Neurobiological findings in posttraumatic stress disorder: a review

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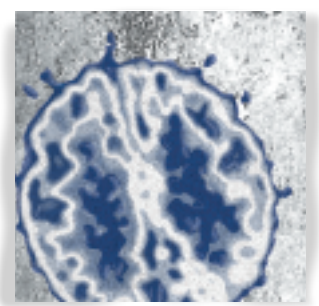

Since posttraumatic stress disorder (PTSD) was first recognized as a psychiatric disorder, it has generated a great deal of scientific interest. Recent studies on the neurobiology of PTSD provide evidence that PTSD is biologically distinct from other types of traumatic and nontraumatic stress responses. This paper reviews three important directions of neurobiological research in PTSD: noradrenergic axis changes and associated alterations in autonomic responsivity, neuroendocrine changes involving the hypothalamic-pituitary-adrenocortical (HPA) axis, and neuroanatomic changes involving the hippocampus. Each section reviews the salient aspects of preclinical research on the biology of stress and their bearing on the understanding of PTSD, and summarizes prominent findings from clinical biological studies of PTSD. Tentative models that integrate current findings from the clinical study of PTSD are reviewed. To conclude, the important methodological and empirical issues that need to be addressed by future studies are indicated.

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Keywords: *noradrenergic; neuroendocrine; neuroanatomic; stress; mental disorder*

Since posttraumatic stress disorder (PTSD) was first recognized as a psychiatric disorder in the *Diagnostic and Statistical Manual of Mental Disorders,* 3rd edition *(DSM-III)* in 1980,[1] it has generated tremendous scientific and public interest. Research on PTSD has only served to elucidate the great complexity of this disorder. While early theoreticians viewed PTSD as part of the continuum of normal stress responses, recent studies indicate that the biological patterns seen in PTSD are different from biological responses to nontraumatic stress.[2] Researchers have made important advances in characterizing the neurobiological features of PTSD and distinguishing biological features associated with PTSD from patterns associated with other types of reactions to traumatic and nontraumatic stressors. This paper reviews three important directions of neurobiological research in PTSD: noradrenergic axis changes and associated alterations in autonomic responsivity, neuroendocrine changes involving the hypothalamic-pituitary-adrenal (HPA) axis, and neuroanatomic changes involving the hippocampus.

Noradrenergic axis function in PTSD

To react appropriately to danger, both animals and humans must rapidly marshal a complex set of behavioral responses. The locus ceruleus (LC), which is located in the dorsal pons, plays a crucial role in activating central and peripheral nervous system responses to threat. Through its broad connections with cortical structures, the hippocampus, hypothalamus, amygdala,

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Selected abbreviations and acronyms

ACTH	*adrenocorticotropic hormone*
CRH	*corticotropin-releasing hormone*
HPA	*hypothalamic-pituitary-adrenocortical (axis)*
LC	*locus ceruleus*
MRSI	*magnetic resonance spectroscopy imaging*
NE	*norepinephrine*
PTSD	*posttraumatic stress disorder*

and spinal cord, the LC organizes affective, cognitive, and motor responses to acute stressors.[3] Activation of LC neurons leads to secretion of norepinephrine (NE), which recruits the multiple pathways involved in modulating behavioral responses to acute stressors. For example, upon receiving electrical stimulation to their locus ceruleus, restrained monkeys will immediately wake up and exhibit behaviors such as head and body turning, eye scanning, tongue movement, hair pulling, and escape struggling. These behavioral responses are similar to those elicited when they are threatened in their natural environment.[4]

The noradrenergic system also modulates cognitive and behavioral adaptations to chronic stressors. Repeated exposure to a stressful stimulus leads to increased NE secretion and facilitates the process of behavioral stress sensitization, whereby the animal develops a heightened behavioral response to further presentations of the same stimulus. Exposure to severe and repeated stress depletes brain NE concentrations and leads to behavioral changes such as decreased exploration in a plus-maze novelty task, decreased appetite, and deficits in previously well-learned behavioral tasks.[5] Such behavioral changes induced by chronic stress have been characterized by the term "learned helplessness."[6] These animal models differ from PTSD in that the development of stress sensitization and learned helplessness requires repeated exposure to stressful stimuli, while PTSD can develop after only a single exposure to traumatic stress. Despite this important difference, stress sensitization and learned helplessness models are useful in explaining behavioral changes associated with PTSD, such as heightened reactions to trauma-related stimuli and decreased interest in usual-life activities.[7]

Through its reciprocal connections with the amygdala, the LC/NE axis also mediates classically conditioned fear responses in animals. In this model, the repeated pairing of a neutral stimulus such as a bright light with a noxious stimulus, such as an electrical shock, eventually results in a conditioned fear response to the previously neutral stimulus when it is presented alone.[8] Reactivation of the neuronal connections between the LC and amygdala that are established during acute stress exposure may explain the failure of animals to extinguish stress-related associations. Conditioned fear patterns may underlie features of PTSD such as heightened arousal responses to ordinary noises and increased avoidance behaviors, while failure of extinction may subserve persistent alarm reactions to reminders of past trauma.

Research on noradrenergic function in PTSD includes hormone- and receptor-binding assays, assessment of autonomic reactivity, and pharmacological probes involving central α_2-adrenergic receptor agonists. One method to assess noradrenergic function in PTSD has been to measure plasma NE levels or levels of NE metabolites in 24-hour urine collections. Studies have found increased urinary concentrations of NE among hospitalized PTSD patients compared with hospitalized patients with other mental disorders.[9] Similar findings have been reported in sexually abused children compared with healthy controls.[10] Other investigators have noted decreases in the density of platelet cell α_2-adrenergic receptors in combat veterans with PTSD and in traumatized children.[11,12] Reduction of these NE-binding receptors may indicate an adaptive downregulation in response to chronically elevated plasma NE levels.

Since the noradrenergic axis also modulates peripheral autonomic responses, investigators have also assessed noradrenergic function in PTSD by comparing autonomic responses in PTSD subjects and controls. Autonomic measures in these studies have included heart rate, systolic and diastolic blood pressure, and galvanic skin responses. While early studies[13,14] noted baseline autonomic differences between combat veterans with PTSD and non-PTSD controls, later studies[15-17] did not replicate these findings. This may be due to the fact that earlier studies did not control for the effects of anticipatory anxiety and study demand characteristics.[18,19] Studies that have compared autonomic responses in PTSD and non-PTSD subjects to stressful but nontraumatic stimuli such as having to perform arithmetic calculations[20,21] or watch

unpleasant films[16,22] have not identified autonomic differences between PTSD subjects and controls. Thus, there is little evidence to suggest that PTSD involves changes in resting autonomic function or in autonomic responsivity to nontraumatic stimuli.

In contrast to these negative findings, there is compelling evidence to indicate that individuals with PTSD exhibit an increased autonomic responsivity to trauma-related stimuli. Compared with trauma-exposed controls, PTSD subjects exhibit greater autonomic arousal to trauma-related stimuli such as audiotapes of combat sounds,[13,14,23] videotapes of war zone scenes,[16,24] and trauma-related smells.[25] Pitman et al[22] noted increased autonomic arousal in PTSD subjects using a script-driven imagery technique in which trauma survivors listened to their own trauma narrative while viewing trauma-related slides. These findings prompted a multisite Veterans Affairs Cooperative Study to evaluate the diagnostic utility of psychophysiological assessments in Vietnam combat veterans with PTSD.[21] This study included three groups: veterans with current PTSD (n=778), veterans with lifetime but not current PTSD (n=181), and veterans who never had PTSD (n=369). Using physiological variables alone, researchers correctly classified 67% of the current PTSD group and a similar percentage of the non-PTSD group. Collectively, these studies suggest that increased autonomic reactivity to traumatic stimuli is an important feature of many individuals with PTSD.

Investigators have also examined noradrenergic axis activity in PTSD using pharmacologic probes such as yohimbine, which activates noradrenergic neurons in the LC region by blocking inhibitory α_2-adrenergic autoreceptors at the presynaptic terminal.[26] Southwick et al[27] found that after receiving yohimbine, a subset of PTSD patients not only exhibited physiological arousal such as increased heart rate and blood pressure, but also developed severe anxiety symptoms including acute panic attacks and increased PTSD symptoms such as intrusive thoughts, flashbacks, and emotional numbing. Yohimbine did not elicit similar responses in trauma-exposed controls without PTSD. Morgan et al[28] demonstrated that yohimbine infusion enhanced acoustic startle responses in combat veterans with PTSD, but did not affect startle responses in combat veterans without PTSD. Consistent with psychophysiologic findings, these result further support the hypothesis that increased noradrenergic responsivity is a core biological feature of PTSD.

Neuroendocrine changes in PTSD

Baseline neuroendocrine changes

In addition to activating the noradrenergic system, exposure to acute stress elicits important neuroendocrine changes that are modulated by the HPA axis. In response to acute stress, corticotropin-releasing hormone (CRH) is released from nuclei in the hypothalamus, amygdala, and cortex.[29] CRH is a 41–amino-acid peptide that is transported to the anterior lobe of the pituitary gland where it stimulates pituitary secretion of adrenocorticotropic hormone (ACTH). ACTH enters the systemic circulation and binds to cells in the adrenal cortex, thereby stimulating the secretion of cortisol. Cortisol is the primary stress hormone. Cortisol binds to the type I and type II glucocorticoid receptors that are present on cell membranes and activates a cascade of physiologic stress responses involving altered metabolism, increased cellular uptake of glucose, modulation of immune activity, and induction of hepatic enzymes. This has been reviewed by Michelson et al.[30] Cortisol also blocks further secretion of CRH and ACTH, thereby curtailing the acute stress response once the stress is over. This is a crucial function of cortisol, since uncontrolled activation of acute stress hormones can significantly harm host tissue. There is clear evidence from animal studies that persistent activation of the HPA axis by chronic and repetitive stress can have deleterious effects such as the acceleration of aging, disruption of reproductive function, immunosuppression, and reduced ability to fight cancers: these findings have been reviewed by Johnson et al.[31]

Noting that increased HPA axis activity is associated with chronic stress in preclinical studies, investigators initially predicted that individuals with PTSD would have elevated plasma cortisol levels and would fail to suppress cortisol levels after being administered dexamethasone.[32-34] However, evidence indicates that HPA axis patterns in PTSD are quite different from patterns seen in studies of chronic nontraumatic stress. Mason and colleagues[32] first noted that veteran inpatients with PTSD had lower 24-hour urinary cortisol levels than other psychiatric inpatients. This finding has been replicated in studies involving both psychiatric[35,36] and

healthy[35,37-39] controls and in other trauma-exposed populations such as holocaust survivors,[39] rape victims,[34,40] and adolescents exposed to a natural disaster.[41] This literature has been reviewed in detail by Yehuda.[42] However, not all studies have obtained similar findings.[11] Differences in study results may reflect differences in study settings, different assay techniques, and patient differences such as inpatient versus outpatient status, obesity, substance abuse, use of medications, and comorbid illnesses.[43] Associated research has examined diurnal fluctuations in plasma cortisol levels in PTSD. Two studies have found that cortisol release in PTSD patients is comparable to that of healthy subjects during the daytime (7 AM to 7 PM), but significantly lower during the late evening and early morning, leading to wider diurnal fluctuations in the PTSD group.[36,44] Other studies have examined target receptor alterations in PTSD and have identified increased glucocorticoid receptors on lymphocyte cell membranes in PTSD subjects compared with controls.[45-48] Collectively, these studies indicate that basal cortisol secretion is altered in PTSD.

Changes in dynamic neuroendocrine responses

To evaluate the dynamic responsivity of the HPA axis in PTSD, investigators have used exogenous hormones that stimulate or inhibit the HPA axis at a specific locus. A well-established paradigm involves measuring ACTH and cortisol levels after administering dexamethasone.

- ***Dexamethasone*** is a synthetic glucocorticoid that mimics the negative feedback effects of cortisol on the HPA axis. It inhibits ACTH release from the pituitary gland, which subsequently leads to a decrease in serum cortisol levels. Four studies have reported that, in response to dexamethasone, individuals with PTSD demonstrate a more robust suppression of ACTH and cortisol release that normal controls.[48-50] This contrasts with the nonsuppression of cortisol levels seen in almost half of all depressed patients after dexamethasone administration.[51]
- Other studies have measured ACTH and cortisol levels after infusing ***CRH***, which stimulates the pituitary gland to release ACTH. Two studies found decreased ACTH responses to CRH infusion in adult PTSD subjects compared with controls,[49,52] while another study[10] found no differences in ACTH response to CRH infusion in sample of adolescent girls.
- Finally, ***metyrapone***, which blocks the synthesis of cortisol in the adrenal gland, has been used to examine hypothalamic and pituitary responses to decrease cortisol in PTSD. One study found that PTSD patients show larger increases in ACTH levels following metyrapone administration that do normal controls.[53]

These findings led Yehuda and colleagues[42] to propose that PTSD may involve an HPA axis that is characterized by enhanced sensitivity to feedback inhibition. According to this model, individuals with PTSD experience chronic and recurrent stress events that lead to increased secretion of CRH. Pituitary sensitivity to CRH decreases the need to compensate for increased CRH release, as reflected by blunted ACTH responses to CRH infusion. To protect against the toxic effects of elevated cortisol, the HPA axis in PTSD becomes increasingly sensitized to feedback inhibition from cortisol through upregulation of glucocorticoid receptors and other mechanisms. This is evidenced by low baseline ACTH and cortisol levels and robust suppression of ACTH and cortisol release after dexamethasone administration. By tightly controlling cortisol secretion and responding aggressively to acute rises in cortisol levels, the neuroendocrine system may serve to buffer vulnerable neuronal structures such as the hippocampus from cellular toxicity induced by elevated serum cortisol levels.[54,55]

Neuroanatomic changes in PTSD

While evidence that severe stress can affect noradrenergic and neuroendocrine function has been well-established, recent animal studies have identified important neurotic effects of stress-mediated increases in glucocorticoid levels. One neuroanatomical structure that appears to be particularly susceptible to stress-induced damage is the hippocampus, which is involved in learning and memory circuits. Studies of monkeys exposed to the stressors of disrupted attachment found damage to cells in the hippocampal region[56]; similar patterns of cell damage could be induced by implanting glucocorticoids directly into the hippocampus.[57] This suggests that elevated glucocorticoid levels, such as might occur acutely during exposure to traumatic stress, could lead

to hippocampal damage. Other studies examining stress-induced hippocampal damage in mice have identified important memory deficits that are correlated with the extent of hippocampal damage,[58] suggesting that structural damage to the hippocampus may also be associated with functional memory deficits.

These findings have led investigators to hypothesize that PTSD may be associated with hippocampal changes resulting from either the acute neurotoxic effects of elevated serum cortisol during exposure to traumatic stress or the gradual deterioration resulting from glucocorticoid-mediated effects of chronic stress. Using magnetic resonance imaging (MRI) techniques to measure hippocampal volume, Bremner et al[59] compared hippocampal size in 26 male Vietnam combat veterans with PTSD and 22 healthy controls, and found a statistically significant 8% reduction in right hippocampal volume in the PTSD group. However, this difference was not associated with PTSD symptoms or combat exposure. Gurvits and colleagues[60] compared hippocampal volumes in veterans with PTSD (n=7) and matched controls (n=7). The PTSD group showed bilateral reductions in hippocampal size (26% on the left, 22% on the right), which remained significant after controlling for age, brain volume, drinking history, and combat exposure. Total hippocampal size was negatively correlated with combat exposure (r=-0.72, P=0.003) and number of PTSD symptoms (r=-0.78, P=0.001), but only weakly associated with memory performance. Examining a different population, Bremner et al[61] compared hippocampal volumes in adult child abuse survivors with PTSD (n=17) versus healthy controls (n=17) and found a statistically significant 12% reduction in left hippocampal size in the PTSD group after controlling for alcohol use, age, and educational status. However, hippocampal volume was not associated with memory deficits, number of PTSD symptoms, or exposure. Finally, Stein et al[62] examined hippocampal volumes in 21 female survivors of childhood sexual abuse with PTSD and 21 nonvictimized controls, and noted a statistically significant 5% reduction in left hippocampal size in the abused group. Combining MRI measurements with proton magnetic resonance spectroscopy (MRSI), Schuff et al[63] observed a 6% decrease in right hippocampal volume which was associated with an 18% decrease in hippocampal activity as measured by the ratio of *N*-acetyl aspartate signal activity to that of choline and creatinine. Their results suggest that utilizing MRSI measurement may enhance our ability to detect subtle hippocampal changes in PTSD. While the above studies included only adults, De Bellis et al[64] compared hippocampal size in 43 abused children with PTSD and 61 matched controls, and found no corresponding decrease in hippocampal volume in the PTSD group. Collectively, these studies provide preliminary evidence that changes in hippocampal size and function may be an important feature of chronic PTSD.

Conclusion and future directions

The findings reviewed in this paper provide tantalizing new insights into PTSD and offer the promise of a richer understanding of this complex disorder. However, for these findings to be truly meaningful, important empirical questions need to be addressed. Most studies have employed a cross-sectional design and included PTSD subjects who suffer from comorbid disorders such as major depression or alcohol abuse. This makes it difficult to identify whether a biological finding associated with PTSD represents a premorbid condition, reflects the impact of a comorbid disorder, or actually results from PTSD. There is a need for prospective longitudinal studies to measure biological variables prior to the onset of PTSD and track their change across time. Furthermore, animal models of PTSD have primarily examined biological responses that develop over days to weeks: findings from such animal models may be less applicable to a disorder such as PTSD, which develops over a period of months to years. Improved animal paradigms are needed to anchor future research in the biology of PTSD.[65] Another critical issue is to determine which biological responses in PTSD are similar to biological stress responses in other populations, and which biological patterns are uniquely associated with PTSD. Exciting research lies ahead and promises to advance our scientific understanding of this major public health challenge. ❑

Hallazgos neurobiológicos en el trastorno de estrés postraumático: una revisión

Desde que fue reconocido por primera vez el trastorno de estrés postraumático (TEPT) como una patología psiquiátrica, se ha generado bastante interés científico. Estudios recientes acerca de la neurobiología del TEPT aportan evidencias que el TEPT es biológicamente distinto de otros tipos de respuestas de estrés traumático o no traumático. Este artículo revisa tres importantes líneas de la investigación neurobiológica en el TEPT: a) cambios en el eje noradrenérgico y alteraciones asociadas a la respuesta autonómica, b) cambios neuroendocrinos en el eje hipotálamo-hipófisis-adrenal (HHA) y c) cambios neuroanatómicos que afectan al hipocampo. Cada sección revisa los aspectos más destacados de la investigación preclínica en la biología del estrés y su relación con la comprensión del TEPT, y resume los hallazgos principales de los estudios clínico biológicos del TEPT. También se revisan algunos modelos tentativos que integran los hallazgos actuales de los estudios clínicos del TEPT. Para concluir, se mencionan los temas importantes metodológicos y empíricos que requieren ser abordados en futuros estudios.

Données neurobiologiques dans les états de stress post-traumatique : revue

Depuis que les états de stress post-traumatique (ESPT) ont été assimilés à une maladie psychiatrique, ils ont suscité un intérêt scientifique important. Des études récentes portant sur la neurobiologie des ESPT ont apporté la preuve que cette pathologie est biologiquement distincte des autres types de réponses à un stress traumatisant ou non traumatisant. Cet article passe en revue trois importantes voies de recherche en neurobiologie des ESPT : les modifications de l'axe noradrénergique et les altérations associées de la réponse autonome, les modifications neuroendocrines impliquant l'axe hypothalamo-hypophyso-surrénalien, et les modifications neuroanatomiques impliquant l'hippocampe. Chaque partie examine les aspects marquants de la recherche préclinique de la biologie du stress et leur contribution à la compréhension des ESPT, et fait le point sur les principaux résultats issus des études biologiques et cliniques des ESPT. Des modèles provisoires intégrant ces résultats sont suggérés. Enfin, les problèmes méthodologiques et empiriques qu'il sera important de prendre en compte dans les études à venir sont indiqués.

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