What Might the Psychobiology of Posttraumatic Stress Disorder Teach Us About Future Approaches to Pharmacotherapy?

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This review considers future directions for developing effective drugs for posttraumatic stress disorder (PTSD). At present, we have embarked upon an empirical approach in which pharmacologic research consists of clinical trials with agents, such as antidepressants, anxiolytics, and anticonvulsants, initially developed for different purposes. The approach taken here is theoretical rather than empirical, starting with what is known about the unique pathophysiology of PTSD and then predicting the types of pharmacologic agents that might prove effective in the future. Such classes of compounds include corticotropin-releasing factor antagonists, neuropeptide Y enhancers, antiadrenergic compounds, drugs to down-regulate glucocorticoid receptors, more specific serotonergic agents, agents normalizing opioid function, substance P antagonists, *N*-methyl-D-aspartate facilitators, and antikindling/antisensitization anticonvulsants. *(J Clin Psychiatry 2000;61[suppl 7]:44–51)*

The pathophysiology of posttraumatic stress disorder (PTSD) is very complex. Patients with the disorder exhibit abnormalities in many psychobiological systems.[1,2] Such findings provide important information that should guide current pharmacologic practice and the future development of new drugs. The aim of such a rational pharmacologic strategy is to identify drugs whose actions can normalize the specific psychobiological alterations associated with PTSD.

The current approach to PTSD pharmacotherapy has been empirical rather than theoretical. A number of drugs, proven safe and effective for other disorders, are now being tested on PTSD patients. The majority of these are antidepressants that potentiate serotonergic mechanisms through presynaptic selective serotonin reuptake inhibition or by combining this action with blockade at postsynaptic serotonin-2 (5-HT_2) receptors (e.g., nefazodone). It is certainly reasonable to test such drugs in PTSD since (1) PTSD patients exhibit abnormalities in 5-HT function and (2) PTSD patients often exhibit comorbid disorders that are responsive to such medications. As I have pointed out elsewhere, "the fact that an SSRI [selective serotonin reuptake inhibitor] might produce symptom relief does not necessarily mean that the primary problem is a 5-HT system abnormality. It may mean that 5-HT neurons exert indirect rather than direct effects through their modulation of other neurobiologic systems."[3(pp464–465)] Indeed, an indirect rather than direct action might explain why SSRI treatment is often palliative rather than curative. Perhaps we would have better success if we could develop medications that directly reverse PTSD-related psychobiological abnormalities since such agents might be expected to have the greatest clinical efficacy.

We will now undertake such a conceptual approach. Instead of a typical review in which we begin by listing different classes of drugs and discuss the empirical literature on their efficacy against PTSD symptoms, we will begin with the pathophysiology itself. In other words, we will begin with key components of the human stress response that appear to be expressed differently among people with PTSD. Those include corticotropin-releasing factor (CRF), the adrenergic nervous system, and the hypothalamic-pituitary-adrenocortical (HPA) axis. We will also consider other mechanisms involved in the human stress response, which, although less well studied, may be important in the development of novel drugs for PTSD.

CORTICOTROPIN-RELEASING FACTOR

CRF is the ignition switch for the human stress response. It stands at the head of the cascade of adrenergic, HPA, immunologic, and other neurohumoral responses that

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have evolved for coping and adaptation to stress. If a fundamental aspect of the pathophysiology of PTSD is an altered stress response, one would predict that CRF function would be abnormal in people with the disorder. Indeed, that has been shown to be the case in the one study on this question, in which Bremner et al.[4] observed elevated CRF levels among Vietnam veterans with PTSD. Should this finding be replicated with other PTSD cohorts, it would confirm the hypothesis that the pathophysiology of PTSD is unique from that of other psychiatric disorders and that it can be partially understood within the theoretical context of the human stress response. It would also suggest that an effective treatment strategy would be to block excessive CRF before it ignites the cascade of adrenergic, HPA, immunologic, and other downstream mechanisms. CRF antagonists are one class of drugs that might perform such a function. A number of experimental CRF antagonists are currently being developed, and it will be exciting to see how they perform clinically as soon as they are safe for testing in humans with PTSD.

NEUROPEPTIDE Y

A second class of drugs that might also prove effective in the treatment of PTSD is neuropeptide Y (NPY) enhancers. NPY is heavily concentrated in the brain stem, amygdala, hypothalamus, and cortex and is believed to function as an endogenous anxiolytic. It appears to attenuate the actions of CRF and other stress-released peptides. Animal research suggests that NPY buffers the impact of the stress response.[5] Preliminary trials with military personnel undergoing arduous basic training have shown that those individuals with the highest NPY levels tolerated excessive stress better than those with lower levels.[6] This intriguing finding suggests that a pharmacologic agent that could promote higher NPY levels might provide clinically significant protection against excessive CRF secreted during abnormal stress responses such as PTSD. From the perspective of the present review, it suggests that a high priority in the future development and testing of drugs for PTSD should be agents that enhance NPY function, thereby reducing the production, secretion, or actions of CRF.

THE ADRENERGIC SYSTEM

One of the most robust findings in PTSD research has been heightened and dysregulated adrenergic function. This abnormality is indicated by hyperresponsiveness of the sympathetic nervous system, by elevated 24-hour urinary catecholamine levels, and by abnormal sensitivity to the adrenergic α_2 antagonist yohimbine. In contrast to non-PTSD subjects, PTSD patients who have been administered yohimbine exhibited excessive startle responses, panic attacks, dissociative symptoms, and abnormalities in cerebral blood flow.[7]

This finding is entirely consistent with the conceptual perspective that the pathophysiology of PTSD reflects abnormalities in the human stress response. Indeed, the first research in this area was by Walter Cannon,[8] whose "flight or fight response" was the first scientific description of the excessive adrenergic response to threat that is a major component of the human stress response. We have learned much more since Cannon's day about the neuroanatomy and neurophysiology of this mechanism. Aston-Jones and associates[9] have shown that CRF activates the adrenergic component of the stress response through a direct action on the locus ceruleus, the nucleus containing the majority of adrenergic neurons in the brain. In addition to mobilization of autonomic, motor, and emotional reactions to threat, excessive adrenergic activity appears to be implicated in a number of abnormal responses that are of clinical significance in PTSD. These include hyperreactivity associated with hyperarousal (DSM-IV Criterion D) symptoms, indelible memories associated with intrusion (Criterion B) symptoms, and dissociation associated with avoidant/numbing (Criterion C) symptoms. Although anxiety, irritability, insomnia, and hyperreactivity are recognized indicators of excessive adrenergic activity, recent findings with Israeli patients seeking emergency room treatment (following terrorist attacks, motor vehicle accidents, or other acute events causing bodily harm) suggest that those individuals with an excessive adrenergic response (e.g., elevated pulse rate) were more likely to develop PTSD than others.[10] With regard to memory, animal and human research indicates that adrenergic mechanisms enhance memories of events that provoke a heightened emotional response.[11,12] The adaptive value of such a mechanism is obvious since survival is enhanced when one has a clear memory of previously encountered life-threatening situations. Finally, Southwick and associates[13] have shown that yohimbine infusions can produce PTSD flashbacks, a dissociative reaction, in patients with PTSD.

Taken together, these findings suggest that antiadrenergic drugs might have an important role in PTSD as treatment for hyperarousal, intrusion, and dissociative symptoms. In addition, such results suggest that antiadrenergic drugs might have utility as prophylactic agents for acutely traumatized individuals by preventing an excessive sympathetic response[14] and by preventing the overconsolidation of traumatic memories.[15]

Given all of these reasons, it is surprising that so little attention has been paid to safe and effective β-adrenergic antagonists such as propranolol and α_2 agonists such as clonidine and guanfacine, which have proven clinical efficacy as antiadrenergic agents. Indeed, there are no randomized trials with any of these drugs and only a few open trials. One trial with propranolol[16] had an A-B-A design (6 weeks baseline—6 weeks on drug—6 weeks off drug) with 11 abused children with PTSD, in which each child served as his/her own control. During the drug phase, most

children reported significant reductions in intrusion and arousal symptoms, which relapsed to pretreatment severity after propranolol was discontinued.[16] In 2 other small trials, propranolol was an effective PTSD treatment for Vietnam veterans but not for Cambodian refugees.[17]

Clonidine has been more consistently successful in 4 small trials with Vietnam veterans, Cambodian refugees, and abused children,[17] but has not been subjected to a rigorous drug trial. Guanfacine, another α_2 agonist that has recently drawn attention because it has a more sustained duration of action than clonidine, is currently being tested. Finally, clonidine was used successfully in an augmentation study with Cambodian refugees in which a clonidine/imipramine combination was more effective than either drug alone.[18] Given the modest success of monotherapy in PTSD with most drugs tested to date, augmentation strategies may be an important approach to explore systematically in future clinical pharmacologic research.

To summarize, although propranolol and clonidine can hardly be considered drugs of the future (like CRF antagonists and NPY enhancers), they are relatively new as far as PTSD treatment trials are concerned. The more we learn about the major contribution of adrenergic dysregulation to the pathophysiology of this disorder, the more imperative it becomes to begin systematic testing of these agents.

HPA AXIS

HPA axis dysregulation is a distinctive abnormality of PTSD that sets it apart from other psychiatric disorders.[2] HPA axis activation is a key component of the human stress response and has been recognized as such since the seminal work of Hans Selye,[19] who called it the "general adaptation response." As Yehuda and associates[2,20] have shown, PTSD patients exhibit a unique HPA profile (distinct from that seen in depression) marked by lower cortisol levels, upregulation of glucocorticoid receptors, and supersuppression to dexamethasone. The enhanced negative feedback of the HPA system is a well-established finding that has been replicated in several independent laboratories. What has not been established, however, is the clinical significance of this finding. I have suggested elsewhere that HPA-enhanced negative feedback may underlie the stress intolerance seen in most PTSD patients who characteristically find the normal hassles and vicissitudes of life (e.g., child care, rush hour traffic) excessively upsetting and difficult to cope with.[3]

In the spirit of a conceptual approach that seeks treatments which will normalize the human stress response as early as possible, the first line of defense against the developement of PTSD might be expected to be a CRF antagonist or NPY enhancer, as noted previously. If, however, homeostatic alterations have already occurred, what other new pharmacologic approach might be worth testing? I have suggested elsewhere[3] that a novel and effective approach directly attacking a key pathophysiologic abnormality might be an attempt to down-regulate (and therefore normalize up-regulated) glucocorticoid receptors with a course of prednisone or some other glucocorticoid medication. Since 5-HT modulates HPA function, another possible approach might be to use an SSRI or related compound that is especially effective in producing such down-regulation.

THE SEROTONIN (5-HT) SYSTEM

Although the results of drug trials with SSRIs and other agents affecting 5-HT mechanisms is reviewed elsewhere in this supplement,[21] it is instructive to consider the role of 5-HT in the human stress response. Animal research suggests that 5-HT affects many fundamental brain mechanisms that are altered in PTSD, including sleep regulation, aggression, cardiovascular activity, motor function, anxiety, mood, and neuroendocrine secretion. Most notably, 5-HT neurons have direct effects on both adrenergic and HPA function.[7] In a clinical study of Vietnam veterans with PTSD, Southwick et al.[13] showed that the 5-HT agonist *m*-chlorophenylpiperazine (*m*-CPP), which primarily affects 5-HT_2 and 5-HT_{1C} receptors, produced panic attacks and flashbacks in some but not all research subjects. Of particular interest is that veterans with PTSD who exhibited such a response to *m*-CPP tended to differ from those who exhibited panic and flashbacks in response to yohimbine. This suggests that some PTSD syndromes may result primarily from 5-HT dysregulation, whereas others may be due to abnormal adrenergic mechanisms. The implications of this possibility for pharmacotherapy are enormous, since antiadrenergic agents might be the treatment of choice for one PTSD subtype whereas drugs that specifically target 5-HT might be needed for the other subtype.

With respect to future drug development, there are many different types of 5-HT receptors. Future research may help us identify which 5-HT receptors should be targeted to obtain the best outcomes for PTSD patients. We may hope to improve on the general 5-HT potentiation produced by SSRIs with more specific 5-HT receptor targets in the future.

THE OPIOID SYSTEMS

Opioid peptides include 3 sets of compounds, endorphins, dynorphins, and enkephalins, that bind to a number of different receptors distributed throughout the central nervous system (CNS). Since β-endorphin is derived from the same large precursor molecule, pro-opiomelanocortin, from which adrenocorticotropic hormone originates, it is also activated by CRF stimulation. There is abundant evidence that endogenous opioids play a role during the human stress response, especially with regard to a unique phenomenon called stress-induced analgesia, in which

stressful stimuli such as electric shock, forced swimming, and restraint produce diminished responsiveness to pain. Since stress-induced analgesia can be reversed by narcotic antagonists such as naloxone, it is clear that opioids are important mediators of this stress response.[5]

Opioids also affect posterior pituitary and gonadotropin hormone systems during the human stress response. Dynorphin and enkephalin inhibit the release of oxytocin, while leu-enkephalin and β-endorphin inhibit the secretion of vasopressin. In addition, CRF stimulation of opioid peptide–containing interneurons inhibits gonadotropin-releasing hormone. One clinical manifestation of this action is the amenorrhea or disrupted fertility sometimes seen in women who have been exposed to excessive psychological stress.[5]

For all these reasons and because there are many drugs that activate or antagonize opioid receptors, it is appropriate to consider opioid mechanisms in PTSD. Unfortunately, there are very little experimental data in this regard. Summarizing such research, it has been shown that PTSD patients exhibit lower pain thresholds, lower β-endorphin levels, decreased production and release of methionine-enkephalin, and (possibly) stress-induced analgesia.[17] With respect to the latter finding, Vietnam veterans exposed to a movie about combat (e.g., the movie *Platoon*), exhibited a naloxone-reversible stress-induced analgesia.[22] Unfortunately, this intriguing finding has not been replicated.

An interesting pharmacologic report concerns an open trial in which a narcotic antagonist had a biphasic action on Vietnam veterans with PTSD.[23] Some veterans experienced beneficial effects, reporting that they felt more alive, less numb, and less constricted emotionally. Others experienced intolerable anxiety, panic, arousal, and (in some cases) flashbacks. Glover[23] interpreted his findings as consistent with the hypothesis that opioids play a role in the emotional numbing seen in chronic PTSD. If it is presumed that numbing is an adaptive response that blunts otherwise intolerable PTSD-induced anxiety and arousal, one would certainly expect narcotic antagonists to help "numbed out" veterans with excessive opioid activity. On the other hand, one would predict that narcotic antagonists would precipitate intense anxiety in those veterans with inadequate baseline opioid levels. It does appear that the response to narcotic antagonists was clinically significant for all subjects in this trial, although it was significantly toxic for some and therapeutic for others. Perhaps careful titration with more selective opioid agonists or antagonists might produce more consistent and desirable effects. These findings are certainly intriguing and warrant further investigation.

THYROID FUNCTION

A series of findings that have received relatively little attention indicate that Vietnam veterans with PTSD exhibit excessive thyroid activity. Mason, Wang, and associates[24,25] have reported elevated triiodothyronine (T_3) and thyroxine (T_4) levels among 4 separate cohorts of veterans that, in a few cases, approached the range seen in clinical hyperthyroidism. Furthermore, the researchers found a linear relationship between PTSD symptoms and free T_3 levels.

Putting these findings in the context of the human stress response suggests that elevated thyroid function may really be a secondary effect of the more fundamental abnormalities in PTSD patients. During the normal stress response, thyroid axis function is decreased both with respect to reduced production of thyroid-stimulating hormone (TSH) and reduced conversion of T_4 to the more active T_3. There is evidence that such reduced thyroid axis activity is due to the inhibiting effect of elevated glucocorticoid levels produced by stress-induced HPA activation.[26]

In PTSD, however, the situation is reversed. Basal cortisol levels are lower than normal owing to the enhanced HPA negative feedback.[2,20] Thus, thyroid function may be increased because of reduced glucocorticoid (e.g., cortisol) inhibition. Therefore, the best treatment to correct PTSD-related elevations in thyroid function should focus on normalization of the HPA system rather than on the thyroid axis itself. Therefore, targeting the thyroid system with pharmacotherapy to ameliorate PTSD symptoms does not appear to be a useful strategy.

SUBSTANCE P

Substance P belongs to a family of neuropeptides called tachykinins. Until recently, its primary role was incorrectly understood to be a sensory neurotransmitter in spinal cord dorsal horn afferent unmyelinated C-fibers involved in transmitting painful stimulation. More recently, it has been shown that substance P is often co-located presynaptically in both adrenergic and serotonergic neurons and that substance P receptors are densely concentrated in brain regions that play a major role in the stress response and regulation of affective behavior (such as the amygdala, hippocampus, locus ceruleus, raphe nucleus, periaqueductal gray, hypothalamus, striatum, and nucleus accumbens[27,28]). In short, preclinical studies suggest that substance P may be an important new avenue to explore with respect to PTSD treatment.

Such theoretical speculations have recently become much more relevant given a successful clinical trial of the substance P antagonist MK-869 in depression.[29] In this randomized clinical trial, MK-869 was as effective as the SSRI paroxetine in reducing depressive symptoms as measured on the Hamilton Rating Scale for Depression. Such a study obviously needs replication. For our purposes, however, future testing of the capacity of substance P antagonists to modify the human stress response and ameliorate PTSD symptoms is of great theoretical and clinical signifi-

cance. It can be expected that such drug trials will be initiated within the near future, since substance P antagonists are being developed by a number of pharmaceutical companies for testing in depression, PTSD, and other anxiety disorders.

THE GLUTAMATERGIC SYSTEM

The excitatory neurotransmitter glutamate plays a very important role in the human stress response. Monoaminergic and opioid (e.g., adrenergic, serotonergic, and dopaminergic) responses to stress are modulated by glutamatergic neurons that act on crucial cortical and limbic structures involved in arousal, perception, motor function, information processing, and memory. Several preclinical studies have shown that glutamate function not only increases in response to stress, but that such increases are associated with increased monoaminergic transmission from subcortical nuclei.[30]

It is necessary to distinguish 2 types of glutamate receptors: NMDA and non-NMDA receptors. NMDA receptors mediate long-term changes in synaptic transmission associated with CNS plasticity; such changes underlie crucial information processing functions such as learning and memory. Non-NMDA receptors, on the other hand, are neuromodulators that influence the actions of monoaminergic neurotransmitters through their actions on postsynaptic membrane potentials.[30]

For purposes of this discussion, we will focus on NMDA receptor function because altered information processing is a key factor in the development and maintenance of PTSD-related cognitive psychological and psychobiological alterations through fear conditioning, operant avoidance conditioning, and altered memory function.[31,32] A unique series of experiments by Krystal and associates[30,33] has shown that when NMDA receptor antagonists, such as the anesthetic ketamine, are given to normal human volunteers, they can produce effects resembling the clinical phenomenon of dissociation. Following ketamine administration, healthy research subjects

> reported the sense of tunnel vision or constriction in the field of attention, subjective sense of time slowing, and increases or decreases in sensory activity in both auditory and visual modalities. . . . Subjects also reported changes in the sense of self. These identity alterations included depersonalization and derealization. Ketamine also induced impairments in executive cognitive functions involving planning, abstract reasoning, the control of attention and working memory.[30(p276)]

There is growing recognition that dissociation is a key component of acute stress disorder and, therefore, has prognostic implications for the later development of PTSD after exposure to a traumatic event. Furthermore, dissociation is a prominent and very disruptive symptom in PTSD after prolonged traumatization as in child sexual abuse or repeated torture during political incarceration. Therefore, the capacity to disrupt crucial information processing mechanisms such as perception, attention, judgment, and memory with NMDA antagonists suggests that this area should be a very important one for future drug development, since any pharmacologic agent that can protect against a dissociative response to extreme stress should protect against the development of PTSD, and any drug that can abolish dissociative symptoms would have an important place in PTSD treatment.

SENSITIZATION

One neuroplastic mechanism that has been proposed as an animal model for PTSD is sensitization/kindling. Post and associates[34,35] have been at the forefront of such research, in which it has been shown that repeated administration of a subthreshold excitatory agent such as cocaine produces a progressive increase in neuronal reactivity. As daily dose administration continues, neurons become sensitized so that the once-subthreshold dose can now produce marked neurophysiologic or behavioral effects that were not elicited at the outset. At its most extreme, such sensitization can produce seizures, in which case it is called *kindling*. Sensitization/kindling has been suggested as a model for cocaine dependence, epilepsy, recurrent psychosis, and PTSD. Although altered glutamatergic transmission via both NMDA and non-NMDA receptors appears to be one component of such a profound neuroplastic mechanism, changes in the whole cascade of synaptic messenger systems and regulator genes have been proposed.[34,35]

Clinical interest in sensitization/kindling models as applied to PTSD has led to a few open trials with anticonvulsants such as carbamazepine and valproate because of their efficacy as antikindling agents in laboratory paradigms. Positive results have been reported in these small open trials, especially with respect to PTSD arousal symptoms, but also, in some cases, with intrusion and avoidant/numbing symptoms.[17] Unfortunately, no randomized clinical trials have been carried out with either carbamazepine or valproate in PTSD. There is renewed interest in anticonvulsant treatment for PTSD with industry-sponsored testing of newer agents such as lamotrigine and gabapentin. This area is obviously of great interest and has potential clinical implications.

TOWARD NEW PHARMACOTHERAPY FOR PTSD

Table 1 summarizes the previous discussion and offers a few suggestions for future research and development on pharmacotherapy for PTSD. It is, essentially, a theoretical map that presents our current thinking about pathophysiological abnormalities associated with specific psycho-

Table 1. Toward New Pharmacotherapy for Posttraumatic Stress Disorder (PTSD)[a]

Neurobiological System	Proposed Abnormality in PTSD	Possible Clinical Abnormality	Proposed Treatment
CRF	Elevated	Anxiety, arousal, depression	CRF antagonists
NPY	Reduced?	Anxiety, arousal, depression	NPY enhancers
Adrenergic	Hyperreactive	Hyperarousal, intrusion, dissociation, panic/anxiety	α_2-Adrenergic agonists β-Adrenergic blockers
HPA	Enhanced negative feedback	Stress intolerance	SSRIs? glucocorticoids?
5-HT	Systemic dysregulation	Broad spectrum PTSD symptoms: impulsivity, rage, aggression, depression, panic, obsessional thoughts, chemical dependency	SSRIs, nefazodone, more selective 5-HT agents
Opioid	Systemic dysregulation	Numbing, chemical dependency	More selective opioid agonists or antagonists
Thyroid	Elevated	Hyperarousal	None
Substance P	Elevated?	Anxiety? depression?	Substance P antagonists?
Glutamate	Impaired NMDA receptor transmission	Dissociation, impaired information processing and memory	NMDA facilitators?
Limbic/cortical neuronal excitability	Sensitization/kindling	Hyperarousal, reexperiencing	Anticonvulsants

[a]Abbreviations: 5-HT = serotonin, CRF = corticotropin-releasing factor, HPA = hypothalamic-pituitary-adrenocortical, NMDA = *N*-methyl-D-aspartate, NPY = neuropeptide Y, SSRI = selective serotonin reuptake inhibitor.

biological systems, my own guesses about the clinical significance of such abnormalities, and, finally, theoretically driven suggestions for drug trials that might be expected to reverse such alterations.

SUMMARY

1. CRF

As stated earlier, normalization of CRF function might be the therapeutic target most likely to have the greatest impact, since CRF is the ignition switch for the entire human stress response and sets in motion the complex cascade of downstream reactions. CRF antagonists are currently being developed by a number of pharmaceutical firms, and it is hoped that safe agents will be ready for testing in the near future.

2. NPY

Another class of drugs that would be expected to physiologically antagonize CRF activity are NPY enhancers. Given preliminary findings suggesting that increased NPY levels can buffer or protect against the impact of stress in humans exposed to extreme conditions, it would appear that development and testing of NPY enhancers is a promising direction for future research.

3. Adrenergic System

Adrenergic abnormalities are well-established in PTSD research. Unfortunately, such knowledge has not spurred very many drug trials with antiadrenergic agents. That has begun to change recently because of clinical observations that the α_2-adrenergic antagonist yohimbine can precipitate dissociative symptoms, potentiate the startle response, and alter cerebral blood flow and can increase anxiety, panic, and arousal among PTSD patients.[4,7] Indeed, case reports of successful treatment of these symptoms with α_2-adrenergic agonists such as clonidine and guanfacine promise to stimulate renewed interest in these drugs.

New findings, suggesting that the β-adrenergic antagonist propranolol might have both a protective and therapeutic role in PTSD by preventing both the encoding of traumatic memories[12] and enhanced acute posttraumatic cardiovascular activity,[10] have renewed interest in this drug as well. Indeed, it is ironic that promising open trials with both drugs more than 15 years ago[36] have been largely ignored by clinical pharmacologists. But then again, better late than never.

4. HPA Axis

Normalization of enhanced HPA negative feedback might be accomplished through down-regulation of glucocorticoid receptors. This is, at best, a theoretical prediction that may fail to appreciate the complexity of HPA dysregulation in PTSD. It is, however, a novel approach that targets a major psychobiological abnormality associated with the disorder. Even if one could down-regulate glucocorticoid receptors through a course of treatment with a corticosteroid such as prednisone, could such changes be maintained? In other words, could one reset the glucocorticoid receptor homeostat to its pre-PTSD setting and achieve a sustained normalization of HPA function? These are empirical questions that merit investigation. An alternative strategy would be to effect such change by modifying serotonergic mechanisms that modulate glucocorticoid receptor function. It is possible that agents which target specific 5-HT receptors might be required to accomplish this goal, rather than drugs affecting global serotonin function such as SSRIs.

5. Serotonin System

SSRIs are currently the most effective drugs available for PTSD treatment, as discussed elsewhere in this supplement.[20] Although significant amelioration of all PTSD symptom clusters has been achieved with these drugs in multisite trials, they are not always effective. Therefore, it is reasonable to ask whether future research with more specific serotonergic agents will produce better results.

6. Opioid System

Opioid dysregulation clearly occurs in PTSD, although it has received little attention and is poorly understood. One interpretation of the current literature is that although steady-state opioid function is reduced, it can be episodically elevated during stressful situations. Furthermore, it appears that narcotic agonists and antagonists can produce clinically significant but variable effects in different PTSD patients, even though such effects may exacerbate rather than ameliorate disruptive symptoms. Given the extent of current knowledge about opioid function and the repertoire of pharmacologic agents with actions at opioid receptors, this is clearly an important area for future research.

7. Thyroid System

Enhanced thyroid function appears to be a robust finding in PTSD research, although it has only been demonstrated by one research group who have investigated combat veterans. Even if this finding can be replicated elsewhere, it appears to be a secondary effect due to abnormal CRF and glucocorticoid activity. Therefore, testing drugs whose primary action is on thyroid function does not seem to be a promising strategy for PTSD treatment.

8. Substance P

Substance P antagonists are an exciting theoretical possibility to consider, given the neuroanatomic distribution of substance P neurons and the likelihood that they play a significant role in the human stress response, especially through reciprocal actions with monoaminergic mechanisms. Such interest is fortified by a recent successful trial of a substance P antagonist as an antidepressant.[29] Testing substance P antagonists in PTSD is sure to come in the near future. We will just have to wait and see.

9. Glutamate

Glutamatergic mechanisms play a crucial role in many cognitive functions that are altered in PTSD such as perception, appraisal, learning, and memory. Glutamatergic dysregulation may be at the heart of significant symptoms such as intrusive memories, learning abnormalities, psychogenic amnesia, and dissociation. Better understanding of NMDA and non-NMDA receptor function and development of safe and specific agents that can normalize such psychobiological abnormalities should prove to be an exciting and relevant focus in pharmacologic research and development.

10. Anticonvulsants

Given the promise of open-label studies with carbamazepine and valproate and the theoretical implications of such findings, drugs affecting the complex processes of sensitization and kindling should be tested systematically in future drug trials for PTSD treatment.

CONCLUSION

The purpose of this brief review is to stimulate new approaches to the pharmacotherapy of PTSD. Given the unique pathophysiology of this disorder, it seems that careful consideration of PTSD-related abnormalities in the human stress response should provide valuable hints for future pharmacotherapy of this disorder.

Drug names: carbamazepine (Tegretol and others), clonidine (Catapres and others), gabapentin (Neurontin), guanfacine (Tenex and others), lamotrigine (Lamictal), naloxone (Naprosyn and others), nefazodone (Serzone), paroxetine (Paxil), propranolol (Inderal and others), yohimbine (Yocon and others).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, the following agents are not approved for the treatment of posttraumatic stress disorder: carbamazepine, clonidine, gabapentin, guanfacine, lamotrigine, nefazodone, paroxetine, prednisone, propranolol, valproate.

REFERENCES

1. Friedman MJ. Progress in Psychobiological Research on PTSD. Seminars in Clinical Neuropsychiatry. Philadelphia, Pa: WB Saunders; 1999
2. Yehuda R. Biology of posttraumatic stress disorder. J Clin Psychiatry 2000; 61(suppl 7):14–21
3. Friedman MJ. Current and future drug treatment for posttraumatic stress disorder patients. Psychiatr Ann 1998;28:461–468
4. Bremner JD, Licinio J, Darnell A, et al. Elevated CSF corticotropin-releasing factor concentrations in post-traumatic stress disorder. Am J Psychiatry 1997;154:624–629
5. Stout SC, Kilts CD, Nemeroff CB. Neuropeptides and stress: preclinical findings and implications for pathophysiology. In: Friedman MJ, Charney DS, Deutch AY, eds. Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to PTSD. Philadelphia, Pa: Lippincott-Raven; 1995:103–123
6. Morgan CA, Wang S, Southwick SM, et al. Plasma NPY in humans experiencing acute uncontrollable stress. Biol Psychiatry. In press
7. Southwick SM, Paige SR, Morgan CA, et al. Adrenergic and serotonergic abnormalities in PTSD: catecholamines and serotonin. Semin Clin Neuropsychiatry 1999;4:242–248
8. Cannon WB. The Wisdom of the Body. New York, NY: Norton; 1932
9. Aston-Jones G, Valentino R, Van Bocksteele. Locus coeruleus, stress, and PTSD: neurobiological and clinical parallels. In: Murburg MM, ed. Catecholamine Function in Posttraumatic Stress Disorder: Emerging Concepts. Washington, DC: American Psychiatric Press; 1994:17–62
10. Shalev A, Freedman SA, Peri T, et al. Prospective study of posttraumatic stress disorder and depression following trauma. Am J Psychiatry 1998; 155:630–637
11. Gold PE, McCarty RC. Stress regulation of memory processes: role of peripheral catecholamines and glucose. In: Friedman MJ, Charney DS, Deutch AY, eds. Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to PTSD. Philadelphia, Pa: Lippincott-Raven; 1995:151–162
12. Cahill L. A neurobiological perspective on emotionally influenced, long-term memory. Semin Clin Neuropsychiatry 1999;4:266–273
13. Southwick SM, Krystal JH, Bremner JD, et al. Noradrenergic and serotonergic function in posttraumatic stress disorder. Arch Gen Psychiatry 1997; 54:749–758

14. Pitman R, Shalev AY, Orr SP. Posttraumatic stress disorder: emotion, conditioning, and memory. In: Gazzaniga MS, ed. The New Cognitive Neurosciences. 2nd ed. Cambridge, Mass: MIT Press; 2000:1133–1147
15. Cahill L. The neurobiology of emotionally influenced memory: implications for the treatment of traumatic memory. Ann N Y Acad Sci 1997;821: 238–246
16. Famularo R, Kinscherff R, Fenton T. Propranolol treatment for childhood post-traumatic stress disorder, acute type: a pilot study. Am J Dis Child 1988;142:1244–1247
17. Friedman MJ, Southwick SM. Towards pharmacotherapy for PTSD. In: Friedman MJ, Charney DS, Deutch AY, eds. Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to PTSD. Philadelphia, Pa: Lippincott-Raven; 1995:465–481
18. Kinzie JD, Leung P. Clonidine in Cambodian patients with posttraumatic stress disorder. J Nerv Ment Dis 1989;177:546–550
19. Selye H. The general adaptation syndrome and the diseases of adaptation. J Clin Endocrinol 1946;6:117–230
20. Yehuda R, Southwick SM, Krystal JH. Enhanced suppression of cortisol following a low dose of dexamethasone in combat veterans with posttraumatic stress disorder. Am J Psychiatry 1993:150:83–86
21. Pearlstein T. Antidepressant treatment of posttraumatic stress disorder. J Clin Psychiatry 2000;61(suppl 7):40–43
22. Pitman RK, van der Kolk BA, Orr SP, et al. Naloxone-reversible analgesic response to combat-related stimuli in post traumatic stress disorder. Arch Gen Psychiatry 1990; 47:541–544
23. Glover H. A preliminary trial of nalmefene for the treatment of emotional numbing in combat veterans with post-traumatic stress disorder. Isr J Psychiatry Relat Sci 1993;30:255–263
24. Mason JW, Wang S, Yehuda R, et al. Some approaches to the study of the clinical implications of thyroid alterations in post-traumatic stress disorder. In: Friedman MJ, Charney DS, Deutch AY, eds. Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to PTSD. Philadelphia, Pa: Lippincott-Raven; 1995:367–380
25. Wang S, Mason J. Elevations in serum T_3 levels and their association with symptoms in World War II veterans with combat-related posttraumatic stress disorder: replication of findings in Vietnam combat veterans. Psychosom Med 1999; 61:131–138
26. Michelson D, Licinio J, Gold PW. Mediation of the stress response by the hypothalamic-pituitary-adrenal axis. In: Friedman MJ, Charney DS, Deutch AY, eds. Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to PTSD. Philadelphia, Pa: Lippincott-Raven; 1995:225–238
27. Otsuka M, Yoshioka K. Neurotransmitter functions of mammalian tachykinins. Physiol Rev 1993;73:229–308
28. Rosen A, Brodin K, Eneroth P, et al. Short-term restraint stress and s.c. saline injection alter the tissue levels of substance P and cholecystokinin in the peri-aqueductal grey and limbic regions of rat brain. Acta Physiol Scand 1992;146:341–348
29. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism for antidepressant activity by blockade of central Substance P receptors. Science 1998; 281:1640–1645
30. Chambers RA, Bremner JD, Moghaddam B, et al. Glutamate and PTSD: toward a psychobiology of dissociation. Semin Clin Neuropsychiatry. 1999; 4:274–281
31. Foa EB, Kozak MJ. Emotional processing of fear: exposure to corrective information. Psychol Bull 1986;99:20–35
32. Brewin CR, Dalgleish T, Joseph S. A dual representational theory of posttraumatic stress disorder. Psychol Rev 1996;103:670–686
33. Krystal JH, Bennett A, Bremner JD, et al. Toward a cognitive neuroscience of dissociation and altered memory functions in post-traumatic stress disorder. In: Friedman MJ, Charney DS, Deutch AY, eds. Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to PTSD. Philadelphia, Pa: Lippincott-Raven; 1995:239–270
34. Post RM, Weiss SRB, Smith MA. Sensitization and kindling: implications for the evolving neural substrate of PTSD. In: Friedman MJ, Charney DS, Deutch AY, eds. Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to PTSD. Philadelphia, Pa: Lippincott-Raven; 1995:203–224
35. Post RM, Weiss SRB, Li H, et al. Sensitization components of posttraumatic stress disorder: Implications for therapeutics. Semin Clin Neuropsychiatry. 1999;4:282–294
36. Kolb LC, Burris BC, Griffiths S. Propranolol and clonidine in the treatment of the chronic post-traumatic stress disorders of war. In: van der Kolk BA, ed. Post-Traumatic Stress Disorder: Psychological and Biological Sequelae. Washington, DC: American Psychiatric Press; 1984:97–107