

Neurobiology of posttraumatic stress disorder

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Recent advances on the neurobiology of posttraumatic stress disorder include: the utilization of functional brain imaging; the incorporation of cross-system research including neuroendocrine (hypothalamic–pituitary–adrenal and hypothalamic–pituitary–thyroid axes), neurochemical (corticotropin-releasing factor, norepinephrine, serotonin, endogenous opiates), and neuroimmunological (humoral and cellular immunity) systems; the expansion beyond exclusive study of combat veterans to include posttraumatic stress disorder patients suffering from noncombat traumas; and the development of animal models of traumatic stress.

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Abbreviations

5HT	5-hydroxytryptamine (serotonin)
ACTH	adrenocorticotropin hormone
CRF	corticotropin-releasing factor
CSF	cerebrospinal fluid
DA	dopamine
DSM III	Diagnostic and Statistical Manual of Mental Disorders III
DST	dexamethasone suppression test
EPI	epinephrine (adrenalin)
fMRI	functional magnetic resonance imaging
GABA	γ-aminobutyric acid
HPA	hypothalamic–pituitary–adrenal (axis)
HPT	hypothalamic–pituitary–thyroid (axis)
NE	norepinephrine (noradrenalin)
PET	positron emission tomography
PTSD	posttraumatic stress disorder
SPECT	single photon emission computed tomography
TBG	thyroxine-binding globulin
TRH	thyrotropin-releasing hormone
TSH	thyrotropin-stimulating hormone

Introduction

Once a diagnosis shrouded in controversy, posttraumatic stress disorder (PTSD) is now not only generally accepted as a valid diagnostic entity but also is accumulating a significant database of neurobiological research. The neurobiology of PTSD bears striking similarities to that of major depression; however, there are differences that underscore the uniqueness of PTSD as a stress-induced syndrome distinct from depression. Like depression studies, PTSD studies have focused upon the two biological systems with the richest traditions in stress-related research: the hypothalamic–pituitary–adrenal (HPA) axis and the catecholamine/sympathetic nervous system. Both depression and PTSD are associated with hyperactivity in these two systems; however, PTSD bears the noteworthy

distinction of being associated with normal to low cortisol levels (hypocortisolaemia) despite hypersecretion of corticotropin-releasing factor (CRF).

Recent advances in PTSD research have extended these findings on several fronts. First, the function of the HPA axis is being more closely scrutinized in an effort to elucidate the underlying pathophysiology that might explain the frequently reported hypocortisolemia in patients with PTSD. Second, animal models are increasingly being used to incorporate novel stress protocols (such as predator exposure) and biological studies (such as hippocampal receptor assays) that would be impractical in humans. Third, the almost exclusive study of combat veterans in PTSD research is giving way to the study of other patient groups suffering from non-combat traumas such as rape or child abuse. In fact, some of the first research in children with PTSD is just now being reported. Fourth, other biological systems including the immune system, the endogenous opiates, and the serotonin system are beginning to receive attention from PTSD researchers. Finally, functional brain imaging is providing our first glimpse into the dysfunction of specific neuroanatomical loci during stimulus processing and symptomatic exacerbation in patients with PTSD. During imaging, symptomatic states can be manifested by intrusive memories of the trauma or by evidence of physiological arousal such as increased heart rate and sweating. PTSD symptoms can be provoked during an imaging session by exposure to a trauma-related cue (e.g. recordings of combat sounds) or by guided mental imagery (e.g. imagining the trauma). As these data continue to accumulate, the role of pharmacological interventions for treating PTSD — including the forthcoming CRF receptor antagonists — can be refined, allowing significant treatment advances in the near future.

As early as the American Civil War, physicians were documenting the finding that persistent psychological distress often follows exposure to war-related trauma. It was soon realized that other traumatic experiences such as natural disasters or serious accidents could produce similar long-lasting psychological symptoms. Previously known by a variety of combat-related colloquialisms such as shell shock, war neurosis, and battle fatigue, it was not until the introduction of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in 1980 that PTSD was included among the recognized psychiatric disorders.

PTSD is characterized in the DSM-III by a phenomenological triad incorporating the symptoms of re-experiencing, avoidance, and hyperarousal. The re-experiencing symptoms of PTSD include nightmares, intrusive memories and flashbacks of the trauma. The avoidance symptoms

include amnesia for the trauma or a reluctance to discuss or think about the trauma. Finally, the hyperarousal symptoms include an exaggerated startle response, fitful sleep and poor concentration. Despite this comprehensive description, the inclusion of PTSD in the DSM-III produced considerable controversy in the field, largely on phenomenological grounds. Some contended that the disorder overlapped so greatly with other anxiety and mood disorders that it was superfluous to psychiatric nosology [1]. There were even implications that political pressures unduly contributed to its inclusion in the DSM-III [2,3]. In addition, others debated whether PTSD belonged among the anxiety disorders, the mood disorders, or a unique class of stress response disorders [4].

Some researchers now contend that the neurobiological uniqueness of PTSD validates it as a distinct diagnostic entity [1,5]. This is indeed ironic when we recognize that the earliest attempts at developing an etiology-based psychiatric nosology were abandoned in the DSM-III — the same edition that first included PTSD — due to the inherent difficulty of demonstrating the underlying biology of psychiatric illnesses. Although a comprehensive neurobiology of PTSD remains to be definitively elucidated, the argument that its unique neurobiology validates its nosological classification may be a harbinger to a day when psychiatric diagnostic schemes again rely more upon the pathophysiology of an illness.

The bulk of PTSD neurobiological research has focused upon the HPA axis and the catecholamine/sympathetic nervous system, with Vietnam combat veterans comprising the largest contingent of research participants. However, PTSD research is now expanding in several domains. First, recent studies incorporate non-combat related PTSD (e.g. victims of rape, child abuse, natural disasters or terrorism). Second, inquiry has extended into other stress-responsive neurobiological systems. Third, new investigative tools such as functional brain imaging are being increasingly utilized. Fourth, several researchers are conducting laboratory animal studies to remedy the long-recognized deficiency of animal models for PTSD [6]. Finally, novel lines of research are investigating the contribution of childhood trauma to the diathesis for adulthood PTSD [7–10].

In this review, we offer an update of the major contributions to the literature on the neurobiology of PTSD that have appeared in the past year. This article will survey new research into the neurocognition and functional neuroanatomy of PTSD, the neuroendocrinology of PTSD, neurotransmitter studies of PTSD, and finally the immunological sequelae of PTSD. Previous reviews of PTSD neurobiology can be consulted for a more comprehensive review of research published prior to 1999 [1,6,11,12,13^{**},14].

Neurocognition and functional neuroanatomy

Many of the hallmark symptoms of PTSD (e.g. nightmares, flashbacks, amnesia for the traumatic event,

dissociative episodes, exaggerated startle response) represent, at least in part, disturbances in neurocognitive processing. In particular, sensory input and memory processing appear to be awry in PTSD. Not only are pharmacological probes being used to investigate psychiatric illness at the cellular level, but new tools are also becoming available to investigate brain function in psychiatric disorders. Some of the methods used to investigate neurocognitive processing in patients with PTSD include neuropsychological testing, sensory evoked potentials, electroencephalography, polysomnography, and various modalities for functional brain imaging, including single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI).

Because the clinical course of anxiety disorders like PTSD is marked by periods of symptom quiescence punctuated by acute episodes of symptom exacerbation, it is important that functional brain imaging studies be conducted both in the resting condition and in the symptomatic state. Consequently, imaging studies of patients with PTSD utilize symptom provocation protocols that take one of two forms: trauma stimulus exposure, and guided mental imagery. The most often used trauma stimulus exposure in PTSD research is the playing of combat sounds to war veterans with PTSD. In guided mental imagery, PTSD patients listen to scripts of both neutral (e.g. a beach sunset) and traumatic events. These events may be fictional or may be based upon real events in the patient's life. After listening to the script, the patient is instructed to imagine the events described in the script while the brain imaging is being conducted. Both trauma stimulus exposure and mental imagery of trauma reliably produce both subjective reports and objective physiological measures of anxiety in patients with PTSD.

Disturbances in sensory processing are believed to play a prominent role in the hyperarousal symptoms of PTSD such as the exaggerated startle response. Evoked potentials (also known as event-related potentials) have provided the most important tool to date in the study of sensory processing in PTSD. Previous PTSD studies have reported abnormalities in the P300 component of the evoked potential (so called because it is the major positive deflection that occurs at around 300 ms after the stimulus onset), which measures attention-dependent conscious processing of target and distractor events. These P300 disturbances may in fact reflect attentional deficits, which have also been measured by neuropsychological paradigms such as the Stroop test [15] and digit-recognition tasks [16]. Two studies in 1999 applied the use of evoked potentials to the study of PTSD sensory processing. One study reported that women with sexual-assault-related PTSD displayed abnormalities in evoked potential mismatch-negativity at the P50 time point when compared with controls [17^{**}]. In the mismatch negativity protocol, the subject is presented with two auditory stimuli. The first is

a frequently repeated “standard” sound. The second is an infrequently repeated “deviant” or “oddball” sound that differs in frequency from the standard sound. The electrical activity in the brain provoked by the two sounds produces distinct waveforms that are measured during an evoked potential session. The difference in the amplitude of the waveforms evoked by the two sounds is known as the mismatch negativity. We have known for some time that patients with PTSD exhibit an exaggerated mismatch at the P300 time point. However, the fact that patients with PTSD demonstrate an exaggerated mismatch as early as 50 milliseconds (i.e. P50) after the stimulus exposure (when the sound has not yet reached conscious awareness) indicates that abnormalities in sensory processing occur independently of the attentional deficits previously measured at the P300 time component. A second recent study reported that the P1 (i.e. the first positive deflection) component of an auditory evoked potential exhibited reduced sensory gating both in women with rape-related PTSD and in men with combat-related PTSD [18]. Sensory gating deficits of the P1 auditory evoked potential suggest that patients with PTSD have difficulty filtering incoming auditory stimuli. Future research using fMRI may allow for the identification of the neuroanatomical loci associated with these disturbances in sensory processing.

Memory processing is also disturbed in PTSD. Memory is often conceptually organized into explicit and implicit components. Explicit memory comprises verbal recall and a storage buffer known as working memory. Implicit memory consists of embedded knowledge evident during the performance of learned tasks. The neuroanatomical loci of memory processing include both subcortical structures (e.g. the hippocampus and amygdala) and cortical regions (e.g. the prefrontal, anterior cingulate, and orbitofrontal cortices).

The hippocampus is involved in the verbal recall aspect of explicit memory. Although one recent study detected no difference in hippocampal volume in children with abuse-related PTSD [19], right-sided hippocampal atrophy in adult PTSD patients associated with measurable deficits in verbal recall has been reported [20]. Stress-related hippocampal atrophy appears to be a consequence of increased exposure to excitatory amino acids and glucocorticoids. An earlier report noted increased right parahippocampal activation in a PET study of Vietnam veterans with PTSD when presented with traumatic stimuli. One 1999 PET study reported decreased right hippocampal activation during script-driven guided mental imagery of traumatic experiences in women with childhood abuse-related PTSD when compared to sexually abused women without PTSD [21].

The amygdala plays a key role in consolidating the emotional significance of events. Thus, this region has played a crucial role in our understanding of conditioned fear processing, a process that is important in the pathophysiology of PTSD. In fact, laboratory animal studies have clearly

demonstrated that the central nucleus of the amygdala is one of the critical neuroanatomical loci in the development of the fear-potentiated startle (one of the hyperarousal symptoms of PTSD). In a SPECT study comparing Vietnam combat veterans with PTSD to combat veterans without PTSD and to noncombatant controls, only the PTSD group exhibited left amygdala activation in response to exposure to combat sounds [22].

Of the cerebrocortical regions, the prefrontal cortex appears to play a seminal role in the working memory component of explicit memory and may play a counter-regulatory role in the stress response through inhibitory effects upon the amygdala. Alterations in prefrontal cortical activity may explain the deficits in explicit memory function often seen in PTSD. The anterior cingulate gyrus is responsible for the maintenance of social mores, fear-related behavior, and selective attentional processing (as evidenced by the Stroop task). Anterior cingulate dysfunction may therefore play a role in the re-experiencing phenomena reported in PTSD. Also involved in conditioned fear processing and its extinction is the orbitofrontal cortex. A conditioned fear response occurs when a conditioned stimulus (e.g. a light) is repeatedly paired with an unconditioned stimulus (e.g. a shock) such that the fear response occurs to the conditioned stimulus alone. Extinction (i.e. loss of the fear response to the conditioned stimulus) eventually occurs when the conditioned stimulus is repeatedly shown without the accompanying unconditioned stimulus. Because the orbitofrontal cortex is crucial to the process of extinction, orbitofrontal dysfunction probably contributes to the tenacity of the hyperarousal symptoms such as the exaggerated startle response in patients with PTSD. Finally, explicit memory buffers in the various sensory association cortices and the motor cortex appear to be activated when PTSD patients are exposed to traumatic cues, and thus are likely to play a role in the pathophysiology of re-experiencing.

Several new studies have used functional imaging techniques to study cortical functioning in PTSD patients. For example, the guided mental imagery PET study previously discussed [20] also delineated relatively greater increases in activation of the anterior prefrontal cortex but not the anterior cingulate in PTSD subjects when compared to controls. Another guided-mental imagery PET study comparing women with childhood abuse-related PTSD to abused women without PTSD reported comparatively greater increases in orbitofrontal and anterior temporal cortical activation, comparatively small increases in anterior cingulate activation, and decreases in left inferior frontal activation in PTSD subjects [23*]. Consistent with these results is a PET study [24] in which Vietnam veterans with PTSD were exposed to combat sounds and pictures; decreased medial prefrontal blood flow and relatively smaller increases in anterior cingulate activity were found in PTSD patients when compared with Vietnam combat veterans without PTSD. Two new SPECT studies in which subjects were exposed to combat sounds have

provided contrasting results. In the first study, no differences in cortical activation were found between Vietnam combat veterans with and without PTSD or noncombatant controls [22]. In contrast, in the second SPECT study in which Vietnam veterans with PTSD were exposed to combat sounds, greater increases in medial prefrontal cortical activity in the patients with PTSD were revealed when compared to combat veterans without PTSD and noncombatant controls [25]. Consistent among all these studies is the fact that brain regions involved in the processing of memory, emotion/fear, and visuospatial orientation demonstrate functional aberrations in patients with PTSD.

Psychoneuroendocrinology

Hypothalamic–pituitary–adrenal axis

The classic HPA axis response to stress is hierarchically organized, with increases in hypothalamic CRF secretion that in turn increase the release from the pituitary of adrenocorticotropin hormone (ACTH), and ultimately increase the adrenocortical release of cortisol. Patients with major depression exhibit, as a group, both CRF hypersecretion and hypercortisolemia. Furthermore, negative feedback within the HPA axis has been shown to be dysfunctional in depression (e.g. see [26,27]).

The HPA axis in PTSD patients appears to distinguish this diagnostic group both from healthy volunteers and from patients with depression. Like those with depression, PTSD patients hypersecrete CRF, as evidenced by elevated levels of CRF in cerebrospinal fluid (CSF) and a blunted ACTH response to CRF stimulation. However, the similarities may end here. In contrast to studies of patients with major depression, most PTSD studies have, surprisingly, demonstrated subnormal cortisol levels despite the increased release of CRF. Moreover, studies indicating cortisol ‘super-suppression’ in the dexamethasone suppression test (DST), a test of HPA axis negative feedback) and increased density of glucocorticoid receptors on peripheral lymphocytes suggest that hypocortisolemia in PTSD may be a consequence of exaggerated HPA axis negative feedback. These findings are in stark contrast to the findings in patients with major depression.

There were several key additions in 1999 to the study of HPA axis function in PTSD. Perhaps the most important is a study of CRF hypersecretion, using the technique of serial CSF sampling [28•]. This study reported elevated CSF CRF concentrations collected repeatedly over a 6 hour period, but normal urinary free-cortisol concentrations in combat veterans with PTSD when compared to both noncombatants and combat veterans without PTSD. The use of serial CSF sampling eliminated the potentially confounding effects of procedure-associated anxiety and HPA axis diurnal variation.

Another controversial issue is the amplification of HPA axis negative feedback reported in PTSD patients. Although earlier reports of lymphocyte glucocorticoid

receptor up-regulation suggest a mechanism for this enhanced feedback, no studies have investigated receptor changes within the CNS. A novel laboratory animal study utilizing a stress sensitization model [29•] has attempted to remedy this deficiency by measuring post-stress changes in hippocampal glucocorticoid receptor messenger RNA (mRNA) expression in rats. In comparison to non-stressed animals and those exposed to chronic stress, rats undergoing an acute stress paradigm exhibited the prototypical enhanced HPA axis feedback seen in PTSD. Furthermore, the acutely stressed rats demonstrated increased hippocampal glucocorticoid receptor mRNA expression but decreased hippocampal mineralocorticoid receptor mRNA expression.

The provocation of symptoms by use of psychosocial stress is potentially an important tool in anxiety disorders research. This is particularly true in PTSD, an illness in which symptomatic exacerbation is typically precipitated by trauma-related cues. Recognizing this fact, one study this year used a psychosocial symptom-provocation design, exposing Vietnam veterans with and without PTSD to combat sounds [30]. Combat veterans with PTSD exhibited higher baseline plasma cortisol levels than controls, but no differences in either baseline plasma ACTH levels, ACTH responses to the stressor, or cortisol responses to the stressor. Methodological difficulties unfortunately hindered this study. In particular, the baseline measures were collected just prior to exposure to the stressor. Therefore, these measurements may not represent a true baseline but may be confounded by the anticipatory anxiety of the imminent stress exposure.

Another study published this past year reported the surprising finding of elevated urinary free cortisol in prepubertal children with PTSD when compared to controls and non-traumatized children with another anxiety disorder [31]. It is unclear whether this discrepant finding of elevated cortisol in childhood PTSD indicates that the neurobiology of childhood PTSD is distinct from the frequently reported relative hypocortisolemia of adult PTSD, or whether this is an artifactual consequence of the inherent methodological differences in conducting pediatric as opposed to adult research. Furthermore, it is unknown whether children with PTSD would adapt via maturational processes to the pattern of HPA axis activity reported in adults with PTSD.

Finally, an interesting pilot study of rescue workers endeavors to address the need for early detection in persons at high vocational risk for traumatic exposure [32•]. Although none of the rescue workers in this study fulfilled diagnostic criteria for PTSD, elevations in evening salivary cortisol were correlated with subsyndromal posttraumatic avoidance symptoms. Longitudinal follow-up studies are required in order to ascertain whether these early changes are predictive of subsequent illness. In addition, further prospective study of known high-risk populations (before,

during and after trauma exposure) should provide an opportunity to investigate the pathogenesis of PTSD.

Hypothalamic–pituitary–thyroid axis

Although there is long-standing evidence of an association between traumatic stress and the onset of clinical hyperthyroidism, a paucity of hypothalamic–pituitary–thyroid (HPT) axis research has been conducted in PTSD. The available studies do, however, indicate increased HPT axis activity in PTSD [12,13**]. In particular, peripheral measures of both the total and the free fractions of tri-iodothyronine (T_3) and thyroxine (T_4) show that these are elevated in PTSD patients. Furthermore, T_3 elevations are disproportionately higher than T_4 elevations, suggesting enhanced peripheral deiodination of T_4 to the more biologically active T_3 form of the hormone. Interestingly, in the standard thyrotropin-releasing hormone (TRH) stimulation test, an exaggerated thyrotropin-stimulating hormone (TSH) response has been reported in PTSD patients in contrast to the blunted TSH response observed in depression, although some depressed patients also exhibit an enhanced response.

In this past year's lone contribution to the study of the HPT axis, World War II combat veterans with PTSD were studied [33*]. Paralleling previous findings, baseline measures of both total T_3 and free T_3 were elevated. In addition, these elevations correlated with the severity of PTSD hyperarousal symptoms. By contrast, T_4 and thyroxine-binding globulin (TBG) were not elevated as had been reported in previous studies of Vietnam veterans. This new study incorporates a unique patient sample who were over 50 years removed from their traumatic exposure, thereby further documenting the chronicity of HPT axis changes in PTSD. This study raises the possibility, however, that some of these changes may attenuate over time.

Neurotransmitter studies

Norepinephrine

Norepinephrine (NE) is by far the most thoroughly studied classical neurotransmitter involved in the biological response to traumatic stress. Since World War II, psychophysiological research has demonstrated physical responses to stress suggestive of increased sympathetic tone such as tachycardia, hypertension, diaphoresis, and dizziness. These physiological measures are accompanied by evidence of NE hypersecretion. For example, numerous studies have reported increased urinary concentrations of both NE and epinephrine (EPI) in patients with PTSD. These findings were confirmed by a recent study in children in which those suffering from abuse-related PTSD exhibited higher levels of urinary NE than both controls and children with non-trauma related anxiety [31]. Baseline plasma levels of NE are not elevated; however, physical exercise or exposure to trauma-related stimuli increases plasma concentrations of NE, EPI, and their metabolites in those with PTSD [30]. Previous research has also demonstrated that intravenous administration of

the α_2 receptor antagonist yohimbine, which results in increased NE activity, precipitates flashbacks and panic attacks in most PTSD patients. A case series published this past year indicates that oral yohimbine can also exacerbate PTSD symptomatology [34].

Recent PTSD research has focused on NE receptors and related second-messenger systems. These studies have investigated the density and affinity of both α_2 and β_2 NE receptors with mixed results. Most earlier α_2 receptor studies reported decreases in platelet α_2 receptor density, but measures of α_2 receptor function have produced inconsistent results. The lone 1999 study of α_2 receptors contrasted with previous findings in that the authors reported increased platelet α_2 receptor density in combat veterans with PTSD with no alterations in receptor affinity of G-protein coupling [35]. β_2 receptor measures in PTSD have likewise been inconsistent with studies reporting either impaired or unaltered β_2 -mediated signal transduction. The only 1999 study of β_2 receptors reported increased neutrophil β_2 receptor density and enhanced β_2 receptor G-protein coupling in combat veterans with PTSD [36].

Finally, NE hyperactivity may have an impact on lipoprotein metabolism. One study this year reports that Vietnam veterans with PTSD exhibited elevated total cholesterol, triglycerides and low-density lipoprotein, but reduced high-density lipoprotein, in comparison to civilians participating in a substance abuse treatment program [37*]. Although this study was hindered by confounds in its comparator group, it identifies yet another avenue for investigating the implications of noradrenergic dysfunction in PTSD [30].

Other neurotransmitter systems

Dopamine (DA) and glutamate hyperactivity have also been postulated to play a role in the neurobiology of PTSD. Previous PTSD research has demonstrated increased urinary and serum concentrations of DA and its major metabolite, homovanillic acid; however, this year's contributions bring into question the notion that DA hyperactivity plays a significant role in PTSD [38,39].

Glutamate enhances NE tone and is believed to contribute to the hippocampal atrophy associated with chronic stress. Nevertheless, little research has specifically focused on its role in PTSD. In 1999, an animal predator exposure model potentially relevant to PTSD was used to study glutamate/NMDA-receptor-mediated responses to stress [40**,41*]. These studies demonstrated that pretreatment with a NMDA-receptor antagonist (particularly in the left amygdala) prior to the predator exposure abolished the post-exposure anxiety that had been demonstrated previously. By contrast, administration of an NMDA antagonist after the predator exposure did not block post-exposure anxiety.

Serotonin (5-hydroxytryptamine [5HT]), GABA and endogenous opiates (i.e. endorphins and enkephalins) are

counter-regulatory neurotransmitters that serve to dampen NE neuronal firing in the locus coeruleus. Perhaps the best grounds for proposing that a 5HT dysfunction exists in PTSD resides in the beneficial treatment effects of serotonergic antidepressants; however, other evidence — including decreased serum concentrations of 5HT [42], decreased density of platelet 5HT uptake sites [43], and a blunted prolactin response to D-fenfluramine (indicative of central 5HT hypoactivity) [44] — suggests that 5HT activity is decreased in PTSD patients.

Pharmacological probes of GABA activity (e.g. β -carbolines), animal models of benzodiazepine-receptor mediated GABAergic function, and the clinical efficacy of benzodiazepines in relieving the re-experiencing and hyperarousal symptoms all suggest that GABA function may be impaired in PTSD [45,46].

Endogenous opiates may contribute to the occurrence of stress-induced analgesia, dissociative symptoms, and possibly the high rate of opiate abuse in patients with PTSD. The limited opioid research in PTSD has produced mixed results, indicating decreased baseline levels but increased post-stimulation levels of β -endorphin. These findings are not necessarily contradictory. It is plausible that during acute stress CRF hypersecretion elevates the secretion of opioids; however, chronic CRF hypersecretion might downregulate pituitary CRF receptors, resulting in lower baseline concentrations of β -endorphin. Clearly, further study is needed. Interestingly, an open label trial (i.e. there was no placebo control) of the opioid receptor antagonist naltrexone in patients with PTSD was reported to decrease the frequency of flashbacks and other dissociative phenomena [47].

Psychoneuroimmunology

It has long been assumed that stress has a deleterious impact on the function of the immune system; however, research results have been inconsistent. Investigations of the association between stress and immunological disturbance include measures of both cellular and humoral immunity [48]. Cellular immunity refers to the infection-fighting capacity of immune cells such as lymphocytes, neutrophils, macrophages, and natural killer cells. Measures of cellular immunity include the absolute numbers of cells, the ability of these cells to attack invading organisms, and the ability of these cells to proliferate in response to an invading organism. Humoral immunity refers to the capacity for the immune system to produce substances that ward off invading organisms. Measures of humoral immunity include antibody titers, and concentrations of regulatory cytokines such as the interferons and interleukins. In depression, cellular immunity studies have, on the whole, suggested a pattern of immunosuppression. However, components of the humoral immune system are often activated in depressed patients.

How can immunosuppressive measures such as decreased natural killer cell activity be reconciled with this apparently

contradictory evidence of immunoactivation? One hypothesis is that stress induces bi-directional, homeostatic interactions between the neuroendocrine and neuroimmunological systems. In depression, increased CRF secretion has been associated with humoral immunoactivation, as shown by increased proinflammatory cytokine release. These cytokines, in turn, appear to augment HPA axis function by promoting additional CRF release and by inducing glucocorticoid resistance that impairs negative feedback within the HPA axis. Conversely, HPA hyperactivity also elicits immunosuppression, which is reflected by observations of decreased natural killer cell activity. In summary, depression produces a mixed picture of immunological activation, immunological suppression, and HPA axis hyperactivity.

The limited immunological research database in PTSD patients suggests that immune system alterations in these patients may be distinct from those observed in depressed patients, just as HPA axis pathophysiology appears to be. PTSD studies (including two from this past year [49,50]) demonstrate increased levels of interleukin-6, indicating humoral immunity activation that parallels similar findings in depression. However, cellular immunity measures in PTSD and depression appear to differ. Although most cellular immunity studies in depression indicate immunosuppression, two of three PTSD studies in 1999 suggest that cellular immunity may in fact be activated [51,52,53].

Although these results are clearly preliminary at best, they suggest potential differences in the immune system responses in patients with depression and those with PTSD that are of heuristic value. CRF hypersecretion and humoral immunoactivation are common to both disorders and may represent a shared pathophysiology. In depression, CRF hypersecretion precipitates hypercortisolemia that may, in turn, produce cellular immunosuppression. However, most PTSD studies have demonstrated low to normal cortisol levels despite increased levels of CRF. Consequently, the relative hypocortisolemia of PTSD may preserve or even exaggerate cellular immune activity.

Conclusions

The vast literature regarding the neurobiology of stress and depression has provided a template for PTSD research. Therefore, it is understandable that the bulk of neurobiological research to date has focused upon the NE and HPA axis stress response systems. Although research to date provides an unsatisfyingly incomplete picture, there is increasing evidence that the neurobiology of PTSD is truly distinct from other mental disorders. It remains unclear, however, which of the neurobiological alterations observed in PTSD thus far are a direct consequence of the disorder itself, and which are a consequence of homeostatic adaptations to trauma exposure independent of any illness.

The future of PTSD neurobiological research will undoubtedly center upon efforts to integrate the disparate findings within and among numerous biological systems. Multi-system correlational studies will attempt to delineate not only specific measurable alterations, but also the role that (presumably bi-directional) inter-system mechanisms play in perpetuating the chronic changes witnessed in PTSD neurobiology. A myriad questions remain. How can PTSD be associated with both hypersecretion of CRF and low levels of circulating cortisol? Does the limited data from studies of immune system alterations in PTSD truly indicate that this is an inflammatory disorder? How can we apply our knowledge of the neural circuitry involved in fear responses to the results of functional neuroanatomical studies? The issue of comorbidity, particularly with affective disorders and substance abuse, is a potentially knotty one.

This review obviously is intended not as a definitive treatise on the topic, but instead as a snapshot of the work in progress. There is much to be learned that may ultimately serve not only to increase our knowledge of the neurobiology of stress and anxiety but also to suggest new treatments for this chronic and debilitating illness.

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- of outstanding interest

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