

STRESS

The constancy of the “milieu interieur” is the condition of a free and independent existence.
- Claude Bernard, 1878

Adaptation to changing physical and social demands requires integration of behavioral, neuroendocrine and autonomic responses to maintain homeostasis. Stress, defined as any perturbation of homeostasis, can be psychological or physiological in nature. Thus, heat, cold, and physical trauma are direct physical assaults on homeostasis. Fear, anger, surprise, and other emotions, in response to various external stimuli or events, represent psychological states that also disrupt the internal stability of the body. The most important concept that you will learn concerning stress, and of great clinical relevance, is that the stress response can be both beneficial and detrimental to the organism. There are many complex factors that determine whether the organism's response to stress leads to adaptation and resilience (beneficial), or maladaptation and dysfunction. An appreciation of the concept of stress and its basic biological underpinnings is essential to the understanding of both health and disease processes.

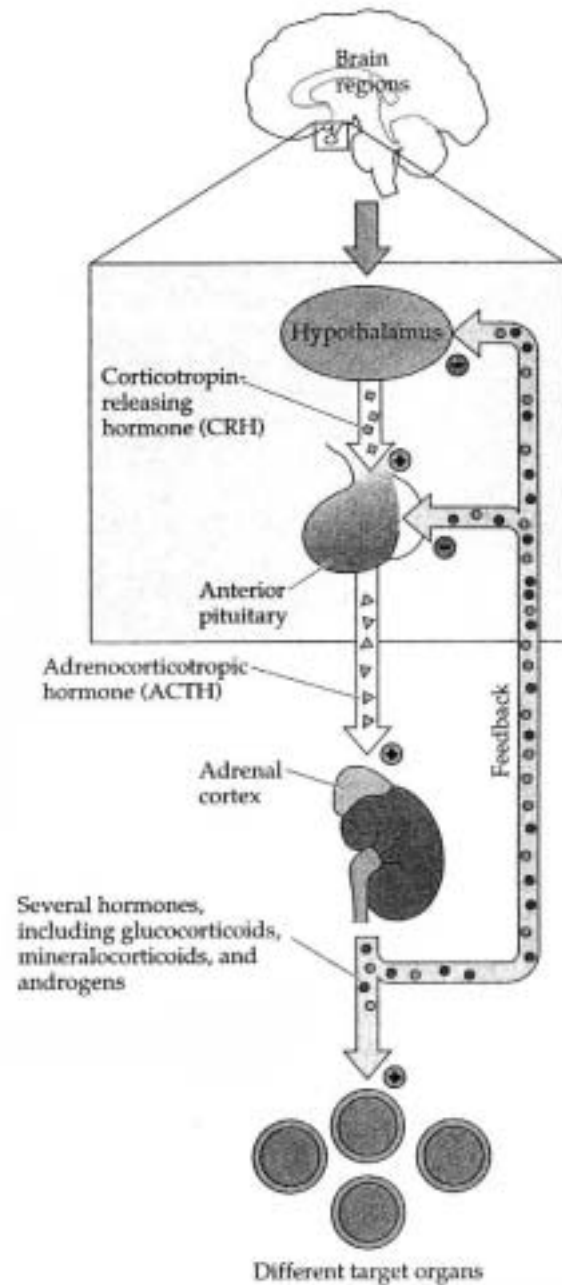
Exposure to moderate levels of stress elicits adaptive (beneficial) responses in both the central and peripheral nervous system that function to maintain homeostasis and return systems to equilibrium. The overall response to stress at the physiological, neural, hormonal, and behavioral level is extremely complex; here we attempt to underscore only the key players. The principal components of the stress response consist of the **hypothalamic-pituitary-adrenal (HPA) system** (most commonly known as the **HPA axis**), the **locus coeruleus-norepinephrine (LC-NE) system**, and the **extrahypothalamic corticotropin releasing hormone (CRH) system**. The HPA system is involved in the secretion of hormones from the pituitary and adrenal cortex. The LC-NE and CRH systems are the major brain pathways that encode the response to stress. In general, stress-induced activation of these systems leads to **sympathetic** activation, characterized by increased flow of glucose and oxygen to the muscles and brain, adrenomedullary discharge of epinephrine, vasoconstriction, increased heart rate and blood pressure, enhanced arousal, and focused attention. In sum, they prepare the body for the classic “fight or flight” response.

Elements of the HPA system

The HPA system is depicted schematically in Fig. 1. The endocrine response to stress is initiated when the organism senses or perceives a stimulus as a threat. Releasing factors are secreted by neurons in the **paraventricular nucleus (PVN)** of the hypothalamus (you know from earlier lectures that the PVN also secretes oxytocin and vasopressin). **Corticotropin-releasing hormone (CRH)** is an example of a releasing factor. The PVN neurosecretory cells project their axons to the portal capillary plexus of the median eminence. CRH is secreted into the portal capillaries and reaches the anterior pituitary, where it stimulates the synthesis and release of **adrenocorticotropin hormone (ACTH)**.

The release of **ACTH** into the blood stream stimulates the synthesis and secretion of **glucocorticoids** from the adrenal **cortex**. In humans, the principal glucocorticoid is **cortisol**. Some of the major functions of glucocorticoids include the modulation of energy utilization and suppression of the inflammatory/immune response.

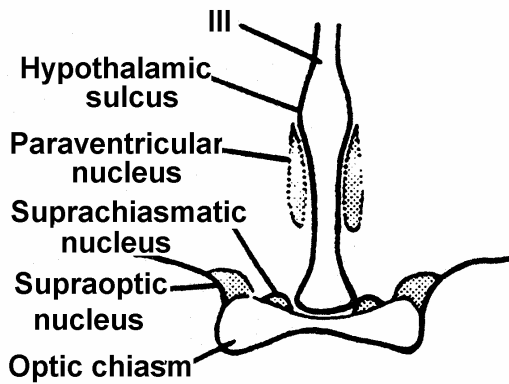
Fig. 1. The hypothalamic-pituitary-adrenal axis (HPA). Adapted from Rosenzweig et al, 1996. Stressful stimuli, processed through brain sensory regions, activate the CRH-releasing cells of the PVN in the hypothalamus. The CRH then initiates a cascade that results in increased plasma levels of cortisol. Cortisol negatively feeds-back to several brain regions to inhibit further production of CRH. An important area for negative feedback in addition to the hypothalamus is the **hippocampus** (memory; not shown), which has high levels of glucocorticoid receptors.



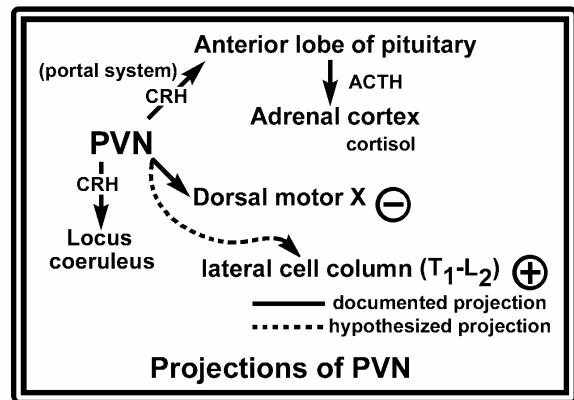
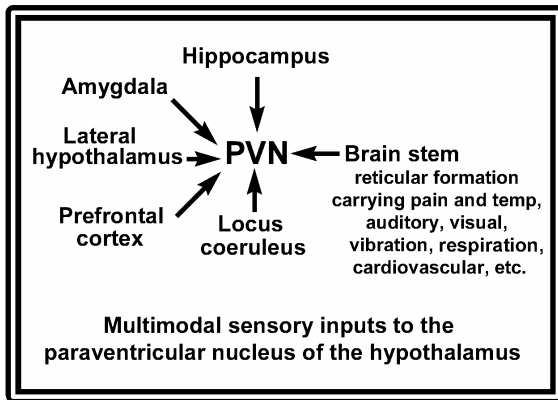
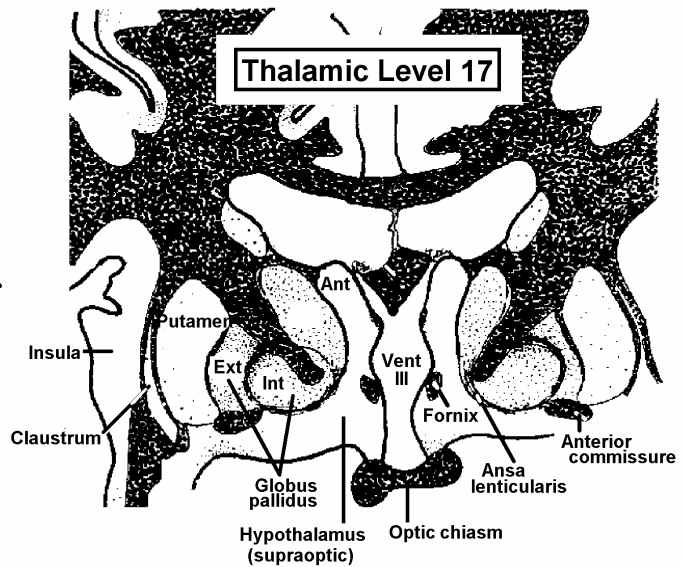
Modulation and termination of the HPA response to stress occurs through a glucocorticoid negative-feedback process, one of the body's primary mechanisms for self-control. This feedback inhibition by circulating glucocorticoids is an important mechanism for controlling HPA activity. Glucocorticoid receptors located in the pituitary, hypothalamus, and limbic brain regions, especially the hippocampus, are activated following the stress-induced increase in cortisol secretion. Through a process that is not fully understood, glucocorticoid receptors on cells in the PVN, anterior pituitary and hippocampus results in negative feedback inhibition of the secretion of cortisol.

Inputs and outputs of the PVN

If the PVN plays such an important role in the modulation of the stress response, how is this accomplished? The exact answer to this question is not known, but the afferent and efferent connections to the PVN provide some clues. The PVN receives an important input from the **amygdala**. The amygdala receives multimodal input from all sensory modalities; therefore the PVN receives indirect sensory input. Stress signals can also activate the PVN via the lateral hypothalamus, which receives input from secondary (higher) sensory cortical areas, and via inputs from the locus coeruleus, the prefrontal cortex, and the hippocampus (memories of stressful things!). In addition to releasing CRH into the portal system and inducing ACTH release, the PVN has strong projections to brain stem autonomic ganglia – i.e. the preganglionic neurons in the dorsal motor nucleus of the vagus (dorsal motor X) and sympathetic preganglionics in the lateral column of the spinal cord (T1-L2).



Cross section through supraoptic region of the hypothalamus



There are many examples of activation of the HPA system during stress. As noted earlier, physical, psychological and social stresses activate the stress hormones. Novelty, uncertainty, threat, conflict, unpredictability, pain and injury are all triggers of the plasma cortisol response. For example, maternal separation results in increased plasma cortisol in the infant monkeys and the rise in cortisol is directly related to the length of separation.

It is important to note that plasma cortisol, as is true of many circulating hormones, has a distinct daily rhythm which is driven by an endogenous clock. Mammals normally exhibit a rise in plasma ACTH and glucocorticoids at the **onset** of wakefulness and a trough (nadir) 12 hours later. It is of significant clinical interest that a hallmark of severe depression is a general **elevation** of plasma cortisol and a flattening of the diurnal rhythm of secretion. Although the mechanism underlying this effect is not known, it suggests that there are marked disturbances in the system that controls the stress response in depression.

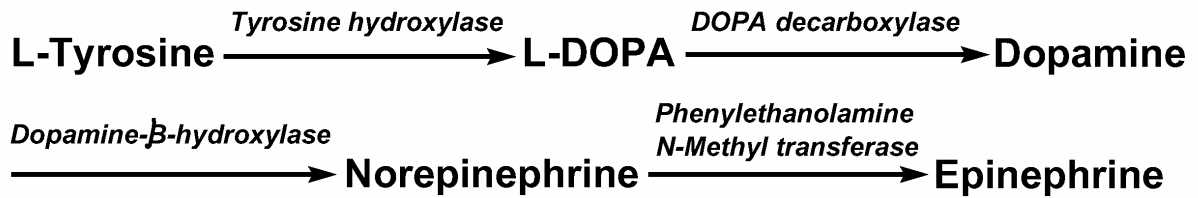
A further important function of glucocorticoids appears to be in learning and memory. Memories of emotionally arousing events are often more vivid and stable than memories of ordinary or neutral events. This makes evolutionary sense since organisms greatly benefit from important events (don't even go near that cave where you nearly got eaten...). It is believed that the brain has evolved memory-modulating mechanisms whereby certain modulators enhance memory formation. The hippocampus, a critical structure for memory, has dense levels of glucocorticoid receptors. Cortisol may be one of several modulators/transmitters to facilitate memory at the level of the hippocampus. Unfortunately, as we all know, too much stress is a bad thing; chronic exposure to high doses of cortisol or stress impairs memory and eventually results in neuronal cell death within the hippocampus. Such hippocampal cell death associated with stress is especially prevalent during the aging process.

The locus coeruleus-norepinephrine (LC-NE) system

Thus far, we have discussed how stressful events or stimuli engage a neuroendocrine system, the HPA axis, which results in a wide range of physiological, endocrine and behavioral effects. In concert with this endocrine activation, stress concurrently engages the **LC-NE system**.

The locus coeruleus (LC) is a small, compact group of **norepinephrine** (NE) concentrating cells located in the pons (see Figs. 2 and 3). There are approximately 20,000 LC cell bodies in the human brain. Translated from Latin, LC means **blue spot**. A section of fresh human brain through the LC shows these blue spots because the LC neurons contain melanin (like pars compacta of the substantia nigra). NE is a neurotransmitter synthesized from dopamine by the enzyme dopamine- β -hydroxylase.

Biosynthesis of Catecholamines



The LC sends widespread, branching projections to **all** areas of neocortex, thalamus, limbic system, hypothalamus, other brain stem nuclei, and the spinal cord (Fig. 3). Within these regions, axons of LC cells branch repeatedly resulting in a wide distribution of NE release. Behavioral and sensory stimuli elicit activation of LC-NE neurons which influence the functional activity of their diverse target sites. The broad nature of NE secretion in terminal regions may serve to alter the tone of global brain functions such as vigilance, attention, and arousal.

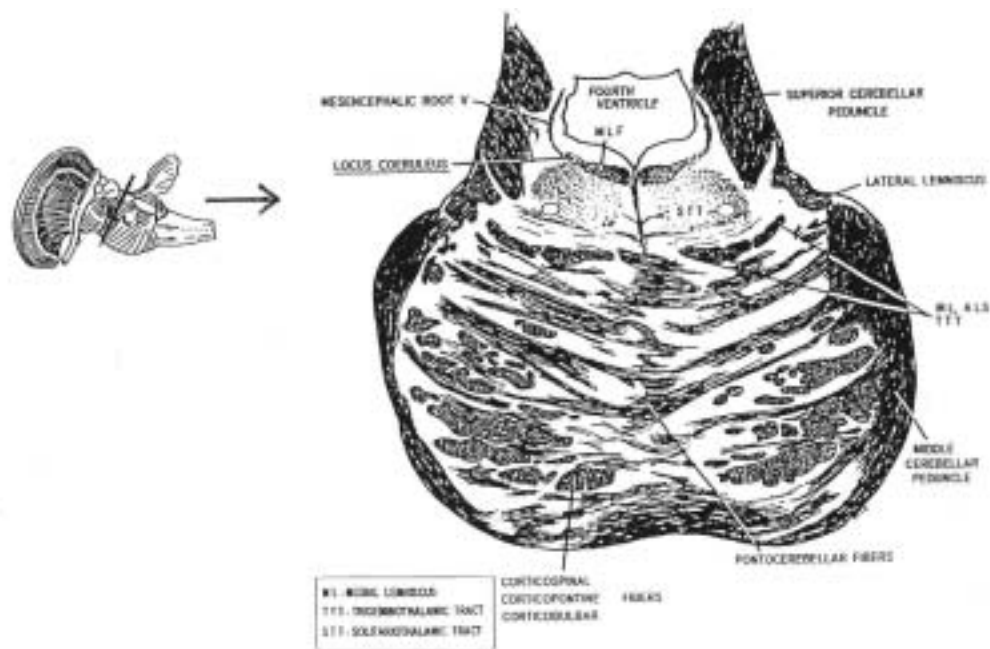


Fig. 2. Location of LC cells in the rostral pons.

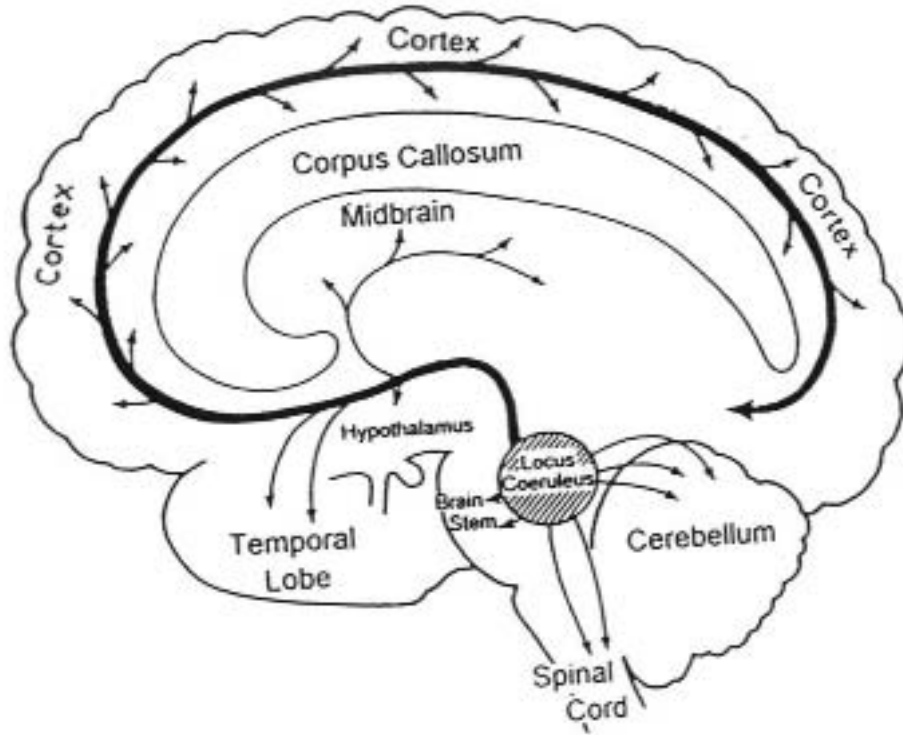
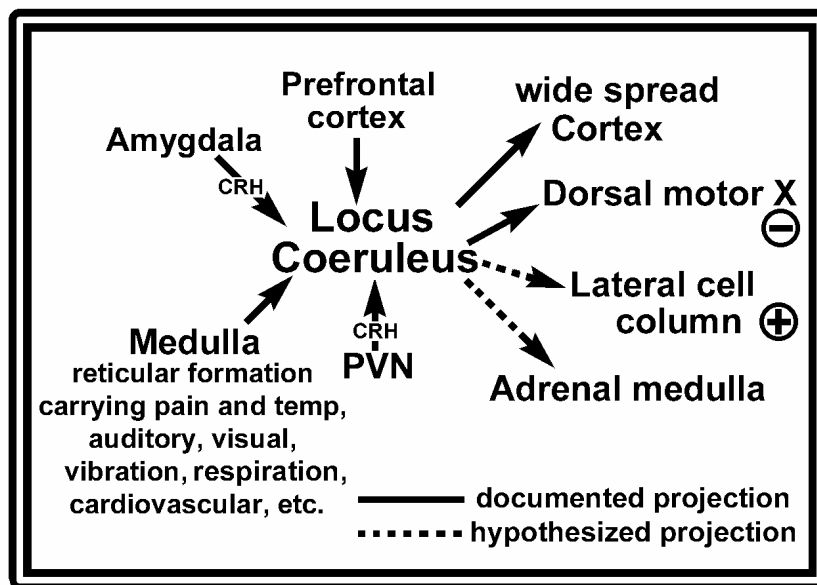


Fig. 3. The LC-NE system. Adapted from Andreasen, NC: The broken brain: the biological revolution in psychiatry. New York, Harper & Row, 1984.

LC cell bodies receive diverse sensory inputs from the medullary reticular formation (collaterals from pathways like the TTT, STT, ML, and ALS reach this area of the medulla [reticular formation] but were not emphasized in the Brain Stem Module). Additionally, LC neurons receive afferents from the prefrontal cortex, amygdala and hypothalamus. Finally, the LC receives fiber input from the PVN itself. All this information therefore includes highly processed cognitive/emotion-related inputs and autonomic related inputs. Outputs go to broad regions of neocortex and limbic system, as well as descending brain stem and spinal areas (Fig.3). A further important output is to sympathetic preganglionic neurons in the lateral cell column of the spinal cord (T1-L2).



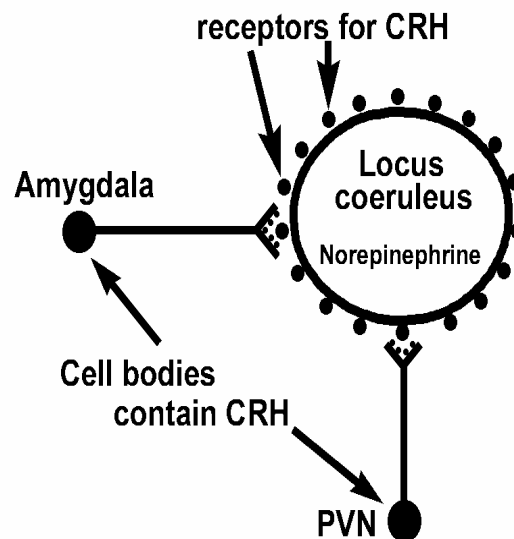
Their strategic position in the brain stem and their innervation of virtually all areas of the nervous system would suggest that the LC neurons are in a strategic position to exert a broad influence over CNS function. The main role ascribed to LC neurons is in the integration and orchestration of the adaptive CNS response to various stressors or challenges. For example, LC neurons burst fire to a variety of arousing stimuli (“**attention-grabbing**”) loud clicks or bright flashes, noxious stimuli, or physiological challenges such as hypoxia or hypoglycemia. They are very active when the animal is orienting and attending to such stimuli, in a highly aroused, vigilant state. In contrast, their activity is at a very low level when the animal is quietly resting, grooming, or feeding. When the animal is asleep, the neurons shut off their activity altogether.

Extrahypothalamic CRH Systems

The CRH system associated with the PVN of the hypothalamus is involved primarily in the regulation of pituitary ACTH secretion. There are, however, other CRH systems located throughout the brain. There are several brain regions where CRH may play a role in this regard. These systems are sometimes called **extrahypothalamic CRH** systems, but this is something of a misnomer, as there is extensive overlap between the “classic” HPA-CRH systems and the CRH in other pathways. In the pons, CRH-containing **terminals** are associated with CRH receptors on **LC** neurons. These terminals arise from CRH producing cells in PVN and the amygdala. Studies have shown that application of CRH to LC neurons results in **increased** firing of LC neurons. The **opposite** effect occurs after administration of a CRH antagonist into the LC, which blocks these receptors. Thus, the CRH action on LC-NE cell bodies serves to increase the level of arousal (via activation of autonomic response) and vigilance (LC projects to cortex) during a state of stress.

In summary, CRH systems play a role in coordinating various facets of the stress response. The hypothalamic-CRH system serves to regulate secretion of pituitary ACTH secretion, and thus initiates the endocrine response to stress. The extrahypothalamic systems function to promote the activation of the peripheral autonomic responses and vigilance associated with cortical activation.

Extrahypothalamic CRH systems



Although stress rapidly elicits physiological and behavioral responses, the long-term consequences of that stress exposure are modulated by psychological factors. It is now known that **predictability** and **controllability** of stress, as opposed to the stress itself, are extremely important factors in the stress response. The psychological effects were first demonstrated in research using dogs at the University of Pennsylvania. In this experiment, two groups of dogs were exposed to an environment in which they were administered electric shocks. One group of dogs was able to escape from the shocks by pushing a panel, whereas the other group had no control over the termination of the shocks. Both the number and duration of shocks were exactly the same for both groups of dogs. This was achieved by having the fate of one dog controlled by its partner. That is, when one dog was shocked, so was the other. When one dog terminated the shock, the shock was also terminated for the partner. This procedure (called a “yoked control”) guaranteed that stress exposures were exactly the same for both dogs. The difference was that one dog exercised some control over the stress, whereas the other dog was exposed to chronic stress that was uncontrollable.

The dog with uncontrollable (unpredictable) chronic stress had **elevated** cortisol and **decreased** NE, while the dog with controllable (predictable) chronic stress had **normal** cortisol and NE levels. The uncontrollable stress also resulted in hypertrophy of the adrenal gland.

Both groups of dogs were subsequently placed in a new situation that provided them with the opportunity to help themselves by escaping the presentation of shocks by jumping a hurdle. The dogs that previously controlled their shock experience were able to learn as rapidly as naive dogs that had no previous shock experiences. However, dogs that were previously exposed to uncontrollable shocks behaved very differently. They became passive and failed to jump the hurdle to escape from shock. This failure to respond adaptively to new situations after exposure to uncontrollable stress is called “**learned helplessness**.” The phenomenon of learned helplessness illustrates how an individual's perception of a stressful event and not the event, per se, is important in determining the consequences of stress, as well as influencing future behavior.

It has been suggested that the mechanisms underlying learned helplessness (chronic uncontrollable stress) may be similar to those occurring in certain kinds of depression. Not only is learned helplessness a model of depression, but it also has important implications for how brain function regulates adaptation to stress, and how coping or cognitive styles may alter brain neurochemical systems. The learned helplessness theory as applied to depressive disorders hypothesizes that the experience of “**noncontingency**”- the lack of a relation between responding and outcome- shapes an individual's ability to deal with aversive or stressful events. Experiencing helplessness or an inability to alter a bad situation undermines the motivation to respond positively, to cope effectively, or to believe that behavior can affect outcome. In other words, perceived or actual loss of control over important life events may be a major precipitating factor of depression.

Interestingly, animals that have experienced control over a stress are **less** likely to have a reduction in brain NE levels when exposed subsequently to an uncontrollable chronic stressor. In effect, animals with a history of stressor controllability appear to be “immunized” from the effects of uncontrollable stressors.

Positive experience can have protective effects on the stress response. In a recent study that received much attention, researchers found that adult rats whose mothers had licked and groomed them more (i.e. they received more attachment behaviors) showed a reduced adrenocortical response to stress, compared with a group of rats whose mothers showed low levels of maternal behaviors. Thus, early life experiences during critical periods in development may participate in shaping the reactivity to stress in adulthood.

Posttraumatic Stress Disorder (PTSD)

The diagnosis of **PTSD** consists of exposure to a traumatic event in which 1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others and 2) the person's response involved intense fear, helplessness, or horror. As a result of this, the patient persistently re-experiences the event in one or more of the following ways; recurrent or intrusive distressing recollections of the event, including images, thoughts, or perceptions, recurrent distressing dreams of the event, acting or feeling as if the traumatic event were recurring (including a sense of reliving the experience, illusions, hallucinations, and dissociative flashbacks), or an intense psychological distress or psychological reactivity at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event. The patient also exhibits persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness as indicated by efforts to avoid thought, feelings, or conversations associated with trauma, efforts to avoid activities, places, or people that arouse recollections of the trauma, inability to recall an important aspect of the trauma, markedly diminished interest or participation in significant activities, feeling of detachment or estrangement from others, restricted range of affect, or sense of foreshortened future.

These patients exhibit psychological signs of **increased** arousal, which include difficulty falling asleep, irritability or outbursts of anger, difficulty concentrating, hypervigilance, or exaggerated startle response. This increase in arousal level is associated with an **increase** in the levels of NE in the blood and urine and increases in heart rate and blood pressure. Thus, PTSD patients have abnormally elevated behavioral, cardiovascular and biochemical responses to the alpha-2-NE **antagonist** yohimbine, which stimulates central NE release, compared with healthy controls. Beta-adrenergic blockers can block the effect of increased NE and are often used in the treatment of PTSD for that reason.

Interestingly, patients with PTSD have **lower** cortisol levels. That is, it appears that with PTSD, the brain may become hypersensitive to the effects of cortisol. Cortisol is essential in times of stress, and as a result, PTSD sufferers often have difficulty in stressful situations. It has been shown that there is an increase in cortisol receptors on ACTH producing cells. This would increase the negative feedback on the secretion of cortisol by the adrenal gland. You will remember that there is an increase in cortisol in chronic mood disorders. Thus, the hypothalamic-pituitary-adrenal (HPA) axis appears to work differently in people with PTSD.

You will learn that the hippocampus is involved in the storage and retrieval of memories, and receives input from the locus coeruleus (NE). Hyperactivity at the locus coeruleus may result in damage in these regions. Memories are not integrated properly and instead take the form of nightmares, flashbacks, or physical symptoms. MRI comparisons have shown an approximate 10% decrease in volume of the hippocampus in PTSD patients. There is also some evidence that communication between brain hemispheres is impaired in PTSD patients. The "right brain" has typically been associated with emotions and the development of social skills. If the right side is damaged or is unable to communicate with the "cognitive" left side, the result is memories or emotions that the patient is unable to verbalize or work through on their own. The event is essentially trapped in the subconscious.

Problem Solving

1. Which of the following statements is **TRUE** regarding learned helplessness?
 - A. results from chronic uncontrollable stress
 - B. associated with increased cortisol levels
 - C. associated with decreased NE
 - D. associated with increased NE
 - E. three of the above are **TRUE**

2. Glucocorticoids:
 - A. are released by the adrenal medulla in response to stress
 - B. have receptors on hippocampal neurons
 - C. activate the anterior pituitary
 - D. are released by the adrenal cortex in response to stress
 - E. two of the above are **TRUE**

3. Chronic uncontrollable stress:
 - A. can result in adrenal gland hypertrophy
 - B. results in continuing low levels of NE
 - C. results in increase in cortisol
 - D. can result in death of hippocampal neurons
 - E. all of the above are **TRUE**

4. Which of the following is **FALSE** regarding extrahypothalamic CRH?
 - A. increases the cardiac response to stress
 - B. increases firing rate of LC neurons
 - C. increases levels of NE
 - D. receptors are found on LC neurons
 - E. found in LC terminals

5. The following neurotransmitter profile would be most likely to characterize the brain of an infant monkey recently separated from its mother:
 - A. decreased levels of cortisol and adrenaline
 - B. decreased levels of CRH and norepinephrine
 - C. increased levels of CRH and norepinephrine
 - D. increase adrenaline and decreased CRH
 - E. decreased levels of ACTH

6. Posttraumatic stress disorder (PTSD):
 - A. patients can have flashbacks
 - B. NE levels are increased and there is increased arousal
 - C. patients have exaggerated responses to the alpha-2 NE antagonist yohimbine
 - D. cortisol levels are increased
 - E. three of the above are **TRUE**

7. In the HPA axis:
 - A. CRH is released by the adrenal medulla
 - B. cortisol is released by the pituitary
 - C. glucocorticoids are released by the PVN
 - D. amygdala input can cause the PVN to secrete ACTH
 - E. brain stem inputs can cause the PVN to secrete CRH

8. The locus coeruleus:
 - A. sends widespread dopaminergic projections to neocortex, thalamus, and the limbic system
 - B. sends a very narrowly focused norepinephrine projection to only the hypothalamus
 - C. is involved in vigilance, attention, and arousal
 - D. means “pink spot” in Russian
 - E. two of the above are correct

9. Chronic uncontrollable stress:
 - A. can be protected against by prior exposure to chronic controllable stress
 - B. results in reduced brain NE levels
 - C. may contribute to the development of depression
 - D. results in increased NE levels
 - E. three of the above are correct

10. Corticotropin releasing hormone (CRH):
 - A. is found mainly in the spinal cord
 - B. regulates autonomic but not behavioral responses to stress
 - C. infusion into the brain decreases plasma levels of epinephrine and norepinephrine
 - D. decreases stress-induced arousal by inhibiting LC firing rates
 - E. found in the cells of the amygdala and in PVN terminals ending on LC cells

11. The paraventricular nucleus (PVN) of the hypothalamus:
- A. receives input from the prefrontal cortex, the brain stem and the amygdala
 - B. is inactivated by stress
 - C. receives strong projections from the spinal cord
 - D. lies in the rostral hypothalamus
 - E. two of the above are true
12. Which of the following **connections** is/are **TRUE**?
- A. amygdala projects to the PVN
 - B. brain stem reticular formation projects to the PVN
 - C. prefrontal cortex projects to the PVN
 - D. amygdala projects to the LC
 - E. all are **TRUE**
13. Which of the following **connections** is/are **TRUE**?
- A. LC projects to frontal cortex
 - B. LC projects to dorsal motor X
 - C. LC projects to the lateral cell (sympathetic) column (T1-L2)
 - D. PVN projects to LC
 - E. all are **TRUE**
14. Which of the following statements is **FALSE**?
- A. there are glucocorticoid receptors in the hippocampus, PVN, and anterior pituitary
 - B. cortisol levels are highest around 7AM
 - C. your NE levels would increase if you suddenly heard a bomb go off out side the lecture hall
 - D. NE levels increase during chronic controllable stress
 - E. LC neurons burst fire to a variety of novel stimuli
15. Which of the following statements is **TRUE**?
- A. there are 19, 999 cells in the LC
 - B. repeated controllable stress results in a decrease in NE levels in terminals
 - C. too much cortisol can result in memory problems
 - D. the projections of the LC are limited to the brain stem
 - E. the PVN lies in the caudal hypothalamus
16. Which of the following statements is/are **TRUE** regarding post-traumatic stress disorder (PTSD)?
- A. flashbacks are uncommon
 - B. yohimbine causes an increase in cardiovascular responses in those with PTSD
 - C. has no effect upon cells in the LC
 - D. patients have low levels of circulating NE
 - E. patients exhibit high cortisol levels

PROBLEM SOLVING ANSWERS

1. E (A, B, C)
2. E (B,D)
3. E
4. E
5. C
6. E (A, B, C)
7. E
8. C
9. E (A, B, C)
10. E
11. E (A, D)
12. E
13. E
14. D
15. C
16. B