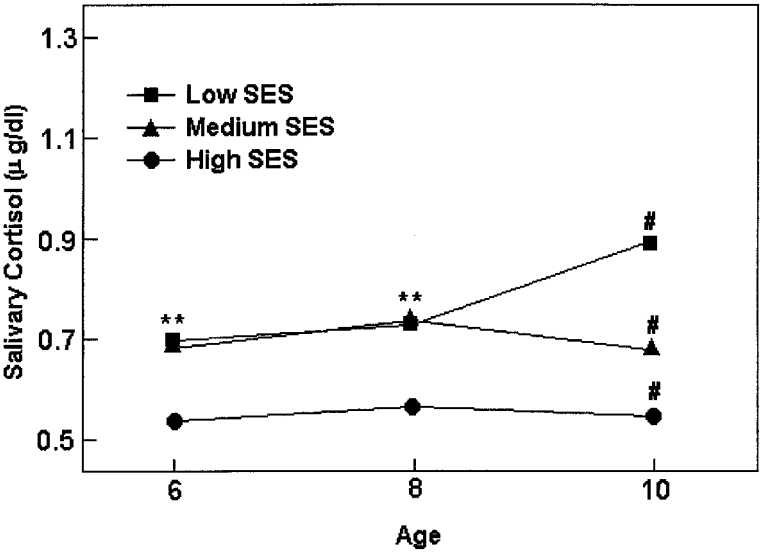

Figure C.2
Cortisol levels in low, medium, and high socioeconomic (SES) groups (Lupien et al., 2000).

nutritional status and fear at home and outside. These may also have an impact on the level of cortisol in this study.

Cortisol is *not* the molecule of fear or stress. Rather, cortisol is the molecule of energy metabolism, and fear is metabolically expensive. Because of its role in energy metabolism, cortisol levels are essential for normal brain function and the regulation of neuropeptides (Herbert, 1993) or neurotransmitters (e.g., Stutzman et al., 1998; Lucas et al., 1998b). In other words, cortisol is released in diverse behavioral, psychological, physiological, and environmental contexts. Cortisol facilitates a wide range of behavioral/psychological events by its effects on the brain (figure C.3) including cognitive functions (Lupien et al., 2002). Understanding these behavioral/psychological events relies on linking the glucocorticoid to the neuropeptides or neurotrans-

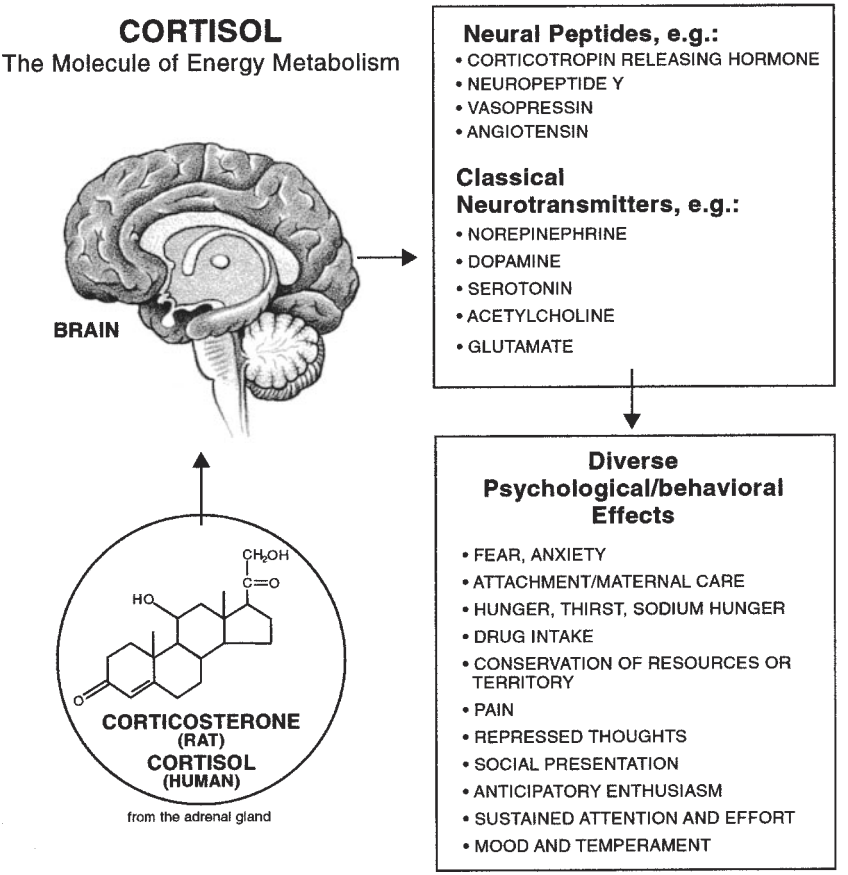

Figure C.3
The diverse effects of glucocorticoids on brain and behavioral/psychological functions. The structural depiction is of the rat's corticosterone (Erickson and Schulkin, unpublished).

mitters that are being synthesized in the brain within the environmental context that the animal is coping with.

Glucocorticoid levels can reflect appetitive states, such as thirst, hunger, sodium hunger, or states such as fear or excitement. It is not the level of cortisol per se that matters, but the effects of cortisol on the brain production of neurotransmitters such as serotonin and dopamine (e.g., Lowry et al., 2001), and neuropeptides such as angiotensin and CRH (e.g., Sumners et al., 1991; Makino et al., 1994a, b) in functional circuits.

Corticotropin-Releasing Hormone and the Amygdala

I have exaggerated the relative importance of CRH. I recognize that it is one peptide among many, and there are compensatory responses that would render CRH unimportant under a number of conditions.[1] Corticotropin-releasing hormone is just one of the peptides that underlie regulatory states such as fear. I have used it to make a point that covers a wide variety of research—fear, trauma, preterm delivery, and addiction. It is one important system among others in maintaining internal stability. A more complete picture will need to embrace the diverse neuropeptides and neurotransmitters that underlie homeostatic and allostatic regulation and that are regulated by internal physiological needs and external contexts.

Moreover, neither glucocorticoids nor CRH (nor the activation of the amygdala) are solely dedicated as signals of fear or adversity. Cortisol is the molecule of energy metabolism and has wide and diverse effects on the brain (see figure C.3). In addition, central CRH can elicit sodium ingestion, and it is important to bear in mind that this peptide is linked to cardiovascular regulation (Denton, 1982; Chrousos et al., 1998). Furthermore, using microdialysis, elevated CRH levels have been discerned in the central nucleus of the amygdala in rats during food ingestion (Merali et al., 1998). Food ingestion places one in

1. In addition, the role of the catecholamines should not be overlooked—see Dave Goldstein's (1995a, 2000) two important books.

a threatening situation—vigilance has to be maintained so as not to become a food source for something else.

That the amygdala is fundamentally tied to vigilance and attention (Whalen, 1998; Gallagher and Holland, 1994; Rosen and Schulkin, 1998; McGaugh, 2000; Davis and Whalen, 2001; Calder et al., 2001) has been recognized by several investigators (see also Flynn, 1972; Baron-Cohen et al., 1999; Schulkin, 2000; Emery et al., 2001). The expression of CRH within this region and others is linked to the animal's sense of adversity and attention to environmental cues (Cook, 2002). Neuropeptides / neurotransmitters regulated by steroid hormones play a fundamental role in the expression of central states.

Chronic Angst, Allostasis, and Pathology

McEwen and his colleagues (McEwen and Stellar, 1993; McEwen, 1998a, b, 1999; McEwen and Seeman, 1999) formulated and developed the terms *allostasis* and *allostatic overload* in an attempt to account for preserving physiological stability amid changing circumstances. For example, when uncertainty persists for long periods or is perceived as going beyond one's control, it results in negative consequences that my colleagues and I called *anticipatory angst* in an earlier paper (Schulkin et al., 1994). There is a plethora of animal and human data on the negative consequences to bodily and psychological health in such a circumstance. This occurs when normal physiological adaptation is run beyond what it was designed to tolerate.

The diverse physiological systems for maintaining bodily viability to acute challenges are reflected in mobilization of cardiovascular function, activation of metabolic fuels, activation of immune defense, and engagement of central nervous systems function (McEwen, 1998a, b; Sapolsky et al., 2000). But the chronic condition (allostatic state; Koob and Le Moal, 2001) can result in allostatic overload and cardiovascular, metabolic, immunological, and neuronal pathology.

Adaptation to uncertainty is a fact of life because uncertainty pervades life. In the short run, allostatic mechanisms can

provide physiological and behavioral resources that help maintain equilibrium. Unfortunately, these resources are finite. Chronic signals from physiological mediators (cytokines, cortisol, catecholamines, etc.) take their toll on bodily function, resulting in vulnerability to a variety of diseases such as those that concerned Sterling and Eyer (1988) and later McEwen and Seeman (1999; including hypertension, diabetes, atherosclerosis, bone loss, sleep disruption, disruption of immune and reproductive functions, inhibition of neurogenesis, aging process; Seeman et al., 2001). Vulnerability to these events can occur from prenatal events (Barker, 1997; Welberg and Seckl, 2001).

Within the literature, something beyond traditional conceptions of homeostasis was needed to account for regulatory events. To Selye and others (Goldstein, 1995a, b, 2000; Chrousos, 1998; Berntson and Cacioppo, 2000), the breakdown of systems was well-known and well-studied. Adaptation can only go so far in the attempt to maintain internal stability amid changing circumstances. The mechanisms for short-term regulation can lead to pathology when pushed beyond their adaptive time frames. To explain wide variation in physiological regulatory events, a biological basis of individual differences was noted.

Anticipatory regulation is a cognitive achievement and built into our brains (Gallistel, 1992; Schulkin, 2000). After all, evolution favored those who could not only react to events but also anticipate them. Thus, it is very reasonable to distinguish reactive from predictive homeostasis (Moore-Ede, 1986). Allostasis accounts for long-term responses—not simply short-term adaptations—and reflects feedforward and cephalic influences over behavioral and physiological events. The concept of allostasis forces one to broaden one's view of maintaining internal viability in changing and uncertain circumstances (but see Goldstein, 2000 for a very detailed depiction of homeostatic systems). But the concept also highlights the regulatory costs, in terms of the initial protective mechanisms and the longer-term damaging consequences of allostatic overload (e.g., the long-term changes in excitatory amino acid by chronic high levels of glucocorticoids; McEwen, 1999, 2001). The time scale in which to envision

regulatory events by the use of the concept of allostasis is expanded quite considerably. What occurs quite naturally is the link between normal variation in use and descent into overload. The mediators of allostasis are different from the standard mediators of homeostasis such as pH, osmolarity, oxygen, and body temperature. Standard homeostatic mediators are less variable in the context of adaptation and bodily viability.

Evolutionary Considerations

Earlier accounts of allostasis overlooked our evolutionary context. When in our evolutionary past have we had prolonged periods of restfulness (Wingfield and Ramenofsky, 1997; Wingfield and Romero, 2001)? We need to take evolution into account as we consider homeostasis, stress, allostasis, and allostatic overload. For example, high levels of corticosterone can favor or support animals in a wide variety of contexts; in a number of species, levels of corticosterone or cortisol can be adjusted in the short term by both behavioral and physiological means (Wingfield and Ramenofsky, 1997). In the short term, glucocorticoids are protective and facilitate normal physiological and behavioral adaptation. But in the long run, high levels of corticosterone interfere with a number of regulatory functions (McEwen, 1998a, b, 2000).

Constant stimulation is not new; our increasing life expectancy is. Tissue declines with age. Rousseau (1762) asked the question, "Why are men in chains when they are born free?" Perhaps an analogous question is, Why is there so much worry when we have so much? One reason is that if we don't find worry, we are very good at constructing it. This is not just a piece of pathology.

The dominant theme that led to the concept of allostasis is that chronic arousal of the brain drives increases in regulatory physiology to a point beyond what is acceptable for normal function. Evolution favored a number of specialized mechanisms in the brain in regulating both behavioral and physiological functions. When activated inappropriately, normal

maintenance turns into pathological vulnerability and expression (figure C.4).

Allostasis—A Plausible Concept

The concept of allostasis has brought about new research under the rubric of a concept that is useful because it provides a plausible hypothesis for connecting what might seem to be unrelated events. For example, we now have discussions about allostasis, allostatic state, and allostatic overload in the context of drug use and sensitization (Koob and Le Moal, 2001) and in preterm delivery of babies (Schulkin, 1999a). The larger rubric is that of regulatory physiology, and both the concepts of homeostasis and allostasis are nominally related to physiological function. There is no isomorphic relationship between the concepts and the regulatory physiological systems.

The induction of neuropeptides by steroids is not an aberration in the behavioral activation that serves physiological and long-term viability. These events, contrary to how positive induction (feedforward mechanisms) is usually or has been construed (Goldstein, 1995a, b, 2000), are not necessarily instances of pathological breakdown and perhaps not any more vulnerable to dysfunction (Korte, 2001) than other regulatory systems. They represent one mechanism by which the brain orchestrates behavioral events that sustain the animal. Negative restraint is only one endocrine mechanism, and positive induction is not an aberration. In a number of regulatory events, there are feedforward mechanisms that underlie the central state.

Allostatic regulation can reflect short-term needs, such as avoiding predators and finding food, as well as intermediate needs, such as conservation of social space or environmental defense. Allostatic regulation is also evident in longer-term needs, such as successful reproduction. In each of these cases, the steroid acts to facilitate or sustain neuropeptide expression—feedforward mechanisms (Pfaff, 1980; Herbert, 1993; Schulkin, 1999a).

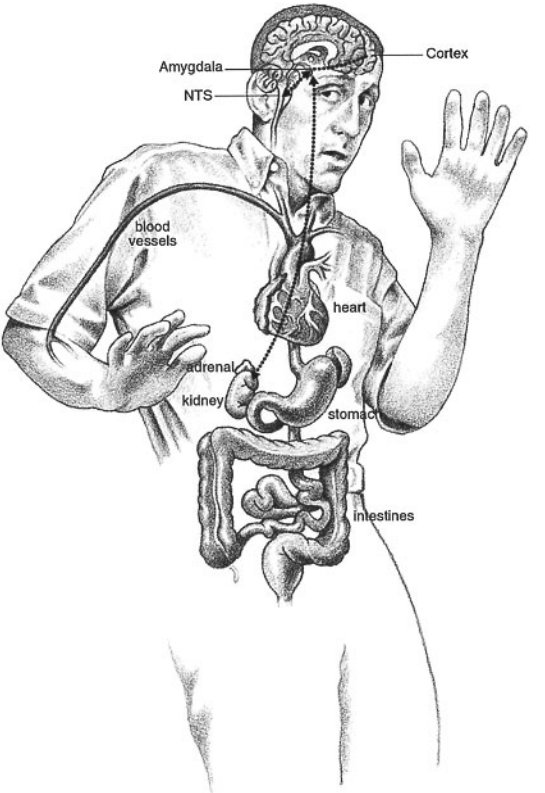

Figure C.4
Cortical, amygdala, brainstem (e.g., solitary nucleus, NTS), and peripheral organs (Yansen and Schulkin, unpublished).

Balancing internal demands with external contexts (what is available, is it safe, what is the probability of being eaten?) is an everyday occurrence for most species. This is achieved by the integration of a number of appraisal mechanisms and balancing competing motivations (McFarland, 1991; Berntson and Cacioppo, 2000) that are then integrated within the nervous system. Social contact, approach, and avoidance mechanisms reflect in part the expression and regulation of neuropeptide and receptor sites by steroid hormones, many of which are important in regulating social behaviors (Insel, 1992; Bridges and Freemark, 1995; Carter et al., 1999). In turn, social behaviors are regulating internal physiology (Hinde, 1968, 1970; Levine, 1975; Levine et al., 1989; Blass et al., 1995; Gunnar and Davis, 2001). The search for social contact and closeness can reduce the level of cortisol and decrease the central nervous system production of CRH, for example, in extrahypothalamic sites. Social engagement is the way by which contact and cooperation serve more than one individual, both in terms of short- and long-term goals (mothers and their offspring; Hofer, 1994; Hofer and Sullivan, 2001). Regulatory physiology is broad in the context of trying to maintain internal viability.

Concluding Remarks

It is beneficial to look at the context in which the terms *homeostasis* and *allostasis* are used in our scientific lexicon. Both homeostasis and allostasis function as heuristics for inquiry, somewhat like other broad biological categories (e.g., *adaptation*). They are scientific concepts, but are not as clear as one would like them to be. Nonetheless, they are useful, for they guide inquiry and provoke a degree of musing.

One could argue that the concept of homeostasis was construed too narrowly, that homeostasis can reflect both predictive and reactive mechanisms (Moore-Ede, 1986), both short-term and long-term regulation of the internal milieu. In fact, it does. The concept of allostasis here is presented in the context of what the philosopher Peirce used to call "a humble argument" (see

the new anthology of his works, 1992–98). One looks at the field and realizes that in the context of what is known about the anatomical connectivity of peripheral sites with the central nervous system (and from brainstem to cortex; Blessing, 1997), that another concept, one expanded beyond what homeostasis has meant to investigators, was necessary to account for emerging data of regulatory systems. It is in this spirit that allostasis is suggested for understanding regulatory physiology and behavioral or systems neuroscience.

Concepts like homeostasis and allostasis function in the context of regulatory physiology. In this great age of molecular biology, whole-body physiological analysis is essential and integrative. These force us to consider end-organ systems together as functioning wholes in maintaining bodily health. They serve to unify and bring into perspective a wide range of physiological data. These concepts play a functional role in biological inquiry and insofar as they further inquiry into understanding bodily stability amid change, they have played an important role.

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Name Index

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Subject Index