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Neurobiology of Posttraumatic Stress Disorder

Implications for Treatment

J. Douglas Bremner, Dennis S. Charney

Department of Psychiatry, Yale University School of Medicine, National Center for Posttraumatic Stress Disorder and West Haven VAMC, West Haven, Conn., USA

Posttraumatic stress disorder (PTSD) can occur with exposure to any extreme traumatic stressor, including combat, torture and imprisonment, natural disasters, such as floods and earthquakes, childhood physical and sexual abuse, rape and motor vehicle accidents. Patients with PTSD suffer from intrusive memories and dissociative flashbacks over which they have little or no control, nightmares, sleep disturbance, abnormal startle reaction, increased vigilance, physiological hyperresponsiveness to reminders of the original trauma, avoidance reactions, restriction of emotional expression, social dysfunction and guilt. Studies of the current prevalence of PTSD in the United States range from 1% of the general population [1] to 9% of urban youth [2] and 15% of Vietnam combat veterans [3]. Given the magnitude of the problem, it is important to have a better understanding of the neurobiology of PTSD. This in turn may promote the development of new treatments for this disorder. However, due to the fact that PTSD has only relatively recently been addepted as a valid diagnosis, little is known about its neurobiology and pharmacological treatment.

Stress affects multiple neurobiological systems. These include norepinephrinc, hypothalamic-pituitary adrenal axis (HPA)/corticotropin releasing factor (CRF), benzodiazepine, dopamine, opiate and serotonin brain systems [reviewed in ref. 4–7]. In addition, stress affects brain structures involved in memory, such as the amygdala and hippocampus. The lack of research on the effects of stress on humans can be contrasted with the large amount of research which has examined

Table 1. Changes in brain neurotransmitter and neurohormonal systems with stress

Neurotransmitter	Acute stress	Chronic stress	Brain regions involved	PTSD symptoms
Norepinephrine	increased turnover	increased responsiveness of LC neurons	Hipp, Hypo, LC, Cor, Amyg, Thal	anxiety, fear, hypervigilance, hyperarousal, irritability, encoding of traumatic memories
Dopamine	increased release	increase	PFC, NA	
CRF/HPA axis				
Brain CRF	increase	increase/ decrease	Hipp, Hyp, Cor, LC, Amyg	metabolic activation, anxiety/fear
Peripheral ACTH	increase	increase/ decrease		memory alterations
Peripheral cortisol	increase	increase/ decrease		hyperarousal
Benzodiazepines	decreased binding	decreased binding	Hipp, Cor	alterations in memory, anxiety and fear
Endogenous opiates	increased release	decrease[a]	MB, Hipp, Cor	analgesia, emotional blunting, encoding of traumatic memories

Hipp = Hippocampus; Hypo = hypothalamus; LC = locus ceruleus; Cor = cerebral cortex; Amyg = amygdala; PFC = prefrontal cortex; NA = nucleus accumbens; MB = midbrain; Thal = thalamus.

[a] Decrease in receptor binding measured by B_{max}.

the effects of stress on animals. This research can be used to piece together a model for how stress can affect neurobiological systems in humans, and to formulate hypotheses for testing in patients with PTSD. It is hoped that an increase in knowledge about the neurobiology of PTSD may lead to advances in treatment, for example, through the development of pharmacological regimens which target specific brain systems affected by stress. This paper will briefly summarize laboratory findings in animals related to each brain system affected by stress, with findings in humans in PTSD when such studies have been conducted (table 1). Because of the fact that the few human studies performed to date have examined alterations in noradrenergic and HPA/CRF systems, as well as brain memory systems, this paper will have an increased emphasis in these areas. Finally, what is known about the neurobiology of PTSD will be reviewed in relation to the few controlled studies of the psychopharmacology of PTSD, and future avenues for the development of psychopharmacological treatments of PTSD will be discussed.

TSD symptoms

nxiety, fear, hyper-
igilance, hyperarousal,
ritability, encoding of
raumatic memories

etabolic activation,
nxiety/fear
emory alterations

yperarousal

terations in memory,
nxiety and fear
nalgesia, emotional
unting, encoding of
aumatic memories

ex; Amyg = amygdala;

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Noradrenergic Brain Systems

Accumulated evidence supports a relationship between alterations in noradrenergic brain systems and stress. The majority of norepinephrine cell bodies in the brain are located in the locus ceruleus (dorsal pons) and in the lateral tegmental area [reviewed in ref. 8], with projections to diffuse cerebral cortical areas, cerebellum, cingulate gyrus, thalamus, hippocampus, hypothalamus, amygdala, bed nucleus of the stria terminalis, and nucleus accumbens, as well as descending projections which synapse at the level of the thoracic spinal cord [reviewed in 9, 10]. The norepinephrine system plays an important role in the stress response. Animals exposed to electric shock which they cannot escape from develop specific behavioral patterns which include conditioned fear responses and learned helplessness. Exposure to inescapable stress in the rat results in increased turnover and release of norepinephrine in cerebral cortex [11–13], hippocampus [13–15], amygdala [16], hypothalamus [12], locus ceruleus [11], thalamus and pons [12]. Chronic stress in the form of re-exposure to foot shock in the rat after a period of time without shock results in an increased turnover and release of norepinephrine in the hippocampus [13, 17], hypothalamus [13], cortex [13, 18] and locus ceruleus [19]. Chronic stress results in an eventual depletion of norepinephrine in many of these brain areas when synthesis is not able to keep up with demand [12, 13, 18, 20]. These studies suggest that noradrenergic brain systems are activated by stress, resulting in increased norepinephrine synthesis, release and metabolism in the brain.

Stress is also associated with an increase in firing of locus ceruleus neurons, which appears to play a role in the generation of behaviors specific to the stress response. Locus ceruleus neurons at rest typically discharge in a slow, phasic manner [21]. A 2- to 3-fold increase in locus ceruleus activity in the cat, associated with defensive behaviors such as arched back, piloerection, flattened ears, increased heart rate and blood pressure, and mydriasis, follow stressors such as visual threat [22] or seeing a dog or an aggressive cat [23]. Behaviorally activating but nonstressful stimuli, such as seeing an inaccessible rat, do not result in activation of these neurons [22, 24]. In the awake monkey, threatening and novel situations result in an increase in firing of the locus ceruleus [9, 25, 26]. Electrical stimulation of the locus ceruleus in seat-restrained monkeys is associated with behavioral effects such as head and body turning, eye scanning, tongue movement, scratching, jerking, hand-wringing, escape struggling and pulling hair and skin, which are consistent with fear-related behaviors [27]. These studies suggest that an increase in locus ceruleus activity, with increased norepinephrine release in the brain, may play a role in fear and axiety-related behaviors.

Considerable interest has been focused on possible noradrenergic contributions to PTSD. Increase in plasma and urinary norepinephrine and epinephrine

are associated with stressful situations in healthy human subjects [28, 29]. Many of the symptoms of PTSD, including sleep disturbance, hypervigilance, physiological arousal, and exaggerated startle response, could possibly be related to alterations in noradrenergic systems [30]. PTSD patients have been shown to have an increase in resting heart rate and blood pressure in comparison to normal controls and combat veterans without PTSD [31, 32]. Increases in heart rate and systolic blood pressure following exposure to combat sounds or 'scripts' of traumatic events have been found in Vietnam veterans with combat-related PTSD in comparison to non-PTSD combat veterans [33, 34], Vietnam veterans with other psychiatric disorders [34] and healthy controls [35–37]. An increase in urinary norepinephrine and epinephrine has been found in PTSD patients in comparison to patients with other psychiatric disorders and healthy controls [38, 39]. Other investigators, however, have found no difference in urinary levels of norepinephrine or cortisol in patients with PTSD in comparison to Vietnam veterans without PTSD [40] or in plasma levels of norepinephrine at baseline in Vietnam veterans with PTSD in comparison to healthy controls [41, 42]. An increase in plasma epinephrine [36] and norepinephrine [42] has been shown following exposure to traumatic reminders in Vietnam veterans with PTSD in comparison to healthy subjects. A decrease in platelet adrenergic α_2 receptor number as measured by total binding sites for the α_2 antagonist [^{3}H]rauwolscine, possibly secondary to high levels of circulating catecholamines, has been observed in PTSD patients in comparison to healthy controls [43]. Although these studies do not consistently support an increase in basal sympathetic function in PTSD, they do suggest that patients with PTSD may have an increased responsiveness of the sympathoadrenal system.

Pharmacological studies are also consistent with alterations in noradrenergic function in patients with PTSD. The α_2 antagonist, yohimbine, blocks the noradrenergic presynaptic autoreceptor, resulting in an increase in firing of noradrenergic neurons and an increased release of norepinephrine in the brain. Yohimbine administration results in flashbacks in 40% and panic attacks in 70% of Vietnam veterans with combat-related PTSD, an increase in PTSD-specific symptomatology, increased MHPG, blood pressure and heart rate response in patients with PTSD in comparison to normal healthy controls [44]. We are currently studying Vietnam combat veterans with PTSD (n = 10) and healthy subjects (n = 10) using PET [^{18}F]2-fluoro-2-deoxyglucose technique and coregistered MRI scans during administration of yohimbine and placebo. This PET technique allows for quantitative measurement of cerebral glucose metabolism. Norepinephrine release in the brain has been shown in preclinical studies to drive down brain metabolism in several brain regions which receive noradrenergic innervation, with decreases in temporal, parietal, frontal, orbitofrontal and occipital cortex, as well as caudate, following administration of yohimbine in ani-

mals. We hypothesize that administration of yohimbine will be associated with a relative decrease in metabolism in these brain regions in patients with PTSD in comparison to controls.

The Corticotropin-Releasing Factor/Hypothalamic-Pituitary-Adrenal Axis System

The CRF/HPA system plays an important role in the stress response. Exposure to stressful situations is associated with a marked increase in cortisol release from the adrenal. Cortisol release from the adrenal is regulated by adrenocorticotropin-releasing hormone (ACTH) release from the pituitary, which in turn is primarily regulated by CRF release from the paraventricular nucleus of the hypothalamus. CRF is distributed in several brain areas, in addition to the paraventricular nucleus, which have been implicated in the behavioral and physiological responses to stress, including the central nucleus of the amygdala, hippocampus, prefrontal and cingulate cortices, locus ceruleus, thalamus, periacqueductal gray, and cerebellum [reviewed in ref. 45]. Intraventricular injection of CRF results in a series of physiological and behavioral responses which are adaptive during stress and which are considered to be characteristic of anxiety responses. These behaviors include increased locomotion and grooming in an open field environment, a decrease in punished responding and time spent on the open arms of an elevated plus maze. CRF injected into the central nucleus of the amygdala results in an increase in the magnitude of the startle response and significantly improves retention of the inhibitory avoidance response, a measure of learning and memory [reviewed in ref. 46].

The CRF/HPA system appears to stimulate brain norepinephrine systems, and conversely, brain norepinephrine systems appear to stimulate CRF/HPA systems. CRF-containing neurons from the paraventricular nucleus of the hypothalamus project to the locus ceruleus, and noradrenergic neurons from the locus ceruleus project to the paraventricular nucleus. Intraventricular administration of CRF results in an increased discharge rate of locus ceruleus neurons. Administration of norepinephrine, in turn, stimulates release of CRF [reviewed in ref. 46].

Exposure to acute stress results in an increase in glucocorticoids in laboratory animals which is probably mediated by CRF and ACTH (reviewed in ref. 47]. Glucocorticoids are important in effecting many of the expressions of the stress response, such as increased gluconeogenesis, inhibition of growth and reproductive systems, and containment of inflammatory responses. Different effects result from exposure to chronic stress. Chronic stress has been shown to result in a decrease in glucocorticoid levels in some studies, while other studies have shown an increase. Animals with a history of prior exposure to stress respond to subse-

quent stressors with a delay in the return of glucocorticoids to baseline following exposure to the stressor [reviewed in ref. 45].

Several clinical studies suggest that alterations in HPA function may be associated with PTSD. A decrease in urinary cortisol levels has been found in Vietnam veterans with chronic PTSD in comparison to controls and patients with other psychiatric disorders [48]. PTSD patients have been shown to suppress normally with the standard 1 mg dexamethasone suppression test [49]. Studies utilizing lower doses of dexamethasone (0.5 mg) suggest that PTSD may be associated with a supersuppression of the cortisol response in comparison to normal controls [50], which appears to be the opposite of patients with major depression who are nonsuppressors with the standard 1 mg dexamethasone suppression test. PTSD patients have also been found to have a significantly lower ACTH response to CRF than controls, suggesting a blunted ACTH response to CRF [51], and an increase in lymphocyte glucocorticoid receptors in comparison to controls [52]. These studies suggest that alterations in cortisol and HPA axis function may be associated with PTSD. One possible explanation of clinical findings to date is an increase in central glucocorticoid receptor responsiveness. An increase in glucocorticoid responsiveness in brain structures such as the hippocampus may lead to a heightened negative feedback system, with the net result of a decrease in peripheral cortisol, and a heightened suppression of cortisol in comparison to normal sujects. It is important to note, however, that there are inconsistencies in findings from preclinical and clinical studies on CRF/HPA changes associated with stress that prevent the formulation of a single hypothesis which can explain all of the findings. Clearly further studies are required in this important area.

Dopaminergic Brain Systems

Accumulating evidence suggests that dopaminergic brain systems are involved in the neurobiologic response to stress. Mild and brief stress in the form of foot shock results in a selective activation of the dopaminergic neurons of the medial prefrontal cortex [53]. Daily treatments of inescapable foot shocks to rats result in increased levels of the dopamine metabolites, DOPAC, in the prefrontal cortex, and HVA, in the nucleus accumbens [54]. The dopamine innervation of the medial prefrontal cortex appears to be particularly vulnerable to stress, however stress can enhance dopamine metabolism and release in other areas receiving dopamine innervation, such as the nucleus accumbens, providing that greater intensity or longer duration stress is used [55]. Following lesions of the prefrontal cortex, foot shock results in significant increases in dopamine levels in the nucleus accumbens [56]. These studies suggest that stress results in a preferential increase in mesoprefrontal cortical dopamine release.

Stress-induced increases in mesoprefrontal cortical dopamine release is susceptible to modulation by several neurotransmitter systems. N-methyl-*D*-aspartate and opiate receptor blockade in the ventral tegmental area prevents stress-induced activation of the cortical dopamine system [57]. In addition, preadministration of benzodiazepines prevents attenuation of stress-induced activation of dopamine neurotransmission [55]. These studies suggest that dopamine is involved in an interregulatory process with other chemical mediators of the stress response.

No studies have directly examined dopaminergic brain systems in patients with PTSD. The prefrontal cortex has been suggested to play a role in 'working memory' in conjunction with other brain areas such as the hippocampus. Clinical studies have provided evidence consistent with alterations in attention and memory in PTSD patients [58]. One possible system which may be involved in alterations in working memory in patients with PTSD is the mesocortical dopaminergic system. In addition, administration of cocaine and amphetamine, which both stimulate endogenous dopamine release, results in an increase in paranoid and vigilance behaviors. One could speculate that alterations in dopamine systems may play a role in the pathophysiology of these particular symptoms in patients with PTSD.

Benzodiazepine Brain Systems

Benzodiazepine brain systems have been hypothesized to play a role in the neurobiology of stress and anxiety [59]. Central benzodiazepine receptors and receptors of the inhibitory neurotransmitter system, γ-aminobutyric acid type A, are part of the same macromolecular complex. These receptors have distinct binding sites, although they are functionally coupled and regulate each other in an allosteric manner. Benzodiazepines potentiate and prolong the synaptic actions of the inhibitory neurotransmitter γ-aminobutyric acid [reviewed in ref. 59]. The relationship between benzodiazepine receptor function and stress is of importance considering the fact that the anxiety symptoms associated with PTSD often show improvement with administration of benzodiazepine medication.

Preclinical studies are consistent with a relationship between alterations in benzodiazepine receptor function and stress. Animals exposed to inescapable stress in the form of cold swims or foot shock develop approximately a 30% decrease in benzodiazepine receptor binding (B_{max}) in cortical brain tissue [60–63] and hippocampus [60, 61, 64]. Conflicting results have been obtained on the effects of stress on the hypothalamus [64]. Studies have not shown an effect of stress on benzodiazepine receptor binding in amygdala, thalamus [60], midbrain [64], pons, striatum [60, 64] and cerebellum [60, 64]. Chronic inescapable stress

in the form of foot shock or cold swim is also associated with decreases in benzodiazepine receptor binding in cortex, hippocampus and hypothalamus, in addition to midbrain, with no effects seen in pons, and conflicting results on the effects in striatum and cerebellum [64–66]. These changes have been associated with alterations in memory manifested by deficits in maze escape behaviors [65, 66]. In addition, deficits in short-term memory associated with stress are prevented by preadministration of benzodiazepines [67]. Decreases in benzodiazepine receptor binding appear to be specific to certain types of stress, such as foot shock or swim stress, as opposed to other types of stress, such as defeat stress [68] and to uncontrollable stress as opposed to controllable stress [67]. A decrease in benzodiazepine receptor binding (B_{max}) has been demonstrated in the so-called Maudsley genetically fearful strain of rat in comparison to nonfearful rats in several brain structures including the hippocampus [69], suggesting the possibility that there may be genetically determined individual variations in benzodiazepine receptors which could translate into varying degrees of risk for the development of pathology following exposure to extreme stress. In summary, these findings suggest a decrease in benzodiazepine receptor binding with stress.

No studies have examined benzodiazepine receptors in clinical populations of patients with PTSD. If findings from animal studies extend to humans, it is possible that stress may be associated with a functional deficit of bound benzodiazepine, which may explain the efficacy of benzodiazepine medication, as a sort of 'replacement' therapy, in patients with PTSD and other anxiety disorders. The fact that these patients appear to have an obvious preference for benzodiazepine medications which may diminish many symptoms, including startle and hyperarousal, suggests that alterations in benzodiazepine receptors may play a role in the symptomatology of PTSD. New advances in neuroimaging methods have made possible the assessment of central benzodiazepine receptors with single photon emission computed tomographic measurement of the benzodiazepine receptor ligand [^{123}I]iomazenil [70], and more recently studies have been initiated with [^{11}C]-labelled forms of iomazenil using PET. Clearly, future research should examine benzodiazepine receptors in patients with PTSD.

Endogenous Opiate Systems

Endogenous opiate systems are also involved in the stress response. Exposure to stress results in an increased release of opiate peptides and the development of an analgesia to pain known as stress-induced analgesia which can be blocked by administration of the opiate receptor antagonist naltrexone [71]. Rats exposed to inescapable stress develop decreased binding of the μ-opiate receptor agonist DAGO in midbrain [72]. In addition, preadministration of morphine to rats

exposed to inescapable stress attenuates the stress-induced release of norepinephrine in hypothalamus, amygdala, midbrain and thalamus [14]. Opiates cause a decrease in firing from the locus ceruleus; this provides an explanation for the favorable response of hyperarousal symptoms of PTSD to opiates such as heroin.

Several lines of evidence suggest that alterations in endogenous opiate systems may be associated with the clinical symptomatology of patients with PTSD. Since the time of World War II, surgeons working on the battlefield have noted that wounded soldiers have a reduced need for opiate analgesic medication, suggesting that the stress of combat is associated with an increase in endogenous opiate release. Vietnam veterans with combat-related PTSD have been shown to have high rates of heroin abuse and dependence [3]. These patients appear to prefer opiates as substances of abuse to other substances, such as cocaine. In addition, Vietnam veterans with PTSD have been found to have a reduced sensitivity to pain during exposure to traumatic reminders in the form of a videotape with combat-related scenes [73]. This analgesia to pain is reversible with the opiate antagonist, naloxone, which prompted the authors to point out the parallel between their finding and the stress-induced analgesia response in animals [74].

Stress and Memory

The relationship between stress and memory is highly relevant to the neurobiology of patients with PTSD. The hippocampus and adjacent perirhinal, entorhinal and parahippocampal cortices plays an important role in learning and memory, as well as being a major target organ in the brain for glucocorticoids [reviewed in ref. 47]. Studies in a variety of animal species suggest that increased levels of glucocorticoids seen during stress are associated with damage to hippocampal neurons [75]. We have found evidence for deficits in short-term memory in Vietnam combat veterans with PTSD (n = 26) in comparison to controls (n = 15) as measured by the logical memory component of the Wechsler Memory Scale, and the visual and verbal components of the Selective Reminding Test. There was no difference in scores on the Wechsler Adult Intelligence Scale-Revised between PTSD patients and controls. In addition, level of current PTSD symptomatology as measured by the Mississippi Scale for combat-related PTSD was correlated with degree of memory impairment as measured by the Wechsler Memory Scale [58].

Conditioned fear represents a form of memory which is central to the stress response. Animals exposed to a neutral stimulus in conjunction with an aversive unconditioned stimulus will exhibit a conditioned emotional reaction of fear or anxiety to the neutral stimulus alone, often for years after exposure to the original

aversive stimulus [reviewed in ref. 6]. The amygdala plays an important role in the acquisition of conditioned fear. Acquisition of conditioned fear is associated with an increase in the amplitude of the acoustic startle reflex, which in turn is mediated by the amygdala [76]. The amygdala integrates sensory input and mediates expression of the fear response through activation of the peripheral sympathetic nervous system. For instance, pathways from the amygdala to the lateral hypothalamus mediate sympathetic responses to stress [77]. Electrical stimulation of the amygdala in cats results in the 'sham rage' and defensive behavioral reactions, characterized by peripheral signs of autonomic hyperactivity, alerting, chewing, salivation, piloerection, turning, facial twitching, arching of the back, hissing, snarling and poorly directed outbursts of aggressive behavior [78]. Considering the important role which conditioned fear responses play in the symptomatology of patients with PTSD, studies in this area should help improve our understanding of this disorder.

Neurobiology of Posttraumatic Stress Disorder: Applications to the Development of Psychopharmacological Treatments

The development of a knowledge base related to the neurobiology of PTSD may be useful in the development of treatments for this disorder. The targeting of specific brain systems which are affected by stress with specific psychopharmacological agents represents one logical approach to the treatment of PTSD [79]. The fact that multiple neurobiological systems are involved, however, makes this approach complicated. In addition, individual brain systems may exert their effects through modulation of other brain systems. Nevertheless, categorizing the psychopharmacology of PTSD by individual brain systems represents a rational method to begin the development of a body of knowledge related to the psychopharmacological treatment of PTSD.

The few controlled clinical trials in patients with PTSD have been conducted with tricyclic and monoamine oxidase inhibitor medications, which act on noradrenergic and serotonergic brain systems (table 2). The fact that tricyclic antidepressants such as imipramine reduce firing of locus ceruleus neurons and result in a downregulation of postsynaptic β receptors [reviewed in ref. 80] suggests that these medications may be beneficial in the treatment of PTSD. The few controlled clinical trials which have been conducted in PTSD, however, have not shown marked improvement in symptomatology with tricyclic and monoamine oxidase inhibitor medication in comparison to administration of placebo. In a double-blind placebo-controlled trial of phenelzine and imipramine in 34 Vietnam combat veterans with SCID-diagnosed PTSD, patients treated with imipramine 300 mg a day for 8 weeks (n = 12) showed a significant 20% decrease in

Table 2. Psychopharmacology of PTSD

Medication	Neurotransmitter	Controlled trials	Efficacy
Tricyclics			
Amitriptyline	NA/serotonin	1	+
Imipramine	NA/serotonin	1	+
Desipramine	NA	1	–
Doxepin	NA/serotonin	0	+
Monoamine oxidase inhibitors			
Phenelzine	NA/serotonin	2	++
α_2 antagonists			
Clonidine	NA	0	+
β antagonists			
Propanolol	NA	0	+
Benzodiazepines			
Alprazolam	benzodiazepine	0	+
Antiepileptics			
Carbamazepine		0	+
Valproic acid		0	+

NA = Norepinephrine; – = no efficacy; + = mild efficacy; ++ = moderate efficacy.

PTSD symptomatology as measured by the Impact of Events Scale (IES) with no significant decreases in rated anxiety or depression. Patients treated with phenelzine (n = 11) showed a significant 50% decrease in IES score and no significant decreases in anxiety or depression, and patients treated with placebo (n = 11) showed no change in IES, anxiety, and depression ratings [81]. In an 8-week double-blind trial of amitriptyline and placebo in Vietnam combat veterans with PTSD (n = 40), patients showed a significant decrease in total IES (30%) and Hamilton Depression Scale scores (43%), with no change in Hamilton Anxiety Scale score, after 8 weeks of treatment with medication, in comparison to patients treated with placebo, who had no change in symptomatology [82]. In a 4-week double-blind crossover trial of desipramine 200 mg/day and placebo in patients with PTSD (n = 18), desipramine caused a significant reduction in Hamilton Depression Scale score (25%), but not Hamilton Anxiety Scale or IES scores, in comparison to placeo [83]. A double-blind trial of phenelzine in PTSD patients showed no significant improvement in symptomatology in comparison to place-

bo, although patients were treated for only 5 weeks [84]. In summary, in the only four placebo-controlled double-blind trials of medication for PTSD which, to our knowledge, have been published to date, there are only modest improvements in PTSD and depressive symptomatology, and no improvement in anxiety, with tricyclic and monoamine oxidase inhibitor medications.

No controlled trials have been conducted utilizing medications which act on other brain systems. Open trials of the serotonin reuptake inhibitor, fluoxetine, have shown improvement in symptoms of PTSD, and double-blind placebo-controlled trials of this medication are currently in progress. Clinical experience suggests that benzodiazepine medications are efficacious for many of the symptoms of PTSD, but most clinicians do not frequently prescribe benzodiazepines because of the high comorbidity with alcoholism and substance abuse in patients with PTSD, and no controlled trials have been conducted with this class of medication. Open trials of the α_2 agonist clonidine, which has actions opposite of yohimbine, decreasing norepinephrine release through activation of the norepinephrine autoreceptor, have suggested that this medications is possibly efficacious [31, 85]. This medication is currently being evaluated with a double-blind placebo-controlled trial. Open trials have also suggested some efficacy with the β-adrenergic receptor antagonist, propanolol [31] as well as with carbamazepine [86] and valproic acid [87].

Concluding Comments

In spite of the fact that there is a wealth of research information on the effects of stress on animals, studies have only recently begun to investigate the effects of stress on humans exposed to extreme stress with the diagnosis of PTSD. An understanding of the neurobiology of PTSD may be useful for the development of pharmacological treatments for this disorder. Stress affects multiple brain systems, including norepinephrine, CRF/HPA, benzodiazepine, dopamine and opiate brain systems. Studies in humans have provided some evidence for alterations in norepinephrine and CRF/HPA systems in patients with PTSD. Targeting pharmacological interventions toward specific brain systems represents one rational approach to the treatment of PTSD. However, the fact that stress affects multiple brain systems complicates this approach. This may account for the fact that the only four placebo-controlled double-blind trials of medication in patients with PTSD have not shown robust effects. Future studies should further delineate alterations in neurobiological systems in patients with PTSD with the goal of developing new pharmacological treatments for patients with PTSD.

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J. Douglas Bremner, MD, 116a West Haven VAMC, 950 Campbell Avenue,
West Haven, CT 06516 (USA)