■ REVIEW

The Neurobiological Basis of Anxiety and Fear: Circuits, Mechanisms, and Neurochemical Interactions (Part II)

DENNIS S. CHARNEY, CHRISTIAN C. G. GRILLON, and J. DOUGLAS BREMNER
Yale University School of Medicine
Department of Psychiatry
New Haven, Connecticut

This article is Part II of a review of the neuronal circuits, neural mechanisms, and neuromodulators that seem to be involved in anxiety and fear states. Part I focused on the specific brain structures, including the roles of the amygdala, locus coeruleus, hippocampus, and various cortical regions and the neural mechanisms of fear conditioning, extinction, and behavioral sensitization in mediating the signs and symptoms of anxiety and fear. Part II attempts to develop a better understanding of neurochemical mediation of traumatic remembrance and the neurobiological consequences of stress, particularly when experienced early in life. Finally, the data is synthesized to provide a basis for understanding the pathophysiology of anxiety disorders, such as Panic disorder and Posttraumatic Stress Disorder. NEUROSCIENTIST 4:122–132, 1998

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Anxiety disorders such as Posttraumatic Stress Disorder (PTSD) and Panic disorder are characterized by memories of the traumatic experience or original panic attack that remain indelible for decades and are easily reawakened by all sorts of stimuli and stressors. The strength of traumatic memories relates in part to the degree to which certain neuromodulatory systems, particularly catecholamines and glucocorticoids, are activated by the traumatic experience (1, 2). Experimental and clinical investigations suggest that memory processes remain susceptible to modulating influences after information has been acquired.

Many investigations in laboratory animals have shown that alterations in brain catecholamine and glucocorticoids affect the consolidation, storage, and retrieval of emotional memories (3–5). Locus coeruleus (LC) activation by electrical stimulation or α_2-adrenergic receptor antagonists enhance memory retrieval (6, 7). The memory enhancing effects of increased noradrenergic (NE) activity may be mediated by β-noradrenergic receptors within the amygdaloid complex (1, 2). Glucocorticoids influence memory storage via activation of glucocorticoid receptors in the hippocampus. Basolateral amygdala lesions block the memory enhancing effects of glucocorticoid administration in the dorsal hippocampus (5).

There are important functional interactions between the sympathoadrenal and adrenocortical systems. Adrenocortical suppression blocks the memory-enhancing effects of amphetamine and epinephrine. The mechanisms responsible for this effect likely involve the hippocampus and amygdala (8). Glucocorticoids released from the adrenal glands in response to aversive training can enhance memory storage. The β receptor antagonist, propranolol, infused into the basolateral nucleus of the amygdala, antagonizes glucocorticoid induced memory enhancement. These results suggest that NE mechanisms in the amygdala are critically involved in glucocorticoid mediated memory storage (9).

The hypothesized involvement of the NE system in the storage and retrieval of traumatic memories is supported by recent clinical investigations. Yohimbine induces vivid traumatic memories in patients with PTSD (10). In healthy subjects, propranolol impairs memory for an emotional story, but not for a neutral story (11). These data suggest that some of the acute responses to trauma (i.e., release of high levels of glucocorticoids and NE) may facilitate the encoding of traumatic memories.

Neurobiological Consequences of Stress

Stress produces profound alterations in multiple neurotransmitter systems. In the following section, we evaluate the effects of stress on NE neurons, corticotropin releasing hormone (CRH), and the hypothalamic-pituitary-adrenal axis (HPA). These systems that have been studied extensively, have regulatory effects on brain structures implicated in anxiety and fear, and seem to be involved in the neural mechanisms of fear conditioning, extinction, sensitization, and traumatic remembrance.

The original view that stress results in a general adaptation syndrome has been replaced by the hypothesis

Address reprint requests to: Dennis S. Charney, M.D., Yale University School of Medicine, Department of Psychiatry, 25 Park Street, New Haven, CT 06510 (E-mail: dennis.charney@yale.edu).

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that the response to stress involves a constellation of adaptive alterations that are idiosyncratic to each individual and are influenced by innate characteristics as well as past experiences. Neurobiological responses to severe stress are clearly adaptive and have survival value, but they also can have maladaptive consequences when they become chronically activated. Examination of the preclinical data concerning neurochemical substrates of the stress response, the long-term impact of early exposure to stress, and possible stress-induced neurotoxicity provide a context for clinical investigations of the pathophysiology of PTSD and Panic Disorder.

NE System

Stressful stimuli of many types produce marked increases in brain NE function. Stress produces regional increases in NE turnover in the LC, limbic regions (hypothalamus, hippocampus, and amygdala), and cerebral cortex. Immobilization stress, foot-shock stress, tail-pinch stress, and conditioned fear increase NE metabolism in the hypothalamus and amygdala (12).

Neurons in the LC are activated in association with fear and anxiety states (13, 14) and the limbic and cortical regions innervated by the LC are thought to be involved in the elaboration of adaptive responses to stress (15). A particularly dramatic example was the demonstration that LC-NE neurons in freely moving cats were activated twofold to threefold by confrontation with either a dog or an aggressive cat, although exposure to other novel stimuli (such as a nonaggressive cat) did not increase the firing rate (16).

Certain stressors elicit increased responsiveness of LC neurons to excitatory stimulation. Antagonism of α_2 adrenergic-receptors with idazoxan or yohimbine increases the response of LC neurons to excitatory stimuli without altering their baseline firing rate (17, 18). Consistent with these findings, acute cold-restraint stress results in decreased density of α_2-receptors in the hippocampus and amygdala (19). Further, in chronically cold-stressed rats, the release of norepinephrine, produced by yohimbine in the hippocampus, is enhanced (20).

In the case of uncontrollable stress, concurrent alterations in catecholamine systems may become maladaptive. Exposing rats to uncontrollable stress produces fear and anxiety and can lead to a chronic enhancement of responsiveness of LC neurons to excitatory stimulation because of decreased stimulation of "functional blockade" of α_2 receptors after norepinephrine depletion (17).

Neuropharmacological studies of noradrenergic function. The findings that stress increases NE function and that fear conditioning and behavioral sensitization are related to alterations in NE activity may have important implications for understanding the pathophysiology and course of Panic disorder and PTSD. Many of the chronic symptoms experienced by these patients, such as panic attacks, insomnia, startle, and autonomic hyperarousal, are characteristic of increased NE function (21–23).

Stress-induced increases in NE function may be related to abuse of alcohol, opiates, and benzodiazepines by patients with PTSD in attempts to relieve their symptoms. Acute alcohol administration has been reported to reduce stress-induced increases in NE turnover in the amygdala and the LC, but not in the hypothalamus, hippocampus, and cerebral cortex (24). Opiates, such as morphine, decrease stress-induced increases in NE release in the amygdala, hippocampus, hypothalamus, thalamus, and midbrain (25). Benzodiazepines, including diazepam, attenuate stress-induced increases in NE release in the hypothalamus, hippocampus, cerebral cortex, and the LC region (26).

Well-designed psychophysiologic studies have documented heightened autonomic or sympathetic nervous system arousal in combat veterans with chronic PTSD. Combat veterans with PTSD have a higher resting mean heart rate and systolic blood pressure and greater increases in heart rate when exposed to visual and auditory combat-related stimuli compared with combat veterans without PTSD, patients with generalized anxiety disorder, or healthy subjects (27, 28). Furthermore, they display hyperreactive responses to combat-associated stimuli but not to other stressful non–combat-related stimuli (29). Because central NE (LC) and peripheral sympathetic systems may function in concert (30), these data are consistent with the hypothesis that NE hyperreactivity in patients with PTSD may be associated with the conditioned or sensitized responses to specific traumatic stimuli.

Peripheral Sympathetic Dysfunction

Neuroendocrine studies and investigations of peripheral catecholamine receptor systems have also provided evidence of dysregulated peripheral sympathetic nervous system activity in PTSD. Several studies have found significantly elevated 24-hour urine NE excretion in PTSD (31). Consistent with this observation, it has been reported that the density of platelet α_2-adrenergic receptors is reduced, perhaps reflecting adaptive "downregulation" in response to long-standing elevated levels of circulating endogenous catecholamines (32).

NE function has also been probed by determining the behavioral, biochemical, and cardiovascular responses to the α_2-adrenergic receptor antagonist yohimbine. As predicted from the preclinical studies reviewed above, clinical investigations of combat veterans with PTSD have exhibited markedly enhanced behavioral, biochemical, physiological, and cardiovascular responses to yohimbine (10, 33, 34). Moreover, a recent PET study demonstrated that PTSD patients have a cerebral metabolic response to yohimbine, consistent with increased norepinephrine release (34).

There is considerable evidence that abnormal regulation of brain NE systems is also involved in the pathophysiology of Panic disorder. Panic disorder patients are very sensitive to the anxiogenic effects of yohimbine and

have exaggerated plasma 3-methoxy-4-hydroxyphenylethylene glycol, cortisol, and cardiovascular responses to yohimbine (21, 22, 35, 36). The responses to the α_2-adrenergic receptor agonist clonidine are also abnormal in Panic disorder patients. Clonidine administration caused greater hypotension, greater decreases in plasma MHPG, and less sedation in panic patients than in control subjects (36–39). These findings suggest that PTSD and Panic disorder may have similar pathophysiologic dysfunctions in the regulation of NE function. However, the causes of the two syndromes may differ, with Panic disorder more closely associated with genetic factors and PTSD with the effects of severe psychological trauma.

CRH

Although CRH is an important component of the HPA axis, the most salient behavioral actions of CRH are mediated outside the axis. The actions of CRH in the brain are mediated through multiple binding sites. There is heterogeneity of CRH binding sites with respect to sequence, pharmacology, and tissue distribution. There are at least three receptors, CRH_1, CRH_{2A}, and CRH_{2B}, each of which is composed of seven putative transmembrane spanning domains characteristic of G_s-coupled receptors.

CRH_1 receptors are most abundant in neocortical, cerebellar, and sensory relay structures. CRH_2 receptors are generally localized to specific subcortical structures, most notably lateral septal nuclei, choroid plexus, olfactory bulb, specific amygdaloid nuclei, and various hypothalamic areas.

The anatomical distribution of CRH_1 and CRH_2 receptors may be relevant to the function of CRH receptor subtypes. Within the pituitary, CRH_1 expression predominates over CRH_2 expression, which suggests that CRH_1 receptors may mediate CRH induced changes in ACTH release. The role of the CRH receptor subtypes in anxiety and fear remains to be established. The high level of CRH_2 receptors in hypothalamic and amygdaloid nuclei suggests that CRH_2 receptors may mediate the anxiogenic effects of CRH. However, there is behavioral evidence that CRH_1 receptors may also be involved in the mediation and expression of anxiety-related behavior (see below) (40).

An enormous body of evidence indicates that the release of CRH release represents a major component of neurobiological response to stress (41). Central administration of CRH produces "anxiety-like" behavioral and autonomic effects that are not suppressed by hypophysectomy (42, 43). Intracerebroventricular injection of CRH produces a marked, long-lasting, and dose-dependent elevation of startle amplitude (44) which is reduced by the anxiolytic compound chlordiazepoxide (45). The anxiogenic effects of CRH can be attenuated by α-helical CRH, a CRH receptor antagonist (46, 47). CRH antisense oligodeoxynucleotide treatment attenuates social defeat-induced anxiety elevation of CRH on RNA and CRH in the hypothalamus (48).

The precise brain sites where CRH exerts its anxiogenic effects are under active investigation. CRH acts through extensive extrahypothalamic connections with several brain structures implicated in stress, including the central nucleus of the amygdala, bed nucleus of stria terminalis (BNST), hippocampus, paraventricular nucleus of the hypothalamus (PVN), and LC. The amygdala is thought to be an important site of CRH effects. Stress increases the release of CRH into the amygdala (49). CRH injection into the amygdala reduces exploratory behaviors (50). Chronic infusion of the CRH_1 receptor antisense oligodeoxynucleotide into the central nucleus of the amygdala reduced anxiety-related behavior in socially defeated rats (51). Restraint stress results in increased CRF levels in the amygdala (49).

The amygdala is not the only mediating site for the anxiogenic effects of CRH. Lesions of the central nucleus of the amygdala attenuate CRH facilitation of startle (44), but local injection of CRH into the amygdala does not significantly elevate startle. This suggests that the amygdala is only one component of the neural circuit necessary for CRH to elevate startle. Lesions of either the hippocampus or BNST completely block the CRH-enhanced startle. The BNST has been shown to be involved in the response to various stressors (52, 53). It has extensive efferent projections into the PVN (54) and has anatomical similarities with central and medial nuclei of the amygdala. The BNST has brain projections into hypothalamic and brainstem sites that are essentially the same as the central nucleus of the amygdala, and it receives direct projection from the amygdala and the hippocampus, which suggests that the BNST may play a crucial role in behavioral and hormonal responses to stress. Lee and Davis have recently suggested that the BNST might be a primary site for the effect of CRH to enhance startle (55).

Functional Interactions between the LC and CRH

Mounting experimental evidence suggests that the LC NE neurons may play a pivotal role in the anxiogenic properties of CRH (56, but see 57). Stressful conditions robustly increase CRH concentrations in the LC (57); CRH injected into the LC intensifies anxiety-related responses (58, 59). Microinfusion of CRF directly into the LC increase the firing rate of LC neurons in a dose-dependent manner and produces an elevation of norepinephrine, as measured by in vivo microdialysis, and NE metabolites in LC projection regions, including the amygdala, hypothalamus, and prefrontal cortex (60–62). LC activation by CRF is also associated with cortical electroencephalogram (EEG) activation. Infusion of the CRF antagonist, α-helical CRF, into the LC attenuates stress induced release of NE in the prefrontal cortex (63). These findings support the notion that CRF serves as an excitatory neurotransmitter in the LC and that these actions are translated into increased cortical NE release and cortical EEG activation.

Repeated stress sensitizes the LC response to CRF. It has been hypothesized that stress-induced sensitization of hypothalamic pituitary function is an adaptation that allows the chronically stressed animal to mount appropriate endocrine responses to threatening stimuli. Similarly, stress-induced sensitization of the LC to CRF allows the LC to continue to respond to novel stressors. However, this effect may have pathological consequences and could relate to the hyperarousal and sleep disturbances seen in stress-related psychiatric disorders such as depression and PTSD (51).

HPA Axis

Acute stress of many types produces increases in ACTH and corticosterone levels in laboratory animals (64). The mechanism responsible for transient stress-induced hyperadrenocorticism and feedback resistance may involve a downregulation of glucocorticoid receptors (65, 66). High glucocorticoid levels (such as those elicited by acute stress) decrease the number of hippocampal glucocorticoid receptors, resulting in increased corticosterone secretion and feedback resistance. After stress termination, when glucocorticoid levels decrease, receptor numbers are increased and feedback sensitivity normalizes (67, 68).

The effects of chronic stress on ACTH and corticosterone secretion vary depending on the experimental paradigm. It has been reported that an adaptation to chronic stress may occur, resulting in decreased plasma ACTH and corticosterone levels compared with levels after a single stressor (69–71). However, other investigations have revealed enhanced corticosterone secretion after chronic stressor regimens (71–75). There is also evidence that the experience of prior stress may result in augmented corticosterone responses to a subsequent stress exposure (76). It is not known which factors determine whether adaptation or sensitization of glucocorticoid activity will occur after chronic stress (77).

Interactions between HPA and NE Systems

Chronic hypercortisolemia decreases basal levels and stress-induced increments in indices of the release, metabolism, turnover, and synthesis of catecholamines in the PVN, which suggests that glucocorticoids restrain stress-induced activation of catecholamine synthesis in the PVN (78-82). The HPA and sympathetic nervous system interact in complex ways to maintain homeostasis. Endogenous glucocorticoids restrain catecholamine responses to immobilized stress. This effect may depend on the type of stressor (83). Hypercortisolemic animals have blunted NE responses to yohimbine in brain microdialysate (84). These findings suggest that α_2-adrenergic receptor may be an important site of interaction between catecholamine and HPA systems (85).

Neuroendocrine studies of CRF and the HPA axis. In a recent investigation, PTSD patients were shown to have an elevation in CSF CRH consistent with the hypothesized role of CRH in the stress response (86). Several studies have found evidence for altered HPA/CRF axis function in PTSD, including a blunted ACTH response to CRF (87, 88).

The findings suggest that in patients with PTSD, the HPA is highly sensitized and is characterized by decreased basal cortisol levels, increased number of lymphocyte glucocorticoid levels, and a greater suppression of cortisol to dexamethasone.

Evidence for dysfunction of CRH or HPA systems in Panic disorder has been inconsistent. A preliminary study found normal levels of CSF CRH in Panic disorder patients (89). Blunted ACTH responses to CRH have been reported in some studies (90, 91) but not in others (92, 93). Both normal and elevated rates of cortisol nonsuppression after treatment with dexamethasone have been reported (94). Urinary free cortisol results have been inconsistent (95, 96). Elevated plasma cortisol levels were reported in one study (97) but not another (91). In a recent study of 24-hour secretion of ACTH and cortisol in Panic disorder, only subtle abnormalities were seen. Patients had elevated overnight cortisol secretion and greater amplitude of ultradian secretory episodes. These alterations were modulated by illness severity and treatment seeking (98).

The Neurobiological Consequences of Adverse Early Life Experiences

Recent preclinical studies indicate that early life experiences can have long-term neurobiological consequence on brain NE and CRF systems function and HPA responses. Infant rats exposed to maternal deprivation exhibit alterations in NE, HPA, and CRF systems as adults. Adult male rats previously isolated from their mothers exhibit increases in median eminence and parabrachial nucleus CRH concentrations, increases in basal and stress-induced ACTH concentrations, and reductions in CRH binding sites in the anterior pituitary and dorsal raphe (99).

A recent investigation evaluated the effects of maternal separation on CRH, HPA, and NE systems in adult rats. Rats exposed to maternal separation had decreased numbers of glucocorticoid receptors, as measured by dexamethasone binding in the hippocampus, hypothalamus and frontal cortex, and had increased stressor induced rises in CRH mRNA in the central nucleus of the amygdala, PVN, and BNST. They also had increased NE levels in the PVN as determined by microdialysis. The importance of LC-CRH interactions was supported by increased CRH binding in the LC (Plotsky P, unpublished presentation, 35th Annual Meeting American College of Neuropsychopharmacology, 1996 Dec, San Juan, PR). These findings are consistent with an earlier report that early postnatal adverse experiences alters hypothalamic CRF mRNA, median eminence CRH content, and stress-induced CRH release in male rats (100), and sug-

gest that early adverse experience may permanently alter CRH circuits.

In nonhuman primates, adverse early experiences induced by variable maternal foraging requirements result in profound behavioral disturbances (more timid, less social, and more subordinate) years later (101). Adult monkeys raised in the variable foraging maternal environment also were hyperresponsive to yohimbine and had elevated levels of CSF CRH (102).

Clinical Studies of Early Life Stress Exposure

Childhood physical and sexual abuse is now recognized as a significant public health problem. Clinical studies have shown that exposure to a previous stressor increases the risk of developing PTSD after exposure to a subsequent stressor (103). It has recently been demonstrated that adult survivors of child abuse with PTSD have reduced left hippocampal volume (see below). There are also preliminary observations of impaired HPA and catecholamine function in victims of child abuse (104–106).

Positive early life experiences and responses to stress. It is possible that positive early life experiences during critical periods of development may have long term beneficial consequences on an animal's ability to mount adaptive responses to stress or threat. Postnatal handling provides an animal model that may be of use in studying this phenomenon. Postnatal handling has important effects on the development of behavioral and endocrine responses to stress. For example, postnatal handling, which seems to increase maternal contact, results in decreased hypothalamic CRH mRNA expression and reduced HPA responses to stress (107). Handled rats have increased densities of glucocorticoid receptor binding and glucocorticoid mRNA levels in the hippocampus. This effect increases the sensitivity of the hippocampus to circulatory glucocorticoids, enhancing the efficacy of negative feedback inhibition. The increased glucocorticoid receptor signal at the level of the hippocampus is associated with decreased ACTH and CRF responses to stress.

Handled rats also have higher levels of benzodiazepine receptors on the central nucleus of the amygdala and LC compared with nonhandled rats, which suggests that extrahypothalamic regions play an important role in the ability of handled rats to inhibit anxiogenic NE responses to stress (108).

Considered together, these findings suggest that early in the postnatal period, there is a naturally occurring brain plasticity in key neural systems that may "program" an organism's biological response to threatening stimuli. Clinical studies should be designed to test this possibility.

Stress, neurotoxicity and the hippocampus. Considerable evidence in animals indicates that stress is associated with damage to hippocampal neurons. Most studies have focused on the role that glucocorticoids, which are released during stress, play in hippocampal damage. Monkeys who died spontaneously after exposure to severe stress were found upon autopsy to have multiple gastric ulcers, which suggested exposure to chronic stress, and hyperplastic adrenal cortices, consistent with sustained glucocorticoid release. These monkeys also had damage to the CA3 subfield of the hippocampus (109). Follow-up studies suggested that hippocampal damage was associated with direct exposure of glucorticoids to the hippocampus (110).

Glucocorticoids appear to exert their effect through disruption of cellular metabolism (111) and by increasing the vulnerability of hippocampal neurons to a variety of insults, including endogenously released excitatory amino acids (110, 112). The atrophy produced by 21 days of daily restraint stress suggests that corticosterone secretion and excitatory mechanisms involving NMDA receptors play a major role in driving the atrophy (113). A similar degree of dendritic atrophy of CA3 hippocampal neurons was produced by restraint stress or chronic multiple stress (shaking, restraint, surviving each day). The two stress paradigms differed in the degree of adrenal activation, with multiple stress being a more potent stressor of corticosterone, which suggests that adrenocortical secretion and adrenal responses play a permissive role in enabling another agent (i.e., excitatory amino acids) to produce the final effect (114). Glucocorticoids augment extracellular glutamate accumulation (115). There are ultrastructural changes in the major excitatory input to CA3 pyramidal neurons, the mossy fiber projection from the granule cells in the dentate gyrus, after repeated stress, and it has been suggested that these changes may be associated with enhanced glutamate release (116). Furthermore, reduction of glucocorticoid exposure prevents the hippocampal cell loss associated with chronic stress (117, 118). The hippocampal findings have been associated with deficits in spatial memory (119, 120).

Neurotoxic effects of prenatal administration of dexamethasone has been examined in fetal monkey brain at 135 and 162 days of gestation. In fetal monkey brain there were decreased numbers of pyramidal cells in the hippocampal CA3 regions and granular regions in the dentate gyrus associated with degeneration of neuronal perikarya and dendrites. Axodendritic synaptic terminals of the mossy fibers in CA3 hippocampal region showed pronounced degeneration (121).

Clinical Studies of Hippocampal Structure and Function. Based upon the preclinical studies noted above, imaging studies have been conducted to determine if patients with PTSD have altered hippocampal structure and function. An initial investigation in patients with PTSD related to Vietnam combat found smaller right hippocampal volume as measured with MRI (122). This work has now been replicated in sexually abused women, combat

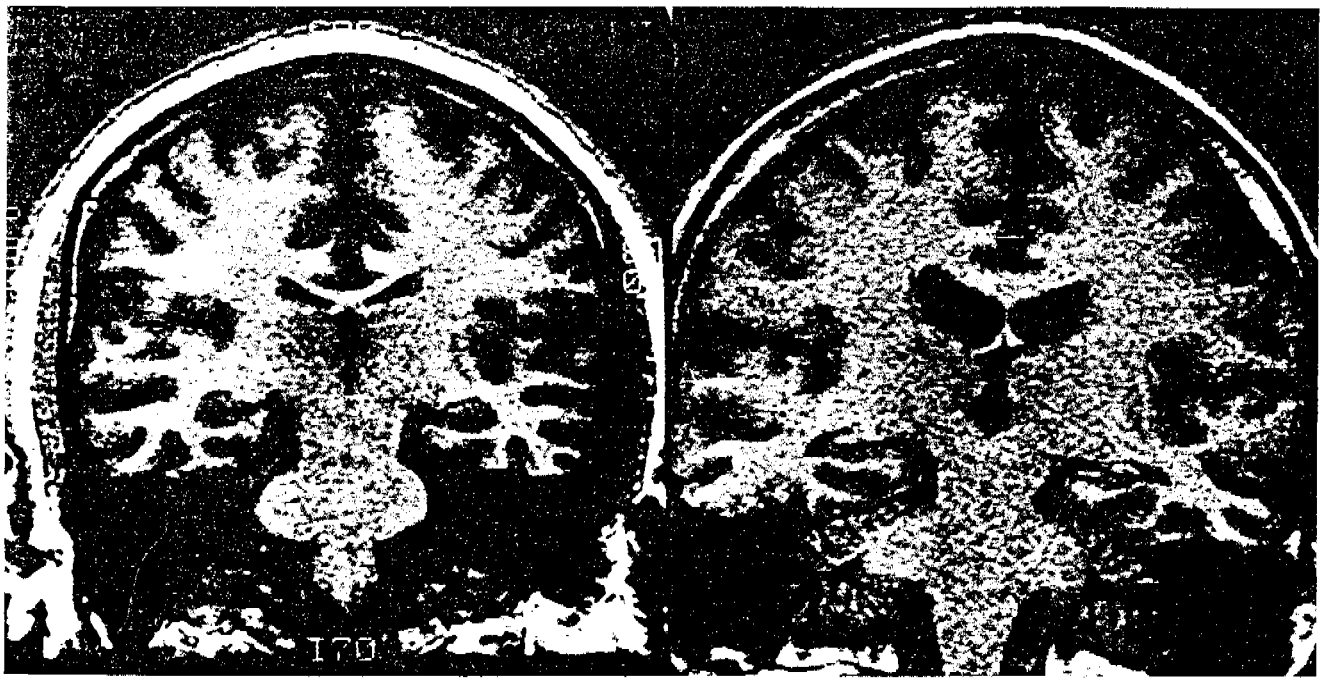

Fig. 1. Magnetic resonance images (MRI) of the hippocampus in a normal subject (a) and a patient with posttraumatic stress disorder (PTSD) (b). The hippocampus is outlined in red in the PTSD patient. Atrophy of the hippocampus is seen in the PTSD patient, but not the normal control.

veterans, and victims of child abuse (123, 124) (Figure 1). Memory disturbances have been identified in patient groups with PTSD, including Korean War prisoners of war (125), Vietnam veterans (126–128), and adult survivors of child abuse (129).

As noted above, several clinical studies indicate that acute stress is associated with a surge in cortisol release. One explanation for observed MRI and memory findings is that acutely elevated cortisol produced by psychological trauma is responsible for hippocampal damage. Alternatively, individuals with genetically determined hippocampal insufficiency may be more vulnerable to psychopathology as a consequence of traumatic stress.

An important question requiring further study is whether the vulnerability of the hippocampus to stress-induced damage is related to the stage of neuronal development or degeneration associated with aging. For example, it is not known if prenatal administration of dexamethasone has neurotoxic effects on the hippocampus in offspring. Further work is needed to understand how stress at different points in the life cycle may affect the structure and function of the hippocampus (Table 1).

Conclusion

The proposed functional neuroanatomy and neural mechanisms related to anxiety and fear provide a basis for understanding the pathophysiology of anxiety disorders. Several levels within the neural circuitry of anxiety and fear may be dysfunctional in anxiety disorders. There may be abnormalities in peripheral sensory receptor systems, the relay of sensory information through the thalamus, the processing of sensory data in cortical and subcortical structures, the attachment of affect based upon prior experience by the amygdala, and the autonomic, neuroendocrine, neurochemical, and neuromotor efferent responses.

Panic disorder, which is characterized initially in most patients by spontaneous panic attacks, may be caused by dysfunction in a variety of brain structures in the stimulus processing or the efferent arm of the circuit. Spontaneous panic attacks may be mediated by subcortical structures, because decorticate animals still have marked anxiety and fear responses (37). For example, abnormal regulation of the locus coeruleus-norepinephrine system, which has been proposed to be involved in the pathophysiology of Panic disorder, may be part of the spontaneous panic attack circuit. Situational panic attacks and agoraphobia are most probably caused by modality-specific and contextual fear conditioning, which are mediated by the associated brain structures and neuromodulators.

Posttraumatic stress disorder is characterized by intrusive traumatic memories manifested by recurring dreams, flashbacks, and psychological distress after exposure to events that symbolize or resemble the original trauma, persistent avoidance of stimuli associated with the trauma or a numbing of general responsiveness, and chronic symptoms of increased arousal. The persistence of intrusive memories may be attributable to the strength of neuronal interactions between cortical regions, where many such memories are stored, and subcortical regions, such as the amygdala, which serve to attach affect to the memories. The psychological distress and physiological re-

Table 1. Neurobiological Consequences of Stress: Clinical Implications.

Stress Effect	Clinical Finding or Implications
1. Stress produces acute and chronic alterations in brain noradrenergic function.	1. A variety of clinical investigations indicate that patients with PTSD and panic disorder have hyper-responsive brain noradrenergic symptoms.
2. Enhanced release of CRH is major component of the stress response.	2. Preliminary studies have shown that PTSD patients have elevated levels of CSF CRH and blunted ACTH responses to CRH. CRH antagonist drugs may represent a new class of anxiolytic medications.
3. Preclinical studies suggest early adverse life experiences produce long term changes in brain noradrenergic and CRH systems.	3. There may be critical periods in development that stressors have particularly potent effects on brain function. Given the prevalence of early childhood trauma, clinical studies are badly needed.
4. Psychological stress is associated with damage to the hippocampus which is mediated, in part, by increased exposure to glucocorticoids.	4. Clinical investigations utilizing magnetic resonance imaging indicate that patients with PTSD have reduced hippocampal volume. Determining whether these observations are reversible and are due to acute or chronic stress requires further study. Exposure to glucocorticoid treatments may endanger the hippocampus.
5. The strength of traumatic memories relates to the degree to which catecholamines and glucocorticoids are activated by the traumatic experience.	5. Therapeutic studies utilizing drugs which reduce noradrenergic or glucocorticoid function may have beneficial effects on the encoding, consolidation, or retrieval or traumatic memories.

CRH, corticotropin-releasing hormone; PTSD, posttraumatic stress disorder.

sponses to trauma reminders involve the mechanisms of fear conditioning and extinction. Contextual fear conditioning involving the hippocampus and the bed nucleus of the stria terminalis may be particularly relevant to severe cases of PTSD in which stimulus generalization is a cardinal feature. The autonomic hyperarousal may be mediated by brain structures within the efferent arm of the anxiety circuit.

Coordinated functional interactions among brain CRF, the HPA axis, and NE neuronal systems may be critical in promoting adaptive responses to stress, anxiety, or fear (Figure 2). These interactions are likely to be relevant to the endocrine and cardiovascular responses to stress and the encoding of traumatic memories. As reviewed above, stressful and fear inducing stimuli acutely increase CRH, HPA, and NE functions. CRH has been shown to increase LC firing resulting in enhanced NE release in LC projection areas throughout the brain. Further, norepinephrine increases CRH in the PVN of the hypothalamus. In acutely stressed animals, medullary NE nuclei may make a larger contribution to this effect of NE on CRH (compared with the LC), whereas after repeated exposure to the same stressors, the role of the LC seems to predominate. In chronically stressed animals, LC innervation may facilitate NE activity in the PVN. One consequence of increased levels of CRH in the PVN is stimulation of ACTH secretion from the pituitary and, consequently, elevation of cortisol release from the adrenal gland. High levels of circulating cortisol through a negative feedback pathway decrease both CRF and NE synthesis at the level of the PVN. Glucocorticoid inhibition of NE-induced CRH stimulation may be evident primarily during stressor-induced cortisol release and not under resting conditions. Glucocorticoids exert feedback inhibition on stress-induced CRH release, in part, at least, by attenuating NE activation of the PVN.

The clinical relevance of these functional interactions remains to be established. However, the PVN has a major role in the regulation of neuroendocrine and cardiovascular responses to stress. NE, cortisol, and CRF seem to be tightly linked in a functional system that may have broad homeostatic purposes. High levels of cortisol probably serve to restrain the stress-induced neuroendocrine and cardiovascular effects mediated by the PVN.

Profoundly different but equally important functionally significant interactions occur to influence the encoding of traumatic memories. Cortisol enhances memory at the level of the hippocampus and amygdala and this effect is blocked by the β-adrenergic receptor antagonist, propranolol. Similarly, NE enhances memory through actions at the hippocampus and the amygdala. The facilitation of memory by NE is attenuated by glucocorticoid antagonism. Thus, increased release of cortisol and NE both serve to enhance memory and are probably key mediators of traumatic remembrance. These findings suggest that combined treatment with propranolol and a glucocorticoid antagonist may impair encoding of traumatic events.

Considered together, the functional interactions among cortisol and the CRF and NE systems represent remarkable adaptive mechanisms. In the PVN, cortisol serves to restrain cardiovascular and hormonal responses to stress. In contrast, at the level of the amygdala and hippocampus, cortisol and NE synergize to facilitate the encoding of

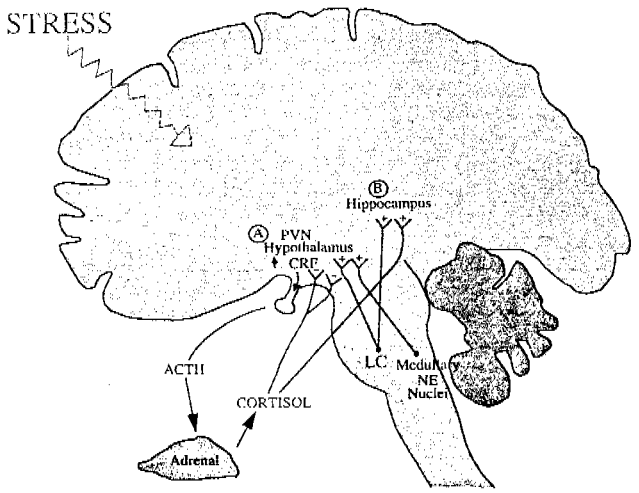

Fig. 2. The functional interactions among cortisol, corticotropin-releasing hormone (CRH), and noradrenergic systems represent remarkable adaptive mechanisms. Stressful and fear inducing stimuli increase CRH, the hypothalamic-pituitary-adrenal (HPA) axis, and noradrenergic (NE) system functions. CRH increases LC firing and norepinephrine (NE) release in projection areas including the paraventricular nucleus (PVN) of the hypothalamus. Norepinephrine increases CRH in the PVN. The CRH stimulates ACTH release from the pituitary, which results in enhanced release of cortisol from the adrenal gland. High levels of cortisol, through negative feedback, decreases both CRF and NE synthesis at the level of PVN, and thereby likely serve to restrain the stress induced neuroendocrine and cardiovascular effects mediated by the PVN (A). In contrast, at the level of the hippocampus, cortisol and norepinephrine act in concert to enhance memory and are probably key mediators of traumatic remembrance (B).

traumatic memories and learning related to the avoidance of dangerous situations.

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