

Research Review

CIRCUITS AND SYSTEMS IN STRESS. II. APPLICATIONS TO NEUROBIOLOGY AND TREATMENT IN POSTTRAUMATIC STRESS DISORDER

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This paper follows the preclinical work on the effects of stress on neurobiological and neuroendocrine systems and provides a comprehensive working model for understanding the pathophysiology of posttraumatic stress disorder (PTSD). Studies of the neurobiology of PTSD in clinical populations are reviewed. Specific brain areas that play an important role in a variety of types of memory are also preferentially affected by stress, including hippocampus, amygdala, medial prefrontal cortex, and cingulate. This review indicates the involvement of these brain systems in the stress response, and in learning and memory. Affected systems in the neural circuitry of PTSD are reviewed (hypothalamic-pituitary-adrenal axis (HPA-axis), catecholaminergic and serotonergic systems, endogenous benzodiazepines, neuropeptides, hypothalamic-pituitary-thyroid axis (HPT-axis), and neuro-immunological alterations) as well as changes found with structural and functional neuroimaging methods. Converging evidence has emphasized the role of early-life trauma in the development of PTSD and other trauma-related disorders. Current and new targets for systems that play a role in the neural circuitry of PTSD are discussed. This material provides a basis for understanding the psychopathology of stress-related disorders, in particular PTSD. Depression and Anxiety 16:14–38, 2002.

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INTRODUCTION

The rapid pace at which our knowledge of stress processing has expanded over the last decade has led to an increase in our understanding of the psychopathology of posttraumatic stress disorder (PTSD). In addition to results from preclinical studies that use a variety of animal models of traumatic stress, there are other factors that have guided recent advances in the neurobiology of PTSD, e.g., utilization of functional brain imaging, the incorporation of cross-system research (including neuroendocrine, neurochemical, and neuro-immunological systems), and an expansion beyond exclusively studying combat veterans to include PTSD in patients suffering from non-combat traumas [Newport and Nemeroff, 2000].

PTSD is the only psychiatric condition whose definition demands that a particular stressor precede its appearance [APA, 1994]. It is characterized by specific symptoms that develop following exposure to

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psychological trauma and where the person's response involved intense fear, helplessness, or horror. Symptoms of PTSD are divided into three categories: 1) re-experiencing of the event, 2) avoidance of stimuli, and 3) persistent symptoms of increased arousal. The critical underlying psychobiological processes have been defined as stress sensitization, fear conditioning, and failure of extinction [Charney et al., 1993]. Studies indicate that chronic combat-related PTSD is frequently associated with other psychiatric disorders. However the course-of-illness onset of PTSD comorbidity often shows that unlike generalized anxiety disorder and past substance use, the mean onset of comorbid disorders occur later than PTSD [Mellman et al., 1992]. PTSD almost always emerges soon after exposure to trauma. Lifetime PTSD appears to be associated with increased risk of lifetime panic disorder, major depression, alcohol abuse/dependence, and social phobia. Current PTSD is associated with increased risk of current panic disorder, dysthymia, social phobia, major depression, and generalized anxiety disorder. Relative to PTSD, the onset of the comorbid disorders is major depression, alcohol abuse/dependence, agoraphobia, social phobia, and panic disorder [Engdahl et al., 1998].

The pathophysiology of PTSD reflects long-lasting changes in the biological stress response systems that underlie many of the symptoms of PTSD and other trauma-related disorders [see also Friedman et al., 1995; Charney et al., 1998a,b; Charney and Bremner, 1999; McEwen, 2000a,b]. Specific brain areas that play an important role in mediating the biological stress response are involved in processes of learning and memory and are preferentially affected by stress, including hippocampus, amygdala, hypothalamus, medial prefrontal, and cingulate [Bremner et al., 1999a; McEwen, 2000a].

This paper reviews theory-driven research, derived from animal models in the field of PTSD. Alterations in affected neural systems in PTSD are reviewed (hypothalamic-pituitary-adrenal axis (HPA-axis), catecholaminergic and serotonergic systems, endogenous benzodiazepines, neuropeptides, hypothalamic-pituitary-thyroid axis, and neuroimmunological alterations). A working model for the neural circuits and systems that are involved in the psychopathology of PTSD is described, which can also be applied to other stress-related disorders. The clinical correlation of alterations in systems involved in learning and memory are reviewed, as well as the role of early trauma in development of PTSD. The rapid growth of neuroimaging has led to new findings and substantiated some earlier hypotheses. These studies are reviewed. Based upon findings from preclinical studies (reviewed in a companion paper: Vermetten and Bremner, 2002) several drugs have been used in the pharmacological treatment of PTSD with varying efficacy. Several new targets and agents, among which are specific seroto-

nergic agents, CRF antagonists, anti-adrenergic compounds, opiate antagonists, neuropeptide Y enhancers, drugs to down-regulate glucocorticoid receptors, substance P antagonists, N-methyl-D-aspartate (NMDA) facilitators, and antikingling/antisensitization anticonvulsants have been developed that may be efficacious in treatment of PTSD [see Friedman, 2000].

A WORKING MODEL FOR A NEURAL CIRCUITRY IN PTSD

Based on studies of the effects of stress on animals and emerging work in clinical neuroscience of PTSD, a working model for a neural circuitry of anxiety and fear that is also applicable to PTSD can be described. This model is based on work of Charney and Bremner [1999]. The brain structures that constitute a neurological working model for traumatic stress should have several features: 1) sufficient afferent input should be provided to permit assessment of the fear-producing nature of the event; 2) the neuronal interactions among the brain structures must be capable of incorporation of a person's prior experience into the cognitive appraisal of stimuli; 3) it is critical to effectively lay down memory traces related to a potential threat; and 4) efferents projecting from the brain should be able to mediate an individual's neuroendocrine, autonomic, and motor responses. Critical brain structures involved in mediating anxiety and fear behavior that result from traumatic stress are locus coeruleus (LC), hippocampus, amygdala, prefrontal cortex, thalamus and hypothalamus, and periaqueductal gray (PAG) that will contribute to neural mechanisms of fear conditioning, extinction, and behavioral sensitization in case of persistent symptoms of traumatic stress (see Fig. 1).

The model provides the neural circuitry that plays a role in describing how information related to a threatening stimulus (e.g., being threatened by someone at gunpoint or witnessing a deadly car accident) enters the primary senses (smell, sight, touch, and hearing), is integrated into a coherent image that is grounded in space and time, activates memory traces of prior similar experiences with the appropriate emotional valence (necessary in order to evaluate the true threat potential of the stimulus), triggers a stress response, and subsequently triggers appropriate and adaptive behavioral response, such as defending yourself, running away, or calling for help.

Afferent sensory input enters through the eyes, ears, smell, touch, the body's own visceral information, or any combination of these. These sensory inputs are relayed through the dorsal thalamus to cortical brain areas, such as primary visual (occipital), auditory (temporal), or tactile (postcentral gyrus) cortical areas. Olfactory sensory input, however, has direct inputs to the amygdala and entorhinal cortex [Turner et al., 1978]. Input from peripheral visceral organs is relayed

It is critical to effectively lay down memory traces related to a potential threat in order to prevent, defend against, or avoid types of threat in the future. The hippocampus and adjacent cortex mediate declarative memory function (e.g., recall of facts and lists) and play an important role in integration of memory elements at the time of retrieval and in assigning significance for events within space and time [Squire and Zola-Morgan, 1991]. The hippocampus also regulates the neuroendocrine response to the stress by its role in glucocorticoid negative feedback. The function of the amygdala in the processing of fear involves conditioning and addition of an emotional valence to the situation. The amygdala also has direct connections that initiate motor responses to fear [Sarter and Markowitsch, 1985]. It is most likely that fearful experiences will be stored in long-term memory. However, amnesia for traumatic events, a widely debated issue regarding memories for childhood abuse, is not an uncommon phenomenon in patients with trauma-related disorders [e.g., Bremner et al., 1996a–c; Chu et al., 1999; van Ommeren et al., 2001] (this is described below). With this long-term storage, memories are felt to be shifted from hippocampus to the neocortical areas where also the sensory impressions take place [Squire and Zola-Morgan, 1991]. In situations of extreme fear, a special “category” of memory is involved, which entails the implicit (probably unconscious) learning and storage of information about the emotional significance of events. The neural system underlying emotional memory involves the amygdala and structures with which it is connected. Afferent inputs from sensory processing areas of the thalamus and cortex mediate emotional learning in situations involving specific sensory cues, whereas learning about the emotional significance of more general, contextual cues involves projections to the amygdala from the hippocampal formation [LeDoux, 1993]. Associative processes can occur during the process of fear conditioning, and these may underlie the long-term associative plasticity that constitutes memory of the conditioning experience [Rogan et al., 1997]. Fear conditioning to explicit and contextual cues has been proposed as a model for intrusive memories that, in a kindling-like process, are reactivated by trauma-related stimuli and hyperarousal, respectively [Grillon et al., 1996]. Clinicians often report that “traumatic cues” such as a particular sight or sound reminiscent of the original traumatic event can trigger a cascade of anxiety and fear-related symptoms in a patient, not rarely without conscious recall of the original traumatic event (R. Loewenstein, personal communication, 2001).

In patients with PTSD, principally, the traumatic stimulus is always potentially identifiable. Symptoms of anxiety in panic or in phobic disorder patients, however, may be related to fear responses to a traumatic cue (in individuals who are vulnerable to increased fear responsiveness, either through constitu-

tion or previous experience), where there is no possibility that the original fear-inducing stimulus will ever be identified.

Frontal cortical areas modulate emotional responsiveness through inhibition of amygdala function, and we have hypothesized that dysfunction in these regions may underlie pathological emotional responses in patients with PTSD, and possibly other anxiety disorders. Medial prefrontal cortex (mPFC) (area 25) (subcallosal gyrus) has projections to the amygdala, which are involved in the suppression of amygdala responsiveness to fearful cues. Dysfunction of this area may be responsible for the failure of extinction to fearful cues, which is an important part of the anxiety response [Morgan et al., 1993; Morgan and LeDoux, 1995]. In extinction, the aversive association in the amygdala seems to be inhibited rather than removed; fear can be rapidly reinstated even long after extinction either by the presentation of the conditioned stimulus in a different context or by a single stimulus-shock pairing [Falls and Davis, 1995]. mPFC is involved in regulation of peripheral responses to stress, including heart rate, blood pressure, and cortisol response [Roth et al., 1988]. Finally, case studies of humans with brain lesions have implicated mPFC (including orbitofrontal cortex, area 25, and anterior cingulate, area 32) in “emotion” and socially appropriate interactions [Damasio et al., 1994]. Auditory association areas (temporal lobe) have also been implicated in animal studies as mediating extinction to fear responses [Romanski and LeDoux, 1993]. As reviewed later, we found dysfunction of medial prefrontal cortex and auditory cortex with traumatic reminders in PTSD [Bremner et al., 1999a,b].

A final component of the stress response involves preparation for a response to potential threat. Preparation for responding to threat requires integration between brain areas involved in assessing and interpreting the potentially threatening stimulus, and brain areas involved in response. For instance, prefrontal cortex and anterior cingulate play an important role in the planning of action and in holding multiple pieces of information in “working memory” during the execution of a response [Goldman-Rakic, 1988]. Parietal cortex and posterior cingulate are involved in visuo-spatial processing that is an important component of the stress response. Motor cortex may represent the neural substrate of planning for action. The cerebellum has a well-known role in motor movement, which would suggest that this region is involved in planning for action; however recent imaging studies are consistent with a role in cognition as well [Akshoomoff and Courchesne, 1992]. Connections between parietal and prefrontal cortex are required in order to permit the organism to rapidly and efficiently execute motor responses to threat. It is therefore not surprising that these areas have important innervations to precentral (motor) cortex, which is responsible for skeletal motor responses to threat, which facilitate survival. The

striatum (caudate and putamen) modulates motor responses to stress. The dense innervation of the striatum and prefrontal cortex by the amygdala indicates that the amygdala can regulate both of these systems. These interactions between the amygdala and the extrapyramidal motor system may be very important for generating motor responses to threatening stimuli, especially those related to prior adverse experiences [McDonald, 1991a,b].

The organism must also rapidly effect peripheral responses to threat, which are mediated by the stress hormone, cortisol, and the sympathetic and parasympathetic systems. Stimulation of the lateral hypothalamus results in sympathetic system activation producing increases in blood pressure and heart rate, sweating, piloerection, and pupil dilatation. Stress stimulates release of CRF from the hypothalamic paraventricular nucleus (PVN), which in turn increases peripheral ACTH and cortisol levels. The mPFC, as mentioned above, also mediates increased blood pressure and pulse as well as elevations in cortisol in response to stress. Striatum, amygdala, and bed nucleus of the stria terminalis also affect peripheral responses to threat through the lateral nucleus of the hypothalamus [Sawchenko and Swanson, 1983; Sawchenko et al., 1983].

The vagus and splanchnic nerves are major projections of the parasympathetic nervous system. Afferents to the vagus include the lateral hypothalamus, PVN, LC, and the amygdala. Efferent connections to the splanchnic nerves have been described occurring from the LC [Clark and Proudfit, 1991]. This innervation of the parasympathetic nervous system may relate to visceral symptoms commonly associated with anxiety, such as gastrointestinal and genitourinary disturbances [Lydiard et al., 1994].

AFFECTED SYSTEMS IN THE NEURAL CIRCUITRY IN PTSD

CRF/HPA-AXIS ALTERATIONS

The corticotropin releasing factor (CRF)/HPA-axis in PTSD has been intensively studied. Accumulated evidence suggests distinct patterns of acute changes and of long-term alterations in HPA-axis in PTSD [reviewed in Yehuda et al., 1995a], which are most probably due to different mechanisms of action for cortisol and its regulatory factors. Findings of urinary cortisol are mixed. In some studies a decrease in urinary cortisol levels in PTSD has been found [Mason et al., 1986; Yehuda et al., 1990, 1995b] but not in others [Pitman and Orr, 1990; Mason et al., 1988; Maes et al., 1998]. Decreased plasma cortisol was found in 24-hr sampling in patients with combat-related PTSD relative to healthy controls and patients with depression [Yehuda et al., 1994]. On the other hand, women with a history of childhood sexual abuse-related PTSD [Lemieux and Coe, 1995] and patients with PTSD

related to a natural disaster [Baum et al., 1993] had elevated levels of urinary cortisol relative to controls. Findings in motor vehicle accident victims subsequently diagnosed with acute PTSD are also mixed with lower levels of cortisol in 15 hr urines in the acute aftermath [Delehanty et al., 2000], as well as elevations in urinary cortisol [Hawk et al., 2000]. It is not clear whether levels of discrepancy can be explained by differences in urine collection alone; other factors must be taken into account as well, such as severity of the disorder, time of collection, type of the trauma [Yehuda et al., 1995a], or specific PTSD symptoms like emotional numbing, which in one of the motor vehicle accident studies predicted a lower cortisol level 6 months after the accident [Hawk et al., 2000]. It has also been suggested that lower urinary cortisol in PTSD reflects an effect of disengagement coping strategies, like disengagement or shame [Mason et al., 2001].

The possibility of enhanced negative feedback sensitivity of the HPA-axis in PTSD has been investigated by using a low dose of dexamethasone. Male patients with combat-related PTSD [Kosten et al., 1990; Kudler et al., 1987; Olivera and Fero, 1990] and female patients with sexual assault-related PTSD [Dinan et al., 1990] have been shown to suppress normally with the standard 1 mg dexamethasone suppression test (DST). Studies utilizing lower doses of DST (0.5 mg) suggest that PTSD may be associated with a super-suppression of the cortisol response in comparison to normal controls [Yehuda et al., 1993; Stein et al., 1997a], which appears to be in contrast to patients with major depression who are non-suppressors with the standard 1 mg DST test. Other neuroendocrine challenge studies have looked at the ACTH response to CRF and β -endorphin, and ACTH response to metyrapone, a drug blocking synthesis from its precursor.

PTSD patients have also been found to have a significantly lower ("blunted") ACTH response to CRF than controls, suggesting an increased release of neuronal CRF [Smith et al., 1989]. PTSD patients were hypersensitive to metyrapone in comparison to healthy volunteers [Yehuda et al., 1996]. This data is consistent with findings of elevated levels of CRF in the cerebrospinal fluid of Vietnam combat veterans with PTSD relative to healthy subjects [Bremner et al., 1997a; Baker et al., 1999]. Other studies have shown that patients with combat-related PTSD had an increase in lymphocyte glucocorticoid receptors in comparison to healthy subjects, non-PTSD combat veterans, and patients with other psychiatric disorders [Yehuda et al., 1991, 1995c]. These studies demonstrate that alterations in cortisol and HPA axis function are associated with PTSD. One possible explanation of the clinical findings to date is an increase in neuronal CRF release, with resultant blunting of ACTH response to CRF, increased central glucocorticoid receptor responsiveness, and resultant

low levels of peripheral cortisol due to enhanced negative feedback. This temporal progressive amplification of responsivity of neurophysiologic, pharmacologic, and behavioral responses has many parallels with the sequence of events that precipitates PTSD and could therefore be viewed as a neurobiological model of sensitization [Friedman, 1994]. An alternative description that has been coined is "allostatic load," which refers to a chemical imbalance centering around the brain as interpreter and responder to environmental challenges and as a target of those challenges [McEwen, 2000b].

The hippocampus is in general felt to have an inhibitory effect on the HPA-axis [McEwen et al., 1992]. Stress-induced impairment in hippocampal function has been shown to be associated with an increase in levels of CRF mRNA in the hypothalamus PVN [Herman et al., 1989] as well as a decrease in the sensitivity of rats to dexamethasone suppression of HPA function [Feldman and Conforti, 1980; Magarinos et al., 1987]. Consistent with this, increased levels of CRF in the cerebrospinal fluid of patients with combat-related PTSD in comparison to controls have been reported [Bremner et al., 1997a] (for an overview of affected systems, see Table 1).

CATECHOLAMINERGIC SYSTEM

Several studies have shown long-term alterations in catecholaminergic systems in PTSD [reviewed in Bremner 1996b,c; Southwick et al., 1997]. PTSD is characterized by tonic autonomic hyperarousal and increases in autonomic system activity in response to trauma-relevant stimuli. The most frequently used measures have been electrodermal activity as presented by skin conductance levels (galvanic skin response); skin temperature; responses of heart rate, systolic and diastolic blood pressure; and electromyography activity of various facial muscles. These variables reflect in part the activity of the peripheral sympathetic system. Exposure to traumatic reminders and neutral scenes utilized in the psychophysiology paradigm have included slides or sounds of scenes similar to the original trauma, and narrative scripts, which are descriptions of what actually happened during the original trauma. Comparisons are either made between exposure to trauma-related material, or both the baseline and the neutral exposures.

Over the past 20 years, a large number of psychophysiology studies have reported heightened sympathetic nervous system activity in veterans with PTSD. Although most studies have found no difference in resting baseline heart rate and blood pressure, the majority of studies have reported exaggerated increases in cardiovascular reactivity among subjects with PTSD compared with normal control subjects when exposed to trauma-specific stimuli such as laboratory-stimulated sights and sounds of combat or tape recordings of personally experienced traumas. Such exaggerated

increases have not been found in combat veterans without PTSD, in combat veterans with anxiety disorders other than PTSD, or in response to generic stressors (such as the film of an automobile accident) that have never been experienced by the trauma survivor. Differences in physiological response to auditory startling tones have shown to develop along with PTSD in the months that follow a traumatic event [Shalev et al., 2000], supporting heightened sympathetic sensitization in the course of development of the disorder.

Studies on autonomic arousal report variable findings. Most of the studies that assess physiological characteristics in PTSD have been conducted with veteran subjects, women with histories of childhood sexual abuse, and victims of motor vehicle accidents [Prins et al., 1995; Carlson et al., 1997; Metzger et al., 1999; Liberzon et al., 1999a; Bryant et al., 2000]. A general finding in these studies was that PTSD patients showed heightened responsivity to trauma-related cues, consistent with increased norepinephrine (NE) responsivity. Patients with combat-related PTSD were found to have elevated norepinephrine and epinephrine in 24 hr urine samples in comparison to normal controls and patients with other psychiatric disorders [Mason et al., 1988; Spivak et al., 1999]. Relative elevations of the norepinephrine metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), were found in nighttime samples in PTSD [Mellman et al., 1995]. No differences were found, however, in urinary norepinephrine between patients with combat-related PTSD and combat-exposed non-PTSD subjects [Pitman and Orr, 1990] or in baseline levels of plasma norepinephrine in combat-related PTSD vs. healthy subjects [Blanchard et al., 1991; McFall et al., 1992; reviewed in Murberg, 1994]. Women with PTSD secondary to childhood sexual abuse had significantly elevated levels of catecholamines (NE, epinephrine, dopamine (DA)) and cortisol in 24 hr urine samples [Lemieux and Coe, 1995]. Hawk et al. [2000] examined the relationship among stress hormone levels, PTSD diagnosis and symptoms, and gender shortly after a common civilian trauma. Catecholamines were related to PTSD diagnosis and symptoms in men (and not in women) who had been in a motor vehicle accident. They exhibited elevated levels of epinephrine and norepinephrine 1 month after the accident and had higher epinephrine levels 5 months later [Hawk et al., 2000]. Sexually abused girls with PTSD excreted significantly greater amounts of catecholamine metabolites, metanephrine, vanillylmandelic acid, and homovanillic acid (HVA) in urine than non-sexually abused girls [De Bellis et al., 1994], and showed a positive correlation with duration of the PTSD trauma and severity of PTSD symptoms [De Bellis et al., 1999a,b]. Exposure to traumatic reminders in the form of combat films resulted in increased epinephrine [McFall et al., 1990] and norepinephrine [Blanchard et al., 1991] release, and increased MHPG with physical exercise [Hamner et

TABLE 1. Alterations in biological systems in PTSD in human studies*

| | |
|---|---|
| CRF/HPA-axis alterations | |
| +/- ^a | Alterations in urinary cortisol |
| ++ (dec) | Altered plasma cortisol with 24 h sampling |
| ++ | Super-suppression with 0.5 mg DST |
| ++ | Blunted ACTH response to CRF |
| + | Lower cortisol response to CRF challenge |
| ++ | Elevated CRF in CSF |
| ++ | Increased lymphocyte glucocorticoid receptors |
| Catecholaminergic function | |
| +/- | Increased resting heart rate and blood pressure |
| +++ | Increased heart rate and blood pressure response to traumatic reminders/panic attacks |
| + | Increased resting urinary NA and Epi |
| - | Increased resting plasma NA or MHPG |
| + | Increased plasma NA with traumatic reminders/panic attacks |
| + | Increased orthostatic heart rate response to exercise |
| + | Decreased binding to platelet α_2 -receptors |
| +/- | Decrease in basal and stimulated activity of cAMP |
| ++ | Decreased platelet MAO activity |
| ++ | Increased symptoms, HR, and plasma MHPG with yohimbine noradrenergic challenge |
| + | Differential brain metabolic response to yohimbine |
| Other neurotransmitter systems | |
| <i>Serotonergic function</i> | |
| ++ | Decreased serotonin reuptake site binding in platelets |
| + | Increased cortical 5-HT ₂ receptor binding |
| + | Reduced hippocampal 5-HT _{1A} receptor binding |
| - | Decreased serotonin transmitter in platelets |
| - | Blunted prolactin response to buspirone (5HT _{1A} probe) |
| - | Altered serotonin effect in cAMP in platelets (5HT _{1A} probe) |
| <i>Hypothalamic-pituitary thyroid axis</i> | |
| + | Increased baseline T3, T4, and TBG |
| + | Increased TSH response to TRH |
| <i>Neuroimmunological system; proinflammatory cytokines</i> | |
| + | Elevated serum II-1 β , II-6, and II-6R |
| <i>Neuropeptides</i> | |
| NPY | |
| + | Lower baseline plasma levels NPY |
| + | Blunted yohimbine-stimulated increases in plasma NPY |
| Cholecystokinin | |
| - | Increased anxiety symptoms with CCK administration |
| NT | Anxiolytic effect of CCK antagonist |
| Opiate | |
| ++ | Naloxone-reversible analgesia |
| + | Mean CSF immunoreactive β -endorphins in CSF |
| + | Increased plasma β -endorphin response to exercise |
| Somatostatin | |
| + | Increased somatostatin levels at baseline in CSF |
| Benzodiazepine | |
| - | Increased symptomatology with Bz-antagonist |
| + | Decreased Bz-receptor binding in prefrontal cortex |
| + | Decreased platelet peripheral benzodiazepine receptor density |

* -, One or more studies did not support this finding (with no positive studies) or the majority of studies did not support this finding; +/-, equal number of studies supported this finding as studies that did not support this finding; +, at least one study supports this finding with no studies not supporting the finding; ++, two or more studies support this finding; +++, three or more studies support this finding, with no studies that do not support the finding. NT, not tested to our knowledge.
^a Findings of decreased urinary cortisol in older male combat veterans and holocaust survivors and increased cortisol in younger female abuse survivors, may be explainable by differences in gender, age, trauma type, or developmental epoch at the time of the trauma.

al., 1994] has been found in Vietnam veterans with PTSD in comparison to healthy subjects. Children with PTSD were found to have increased orthostatic heart rate response, suggesting noradrenergic dysregulation [Perry et al., 1994].

Studies of peripheral norepinephrine receptor function have also shown alterations in α_2 -receptor and cyclic adenosine 3',5'-monophosphate AMP (cAMP) function in patients with PTSD, which are similar to those in panic disorder. A decrease in platelet adrenergic α_2 -receptor number as measured by total binding sites for the α_2 -antagonist [3H] rauwolscine [Perry et al., 1987], and a significantly greater reduction in number of platelet α_2 -receptors after exposure to agonist (epinephrine), has been observed in PTSD patients in comparison to healthy controls [Perry et al., 1991]. A decrease in platelet basal adenosine, isoproterenol, and forskolin-stimulated cAMP signal transduction [Lerer et al., 1987], and basal platelet monoamine oxidase (MAO) activity [Davidson et al., 1985] was found in PTSD patients in comparison to controls. These findings may reflect chronic high levels of NE release, which lead to compensatory receptor downregulation and decreased responsiveness.

Patients with combat-related PTSD compared to healthy controls had enhanced behavioral, biochemical (MHPG), and cardiovascular (heart rate and blood pressure) responses to the α_2 -antagonist, yohimbine, which stimulates central NE release [Southwick et al., 1993]. Moreover, as noted previously, a positron emission tomography (PET) study demonstrated that PTSD patients have a cerebral metabolic response to yohimbine, consistent with increased NE release showing failure of activation in medial prefrontal cortex and decreased metabolism in hippocampus [Bremner et al., 1997b]. In summary, although there is inconsistent evidence for elevations in NE at baseline in PTSD, there is cumulative evidence for increased noradrenergic responsivity in this disorder (see Table 1).

Alterations in sleep function may be secondary to altered pontine function and noradrenergic dysregulation in PTSD. Sleep dysfunction has been documented following acute stress and appears to be related to development of chronic PTSD [Mellman, et al., 1995; Jacobs-Rebhun et al., 2000]. PTSD patients have been found to have an increase in phasic rapid eye movement (REM) activity [Ross et al., 1994, 1999], decreased total sleep time, and increased "micro-awakenings" [Mellman et al., 1995] relative to controls. These abnormalities may play a role in trauma-related nightmares in PTSD patients [Ross et al., 1989]. Increased wake-after-sleep-onset has shown to be specifically associated with trauma-related nightmare complaint, which suggests that nightmares in PTSD are both phenomenologically and functionally distinct from normal dreaming [Woodward et al., 2000]. Ross et al. [1989] have reviewed in detail the literature related to sleep dysfunction in PTSD.

SEROTONERGIC FUNCTION

Although there are only a limited number of studies of serotonergic function in PTSD [Davis et al., 1997; Southwick et al., 1997; Maes et al., 1999a], there is a large body of indirect evidence that suggests that this neurotransmitter has a role in the pathophysiology of anxiety, depression, aggressive acting out, alcohol-related syndromes, and disinhibitory disorders, characterized by impulsivity [Ressler and Nemeroff, 2000]. Serotonin seems to play numerous roles in the central nervous system, including regulation of sleep, aggression, appetite, cardiovascular and respiratory activity, motor output, anxiety, mood, neuroendocrine secretion, and analgesia. Evidence of serotonergic dysregulation in PTSD includes frequent symptoms of aggression, impulsivity, depression and suicidality, and clinical efficacy of serotonin reuptake inhibitors. Alterations in NE, epinephrine, and 5-hydroxytryptamine (5-HT) may have relevance for symptoms commonly seen in survivors with PTSD including hypervigilance, exaggerated startle, irritability, impulsivity, aggression, intrusive memories, depressed mood, and suicidality [Southwick et al., 1999].

The animal model of learned helplessness as a behavioral condition induced by exposure to inescapable stress (which models aspects of depression and posttraumatic stress disorder) has been associated with diminished serotonin release and decreased 5-HT_{2A} receptor density in the rat frontal cortex [Petty et al., 1997; Wu et al., 1999]. In humans, diminished 5-HT metabolism has been associated with aggression, impulsivity, and suicidal behavior [De Cuyper, 1987]. Patients with PTSD are frequently described as aggressive or impulsive and often suffer from depression, suicidal tendencies, and intrusive thoughts that have been likened to obsessions.

Stress-induced activation of serotonin may stimulate a system that has both anxiogenic and anxiolytic pathways within the forebrain [Graeff, 1993]. A primary distinction in the qualitative effects of serotonin may be between the dorsal and median raphe nuclei: the two-midbrain nuclei that produce most of the forebrain serotonin. The serotonergic innervation of the amygdala and the hippocampus by the dorsal raphe are believed to mediate anxiogenic effects via 5-HT₂ receptors. In contrast, the median raphe innervation of hippocampal 5-HT_{1A} receptors has been hypothesized to facilitate the disconnection of previously learned associations with aversive events or to suppress formation of new associations, thus providing a resilience to aversive events [Graeff, 1993]. Chronic stress increases cortical 5-HT₂ receptor binding and reduces hippocampal 5-HT_{1A} receptor binding [Mendelson and McEwen, 1991].

Although anxiety and other serotonergic dysfunctions can be understood in terms of a dysfunctional serotonergic system, it is not clear whether these various behavioral manifestations share one common

serotonergic abnormality, or that the different manifestations are linked to a specificity of serotonergic subtypes [van Praag et al., 1990].

ENDOGENOUS BENZODIAZEPINES

Peripheral-type benzodiazepine (Bz) receptors are sensitive to stress. A relationship has been reported between stress and alterations in benzodiazepine receptor binding [Weizman et al., 1994]. Peripheral benzodiazepine binding sites on platelet membranes have been shown to be increased during diazepam treatment of anxious patients [Weizman et al., 1987]. A decreased platelet peripheral benzodiazepine receptor density was observed in the PTSD patients compared to controls [Gavish et al., 1996]. Single photon emission computerized tomography (SPECT) imaging of [(123)I] iomazenil binding with quantitation of Bz binding showed lower distribution volumes in the prefrontal cortex (area 9) of PTSD patients than in comparison subjects, which is consistent with fewer benzodiazepine receptors and/or reduced affinity of receptor binding in the medial prefrontal cortex in patients with PTSD [Bremner et al., 2000].

NEUROPEPTIDE SYSTEMS

NPY. Preclinical studies have shown that injections of neuropeptide Y (NPY) into the central nucleus of the amygdala function as a central anxiolytic and buffer against the effects of stress; NPY has also been shown to inhibit the release of norepinephrine from sympathetic noradrenergic neurons. When plasma NPY responses to yohimbine and placebo were measured, PTSD patients had lower baseline plasma NPY and blunted yohimbine-stimulated increases in plasma NPY compared with healthy control subjects, suggesting that stress-induced decreases in plasma NPY may mediate, in part, the noradrenergic system hyperreactivity observed in PTSD [Rasmusson et al., 2000]. An increase in plasma NPY was found in healthy humans exposed to military survival training. It was suggested that this uncontrollable stress significantly increases plasma NPY in humans and, when extended, produces a significant depletion of plasma NPY [Morgan et al., 2000a]. In this study NPY was positively correlated with both cortisol and behavioral performance under stress. However, the persistence of a decrease in plasma NPY in PTSD may contribute to long-term symptoms of hyperarousal and the expression of exaggerated anxiety reactions in patients with PTSD.

Cholecystokinin. To examine whether panic provoking agents affect PTSD symptoms, PTSD patients received the panicogen cholecystokinin tetrapeptide-4 (CCK-4) intravenously. Despite significant effects of CCK-4 on anxiety and panic symptoms, no significant provocation of flashbacks was observed in the PTSD

group [Kellner et al., 2000]. There was a blunted ACTH response after CCK-4 in PTSD patients compared to controls. While cortisol was similarly increased in both groups after CCK-4, PTSD patients showed a more rapid decrease of stimulated cortisol concentrations.

Opiate. Naloxone increases endogenous CRF release by blocking an inhibitory opioidergic tone on the HPA-axis. Naloxone reversible analgesia has been described in experiments with patients with PTSD when they viewed a videotape of dramatized combat under naloxone hydrochloride. No decrease in pain ratings occurred in the subjects with PTSD in the naloxone condition, while there was a marked reduction in reported pain intensity ratings of standardized heat stimuli in controls after the combat videotape [Van der Kolk et al., 1989; Pitman et al., 1990]. When measuring CSF β -endorphin in PTSD patients, mean CSF immunoreactive β -endorphins in CSF were increased in PTSD patients [Baker et al., 1997]. PTSD patients demonstrated a differential alteration in plasma β -endorphin response to exercise in PTSD. Post-exercise plasma β -endorphin levels were significantly higher than resting levels in the PTSD patients [Hamner and Hitri, 1992].

Somatostatin. Somatostatin plays an important role in mediating responses to acute and chronic stress. Baseline CSF somatostatin concentrations in PTSD patients were found to be higher than those of the comparison subjects [Bremner et al., 1997a].

ALTERATIONS IN OTHER SYSTEMS IN PTSD

Hypothalamic-pituitary-thyroid axis. Thyroid stimulating hormone (TSH) has a range of actions, which include energy utilization within the cell (important in stress) and stress results in long-lived elevations in thyroid hormone [Mason et al., 1968]. Thyroid function tests are frequently abnormal, hyperthyroid in PTSD, and these abnormalities tend to be in an opposite direction from the abnormalities found in depressive disorder [Prange, 1999]. While patients with major depression exhibited a blunted TSH response to thyrotropin releasing hormone (TRH), some patients with PTSD were found to exhibit an augmented response to TRH [Kosten et al., 1990]. Elevated levels of triiodothyronine (T3), total thyroxine (T4), and thyroxine-binding globulin (TBG) with no elevations in free T4 and thyrotropin (TSH) have been described in patients with combat-related PTSD [Mason et al., 1994; Wang and Mason, 1999], supporting the notion that the thyroid system is altered in chronic combat-related PTSD. A significant positive relationship between total and free T3 and PTSD symptoms was found. Hormone profiles of healthy participants in military survival training demonstrated reductions of both total and free T4 and of total and free T3, as well

as increases in TSH [Morgan et al., 2000b]. Recent research includes the involvement of propyl-endopeptidase, a cytosolic endopeptidase that degrades neuropeptides, such as TRH, and that can play a role in stress responsivity PTSD [Maes et al., 1999b]. Still, more research in this area is needed.

Neuroimmunological alterations in PTSD. There has been increasing interest in the impact of the nervous system on the development and expression of disorders involving the immune system and the contribution of the immune system to psychiatric disease [see review Miller, 1998]. It is known that a balanced immune response (cell-mediated and humoral immunity) is an important defense mechanism. Stress may influence the onset and/or course of infectious, autoimmune/inflammatory, allergic, and neoplastic diseases. Although the mechanism(s) by which a change in immune system balance occurs is not clear, it may be secondary to stress-induced changes in hormones such as cortisol and catecholamines, both of which have been implicated in altering levels of cellular or humoral immunity [Everson et al., 2000]. Recent evidence indicates that together with histamine, glucocorticoids, and catecholamines can selectively suppress cellular immunity, and favor humoral immune responses, inducing pro-inflammatory activities through neural activation of the CRF-mast cell-histamine axis. This dysregulated balance of cytokines produced by T helper cells of the immune system may play a role in stress-related illnesses [Elenkov and Chrousos, 1999].

PTSD in combat veterans has been associated with enhanced immune responsiveness [Watson et al., 1993; Laudenslager, et al. 1998]. Therefore it seems likely that stress-induced secretion of proinflammatory cytokines is involved in the catecholaminergic modulation of anxiety reactions. Recent work has demonstrated that PTSD is associated with increased secretion of proinflammatory cytokines, such as interleukin-1 β (IL-1 β), IL-6, and probably others. Increased serum IL-1 β , concentrations were found to be significantly higher in patients with PTSD [Spivak et al., 1997]. Maes et al. [1999c] reported significantly elevated serum IL-6 and serum IL-6R concentrations in PTSD patients compared to normal volunteers. A higher index of lymphocyte activation was found in patients with childhood sexual-abuse-related PTSD [Wilson et al., 1999], as well as elevated leukocyte and total T-cell counts in combat-related PTSD [Boscarino and Chang, 1999]. While, as described above, in current PTSD there are findings of enhanced immunological functions, in patients in remission from PTSD immunosuppression (e.g., lower number of lymphocytes, number of T cells, NK cell activity, and interleukine (IL)-4 has been reported [Kawamura et al., 2001]. Investigating the function of the immune system as well as the cytokine patterns associated stages of PTSD is a relatively new field and deserves further exploration.

CLINICAL CORRELATES OF MEMORY IN PTSD

There are a number of reasons why the investigation of memory function is clinically relevant to PTSD. Patients with PTSD demonstrate alterations in memory, including nightmares, flashbacks, intrusive memories, and amnesia for the trauma [Figley, 1981; Egendorf et al., 1981]. In addition, descriptions from all wars of this century document alterations in memory occurring in combat veterans during or after the stress of battle. These include the forgetting of one's name or identity and the forgetting of events, which had just taken place during the previous battle [Archibald et al., 1965; Grinker and Spiegel, 1945; Krystal, 1968]. Vietnam veterans with PTSD have been found to have an increase in current amnesic symptomatology in comparison to Vietnam combat veterans without PTSD as measured with the SCID for Dissociative Disorders [Bremner et al., 1993a]. Amnesic memory disturbances should not be confused with deficits in short-term memory; we have reviewed the distinction between these two phenomena in greater detail elsewhere [Bremner et al., 1995a]. Explicit memory is expressed on tests that require conscious recollection of previous experiences (e.g., free recall). Implicit memory is revealed when these experiences affect performance on a test that does not require conscious recollection (e.g., perceptual identification). PTSD patients have been found to have alterations in both explicit and implicit memory [McNally, 1997].

Examples of explicit or declarative memory dysfunction have been found in several PTSD populations. Danish survivors of the KZ camps in WWII were described to have persistent self-reported difficulties in memory after release from internment [Thygesen et al., 1970]. Korean prisoners of war have been found to have an impairment of short-term verbal memory measured by the Logical Memory component of the Wechsler Memory Scale in comparison to Korean veterans without a history of containment [Sutker et al., 1990, 1991]. We have found deficits in short-term memory in Vietnam combat veterans with combat-related PTSD as measured by the Logical Memory component of the Wechsler Memory Scale, and the visual and verbal components of the Selective Reminding Test. PTSD patients in that study did not have lower scores on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) than controls [Bremner et al., 1993b]. Similar results were found in patients with abuse-related PTSD [Bremner et al., 1995b; Jenkins et al., 1998]. Studies have also found deficits in explicit short-term memory as assessed with the Auditory Verbal Learning Test (AVLT) in Vietnam combat veterans with PTSD in comparison to National Guard veterans without PTSD [Uddo et al., 1993], the California Verbal New Learning Test (CVLT) in Vietnam combat veterans with PTSD in comparison to controls [Yehuda et al., 1995c], and the Rivermead

Behavioral Memory Test in child and adolescent patients with PTSD [Moradi et al., 1999].

In a sample of Lebanese adolescents with and without PTSD and a non-traumatized control group, it was demonstrated that the PTSD group scored significantly lower than the other two groups, where no significant differences were observed when the scores of the traumatized non-PTSD group and the non-traumatized controls were compared [Saigh et al., 1997]. A decrease in IQ in combat veterans with PTSD relative to controls may be due to an increased risk for the development of PTSD with lower IQ or a secondary effect of exposure to trauma [McNally et al., 1995].

Other studies in patients with PTSD have shown enhanced recall on explicit memory tasks for trauma-related words relative to neutral words in comparison to controls [McNally, 1997; McNally et al., 1998]. These findings are consistent with both deficits in encoding on explicit memory tasks and deficits in retrieval, as well as enhanced encoding or retrieval for specific trauma-related material.

HIPPOCAMPAL-DEPENDENT LEARNING AND MEMORY, HIPPOCAMPAL VOLUME, AND CORTICOSTEROID LEVELS

MEMORY AND HIPPOCAMPAL VOLUME

We hypothesized that the earlier described findings are related to stress-induced hippocampal damage [Bremner et al., 1999a]. On a biological level, memory impairments of this kind have been found to be attributable to hippocampal damage specifically and are correlated with hippocampal volumetric cell densities [Sass et al., 1990, 1992, 1995]. In this series of studies, Sass et al. demonstrated in patients with idiopathic left temporal lobe epilepsy statistically

significant correlations between presurgical memory impairment (Long Term Retrieval and percent retention on the Wechsler Memory Scale) and hippocampal volumetric cell densities (in CA1, 2, and 3 areas), showing a structural-functional relationship between memory loss and hippocampal volume. From these and other studies, it can be speculated that the volume of the hippocampal formation can serve as a predictor for some specific acquisition and recall measures.

GLUCOCORTICOID HYPOTHESIS OF HIPPOCAMPAL DAMAGE

As reviewed in the accompanying paper, there is considerable evidence derived from research in animals that suggest that stress is associated with damage to hippocampal neurons. Most studies have focused on the role which glucocorticoids play in hippocampal damage [see review of Sapolsky, 2000]. Glucocorticoids appear to exert their effect through disruption of cellular metabolism [Lawrence and Sapolsky, 1994] and by increasing the vulnerability of hippocampal neurons to a variety of insults, including endogenously released excitatory amino acids [Sapolsky and Pulsinelli, 1985; Sapolsky, 1986; Armanini et al., 1990]. Glucocorticoids have also been shown to augment extracellular glutamate accumulation [Stein-Behrens et al., 1994].

Reduction of glucocorticoid exposure helps prevent the hippocampal cell loss associated with chronic stress [Landfield et al., 1981; Meaney et al., 1988]. In addition, as shown by differing strains of rats that have varying glucocorticoid responses to stress, it seems likely that constitutional factors may influence the glucocorticoid-mediated effects of stress on hippocampal neurons [Dhabhar et al., 1993]. There are also substantial gender differences in the concentrations of glucocorticoid receptors at baseline and in response to stress, suggesting that studies related to this area which are performed exclusively in males will not be applicable to females [McCormick et al., 1994].

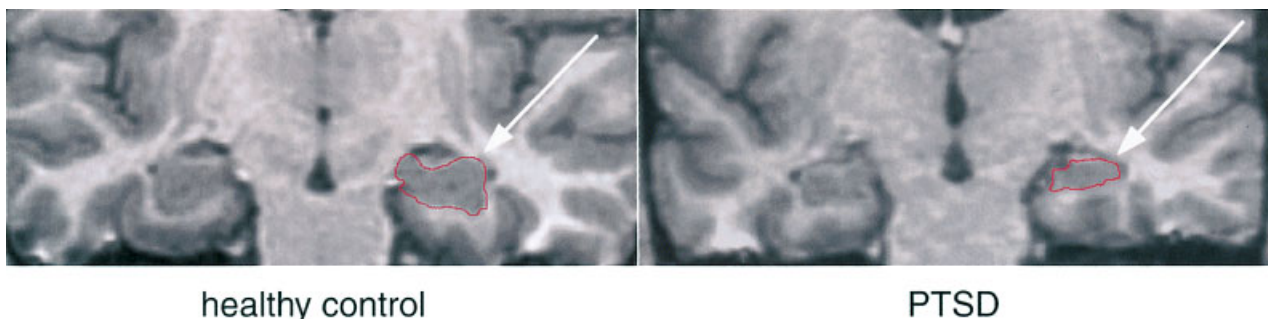


Figure 2. Illustration of volumetric difference between an MRI from a PTSD patient (right) and a healthy control subject (left). Both slices are coronal views, both are resliced to the long axis of the hippocampus and taken from the same anatomical landmarks. The hippocampus can be measured, as indicated by the red line; the white arrow indicates to the left hippocampus on the MRI. In computational analyses, using appropriate software, 3D volume can be calculated by adding the subsequent slices of the MRI.

HIPPOCAMPAL VOLUME IN PTSD

In line with animal findings of impaired hippocampal function and reduced volume, several MRI studies in patients with PTSD have now been performed. In total, four studies have found a reduction in hippocampal volume in both combat-related and civilian PTSD (see Fig. 2).

A reduction of 8% was found in right hippocampal volume in combat veterans with PTSD and 12% in left hippocampal volume in women with childhood sexual abuse-related PTSD. Magnitude of reduction in hippocampal volume in these studies was associated with magnitude of deficits in short-term verbal memory [Bremner et al., 1995c, 1997b]. These volumetric findings have since been replicated. Gurvitz et al. [1996] found a 26% bilateral reduction in combat-related PTSD, and Stein et al. [1997b] reported a 5% reduction in left hippocampal volume in women with child sexual abuse, of which 80% met criteria for PTSD. Currently studies are underway to assess differences in volume before and after treatment, as well as volumetric estimates in mono and dizygotic twins with and without PTSD to assess the differential effect of trauma exposure and PTSD vs. constitutional differences. Meanwhile the etiology of the smaller hippocampal volumes as well as the relationship between the neuroendocrine and neuroanatomic alterations in PTSD are still debated [Yehuda, 1999].

The clinical correlates of these hippocampal volumetric findings are that deficits in short-term memory, abnormal emotional memory for traumatic material, and alterations in neurobiological systems involved in the stress response are an important part of the clinical presentation of patients with PTSD [Pitman, 1989; reviewed in Bremner et al., 1993b; 1995b].

CORTISOL AND HIPPOCAMPAL ATROPHY IN PTSD

Studies showing decreased cortisol in chronic PTSD patients raise the question of how elevated cortisol can represent the etiology of hippocampal atrophy in PTSD. According to Sapolsky's theory of hippocampal damage, this would be due to chronically higher cortisol levels [Sapolsky, 1985]. We have hypothesized that high levels of cortisol at the time of the stressor result in damage to hippocampal neurons, which can persist for many years after the original trauma, leading to reductions in hippocampal volume as measured with MRI [Bremner et al., 1995c, 1997b]. In this scenario, decreased cortisol characterizes the chronic stages of the disorder due to adaptation and long-term changes in cortisol regulation. Longitudinal studies of cortisol in sexually abused girls supports an elevation in cortisol around the time of the stressor, with decreased cortisol developing later in development in patients who develop chronic symptoms of PTSD [Putnam and Trickett, 1997]. An alternative hypothesis for hippo-

campal atrophy is that the enhanced negative feedback is occurring only at the pituitary. Also, another hypothesis that needs to be tested is that hippocampal volume, which is present from birth, can be a risk factor for the development of PTSD; in this scenario, high levels of cortisol associated with stress would have nothing to do with hippocampal atrophy.

Findings of no increase in cortisol levels in the aftermath of rape in women who subsequently develop PTSD [Resnick et al., 1995; Yehuda et al., 1998] have been used to argue against the glucocorticoid hypothesis of stress-induced hippocampal damage. In an initial report, cortisol samples obtained days to weeks after exposure to the trauma of rape found a relationship between low cortisol in the aftermath of rape and prior history of trauma [Resnick et al., 1995]. In a subsequent analysis of samples obtained 8–48 hr after the rape, the authors found a relationship between low cortisol levels in the aftermath of rape and prior history of trauma. However, there was no relationship between cortisol and risk for subsequent development of PTSD [Yehuda et al., 1998]. Given the finding that history of prior trauma increases the risk for PTSD with subsequent victimization, this raises the question of whether these patients had prior PTSD or were physiologically distinct from the non-stress exposed subjects.

GENETIC CONTRIBUTION TO PTSD

Currently, family and twin studies suggest a substantial genetic contribution to the etiology of PTSD. Identification of the nature of the genetic contribution to stress responsivity should enhance understanding of the pathophysiology of stress regulation and stress-related disorder like PTSD, and also has a potential to suggest improved therapeutic strategies for its treatment. Genetic studies of PTSD, however, are complicated by several factors among which are phenotypical differences, requirements for environmental exposure, and high frequency of comorbid psychiatric illness. In addition, genetic heterogeneity, incomplete penetrance, pleiotropy, and the involvement of more than one gene all complicate the genetic analysis of PTSD [Radant et al., 2001].

EARLY LIFE TRAUMA AND NEUROBIOLOGICAL CHANGES

Preclinical studies have demonstrated the effect of early life trauma on neurochemical systems that mediate the stress response [Vermetten and Bremner, 2002]. These findings have been shown to apply to humans as well. Recently, considerable attention has

been given to the observations that adverse experiences early in life can predispose individuals to the development of affective and anxiety disorders in adulthood. There is cumulative evidence that child abuse is associated with markedly elevated rates of PTSD, major depression, and other psychiatric disorders in adulthood [Heim and Nemeroff 1999; Kaufman et al., 2000]. Preclinical studies suggested that stress early in life results in persistent central CRF hyperactivity, increased responsiveness of the HPA-axis, and increased stress reactivity in adulthood [Levine et al., 1993; Plotsky and Meaney, 1993; Ladd et al., 1996; Van Oers et al., 1998; Kaufman and Charney, 1999]. These observations suggest that early adverse experience permanently affects the HPA-axis. In human studies, it was shown that women with a history of childhood sexual abuse-related PTSD were found to have elevated levels of cortisol in 24 hr urine samples [Lemieux and Coe, 1995]. Sexually abused girls had a blunted ACTH response to CRF, consistent with hypersecretion of CRF [De Bellis et al., 1994]. Consistent with this, we found increased levels of CRF in the cerebrospinal fluid (CSF) in PTSD [Bremner et al., 1997a]. Children with PTSD were found to have increased levels of urinary cortisol [De Bellis et al., 1999a,b], a finding that may be explained by the time of the assessment after the trauma and the relation to PTSD symptoms. Children abused within the last couple of months had significantly lower cortisol in comparison to controls [King et al., 2001], a profile that matches findings in adults. Our own preliminary data in women with PTSD related to early childhood sexual abuse show decreased baseline cortisol based on 24 hr diurnal assessments of plasma; cortisol levels were lower at all time points of CRF and ACTH challenge. There was a blunted ACTH response to CRF and normal cortisol response to ACTH challenge. Studies using low doses (0.5 mg) of the dexamethasone suppression test (DST) suggest that adult women with a history of childhood abuse may show a super-suppression of the cortisol response in comparison to normal controls [Stein et al., 1997a], which appears to be the opposite of patients with major depression. Children with abuse-related PTSD had smaller intracranial and cerebral volume as well as smaller hippocampal volume [De Bellis et al., 1999a,b]. These studies demonstrate that alterations in cortisol and HPA-axis function are associated with abuse-related PTSD, with CRF as a central coordinator of the endocrinologic, autonomic, and behavioral stress responses.

FINDINGS FROM FUNCTIONAL NEUROIMAGING IN PTSD

Although there were no published studies using neuroimaging in PTSD as recently as 5–8 years ago, since that time there has been a rapid growth of

research in this area. Several studies have used positron emission tomography (PET) in studies using cognitive activation or pharmacologic provocation that vary from reading narrative scripts, exposing patients to slides and sounds or smells of trauma-related experiences, or administration of yohimbine. In these studies radioactive water ($H_2[O-15]$) or radioactive glucose ($[^{18}F]2$ -fluoro-2-deoxyglucose, or FDG) is used to look at brain blood flow during the cognitive challenge of pharmacologic provocation of PTSD symptoms and traumatic remembrance [Semple et al., 1993; Rauch et al., 1996; Shin et al., 1997, 1999; Bremner et al., 1999b, 1999c]. PET studies demonstrate differences in metabolic response to noradrenergic challenge in PTSD, showing a pattern of decrease in cerebral cortical and hippocampal metabolism, and in normal subjects a pattern of increase in these areas. These findings are consistent with potentiation of central noradrenergic responsiveness in PTSD. Norepinephrine has a U-shaped curve-type of effect on brain function with lower levels of release causing increase in metabolism, while high levels of release cause decrease in metabolism [Bremner et al., 1996b]. Control subjects typically demonstrated increased blood flow in anterior cingulate during these conditions. When personalized scripts of their trauma history were read to female PTSD patients with histories of childhood abuse, blood flow correlates of exposure to these scripts showed decreased blood flow in mPFC (area 24, 25), and failure of activation in anterior cingulate (area 32), with increased blood flow in posterior cingulate and motor cortex and anterolateral prefrontal cortex [Bremner et al., 1999c]. These areas are known to modulate emotion and fear responsiveness through inhibition of amygdala responsiveness. Posterior cingulate plays an important role in visuospatial processing and is therefore an important component of preparation for coping with a physical threat. The posterior cingulate gyrus has functional connections with hippocampus and adjacent cortex, which led to its original classification as part of the “limbic brain.” These women also had decreased blood flow in right hippocampus, parietal, and visual association cortex. These findings replicated earlier findings in combat veterans with PTSD exposed to combat-related slides and sound [Bremner et al., 1999b] (see Fig. 3).

Several studies describe amygdala activation in brain activation in response to fearful stimuli [Rauch et al., 1996, 2000; Liberzon et al., 1999b; Semple et al., 2000]. In general, these findings point to a network of related regions in mediating symptoms of anxiety. Central to symptom mediation is a dysfunction of the mPFC and anterior cingulate, with a failure to inhibit amygdala activation and/or an intrinsic lower threshold of amygdala response to fearful stimuli [Villareal and King, 2001; Pitman et al., 2001]. Dysfunction of the mPFC areas may represent a neural correlate of a failure of extinction/inhibition of fearful stimuli in PTSD (see below).

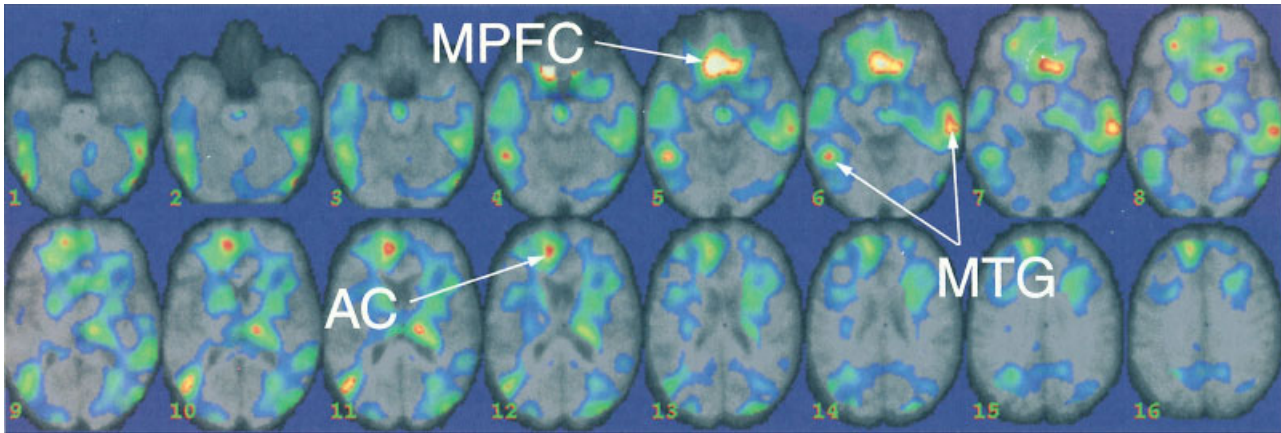


Figure 3. $O^{15}H_2O$ -PET scanning of the brain of a patient with combat-related PTSD during a traumatic reminder (watching combat slides and listening to combat-related sounds) showing decreased blood flow in mPFC (Brodmann's area 25, 32, and 9). The numbers next to the slices refer to different subsequent axial slices through the brain. The decreased blood flow at the time of increased anxiety and fearfulness is indicative of a relative failure to block fear-conditioned processes. The reminder triggered a flashback, with increased heart rate, blood pressure and other psycho(patho)physiological alterations. MPFC, medial prefrontal cortex; MTG, medial temporal gyrus; AC, anterior cingulate.

FAILURE OF INHIBITION OF FEAR IN mPFC

Findings from imaging studies may also be relevant to understand the failure of inhibition of fear responding that is characteristic of PTSD and other anxiety disorders. Although the neural basis of emotional learning has been studied extensively, considerably less is known about the brain systems that might be involved in the inhibition of fear. It is hypothesized that both the dorsal and, to a lesser extent, ventral regions of mPFC play an important role in the regulation of fear extinction [Morgan et al., 1993, 1995; Gewirtz et al., 1997]. Following the development of conditioned fear, as in the pairing of a neutral stimulus (bright light, conditioned stimulus CS) with a fear-inducing stimulus (electric shock, unconditioned stimulus, UCS), repeated exposure to the CS alone would normally result in the gradual loss of fear responding. Extinction to conditioned fear, or "learned inhibition," has been hypothesized to be secondary to the formation of new memories that mask/inhibit the original conditioned fear memory, with a possible role for the hippocampus [Chan et al., 2001]. After all, the extinguished memory can be rapidly reversible following reexposure to the CS-UCS pairing even up to 1 yr after the original period of fear conditioning, suggesting that the fear response does not disappear but is merely inhibited [Falls and Davis, 1995]. It is thought that extinction is mediated by cortical inhibition of amygdala responsiveness [LaBar et al., 1998].

AGENTS AND TARGETS FOR TREATMENT

Numerous psychotropic medications have been reported to have efficacy in PTSD based on non-

controlled studies, but several randomized clinical trials have been performed recently. The empirical status of treatment of the disorder has led to the use of antidepressants, anxiolytics, and anticonvulsants, which were all initially developed for different purposes. New insights in the neural circuitry however have targeted new pharmacotherapeutic interventions and stimulated a more rational pharmacotherapeutic approach. These also have had effects on the development of alternative modes of treatment, which have been developed, such as transcranial magnetic stimulation [Grisaru et al., 1998].

Based upon preclinical studies, new classes of compounds have been recently introduced, including more specific serotonergic agents, CRF antagonists, anti-adrenergic compounds, opioid antagonists, neuropeptide Y enhancers, drugs to down-regulate glucocorticoid receptors, substance P antagonists, NMDA facilitators, and anticonvulsants [Friedman, 2000]. Not all of these have been used in clinical studies; the ones that have been will be discussed below. In case full remission of all symptom areas cannot be achieved with a single type of medication, it can be considered to combine different sorts of medication, such as antidepressants, anxiolytics, adrenergic inhibitors, mood stabilizers, and anticonvulsants. Antidepressant medications are still the mainstay of treatment and are the most studied in controlled clinical trials [Penava et al., 1996; Davidson and Connor, 1999] (see Table 2).

CRF RECEPTOR ANTAGONISTS

Several preclinical studies have been performed in blocking the CRF response to stress. Monkeys that were exposed to an intense stressor after oral

TABLE 2. Overview of neurobiological systems, targets, and drugs in PTSD*

| | | |
|--|---|--|
| CRF/HPA-axis | CRF/CRF antagonists Glucocorticoid receptor | Antalarmin <i>Downregulation glucocorticoid receptor agents</i> |
| Norepinephrine system | Increase in LC/NE; antiadrenergic agents | Propranolol, clonidine, prazosin, (nefazodone) |
| Dopaminergic system | Dopamine turnover/antipsychotics | Risperidone, olanzapine |
| Serotonergic function | Serotonergic depletion | Phenelzine, imipramine, desipramine, amitriptylline, fluoxetine, brofaromine, bupropion, mirtazapine, nefazodone, paroxetine, sertraline |
| Benzodiazepine | Endogenous Bzs/Bz receptor | Alprazolam, buspirone |
| Neuropeptides | NPY CCK/CCK antagonists Endogenous opioids Substance P | NPY enhancers CCK antagonists Nalmefene <i>Substance P antagonists</i> |
| Hypothalamic-pituitary thyroid axis | n/a | n/a |
| Neuroimmunological system; proinflammatory cytokines | n/a | n/a |
| Excitatory amino acids inhibitory amino acids | GABA/glutamate, kindling of limbic structures; antiepileptics | Valproate, carbamazepine, phenytoin, dilantin, Phenobarbital, primidone, <i>oxcarbazepine, felbamate, gabapentin, lamotrigine, topiramate, tiagabine</i> |
| | NMDA receptors | NMDA facilitators |

*The drugs in italics are drugs that have theoretical potential; some have proven efficacy in animal studies.

administration of the CRF₁ receptor antagonist antalarmin showed less body tremors, grimacing, teeth gnashing, urination, and defecation, which can be understood as an inhibition of the usual fear-related behavior. Antalarmin significantly diminished the increases in cerebrospinal fluid CRF as well as the pituitary-adrenal, sympathetic, and adrenal medullary responses to stress. It increased exploratory and sexual behaviors that are normally suppressed during stress [Habib et al., 2000]. Another study looked at the effects of chronic administration of CRF₁ antagonist and found a decreased CRF synthesis in the hypothalamic paraventricular nucleus (PVN). The decrease was dose-dependent and showed decrease in CRF mRNA expression in the PVN and the Barrington's nucleus, there was no alteration of central CRF_{2A} receptor binding or mRNA expression, or urocortin mRNA expression [Arborelius et al., 2000]. In conclusion, CRF receptor antagonists may represent a novel class of antidepressants and/or anxiolytics. Although development is still in its infancy, results from animal studies are promising.

ANTI-ADRENERGIC AGENTS

Anti-adrenergic drugs (such as α_2 -agonists or β -blockers) have as yet received little systematic attention in clinical trials despite evidence for adrenergic dysregulation in PTSD. The first efficacious, reported trials used clonidine in combat-related PTSD in

combination with imipramine [Kinzie and Leung, 1989] and propranolol in children with abuse-related PTSD targeting their hyperaroused agitated state [Famularo et al., 1988]. A recent report demonstrated efficacy of the α_1 -adrenergic antagonist prazosin [Raskind et al., 2000] and guanfacine [Horrigan, 1996; Horrigan and Barnhill, 1996] for the treatment of nightmares in PTSD. For the same indication cyproheptadine, a 5-HT₂ antagonist with antihistaminergic and adrenergic properties has been successfully used [Gupta et al., 1998; Rijnders et al., 2000]. Following earlier reports, some authors recommended starting pharmacotherapy in new PTSD cases with an anti-adrenergic or β -adrenergic agent like clonidine or propranolol [Friedman, 1998]. This medication would need to be commenced immediately after the trauma to block the adrenergic response and prevent the HPA-axis cascade to start. Clonidine can be very effective in this respect, especially as the reduced adrenergic activity often is accompanied by a reduction in anxiety and dissociative symptoms [Friedman, 1998].

DOPAMINERGIC AGENTS/ ANTIPSYCHOTICS

The atypical antipsychotic risperidone has been used in some small studies as adjunct therapy [Lebya and Wampler, 1998; Krashin and Oates, 1999], as well as in treatment for irritability and aggression [Monnelly and Ciraulo, 1999] and for treatment of flashbacks

[Eidelman et al., 2000]. Olanzapine has been described in nightmares and sleep disturbance [Labbate and Douglas, 2000]. The therapeutic effect of these drugs most likely rests on blockade of dopamine (e.g., D₂) as well as the serotonin (e.g., 5-HT₂) receptors.

MAOIs, TCAs, AND OTHER SEROTONERGIC AGENTS

There are now several open label and double-blind placebo-controlled medication trials of serotonergic agents that have been performed in the last 10 years. These trials report the use of monoamine-oxidase inhibitors (MAOI), tricyclic antidepressants (TCA), selective serotonergic reuptake inhibitors (SSRI), and other antidepressants [Shetatzki et al., 1988 (phenelzine); Frank et al., 1988 (phenelzine and imipramine); Reist et al., 1989 (desipramine); Davidson et al., 1990 (amitriptyline); de Boer et al., 1992 (fluvoxamine); Van der Kolk et al., 1994 (fluoxetine); Baker et al., 1995 (brofaromine); Canive et al., 1998; (bupropion); Robert et al., 1999 (imipramine); Connor et al., 1999 (mirtazapine); Brady et al., 2000 (sertraline); Davidson et al., 1998 (nefazodone); Zisook et al., 2000 (nefazodone)]. Most of the MAOI and TCA studies had small sample sizes, were brief (6–12 weeks), and their outcome showed little to modest efficacy or only partial improvement. The largest trials in antidepressants to date showing relatively good efficacy have been with the SSRI. The study of sertraline [Brady et al., 2000] is thus far the largest reported double-blind trial reported with 187 patients distributed over 14 participating sites. This 12-week study resulted in a responder rate of 53% at study-end point compared with 32% for placebo. Sertraline had significant efficacy vs. placebo on the clusters of avoidance/numbing and increased arousal but not on re-experiencing/intrusion. Sertraline was well tolerated, with insomnia the only adverse effect reported, significantly more often than placebo. Emerging data demonstrate efficacy with paroxetine, which may be superior to other serotonergic agents tested to date [Marshall et al., 1998; Bourin et al., 2001]. Only sertraline is yet approved for PTSD in the US. Currently, the SSRI are recommended as a first-line all-round medication for the treatment of PTSD and should be continued for 12 months [Ballenger et al., 2000; Davidson, 2000; Stein et al., 2000].

While with serotonergic agents much emphasis has been given to agents that are predominantly acting on the 5-HT_{1A} receptor, more recent developments are in agents that are more receptor-specific or that have the ability to act on two receptors simultaneously. Nefazodone, an example of a drug that targets both serotonergic and adrenergic systems, has proved useful in sleep-related problems in PTSD [Mellman et al., 1999] and has a broad spectrum of action on PTSD symptoms [Hidalgo et al., 1999].

BENZODIAZEPINES AND AZAPIRONES

The only improvement that was reported in a random-assigned, double-blind crossover trial comparing alprazolam and placebo in PTSD was found in anxiety symptoms during alprazolam treatment, with only modest efficacy in the extension phase [Braun et al., 1990]. However, other studies report improvement on insomnia, flashbacks, and depressed mood using the atypical benzodiazepine buspirone, which has high affinity for 5-HT_{1A} receptor (and moderate affinity for D₂-dopamine receptor) [Duffy and Malloy, 1994; Wells et al., 1991; Fichtner and Crayton, 1994]. The use of benzodiazepines is helpful in reducing physiologic expression of arousal and therefore is recommended as adjunct therapy [Foa et al., 1999]; however, the early administration of benzodiazepines to trauma survivors with high levels of initial distress did not have a salient beneficial effect on the course of their illness [Gelpin et al., 1996].

OPIATE ANTAGONISTS

Based on the hypothesis that emotional numbing is an opiate-mediated phenomenon, Glover reported a trial of nalmefene, a non-FDA approved oral opiate antagonist, showing a favorable response with a marked decrease of emotional numbing and other symptoms of PTSD, including startle response, nightmares, flashbacks, intrusive thoughts, rage, and vulnerability in half of the patient sample [Glover, 1993]. There is some preliminary evidence that increased activity of the opioid system may contribute to dissociative symptoms, including flashbacks, and may respond to opiate antagonists such as naltrexone [Bills and Kreisler, 1993; Bohus et al., 1999].

CCK-ANTAGONISTS

CCK antagonists might have anxiolytic effects and could be a promising new drug. Preclinical studies provide support for the effect of the blocking of CCK_B receptors shortly after a traumatic stressor in mitigating the permanence of PTSD-like symptoms in rats. [Adamec, 1997; Cohen et al., 1999]. Despite these promising reports in animal studies, no human studies have been reported using CCK antagonists.

ANTI-EPILEPTICS/ANTI-KINDLING AGENTS

A number of preclinical studies and preliminary clinical reports have suggested that valproate and carbamazepine may have therapeutic effects in the treatment of certain anxiety disorders [Lipper et al., 1986; Wolf et al., 1988; Keck et al., 1992]. The anti-epileptic drug (AED) lamotrigine has also been used in a 12-week double-blind study of 15 patients, showing improvement on both re-experiencing and avoidance/numbing symptoms compared to placebo patients [Hertzberg et al., 1999]. Another open label trial with 8 weeks of divalproex showed significant decrease of

intrusion and hyperarousal symptoms, while no significant change was seen in avoidance/numbing symptoms [Clark et al., 1999]. Based upon anxiolytic reports of gabapentin in animal studies [de-Paris et al., 2000] and their efficacy in panic disorder [Pande et al., 2000], its first use in PTSD might be efficacious [Brannon et al., 2000]. With their neuroprotective action as the main reason of action, both established AEDs (carbamazepine, phenytoin, valproate, phenobarbital, and primidone) and newer AEDs (oxcarbazepine, felbamate, gabapentin, lamotrigine, topiramate, and tiagabine) might be possible drug treatments for PTSD in future studies.

The majority of the above-described studies used clinical efficacy as the main outcome measure. To better understand the specific effects of pharmacotherapeutic interventions and to enhance our understanding of the effects on different neurobiological circuits and systems, specific studies have started to emerge. These studies compare stress-related parameters before and after treatment. A study of Weizman et al. [1996] reported about a negative finding in the number and affinity of platelet imipramine binding sites, as a marker of the serotonin transporter complex, in PTSD patients before and after phenelzine treatment and in comparison to healthy controls, showing no evidence of a significant difference in the characteristics (B_{max} and K_d) of platelet [3H]imipramine binding between the PTSD patients before and after phenelzine treatment. There was no clinical improvement in the patients on anxiety and depression. [Weizman et al., 1996]. Cohen reported on normalization of autonomic dysregulation in PTSD patients, e.g., heart rate variability with fluoxetine treatment [Cohen et al., 2000]. Other areas of interest of these outcome studies are effects of treatment on immunologic function, cognitive function, gene expression, and HPA-axis after treatment. Neuroimaging studies using PET are promising in the ability to show differences in activation of brain regions that are associated with fear responsivity or extinction of fear.

Another area of interest is the effect of treatment on hippocampal neuronal structure. Animal studies have demonstrated several agents with potentially beneficial effects on the reversibility of the glucocorticoid-mediated stress-induced hippocampal damage. It has been found that phenytoin reverses stress-induced hippocampal atrophy, probably through excitatory amino acid-induced neurotoxicity [Watanabe et al., 1992a]. Other agents, including tianeptine and dihydroepiandrosterone (DHEA), have similar effects [Watanabe et al., 1992b]. Neurons within the hippocampus were found to be unique within the adult brain showing structural plasticity and the capacity to regenerate themselves [Gould et al., 2000] in response to enriching experiences, including learning. Since these are *in vitro* studies that report on neurogenesis in the dentate gyrus of the hippocampus through a regulation of the intracellular brain derived neuro-

trophic factor (BDNF) and cAMP by SSRI, it is implied that these drugs are involved in the processes of neuronal reorganization and strengthening of neural circuits [Duman et al., 1997; Nibuya et al., 1999]. A common action of several serotonergic antidepressants appears to be upregulation of the cAMP response element binding protein (CREB) which facilitates regulation of specific target genes, e.g., in the tyrosine kinase pathway (tyrosine receptor kinase B, trkB). BDNF was found to contribute to reorganization of neural circuits in declarative memory function [Tokuyama et al., 2000], possibly through a modulatory effect on long-term potentiation (LTP), which is important in memory formation [Xu et al., 2000]. The recent report that treatment with antidepressant medication was associated with increased BDNF expression in the hippocampus in postmortem brain supports the notion that CREB levels are indicative of increased BDNF in subjects using antidepressant medication [Chen et al., 2001]. The effects of (serotonergic) antidepressants on synaptic remodeling and function can thus provide a molecular basis for enhanced cognitive processes, such as learning and memory functions [Gomez-Pinilla et al., 2001]. These regulatory processes are slow processes that occur over multiple days. From the above-mentioned animal studies, it appears that chronic, but not acute, administration of antidepressant medication increases the expression of CREB mRNA. Also, it appears that several different classes of antidepressants, including serotonin- and norepinephrine-selective reuptake inhibitors, facilitate the increase in expression of CREB mRNA. Interestingly, in contrast, chronic administration of several non-antidepressant psychotropic drugs did not influence expression of CREB mRNA, demonstrating the pharmacological specificity of this effect [Nibuya et al., 1996]. To summarize, it becomes clear that there is an overlap of plasticity and cell survival pathways, in which disruption of these mechanisms can cause failure of neural plasticity, neuronal atrophy, and death [Duman et al., 2000]. Through the development of these novel drugs, which target cellular processes and molecules involved in neuronal reorganization, neuroplasticity, and cellular resilience, there is a potential that the long-term course and trajectory of PTSD may be modulated [Manji et al., 2000]. It would be promising if it were found that through hippocampal neurogenesis and synaptic remodeling these medications would also have an effect on the glucocorticoid-induced impairment in hippocampal-based declarative memory [Newcomer et al., 1994].

SUMMARY AND CONCLUSION

The contributions of studies to better understand neural circuits and systems in PTSD are rapidly expanding. A biological model to explain psychopathology after traumatic stress involves both brain-

stem circuits, cortical and subcortical regions involved in memory, modulation of emotion, and stress responsiveness. Multiple neurobiological systems, of which the LC/NE system and the CRF/HPA-axis are the key systems, can become sensitized over time by traumatic stress and as a result with other systems contribute to PTSD symptoms such as hypervigilance, poor concentration, insomnia, exaggerated startle response, and intrusive memories.

Increased NE and CRF released in the brain act on specific brain areas, including hippocampus, mPFC, temporal and parietal cortex, and cingulate to mediate symptoms of PTSD. Other neurochemical systems, including Bz_s, opiates, dopamine, CCK, and NPY, also play an important role. Moreover, local tissue modulators—cytokines for the immune response and excitatory amino acid neurotransmitters for the hippocampus—can have an important role in the adaptive function of the brain.

Besides long-term maladaptive processes in neurochemical systems, stress-induced structural changes in brain regions such as the hippocampus as found in both preclinical and clinical studies have important ramifications for PTSD. Preclinical studies have found evidence for plasticity of this brain structure in adult life, which was not thought to be possible until just some years ago. PTSD is also associated with dysfunction of prefrontal cortex, which through failure of inhibition of amygdala function may mediate failure of extinction of fear responses.

An important new development has been the emergence of potential novel mechanisms of action beyond the monoaminergic synapse. The results of recent research have suggested that CRF-antagonists, antiadrenergic compounds, antikindling/antisensitization anticonvulsants, modulators of NMDA, neuropeptide Y enhancers, drugs to down-regulate glucocorticoid receptors, agents normalizing opioid function, and substance P antagonists may provide entirely new sets of potential therapeutic targets.

New research findings on the long-term influence of early traumatic life experiences in the pathogenesis of PTSD also have important ramifications for preventive measures. The cumulative number of studies in PTSD, together with a cross-fertilization of disciplines as has taken place in the last decade in the field of PTSD, have provided exciting new research frontiers that will undoubtedly help to increase our understanding of the long-term consequences of traumatic stress on the brain.

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