The Psychobiology of Posttraumatic Stress Disorder

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Posttraumatic stress disorder (PTSD) develops after exposure to events that are threatening and/or intensely distressing. Accumulating evidence suggests that intense psychological trauma can cause long-standing alterations in the neurobiological response to stress. These alterations translate into a number of symptoms commonly experienced by patients with PTSD. Current treatments for this disorder are only partially effective in managing the disease, and patients have to endure unpleasant symptoms associated with hyperarousal. As a result, they often withdraw from social interaction and increase the use of central nervous system depressants. Data suggest that biological dysregulation of the glutamatergic, amine neurotransmitter (noradrenergic and serotonergic), and neuroendocrine pathways plays a fundamental part in the pathology of PTSD and may cause brain structural as well as functional abnormalities. Knowledge of these pathologic changes in PTSD provides direction for the development of new treatments that will offer more comprehensive management of PTSD and enable patients to enjoy a much improved quality of life. This article reviews current knowledge regarding the psychobiology of PTSD and considers specific agents that are emerging as key modulators of this pathological process. *(J Clin Psychiatry 2000;61[suppl 5]:24–29)*

Posttraumatic stress disorder (PTSD) is a chronic, devastating disorder for which current treatments are only partially effective. Although the psychology of PTSD is well understood, it is important to consider the biology of the disorder if the aim of treating PTSD is to enable patients to live in the present with freedom from feelings or behaviors that belong to the past.[1]

One approach to understanding the neurobiology of PTSD is to review the current knowledge of the normal mechanisms in the brain responsible for the detection of, and response to, imminent harm, danger, or pain. A simplified schematic representation of the normal response to sensory input is shown in Figure 1. Detection of the trauma occurs across a range of modalities including vision, hearing, smell, and touch. This leads to registration of the stressor as memory and promotes a response. The amino acid transmitters, glutamate and γ-aminobutyric acid (GABA), are intimately involved in the process of factual memory registration, and current knowledge suggests that amine neurotransmitters, such as norepinephrine and serotonin, are involved in encoding emotional memory. The acute hormonal response to stress is mediated by hypothalamic peptides such as corticotropin-releasing factor (CRF), arginine vasopressin, and cortisol.

Accumulating evidence suggests that biological dysregulation of the glutamatergic, noradrenergic, serotonergic, and neuroendocrine pathways plays a fundamental part in the pathology of PTSD. These biological changes cause brain structural and functional abnormalities that manifest as symptoms—such as hyperarousal and flashbacks—classically associated with PTSD. This article discusses the current concepts relating to the disrupted psychobiological mechanisms of PTSD and identifies the component agents that are hypothesized to be key modulators in this degenerative process. It also examines the current knowledge relating to structural brain changes induced by these mechanisms.

GLUTAMATERGIC AND GABA PATHWAYS

A large body of evidence supports a role for the glutamatergic and GABA pathways in the psychobiology of PTSD. Adler[2] was the first to observe that prolonged loss of consciousness following terrifying events appears to protect against the development of PTSD. Although coma is not yet fully understood, it is speculated to be partly induced by disruption of the glutamatergic pathway.[1] Additionally, dissociative states associated with the use of glutamate blockers, e.g., ketamine, are likely to be due to drug-induced disruption of glutamatergic transmission in the thalamus. Similarly, GABA-stimulating drugs such as ethanol and benzodiazepines exert some of their effect through suppressing glutamatergic function. These drugs

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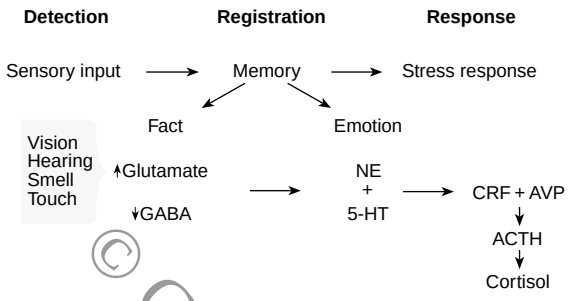
Figure 1. Detection Modalities and Psychobiological Modulators in Stress Response[a]



[a]Abbreviations: ACTH = adrenocorticotropic hormone, AVP = arginine vasopressin, CRF = corticotropin-releasing factor, GABA = γ-aminobutyric acid, 5-HT = 5-hydroxytryptamine, NE = norepinephrine.

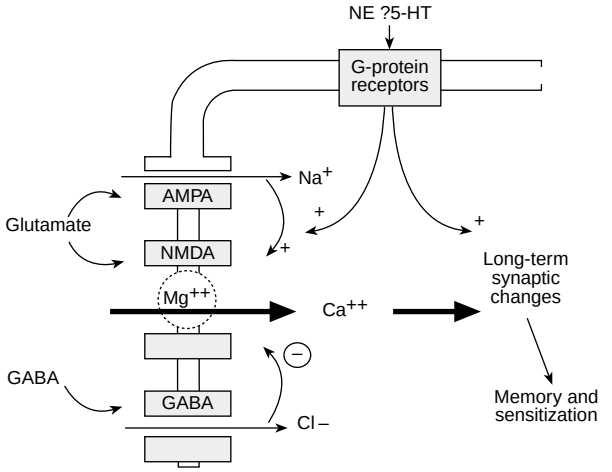
are frequently used by patients with PTSD to prevent the reemergence of previously established memories and possibly the registration of new memories.

Primary sensory transmission involves 2 components: the excitatory amino acid glutamate and the inhibitory amino acid GABA. Glutamate is the primary excitatory transmitter in the brain and plays an intimate role in the processes of consciousness and memory[3] by mediating sensory inputs to the brain. Although glutamate acts on at least 3 receptor subtypes, the 2 of prime importance for the psychobiology of PSTD are the *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. The AMPA receptor is intimately engaged in the processes involved in perception, whereas encoding of factual memory requires coactivation of both the AMPA and the NMDA receptors. GABA exerts its effects through binding to the GABA-A receptor, the most common receptor in the brain, which inhibits the activation of most neurons.

Mechanism for Encoding Memory

At both the cortical and the subcortical levels, glutamate stimulates the AMPA and NMDA receptors, which, in parallel, "feed forward" to stimulate GABA interneurons to release GABA. Hence, glutamate and GABA release always occur in tandem. The glutamatergic input is always excitatory, while the GABA input is inhibitory, and the fine balance between the amino acid transmitters in the brain prevents excessive levels of excitatory transmission from leading to adverse consequences, such as seizures. The consequences of extreme stress are probably mediated by a down-regulation of the GABA system, allowing an excessive activation of the glutamate system that results in the laying down of factual memory (Figure 2). If there is strong stimulation of the postsynaptic neurons, caused either by massive stimulation of the AMPA system or by inhibition of the GABA system, the cell depolarizes, which, in the presence of glutamate, allows activation of the

Figure 2. Mechanism of GABA/Glutamate Pathway in Laying Down Memory of and Sensitization to Stress and Interrelationship of the Pathway With the Neuroamine Transmitter Pathways[a]



[a]Abbreviations: AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid, NMDA = *N*-methyl-D-aspartate. Symbol: ⊖ = inhibitory.

NMDA receptor. The NMDA receptor, like the AMPA receptor, operates a cation channel. However, because conductance through the NMDA channel is greater, it is regulated by a "magnesium gate" (physiologic concentrations of magnesium). For the NMDA receptor to operate, the magnesium gate needs to be deactivated. This can be achieved by either massive stimulation of the AMPA receptor by glutamate or attenuation of the inhibitory GABA system, either of which will lead to marked cell depolarization. Removal of the magnesium blockade initiates influxes of calcium ions through the postsynaptic membrane and causes a transient increase in concentrations of calcium ions within neurons. This process triggers the phosphorylation of proteins, leading to long-term synaptic changes thought to induce memory and sensitization.[3]

There is evidence that in some parts of the brain, e.g., the hippocampus, stimulation of the noradrenergic system can also activate the NMDA system and so lead to long-term synaptic changes. This noradrenergic interaction may explain the linking of emotional responses with factual memory (see Figure 2).

Pathway Dysregulation in PTSD

Acknowledgment of the role played by the glutamatergic and GABA pathways in the normal mechanism for encoding of memory leads to the hypothesis that PTSD is caused by overstimulation of the NMDA system. Excessive influx of calcium ions into the postsynaptic neurons may lead to strongly ingrained memories. This could be a possible mechanism by which the "flash bulb" memories in PTSD are generated. Overstimulation of the NMDA receptors will lead to high levels of calcium ions. These ions

are extremely toxic to cells and eventually will induce cytotoxic cell death, which may be one of the key mechanisms by which brain cells are lost in PTSD. Based on clinical and research observations, it can be hypothesized that abnormalities of GABA inhibition lead to heightened awareness of, or response to, stress.

Other mechanisms have also been proposed as the one through which the GABA receptor contributes to overstimulation of the NDMA system. It has been proposed that endogenous anxiety-producing benzodiazepines that act at the GABA receptor are released during the reexperiencing of traumatic memories.[4] We are currently evaluating this hypothesis with positron emission tomography (PET) using the ligand ^{11}C-flumazenil. If this hypothesis is proved, a benzodiazepine receptor antagonist, e.g., flumazenil, may have beneficial effects in PTSD. This suggestion is already supported by some patient data from a pilot study evaluating the effects of flumazenil in PTSD.[5]

Pharmacologic Intervention

Given the recognition that loss of consciousness protects from PTSD, traditionally the disorder has been managed using amnestic agents: clinicians use medications such as benzodiazepines, and patients typically use alcohol. Both benzodiazepines and alcohol potentiate the effects of GABA; furthermore, alcohol has dual action by additionally blocking the NMDA receptor.[6] However, the critical issue is whether amnestic agents given after the event will prevent the emergence of psychological problems resulting from trauma. Although amnestic agents are effective in producing anterograde amnesia (events which occur after drug administration), they have relatively little effect on the memory for events prior to drug administration (retrograde amnesia). This implies that amnestic agents need to be administered very close to the traumatic event; ideally, they should be given before the experience. However, these agents probably should not be chronically administered after the event, as they may worsen the outcome.[7] In contrast, a cocktail of agents, acting on a range of transmitter systems (e.g., norepinephrine, serotonin) including the GABA system, may be more effective than amnestic agents as postevent treatments.

AMINE NEUROTRANSMITTERS

Norepinephrine

In addition to evidence of glutamatergic dysfunction in PTSD, investigations of neuroendocrine and peripheral catecholamine systems suggest that noradrenergic dysregulation also exists in PTSD.[8] Investigations of α_2-adrenergic receptors in patients with PSTD have shown evidence for a reduced number of receptor sites on platelets compared with those sampled from subjects without PTSD.[9,10] Further evidence from Perry et al.[11] suggests that, compared with normal subjects, patients with PTSD have receptors that are supersensitive to catecholamines, as they are degraded more rapidly by epinephrine. Furthermore, heightened reactivity of the sympathetic nervous system has been consistently reported in combat veterans with trauma-related symptoms.[12,13]

Southwick and colleagues[14,15] have conducted a series of studies in Vietnam combat veterans with PTSD in which they used the noradrenergic probe yohimbine to activate noradrenergic neurons by blocking the presynaptic α_2-adrenergic autoreceptor. In the most recent publication,[15] more than 40% of patients with PTSD experienced yohimbine-induced panic attacks and had significantly greater increases in anxiety, panic, and PTSD symptoms compared with controls. These data suggest that some PSTD patients are relatively supersensitive to noradrenergic stimulation.

Potential treatment strategies. If such intrusive memories and flashbacks can be induced by yohimbine, then it is possible to speculate that attenuation of the noradrenergic system with drugs such as clonidine, which act presynaptically to reduce norepinephrine release, should have clinical utility. Clonidine has been used to a limited extent to stop nocturnal flashbacks,[16,17] while another α_2-agonist, guanfacine, has been reported to have some utility in the suppression of nightmares.[18] Drawbacks with the chronic use of such agents are their hypotensive actions and the tolerance that has been shown to develop to the therapeutic effects. Nevertheless, although they do not seem particularly well suited to long-term treatment, they may have some utility in the acute phase.

The value of pure norepinephrine reuptake blockers in PTSD has not yet been conclusively evaluated. However, predictions based on their pharmacologic effect, the indirect activation of postsynaptic norepinephrine receptors, suggest that, in patients who are supersensitive to noradrenergic stimulation, these agents may cause an initial exacerbation of symptoms. Currently, only one study has been published in this field that compared the effects of desmethylimipramine in non–combat-related PTSD and normal subjects. The study reported that there was no difference in the sensitivity to noradrenergic stimulation between the 2 groups.[19]

Serotonin

Serotonin participates in the modulation of the corticosteroid responses to stress by enhancing secretion of corticotropin-releasing hormone.[20] Although the role of serotonin in PTSD has not been systematically investigated, available data suggest that selective serotonin reuptake inhibitors (SSRIs) are effective treatments for PTSD. Hence, these data justify consideration of a role for this neurotransmitter in this disorder.[21–24] Dow and Kline[24] compared the efficacy of SSRIs and antidepressants that predominantly affect norepinephrine reuptake in PTSD. Their data

suggest that the SSRIs may be more effective. Furthermore, the SSRIs are effective in treating the secondary symptoms of PTSD, especially numbness and avoidance.[25]

To evaluate the potential serotonergic contribution to trauma-related symptoms, Southwick and colleagues[15] administered the mixed serotonin agonist meta-chlorophenylpiperazine (*m*-CPP) to 26 Vietnam veterans with PTSD and measured behavioral and cardiovascular indices. Thirty-one percent of the patients with PTSD experienced an *m*-CPP–induced panic attack and had significantly greater increases in anxiety and PTSD symptoms compared with controls.

Amine Neurotransmitter Subgroups

Southwick and colleagues[15] observed that the subgroup of patients who were sensitive to an *m*-CPP challenge differed from those who were sensitive to a yohimbine challenge. Although these results need to be confirmed, they suggest the presence of 2 neurochemical subgroups of patients with PTSD, similar to those recognized in depression: those with a sensitized noradrenergic system and those with a sensitized serotonergic system. Future research is needed to determine whether *m*-CPP– and yohimbine-sensitive PTSD patients respond differently to an SSRI.

NEUROENDOCRINE ASPECTS

Normal Stress-Response Mechanism

In normal subjects, stress stimulates neurochemicals in the brain to release CRF and other neuromodulators from the hypothalamus and subsequently adrenocorticotropic hormone (ACTH) and cortisol from the pituitary gland and adrenal glands, respectively. These hormones modulate their own release from the hypothalamus-pituitary-adrenal (HPA) system by a negative feedback mechanism.

Dysregulation in PTSD

PTSD patients manifest hypersecretion of CRF[26] but, paradoxically, lower basal cortisol levels[27] and an enhanced negative feedback inhibition of the HPA system. These observations suggest that PTSD is associated with supersensitivity of the HPA system compared with findings in healthy controls.[8] For example, the ACTH response to CRF is blunted in PTSD subjects compared with normal controls. This effect may occur as a result of the hyperresponsivity of the pituitary gland to cortisol and may directly result from an increased number of glucocorticoid receptors on the pituitary gland.[28] Hence, because of a primary alteration in glucocorticoid receptor responsivity, there may be a stronger negative feedback inhibition resulting in attenuated baseline ACTH and cortisol.

Studies have also shown that a larger number of glucocorticoid receptors are present on the lymphocytes of combat veterans with PTSD compared with those who have no psychiatric conditions.[29,30] This difference may be a consequence of up-regulation in response to low cortisol levels, although an alternative hypothesis is that the glucocorticoid receptors modulate hormonal release by modifying the strength of negative feedback.[31] If the latter hypothesis were the case, then increased sensitivity of the glucocorticoid receptor might be the primary alteration in PTSD.[32]

Evidence discussed earlier suggests that an increased activation of the sympathetic nervous system may be associated with PTSD, and the resulting increased levels of catecholamines[33,34] parallel the hyperresponsiveness of the HPA system to neuroendocrine feedback. Additionally, emerging data suggest that distinct abnormalities in the hypothalamic-pituitary-thyroid[35,36] and the hypothalamic-pituitary-gonadal systems[37] are also present in PTSD.

STRUCTURAL BRAIN CHANGES IN PTSD

Mechanisms

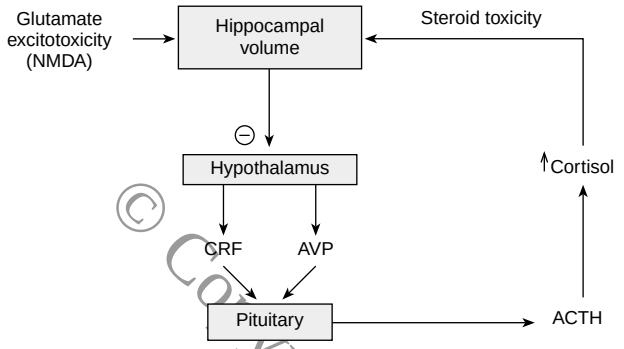
Preclinical research in rodents and primates has shown that experimental stressors can result in functional and morphological changes within the hippocampus.[38,39] Psychobiological research using these animal models has shown that stress-induced elevations of glucocorticoids, e.g., corticosterone, augment the effects of excitatory amino acids, such as glutamate, resulting in structural damage within the brain and abnormal functional brain responses[40,41] (i.e., impaired learning and memory). If hippocampal damage occurs, the normal negative feedback loop of the HPA system is changed to a positive feedback loop that increases exposure of the hippocampus to cortisol toxicity. Together these mechanisms are proposed to perpetuate damage to the hippocampus, resulting in reduced hippocampal volume (Figure 3).

Evidence in Humans With PTSD

A number of studies using magnetic resonance imaging have suggested that reduced hippocampal volume is evident in PTSD or abused subjects.[42–45] Moreover, one of these studies[42] showed that short-term deficits in verbal memory were associated with reduction in hippocampal volume. However, these data do not unequivocally prove that reduced hippocampal volume occurs as a result of exposure to trauma, and it is equally possible that the findings represent a preexisting abnormality that might serve as a risk factor for the development of PTSD following exposure to trauma. Further studies of persons at high risk for trauma (e.g., soldiers), before and after the trauma experience, are necessary to clarify these proposals.

It is likely that other brain regions are damaged in PTSD, resulting in, e.g., reduced temporal lobe volume and frontal lobe loss. Further studies are needed to evaluate these speculations.

Figure 3. Dysregulation of the GABA/Glutamate and Neuroendocrine Pathways Exposes the Hippocampus to Toxicity With a Corresponding Reduction in Cell Volume[a]



[a]These changes exacerbate dysregulation of the neuroendocrine pathway.

BRAIN PATHWAY CHANGES IN PTSD

Normal Mechanisms

The normal format of the brain pathways involved in laying down memory is conceptualized in Figure 4. The sensor is detected through various mechanisms that generate memory of the trauma. Sensory inputs through the thalamus (or equivalent) are laid down as facts within the cortex or hippocampus regions of the brain, whereas emotional memory is laid down in the septo/limbic areas in response to sensory detection by areas of the brain stem, e.g., locus ceruleus. Activation of both these circuits stimulates the hypothalamus and leads to the endocrine response that has been discussed in the previous section. The cortex also modulates output from subcortical structures—e.g., the thalamus, basal ganglia, and the limbic system—through a negative feedback mechanism and suppresses the emotional memory.

Dysregulation in PTSD

Although data are not available to specify what changes in brain pathways occur in PTSD, it may be speculated that dissociation occurs as the result of thalamic transmission. This could be caused by either descending cortical inputs to the thalamus, which would suppress emotional memory, or by excessive noradrenergic input into the thalamus. Desuppression of emotional memory has been observed in combat veterans who experience onset of intrusive nightmares of war trauma after a long period, e.g., 50 years after the trauma experience. This phenomenon has led to the postulate that these symptoms are caused by age-induced cortical loss and a consequent decrease in ability to suppress emotional memory.

Possible mechanisms for the effect on brain pathways of drugs commonly used in the treatment of PTSD are shown in Figure 5.

Figure 4. Brain Pathways That Process Responses to Stress

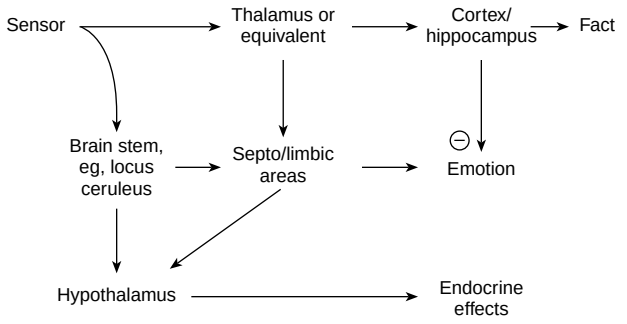
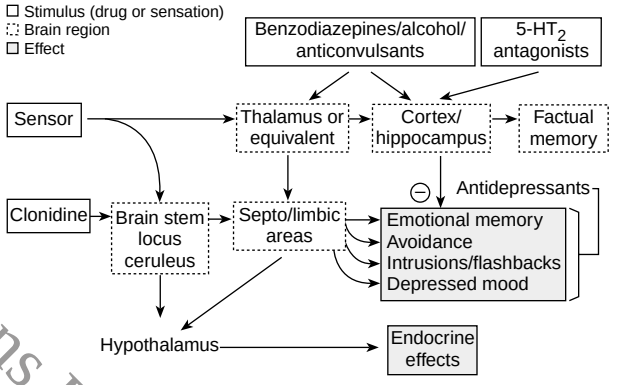


Figure 5. Brain Pathways in PTSD and Possible Sites of Drug Action



CONCLUSION

Biological dysregulation of the glutamatergic and GABA, amine neurotransmitter, and neuroendocrine pathways probably plays a fundamental part in the pathology of PTSD and causes brain structural and functional changes. The concepts discussed in the article have emerged out of advances in physiologic, hormone, and receptor assay methodology. Further advances in neurobiological techniques will facilitate a more detailed understanding of these biological processes and direct the development of more specific, effective treatments to help treat and, hopefully, eventually prevent PTSD.

Drug names: clonidine (Catapres and others), flumazenil (Remazicon), guanfacine (Tenex and others), yohimbine (Yocon and others).

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