Psychobiologic Mechanisms of Posttraumatic Stress Disorder

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Posttraumatic stress disorder (PTSD) is an illness of considerable prevalence, often characterized by high morbidity, treatment resistance, and a chronic course. The core symptoms of PTSD include persistent reexperiencing of the traumatic event, avoidance of stimuli associated with the trauma, and autonomic hyperarousal. We propose several neurobiologic mechanisms that may account for these primary symptoms of PTSD. Preclinical investigations of the effects of stress on learning and memory processes suggest that fear conditioning, behavioral sensitization, and a failure of extinction may be important in the persistence and reexperiencing of traumatic memories and stressor sensitivity. The pathophysiology of PTSD may involve dysfunction of several brain structures, particularly the amygdala, locus coeruleus, and hippocampus, as well as noradrenergic, dopamine, opiate, and corticotropin-releasing factor neurochemical systems. Acutely, severe psychological trauma results in the parallel activation of these systems, producing an array of adaptive behavioral and physiologic responses necessary for survival. In PTSD, however, these acute responses appear to evolve into maladaptive neurobiologic sequelae. These changes may relate to the chronicity of PTSD symptoms and the poor response to treatment given long after the original trauma. Future clinical investigations of the pathophysiology of PTSD should focus on documenting neurobiologic dysfunctions in these patients with an eye toward developing more effective therapeutic approaches that counteract the acute responses to trauma.

I can't get the memories out of my mind! The images come flooding back in vivid detail, triggered by the most inconsequential things, like a door slamming or the smell of stir-fried pork. Last night I went to bed, was having a good sleep for a change. Then in the early morning a storm-front passed through and there was a bolt of crackling thunder. I awoke instantly, frozen in fear. I am right back in Vietnam, in the middle of the monsoon season at my guard post. I am sure I'll get hit in the next volley and convinced I will die. My hands are freezing, yet sweat pours from my entire body. I feel each hair on the back of my neck standing on end. I can't catch my breath and my heart is pounding. I smell a damp sulfur smell. Suddenly I see what's left of my buddy Troy, his head on a bamboo platter, sent back to our camp by the Viet Cong. Propaganda messages are stuffed between his clenched teeth. The next bolt of lightning and clap of thunder makes me jump so much that I fall to the floor .

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Perhaps there are no more vivid memories than those that are stored in the brains of soldiers who have experienced excruciatingly horrible combat situations. Witness the above account of the 48-year-old Vietnam veteran who cannot hear a clap of thunder, see an Oriental woman, or touch a bamboo placemat without reexperiencing the sight of his decapitated friend. Even though this occurred in a faraway place more than 24 years ago, the memory is still vivid in every detail and continues to produce a state of hyperarousal and fear similar to that experienced that fateful day.

Once called combat fatigue, war neurosis, or shell shock, and now posttraumatic stress disorder (PTSD), it is clear that intense trauma can produce vivid memories that can last a lifetime and an increased sensitivity to many types of stress long after the trauma. Although only recognized as a distinct diagnostic entity in 1980, current data suggest that PTSD is a disorder of considerable prevalence and morbidity.[2,3] Posttraumatic stress disorder may be a consequence of other precipitants besides combat, including sexual or physical trauma, but the resulting clinical picture shares common symptomatic elements and, in many patients, may become chronic.[4-10]

In light of the belated recognition of PTSD as a distinct diagnostic entity, it is not surprising that there has been comparatively little research directed toward understanding the phenomenology, course, and neurobiology of PTSD. Few investigations have been conducted to identify vulnerability factors that predispose individuals exposed to trauma to the subsequent development of PTSD. The course of PTSD has not been well characterized, particularly in relation to type, severity, and duration of trauma exposure. Studies that focus on elucidating the pathophysiologic changes that occur in the brain following severe psychological trauma are only now being initiated.

The dearth of clinical neurobiologic research on PTSD stands in contrast to a number of investigations of the behavioral, biochemical, and neurophysiologic effects of fear and stress in laboratory animals. These studies provide insight into certain neural processes that either contribute to the origin of PSTD or alternatively may be involved in the maintenance of pathologic features.[11]

Herein, we attempt to synthesize the findings of preclinical investigations of learning and memory processes and the neurochemical effects of stress with clinical studies of PTSD to develop a set of hypotheses related to the pathogenesis of PTSD. These data suggest that the primary symptoms of PTSD—the persistent reexperiencing of the traumatic event, avoidance of stimuli associated with the trauma, and the symptoms of increased arousal—are related to the neural mechanisms involved in fear conditioning, experimental extinction, and behavioral sensitization, as well as the altered function of specific brain regions and neurochemical systems (Table 1).

Table 1.—Neural Mechanisms Related to Primary Symptoms of Posttraumatic Stress Disorder (PTSD)*

Mechanism	Description	Neurochemical Systems	Brain Regions	Clinical Relevance
Fear conditioning	Animals exposed to emotionally neutral stimulus (conditioned stimulus [CS] in conjunction with an aversive stimulus (unconditioned stimulus [UCS]) will subsequently exhibit a conditioned fear response (CR) to the CS in the absence of the UCS	NMDA receptors, noradrenergic, opiate	Amygdala, locus coeruleus, thalamus, hippocampus	Fear conditioning may account for the common clinical observation in patients with PTSD that sensory and cognitive stimuli associated with or resembling the original trauma elicit symptoms, including anxiety, flashbacks, and hyperarousal; this results in the frequent reexperiencing of the traumatic event, a persistent avoidance of such stimuli, and a compensatory numbing of general responsiveness
Extinction	There is a reduction in the CR when the CS is presented repeatedly in the absence of the UCS; this may result from learning a new inhibitory memory that opposes the original memory	NMDA receptors	Sensory cortex, amygdala	A failure in extinction in PTSD may relate to the persistence in recalling traumatic memories
Sensitization	Increase in response magnitude following repeated administration of a stimulus or presentation of a different strong stimulus	Dopaminergic, noradrenergic, NMDA receptors	Nucleus accumbens, striatum, hypothalamus, amygdala	Sensitization may explain the increased responsiveness of patients with PTSD to stress both related and unrelated to the original trauma; dopaminergic and noradrenergic dysfunction may account for persistent symptoms of increased arousal and the potentiated responses to cocaine; alcohol, opiates, and benzodiazepines may be used to reduce symptoms associated with fear conditioning and sensitization

*NMDA indicates *N*-methyl-D-aspartate.

NEURAL MECHANISMS OF LEARNING AND MEMORY: RELEVANCE TO THE REEXPERIENCING SYMPTOMS OF PTSD

Fear Conditioning and Associative Memories

In patients with PTSD, vivid memories of the traumatic event, autonomic arousal, and even flashbacks can be elicited by diverse sensory and cognitive stimuli that have been associated with the original trauma.[12,13] Consequently, patients begin to avoid these stimuli in their everyday life, or a numbing of general emotional responsiveness occurs. Classic conditioning phenomena, which are easily demonstrated in the laboratory, may explain some of these observations. Animals exposed to an emotionally neutral visual or auditory conditioned stimuli in conjunction with an aversive unconditioned stimulus will subsequently exhibit a conditioned emotional (fear) reaction to the conditioned stimuli in the absence of the unconditioned stimulus. These changes can last for years in laboratory animals[14] and are used to infer that a state of fear has been produced.[15] Hence, neural analysis of fear conditioning in animals can be used to examine the brain mechanisms involved in learning and remembering associations of stimuli with traumatic events.

Several different paradigms have been employed to study the neuroanatomic and neurochemical substrates of fear conditioning. These investigations have demonstrated that fear conditioning to visual and auditory stimuli can be mediated by subcortical mechanisms, involving sensory pathways that project to the thalamus and amygdala.[16] It has been suggested that emotional memories established via thalamoamygdala pathways may be relatively indelible.[17]

The fear-potentiated startle paradigm has been particularly useful for delineation of the mechanisms of fear conditioning because fear is measured by a change in a simple reflex mediated by a defined neural pathway in the brain stem and spinal cord. This test is sensitive to anxiolytic drugs and is disrupted by anatomic lesions known to affect conditioned fear.[18] It also may be relevant to PTSD given that many patients with PTSD exhibit increased startle responses,[19] an abnormality generally not reported in other psychiatric disorders. The central nucleus of the amygdala plays a critical role in the fear-potentiated startle response because it projects directly to one of the brain-stem nuclei necessary for startle,[20] and lesions of this pathway block the ability of conditioned or unconditioned fear stimuli to elevate the startle response.[21,22]

The neurochemical systems involved in the regulation of the fear-potentiated startle response include the noradrenergic, dopaminergic, opiate, and corticotropin-releasing systems.[18] In addition, *N*-methyl-D-aspartate (NMDA) antagonists infused into the amygdala prevent the acquisition of fear-potentiated startle.[23] These data indicate that an NMDA receptor-mediated process at the level of the amygdala may be critical for development of fear conditioning. In fact, recent studies have demonstrated that long-term potentiation, an activity-dependent enhancement of synaptic transmission,[24,25] can be produced in the amygdala measured in brain sections[26] or in vivo following stimulation of the medial geniculate body.[27] Previous work has shown that projections from the medial geniculate body to the amygdala may mediate the formation of memories established by pairing an acoustic stimulus with a footshock.[16] These findings raise the possibility that long-term potentiation in the amygdala may be related to the encoding of the traumatic memories so vividly associated with PTSD.[17]

Other behavioral paradigms indicate that noradrenergic neuronal systems can be activated by neutral environmental stimuli previously paired with shock. Neutral stimuli paired with shock produce increases in brain norepinephrine (NE) metabolism and

behavioral deficits similar to that elicited by the shock.[28,29] In the freely moving cat, the firing rate of cells in the locus coeruleus (LC) can be increased by presenting a neutral acoustic stimulus previously paired with an air puff to the whiskers, which also increases firing and is aversive to the cat.[30] There is also a body of evidence indicating that an intact noradrenergic system may be necessary for the acquisition of fear-conditioned responses.[31,32]

A Possible Failure of Extinction in PTSD

It is possible that the continued ability of conditioned stimuli to elicit traumatic memories and flashbacks in PTSD results from a deficit in the neural mechanisms involved in response reduction or extinction. Experimental extinction is defined as a loss of a previously learned conditioned emotional response following repeated presentations of a conditioned fear stimulus in the absence of a contiguous traumatic event. The form of learning that occurs during extinction is still unclear. Although several different theoretical mechanisms have been proposed, two general classes of theory have emerged.[33] Extinction has been explained in terms of either an "erasure" of the original associations that led to the production of the conditioned response[34] or the acquisition of new associations that compete with or "mask" the expression of the still intact, response-producing associations.[35] Both of these hypothesize that new learning occurs as a result of nonreinforcement but make very different predictions regarding the fate of the conditioned response-producing associations. The erasure hypothesis predicts that following nonreinforcement, the response-producing associations no longer exist, and, therefore, the conditioned response can no longer be performed. The masking hypothesis predicts that the response-producing associations remain after nonreinforcement, and, therefore, if it were possible to temporarily remove the masking associations, the conditioned response could be performed.

Several lines of evidence suggest that the original associations are intact following extinction. For example, Bouton and colleagues[36-38] have shown that the expression of extinction is specific to the stimulus context in which nonreinforcement occurred. Placing the animal into a context different from the one in which nonreinforcement occurred results in a return of the conditioned response. In addition, several experiments have shown that the representation of the unconditioned stimulus following extinction is sufficient for reinstating extinguished responding to some preextinction level.[39-41] In rats, even 1 year after extinction has occurred (ie, more than a third of the lifetime of the animal), the aversive memory can be restored to its original magnitude by a single training trial.[42] This indicates the essentially permanent nature of conditioned fear and the apparent fragility of extinction. This phenomenon may help to explain the common clinical observation that traumatic memories may remain dormant for many years, only to be elicited by a subsequent stressor or unexpectedly by a stimulus long ago associated with the original trauma.[43,44]

These studies indicate that extinction does not erase the original aversive memory but instead involves the learning of a new memory that masks or inhibits the original one. It is important to emphasize, however, that although extinction can be overcome, in healthy animals extinction does result in a reduction of the conditioned fear response. Using traditional measures of conditioned fear, such as freezing, potentiated startle, or autonomic indexes, nonreinforcement leads to a reduction in all of these measures. In healthy humans, many childhood fears become extinguished and do not intrude daily in adulthood. In contrast, patients with PTSD describe persistent traumatic memories that do not extinguish. Thus, it is conceivable that patients with PTSD have deficits in brain systems involved in extinction.

The amygdala is not only involved in the acquisition and expression of conditioned fear responses but may also be necessary for extinction. The NMDA antagonists infused into the amygdala prevent the extinction of fear-potentiated startle.[45] Thus, activity in the amygdala during nonreinforced stimuli presentations may be essential for extinction of conditioned fear stimuli. This may result from processes within the amygdala itself or via structures that project to the amygdala (eg, hippocampus, prefrontal cortex, or septal area) and have been implicated in extinction in several experimental paradigms. Extinction of conditioned fear responses may represent an active suppression by the cortex of subcortical neural circuits (thalamus or amygdala) that maintain learned associations over long time periods.[16,46]

Neural Mechanisms of Behavioral Sensitization and Stress Sensitivity in PTSD

Many patients with PTSD experience chronic symptoms of increased arousal, including insomnia, poor concentration, hypervigilance, exaggerated startle response, and autonomic hyperreactivity. Patients with PTSD demonstrate an increased susceptibility to psychosocial stress in general.[47,48] Several features of behavioral sensitization suggest that this process may account for the persistent symptoms of increased arousal and stress sensitivity in PTSD.

Sensitization generally refers to the increase in response magnitude that occurs following exposure to a stimulus. The response being measured may be neurophysiologic (eg, spike magnitude), behavioral (locomotor activity), or pharmacologic (extracellular dopamine [DA] concentrations). The stimulus may be environmental (eg, footshock) or pharmacologic (eg, amphetamine administration). Moreover, cross-sensitization (augmented response to a different stimulus than the original evoking stimulus) may occur. Although sensitization is frequently considered as an enhancement of response magnitude following repeated presentation of stimuli, a critical variable also involves the time interval between the initial stimulus and subsequent measurements. Thus, a single stimulus can elicit behavioral sensitization, provided that sufficient time has elapsed between the initial presentation and subsequent reexposure.[49]

Posttraumatic stress disorder may occur in response to a single precipitating trauma or alternatively after repeated traumatic events. The symptoms of PTSD persist long after the initial traumatic event(s); sensitization also appears to be an enduring phenomenon. Finally, the stimuli that evoke intrusive memories, flashbacks, and related symptoms in patients with PTSD are often difficult to determine and may bear only a distant association to the initial evoking stimulus. Such cross-sensitization to different stimuli has been extensively documented and suggests a common target structure or system through which the stimuli are processed.

It should be noted, however, that cross-sensitization to different stimuli is not always present. Moreover, the development of a sensitized response to a particular challenge (eg, footshock) following long-term exposure to a different stimulus, such as cocaine administration, may not be present in reverse order, ie, cross-sensitization may not occur if the challenge is cocaine and the chronic stressor is footshock.[50] The observation that there are limitations to the stimuli to which cross-sensitization can occur is similar to that observed in PTSD. Certain environmental stimuli are particularly salient and evoke flashbacks in patients with PTSD, whereas others do not.

A large number of brain structures and neurochemical systems have been implicated in the behavioral sensitization that occurs in response to repeated stress or a single stressor of sufficient magnitude. This is perhaps not surprising given that sensitization can be demonstrated in individual cells. However, the mechanisms of the development and expression of stress-induced sensitization in mammals have been most extensively studied in catecholaminergic systems, particularly in the mesotelencephalic dopaminergic systems.

Single or repeated exposure to a stressor potentiates the capacity of a subsequent stressor to increase DA function in the forebrain[51,52] without apparently altering basal DA turnover.[53] The mechanisms involved in the development and expression of DA-mediated behavioral sensitization appear to be different. The initiation of DA-mediated sensitization is thought to involve the stimulation of D_1 DA receptors in response to increased somato-

Table 2.—Neurochemical Responses to Severe Stress Related to Primary Symptoms of Posttraumatic Stress Disorder (PTSD)

Neurochemical System	Functional Alteration	Brain Regions Involved	PTSD Symptoms
Noradrenergic	Increased regional norepinephrine turnover, increased responsiveness of locus coeruleus neurons	Locus coeruleus, hippocampus, amygdala, hypothalamus, cerebral cortex	Anxiety, fear, hypervigilance, autonomic hyperarousal, "fight or flight" readiness, encoding of traumatic memories, facilitation of sensorimotor responses
Dopamine	Increased dopamine release in frontal cortex and nucleus accumbens, activation of mesocortical dopamine neurons	Prefrontal cortex, nucleus accumbens	
Opiate	Increased endogenous opiate release, decreased density of μ opiate receptors	Periaqeductal gray cerebral cortex, amygdala	Analgesia, emotional blunting, encoding of traumatic memories
Hypothalamic-pituitary-adrenal	Acutely elevated glucorticoid levels, elevated corticotropin-releasing factor	Hippocampus, locus coeruleus, amygdala	Metabolic activation, learned behavior responses, anxiety and fear responses

dendritic release of DA in the midbrain. The increased release of DA from the dendrites of DA neurons may be due to an alteration in γ-aminobutyric acid (GABA) regulation of the DA neurons.[54] The sensitization of D_1 DA receptors may be an NMDA receptor-dependent process.[55] The relevant cellular and transsynaptic effects of D_1 receptor stimulation remain to be clarified.

The expression of behavioral sensitization requires that a sufficient period of time elapse (on the order of several days) for key intercellular and intracellular responses to be mounted that ultimately result in augmented DA function. This may be analogous to the situation in patients with PTSD, in whom a certain interval is interposed between the initial traumatic event and the subsequent appearance of core PTSD symptoms. The increase in effective DA function appears largely attributable to increased release of the amine, although some degree of enhanced receptor sensitivity in the forebrain terminal fields may be present. The augmentation of DA release may occur in response to changes in key afferents to the DA neurons or through reduced autoinhibitory tone.[53]

Behavioral sensitization to stress may also involve alterations in noradrenergic function. Limited shock exposure that does not increase NE utilization in control rats does increase NE release in animals previously exposed to the stressor.[56] Moreover, changes in noradrenergic function in animals subjected to long-term shock require lower shock currents (decreased stressor intensity) than required under acute conditions.[57] An in vivo study observed augmented extracellular NE concentrations in the hippocampus, whereas ex vivo measurements of noradrenergic metabolites in response to chronic stress indicated a sensitized response in the hypothalamus but not hippocampus.[58] It is not clear to what degree this reflects differences in metabolic disposition of NE in the two regions, as opposed to actual differences in sensitization processes. Nonetheless, regional specificity in biochemical indexes of the expression of sensitization may be important. A recent in vivo dialysis investigation demonstrated stress-induced sensitization of NE release in the medial prefrontal cortex.[59]

Neurochemical Effects of Stress and the Primary Symptoms of PTSD

Stress produces profound alterations in multiple neurotransmitter systems. A comprehensive review of these effects is beyond the scope of this review. In the following section, we evaluate the effects of stress on the neurotransmitters and neuropeptides that have been the most extensively studied and appear related to the neural mechanisms of fear conditioning and sensitization. Examination of the preclinical data concerning the neurochemical substrates of the stress response provide a context to consider clinical investigations of PTSD (Table 2).

Noradrenergic System

Stressful stimuli of many types produce marked increases in brain noradrenergic function. Stress produces regional selective increases in NE turnover in the LC, limbic regions (hypothalamus, hippocampus, and amygdala), and cerebral cortex. It has recently been demonstrated that immobilization stress, footshock stress, tail pinch stress, and conditioned fear increase noradrenergic metabolism in the hypothalamus and amygdala.[29,60,61]

The responsiveness of the noradrenergic system to stress is consistent with the notion that the elevated sense of fear or anxiety associated with stress may be a critical factor.[29,60-67] Neurons in the LC are activated in association with fear and anxiety states,[68,69] and the limbic and cortical regions innervated by the LC are those thought to be involved in the elaboration of adaptive responses to stress.[70] A particularly dramatic example was the recent 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.[71]

A series of investigations have shown that certain stressors elicit increased responsiveness of LC neurons to excitatory stimulation.[72,73] These changes have been associated with α_2-adrenergic autoreceptor subsensitivity, similar to that observed by α_2-receptor blockade. In fact, antagonism of α_2-receptors with idazoxan hydrochloride or yohimbine increases the response of LC neurons to excitatory stimuli without altering their baseline firing rate. Chronic blockade of opiate, 5-hydroxytryptamine, and GABA receptors does not appear to influence LC responsiveness.[72,73] Consistent with these findings, acute cold restraint stress results in decreased density of α_2-receptors in the hippocampus and amygdala.[74] The stress-induced increase in NE turnover is also associated with a decrease in postsynaptic beta receptor density.[65,75,76]

Clinical Implications

The findings that stress increases noradrenergic function and that fear conditioning and behavioral sensitization are related to alterations in noradrenergic activity may have important implications for understanding the pathophysiology and course of PTSD (Tables 1 and 2). In particular, many of the chronic symptoms experienced by patients with PTSD, such as panic attacks,

insomnia, startle, and autonomic hyperarousal, are characteristic of increased noradrenergic function.[77-79]

Stress-induced increases in noradrenergic function may be related to frequent 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.[80] Opiates, such as morphine, decrease stress-induced increases in NE release in the amygdala, hippocampus, hypothalamus, thalamus, and midbrain.[81] Benzodiazepine drugs, including diazepam, attenuate stress-induced increases in NE release in the hypothalamus, hippocampus, cerebral cortex, and the LC region.[61]

Pathophysiologic Studies

Most of the early clinical investigations of the pathophysiology of PTSD identified a relationship between severe stress exposure, increased peripheral sympathetic nervous system activity, and conditioned physiologic and emotional responses.[82-84] Since the early 1980s, a series of well-designed psychophysiologic studies have been conducted that have further documented heightened autonomic or sympathetic nervous system arousal in combat veterans with chronic PTSD. Combat veterans with PTSD have been shown to have higher resting mean heart rate and systolic blood pressure, as well as greater increases in heart rate, when exposed to visual and auditory combat-related stimuli compared with combat veterans without PTSD,[85] patients with generalized anxiety disorder,[85] or healthy subjects.[85-90] Furthermore, several psychophysiologic studies have found hyperreactive responses to combat-associated stimuli but not to other stressful non–combat-related stimuli.[91] Because central noradrenergic (LC) and peripheral sympathetic systems may function in concert,[92] these data are consistent with the hypothesis that noradrenergic hyperreactivity in patients with PTSD may be associated with the conditioned or sensitized responses to specific traumatic stimuli. Studies evaluating the efficacy of psychotherapeutic techniques emphasizing desensitization to reduce hyperarousal responses to stimuli associated with the psychological trauma represent a current focus of investigation.[93,94]

Neuroendocrine studies and investigations of peripheral catecholamine receptor systems have also provided evidence of dysregulated peripheral sympathetic nervous system activity in PTSD.[95] Two of three studies have found significantly elevated 24-hour urine NE excretion in combat veterans with PTSD compared with healthy subjects or patients with schizophrenia or major depression.[96,97] Consistent with this observation, it has been reported that the density of platelet α_2-adrenergic receptors is reduced in PTSD, perhaps reflecting adaptive "downregulation" in response to long-standing elevated levels of circulating endogenous catecholamines.[98]

Noradrenergic function has also been probed by determining the behavioral, biochemical, and cardiovascular responses to the α_2-adrenergic receptor antagonist yohimbine.[77,78] As predicted from the preclinical studies reviewed above, combat veterans with PTSD have exhibited enhanced behavioral, biochemical, and cardiovascular responses to yohimbine. The yohimbine-induced increase in plasma 3-methoxy-4-hydroxyphenolglycol was more than twice as great in patients with PTSD as in healthy subjects. Approximately 60% and 40% of the patients experienced yohimbine-induced panic attacks and flashbacks, respectively, that could not be accounted for by comorbid panic disorder.[99] The incidence of yohimbine-induced panic attacks in patients with PTSD approximates that observed in patients with panic disorder.[78,100] In contrast, yohimbine rarely induces panic attacks in healthy subjects or in patients with schizophrenia, major depression, generalized anxiety disorder, or obsessive-compulsive disorder.[101] These findings suggest that PTSD and panic disorder may have similar pathophysiologic dysfunctions in the regulation of noradrenergic function. However, the causes of the two syndromes may differ, with panic disorder more associated with genetic factors and PTSD with severe environmental trauma. The treatment implications of these observations remain to be established but suggest that specific PTSD symptoms (eg, anxiety, panic attacks, flashbacks, and autonomic hyperarousal) may be particularly responsive to drugs that reduce noradrenergic function, such as clonidine hydrochloride.[102-104] It should be noted, however, that patients with panic disorder and those with PTSD have different therapeutic responses to tricyclic compounds. Patients with panic disorder derive great benefit from these drugs, whereas those with PTSD have more modest responses.[105]

DOPAMINERGIC SYSTEM

Acute stress increases DA release and metabolism in a number of specific brain areas.[106-119] However, the DA innervation of the medial prefrontal cortex appears to be particularly vulnerable to stress; sufficiently low-intensity stress (such as that associated with conditioned fear) or sufficiently brief exposure to stress increases DA release and metabolism in the prefrontal cortex in the absence of overt changes in other mesotelencephalic DA regions.[116,118] Stress can enhance DA release and metabolism in other areas receiving DA innervation, provided that greater intensity or longer-duration stress is used.[112,116] Thus, the mesoprefrontal cortical DA innervation is preferentially activated by stress compared with mesolimbic and nigrostriatal systems,[117,119] and the mesolimbic DA innervation appears to be more sensitive to stress than the striatal DA innervation.[116,117,119] The responsiveness of the mesoprefrontal DA system is heterogeneous within the region,[120] reflecting the presence of multiple cortical innervations embedded in this region.[121]

The sensitivity of the mesoprefrontal cortical DA systems to stress appear to be attributable to stress increasing the firing rate of midbrain DA neurons that project to the prefrontal cortex.[112,116,117,122] The enhanced DA responsiveness of subcortical DA systems may reflect in large part changes in release of the amine occurring via presynaptic regulation.[115,116,122]

The stress-induced increases in mesoprefrontal cortical DA neurons appear to be regulated by a number of chemically distinct afferent systems.[116] For example, NMDA and opiate receptor blockade in the ventral tegmental area, the source of the cortical DA innervation, prevent stress-induced activation of the cortical DA system.[123-125] Similarly, immunoneutralization of substance P in the ventral tegmental area prevents the cortical DA response to stress.[126] In addition, stimulation of $GABA_B$ and benzodiazepine receptors in the ventral tegmental area attenuate the stress-elicited activation of DA neurotransmission.[116]

The forebrain DA innervations show an augmented response to repeated stress as well as repeated administration of psychostimulants, such as cocaine and amphetamines. Previous exposure to stress increases the subsequent locomotor response, subserved by DA systems of the nucleus accumbens, to cocaine challenge.[52,127-129] Thus, stress and psychostimulants can, under certain conditions, cross-sensitize.

Clinical Implications

Stress-induced hyperactivity of central DA systems may be linked to specific PTSD symptoms, including generalized anxiety, panic attacks, hypervigilance, and exaggerated startle.[49] The relationship between DA hyperactivity and hypervigilance is supported by the observations that amphetamines and cocaine commonly produce hypervigilance and paranoid behavior.[130] Because chronic stress and cocaine or amphetamine administration have similar effects on DA function, patients with PTSD may have potentiated behavioral response to these drugs and may be more vulnerable to the development of paranoia or psychosis after administration of these agents (Table 1).

The DA innervations of different forebrain sites have been associated with different functions. The prefrontal cortical DA systems appear to be involved in a number of higher-level functions, including attention and "working memory."[131] The stress-induced activation of the prefrontal cortical DA system has been proposed to be involved in the acquisition (but not execution) of

coping responses elaborated in response to stress.[116,132,133] In particular, the prefrontal cortical DA system may be involved in vigilance associated with an individual's initial response to stress and may regulate the activity of corticifugal neurons projecting to a number of sites (eg, the amygdala, entorhinal cortex, or LC) that may be directly involved in the execution of appropriate coping responses.

If excessive responsiveness of dopaminergic systems contributes to the symptoms of PTSD, then drugs that reduce DA function would be expected to alleviate certain symptoms, especially hypervigilance and paranoia. However, prospective studies have not been performed to test this possibility. The only published data, to our knowledge, is a retrospective report of eight patients with chronic PTSD treated with neuroleptics; three (37.5%) of these patients had a moderate to good response to neuroleptic therapy. Neuroleptics are occasionally prescribed for patients with PTSD with psychotic symptoms or severe impulsivity.[134,135]

Endogenous Opiate System

One of the primary behavioral effects of uncontrollable stress is analgesia, which results from the release of endogenous opiates.[136] Substantial analgesia is observed following uncontrollable but not controllable stress[136-139] and also is seen following presentation of neutral stimuli previously paired with aversive stimuli.[140] There is also evidence that sensitization occurs because reexposure to less intense shock in rats previously exposed to uncontrollable shock also results in analgesia.[141]

These effects are likely to be mediated, in part, by a stress-induced release of endogenous opiates in the brain stem because the analgesia is blocked by naltrexone hydrochloride[136,138,141] and shows cross-tolerance to morphine analgesia.[138] Moreover, opiate peptide levels are elevated after acute uncontrollable shock,[142,143] and uncontrollable, but not controllable, shock decreases the density of mu opiate receptors.[144]

Clinical Implications

In nontraumatized human populations, naloxone has been shown to reverse the stress-induced analgesia observed after noxious footshock.[145] Similarly, in Vietnam veterans with PTSD, naloxone has been reported to reverse the analgesia induced by stressful combat films.[146] These findings are consistent with the development of opioid-mediated stress-induced analgesia in PTSD and with the report that wounded combatants during World War II required lower doses of narcotics than civilians with less severe injuries.[147]

It is unknown whether the effects of uncontrollable stress on endogenous opiates are related to the core clinical symptoms associated with PTSD. However, it has been hypothesized that in PTSD traumatic reexposure causes an increase in endogenous opiate levels that might explain compulsive reexposure to traumatic events or "addiction" to trauma.[11] This hypothesis has not been supported by psychophysiologic laboratory studies in which combat films fail to evoke euphoric feelings or emotional responses of calm and control. Instead, the films evoke a numbing or relative blunting of emotional responses. Clinical trials of the opiate antagonist naltrexone may help clarify the involvement of endogenous opiates in PTSD.

A role for endogenous opiates in PTSD is consistent with the clinical observations that opiates are a preferred substance of abuse among many traumatized veterans. The use of opiates by traumatized veterans may represent an attempt to self-medicate or to compensate for dysregulation of the noradrenergic and/or endogenous opiate systems. Opiate withdrawal, on the other hand, is associated with an increase in central noradrenergic activity as well as an increase in PTSD symptoms.[148]

HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS

Unequivocal evidence shows that acute stress of many types produces increases in corticotropin (ACTH) and corticosterone levels in laboratory animals.[149] The mechanism responsible for transient stress-induced hyperadrenocorticism and feedback resistance may involve a downregulation of glucocorticoid receptors.[150-152] High glucocorticoid levels (such as those elicited by acute stress) decrease the number of hippocampal glucocorticoid receptors, resulting in increased corticortrosterone secretion and feedback resistance. Following stress termination, when glucocorticoid levels decrease, receptor numbers are increased and feedback sensitivity normalizes.[152-154]

The effects of chronic stress on ACTH and corticosterone secretion vary depending on the experimental paradigm.[155] It has been reported that an adaptation to chronic stress may occur, resulting in decreased plasma ACTH and corticosterone levels compared with levels following a single stressor.[155-158] However, other investigations have revealed enhanced corticosterone secretion after chronic stressor regimens.[159-165] There is also evidence that the experience of prior stress may result in augmented corticosterone responses to a subsequent stress exposure.[166,167] It is not known which factors determine whether adaptation or sensitization of glucocorticoid activity will occur following chronic stress.[168]

Some of the behavioral deficits produced by stress may be related to effects on HPA axis function. Adrenalectomy has been demonstrated to increase the frequency of behavioral deficits induced by uncontrollable stress; this effect is reversed by corticosterone administration.[169] Data from our study and others suggest that stress-induced corticosterone release may be involved in the central processing of stress-related phenomena and the subsequent learned behavioral responses.

However, there is also evidence that the learning deficits produced by uncontrollable stress may be related to neurotoxic effects of very elevated glucocorticoid levels on hippocampal neurons. The most convincing support for this assertion comes from two recent investigations in vervet monkeys. In one study, vervet monkeys who died spontaneously after experiencing sustained social stress had marked and preferential hippocampal neuronal degeneration.[170] In a subsequent investigation, glucocorticoid administration in vervet monkeys produced similar damage in terms of cell numbers and morphologic features in the hippocampus.[171]

Corticotropin-Releasing Factor (CRF)

Considerable data now indicate that CRF, the hypothalamic hypophysiotropic hormone that activates the pituitary-adrenal axis, is also a neurotransmitter in extrahypothalamic brain sites.[172] In laboratory animals, CRF has anxiogenic-like properties when injected centrally.[173] Furthermore, CRF appears to play an important role in the neuroendocrine, autonomic, and behavioral responses to stress.[174,175] Severe stressors produce increases in CRF concentrations in the amygdala, hippocampus, and LC.[176]

The brain sites mediating the CRF responses to stress have not been established. However, there is accumulating data that these effects of CRF may be produced by interactions with LC noradrenergic neurons; intracerebral ventricular infusion of CRF increases NE turnover in several forebrain areas,[177] CRF in a dose-dependent fashion increases the firing rate of LC-NE neurons,[178] and a stressor that activates NE neurons markedly increases CRF concentrations in the LC.[176] Moreover, it has recently been demonstrated that infusion of CRF into the LC has anxiogenic activity and produces marked increases in levels of the NE metabolite 3,4-dihydroxy phenylglycol in forebrain areas, such as the amygdala and hypothalamus.[179] Bilateral lesions of the amygdala selectively decrease CRF concentrations in the LC.[180] The anxiolytic benzodiazepine alprazolam selectively decreases CRF concentrations in the LC.[181] These data suggest that under stressful conditions, CRF and NE regions, like the LC, may participate in a mutually reinforcing feedback loop.

Also, CRF may have important effects on DA neuronal function. Intraventricular administration of the peptide increases DA metabolism in the prefrontal cortex in a manner similar to stress.[182] It is unclear, however, whether the mechanism through which the prefrontal cortex DA system is activated is the same as that subserving the stress-induced effect.[183]

Neurosteroids

A group of steroid metabolites that are formed in the brain have recently been demonstrated to potentiate GABA-elicited chloride flux.[184-186] Although the precise nature of steroid binding to the $GABA_A$ receptor complex remains unclear, the neurosteroids are thought to recognize a site on the GABA-benzodiazepine/chloride ionophore complex that is distinct from both the benzodiazepine and barbiturate binding sites.[187,188] Although neurosteroids do not bind to the benzodiazepine site, their ability to enhance GABA-elicited chloride ion flux suggests that these compounds may have anxiolytic actions. Consistent with this suggestion is the observation that both brain and plasma concentrations of the neurosteroid metabolites of progesterone and deoxycorticosterone (3a-hydroxy-5a-pregnane-20-one [allopregnanolone] and 3a,21-dihydroxy-5a-pregnane-20-one [alloTHDOC], respectively) increase after exposure to swim stress.[189] In addition, systemic administration of alloTHDOC has been shown to result in anxiolytic effects at doses lower than those required to induce sedation.[190] Recently, intraventricular administration of alloTHDOC has been shown to antagonize the stress-induced increase in prefrontal cortical DA metabolism at doses that do not result in sedation.[191]

Clinical Implications

There is abundant clinical evidence that acute trauma can produce profound increases in glucocorticoid levels.[192] However, it is not known whether the magnitude of these increases is sufficient to produce hippocampal neuronal cell loss, as demonstrated in the nonhuman primate studies. Magnetic resonance imaging studies capable of measuring hippocampal volume in patients with PTSD may be a useful method to evaluate this possibility.

There are comparatively few data on HPA axis function in patients with chronic PTSD. One research group,[193,194] but not another,[195] has found reduced urinary free cortisol levels in patients with PTSD compared with healthy subjects and patients with other psychiatric disorders. Consistent with a decrease in urinary free cortisol concentrations is the finding that lymphocyte glucocorticoid receptors may be increased in PTSD.[196]

Several investigations have been conducted to evaluate HPA system regulatory mechanisms in PTSD. In a small sample of patients, the ACTH response to CRF was reported to be blunted in the presence of normal plasma cortisol levels.[197] Furthermore, preliminary evidence shows that some patients with PTSD may be overly sensitive to the ability of dexamethasone to suppress cortisol.[198] Considered together, these results suggest that certain central inhibitory mechanisms suppressing CRF and ACTH function may be increased in chronic PTSD, resulting in decreased basal cortisol level. This is consistent with preclinical investigations demonstrating adaptive HPA responses to chronic stress.

Despite the above findings, there is also evidence that substantial cortisol level increases can be elicited from patients with PTSD in response to intense emotional stimuli and pharmacologic agents.[99,192] It is possible that patients with PTSD may show exaggerated responses to novel stressors. Thus, more investigation is needed to elucidate HPA axis function in acute and chronic PTSD in relation to alterations in basal activity and regulatory mechanisms following a variety of behavioral and pharmacologic challenges.

As noted above, neurosteroids may serve as endogenous anxiolytic agents. Although there are no data concerning alterations in plasma or cerebrospinal fluid levels of either alloTHDOC or allopregnanalone in patients with PTSD, it is possible that the generation of neurosteroids may be altered in PTSD. Future studies should be devoted to the assessment of this possibility.

CONCLUDING COMMENTS

Preclinical investigations indicate that the neural mechanisms of fear conditioning, extinction, and sensitization may be operative in PTSD. Moreover, strong evidence suggests that noradrenergic, dopaminergic, opiate, and HPA neuronal systems and the LC, amygdala, hypothalamus, hippocampus, and prefrontal cortex are involved in these processes and are important mediators of the stress response.

The acute behavioral responses produced by the parallel activation of these brain structures and neurochemical systems by psychological and physical trauma represent adaptive responses critical for survival in a dangerous environment. For example, autonomic hyperarousal and hypervigilence facilitate appropriate rapid behavioral reactions to threat. The analgesia and blunted emotional responses following trauma produced by increased release of endogenous opioids may increase the chances of survival after serious injury. The trauma-induced increases in cortisol level may promote the metabolic activation necessary for sustained physical demands required to avoid further injury.

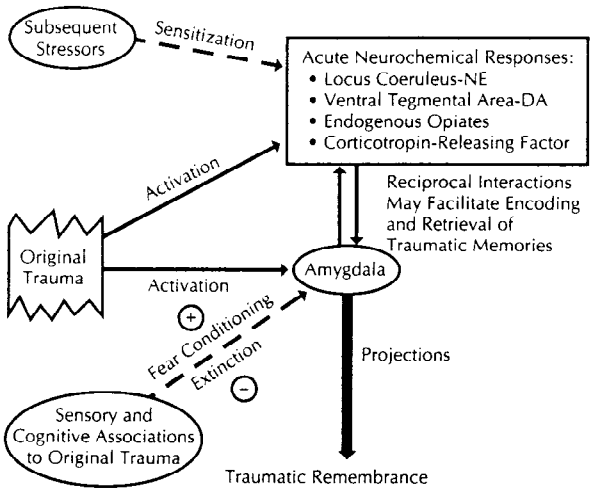
Although initially of benefit, there are long-term negative consequences of the acute neurobiologic responses to stress that may lead to persistent changes in synaptic transmission in limbic and cortical brain sites. A change in excitability of amygdaloid neurons produced by sensitization or fear conditioning would produce changes in a variety of hypothalamic and brain-stem targets that are involved in the somatic and autonomic signs of fear and anxiety.[21] A reduced activation threshold of the LC would result in increased NE release at LC projection sites, including the amygdala, hippocampus, and the cerebral cortex.[61,68,199-201] Similarly, the function of certain distinct mesocortical DA neurons is elevated by fear conditioning and sensitization. Each of these changes in neuronal activity could account for the chronic anxiety symptoms and potentiated stressor sensitivity in patients with PTSD.[47,48]

Emerging evidence suggests learning and memory difficulties in traumatized patients.[202-207] Stress-induced impairment in long-term potentiation, mediated in part by excitatory amino acid, noradrenergic, and opioid receptor systems, may be responsible for the development of learning deficits postulated or observed in PTSD. Because extinction appears to involve an active learning process, deficits in learning may impair normal extinction in patients with PTSD, leading to the abnormal persistence of emotional memories.

TRAUMATIC REMEMBRANCE AND THE AMYGDALA

Perhaps the most characteristic feature of PTSD is that the memories of traumatic experiences 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 are activated by the traumatic experience.[208-210] Evidence from experimental and clinical investigations suggests that memory processes remain susceptible to modulating influences after information has been acquired.[211] Locus coeruleus activation by electrical stimulation or α_2-adrenergic receptor antagonists enhance memory retrieval.[212,213] The memory-enhancing effects of increased noradrenergic activity may be mediated by β-noradrenergic receptors within the amygdaloid complex.[208,209,212] Thus, some of the acute neurobiologic responses to trauma may facilitate the encoding of traumatic memories.[11]

In patients with PTSD, simple sensory phenomena, such as specific smells, sounds, and visions, circumstantially related to the traumatic event persistently produce a



Symptom	Brain Region
Flashbacks, Intrusive Memories	Cortex, Hippocampus
Anxiety, Fear, Hypervigilance	Locus Coeruleus, Ventral Tegmental Area
Facial Expression of Fear	Trigeminal, Facial Motor Nuclei
Anhedonia, Depression	Nucleus Accumbens
Startle	Nucleus Reticularis Pontis Caudalis
Hyperventilation	Parabrachial Nucleus
Sympathetic Activation: Tachycardia, Increased Blood Pressure	Lateral Hypothalamus
Parasympathetic Activation: Diarrhea, Increased Urination	Dorsal Motor Nucleus of the Vagus

A neural model for traumatic remembrance and correlated behaviors. The original trauma produces a parallel activation of key brain regions, including the locus coeruleus, the ventral tegmental area, and the amygdala and associated norepinephrine, dopamine, opioid, and corticotropin-releasing factor systems. Studies have shown that these neurochemical activations produce adaptive behavioral responses and facilitate the encoding of the traumatic memories, possibly at the level of the amygdala. As described in the text, neural mechanisms of fear conditioning, extinction, and sensitization involve these brain regions and neurochemical systems and contribute to the persistence of traumatic memories and many other posttraumatic stress disorder symptoms. The amygdala may play a particularly key role in these processes because of its demonstrated involvement in fear conditioning and extinction and its projections to numerous brain regions (noted in parentheses) and may mediate the associated symptoms evoked by flashbacks and intrusive memories. Posttraumatic stress disorder symptoms are listed with the hypothesized associated brain structures. NE indicates norepinephrine; DA, dopamine.

recrudescence of traumatic memories and flashbacks. The brain regions mediating these processes include the amygdala, LC, hippocampus, and sensory cortex. Most of the evidence points to the amygdala as particularly important in the conditioning and extinction of sensory and cognitive associations to the original trauma and subsequent activation of traumatic memories. NMDA receptors on the amygdala are involved in these processes because NMDA antagonists applied to the amygdala and NMDA lesions of the amygdala prevent the development of fear-conditioned responses and the extinction of fear-potentiated startle.

The suggestion that the amygdala functions to attach fearful or anxious affect to neutral stimuli associated with trauma is supported by data linking the amygdala to anxiety and fear behaviors. Partial or complete destruction of the amygdala causes monkeys to become less fearful than usual.[214]

The amygdala has direct and extensive connections to all of the sensory systems in the cortex. It is likely that many of the memories associated with traumatic events are eventually stored in the cortex.[215] Thus, the functional interchange between the sensory cortices, where memories of each sense may be stored, and the amygdala may be critical for the ability of specific sensory input to elicit traumatic memories. In addition, the highly correlated set of behaviors associated with traumatic memories may result from activation of the amygdala. It projects to a variety of target areas that themselves are critical for the development of these behaviors[216] (Figure).

Table 3.—Therapeutic Implications of a Psychobiologic Model of Posttraumatic Stress Disorder (PTSD)

1. Early treatment intervention may prevent the negative consequences of fear conditioning, sensitization, and other neurochemical responses to acute stress; symptoms of PTSD may respond to medications that counteract the acute stress response when these drugs are prescribed shortly after the traumatic stress.
2. A rational, targeted pharmacotherapy for PTSD may be identified by the development of drugs that act on key brain structures altered by stress and involved in fear conditioning, behavioral sensitization, and extinction (ie, locus coeruleus, amygdala, and hippocampus).
3. Psychotherapies designed to prevent or reverse the effects of fear conditioning may be most effective; cognitive-behavioral therapies using exposure techniques to extinguish the effects of conditioned stimuli should be evaluated.
4. Medications and psychotherapy effective for acute PTSD may be less effective or ineffective for chronic PTSD because of altered neurobiologic state and the development of secondary symptoms, such as depression, guilt, and hostility.

IMPLICATIONS FOR PATHOPHYSIOLOGIC AND TREATMENT STUDIES OF PTSD

Many of the hypotheses described above can be tested in clinical research studies and may have therapeutic relevance (Table 3). Most of the neurobiologic research has been conducted in patients with chronic PTSD. Investigations are required involving patients with acute PTSD. Vulnerability factors that result in the development of acute and chronic PTSD in traumatized individuals need to be identified. Clinical investigations designed to assess the neurobiologic mechanisms associated with fear conditioning and sensitization are indicated. With the use of imagery,[217] negative affective slides,[218] or threat of shock,[219] it is possible to measure fear-potentiated startle in healthy controls as well as in patients with PTSD. Such procedures may provide an objective method to evaluate whether patients with PTSD have deficits in extinction or a lack of sensitivity to conditioned inhibitors. If so, then an understanding of the basic mechanisms in animals that mediate extinction or a reduction in fear by conditioned inhibitors may have direct relevance to PTSD.

A potentially fruitful therapeutic approach is to develop drugs that specifically block conditioned fear. Considerable data suggest that sensory and cognitive associations produce a state of fear or anxiety via direct anatomic pro-

jections from cortical and subcortical brain structures to the amygdala (Figure). Drugs that act on receptors located on amygdaloid neurons themselves (eg, benzodiazepines) may be effective in reducing both conditioned fear and generalized anxiety, because both are assumed to be related to activation of the amygdala. However, under conditions of extreme stress increases in amygdala function (eg, by vivid traumatic memories), these drugs may simply be incapable of preventing stimulation of amygdaloid neurons, except at hypnotic doses. On the other hand, drugs that act selectively on the sensory pathways afferent to the amygdala (eg, by presynaptically decreasing the release of transmitters connecting cortical or subcortical afferents to the amygdala) could be much more effective in blocking conditioned fear, one of the core symptoms of PTSD. In fact, depending on the specificity of these afferent connections and the specificity of the drugs, selective decreases in conditioned fear might be achieved without concomitant effects on alertness and motivation. Drugs that alter function in brain regions to which the amygdala projects may be effective in blocking other specific signs and symptoms of PTSD. Thus, the proposed relationships among dysfunction of specific brain structures and neurochemical systems and clinical symptoms raise the possibility of discovering a rational, targeted pharmacotherapy for PTSD.

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