Research Review

NORADRENERGIC DYSFUNCTION AND THE PSYCHOPHARMACOLOGY OF POSTTRAUMATIC STRESS DISORDER

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The catecholamine norepinephrine is a critical effector of the mammalian stress response and has been implicated in the pathophysiology of posttraumatic stress disorder (PTSD)—a syndrome intrinsically related to the experience of extraordinary stress. Symptom-linked hypernoradrenergic derangements have been observed in PTSD and several studies have examined the potential therapeutic effects of agents that dampen the centrally hyperactive noradrenergic state. These agents include compounds that decrease norepinephrine release (e.g. centrally acting α_2 agonists such as clonidine) and those which block postsynaptic norepinephrine receptors (e.g. centrally acting α_1 or β receptor antagonists such as prazosin or propranolol). In this article, we review studies of central noreadrenergic hyperactivity under both basal and challenge conditions and explore the evidence for these derangements as potential psychopharmacologic targets in patients with PTSD. Given the significant involvement of CNS norepinephrine hyperactivity in PTSD, and its link to intrusive and hyperarousal symptoms, it is not surprising that interventions directed at this system have therapeutic potential in PTSD. The utility of these anti-adrenergics in the clinical treatment of PTSD remains to be determined, though it is possible that they may prove to have primary roles in a disorder that is only modestly responsive to antidepressant treatment. Depression and Anxiety 0:1–12, 2007. *Published 2007 Wiley-Liss, Inc.*[†]

Key words: *posttraumatic stress disorder; anxiety disorders; cerebrospinal fluid; norepinephrine; β-blocker; α-blocker; central nervous system*

INTRODUCTION

The catecholamine norepinephrine (NE) plays a critical role as one of the principal mediators of the mammalian response to stress. Its potential role in the pathophysiology of posttraumatic stress disorder (PTSD)—a syndrome intrinsically related to the experience of extraordinary stress—has been under direct investigation for more than two decades [Bremner et al., 1996a; Kosten et al., 1987; Perry et al., 1987; Ressler and Nemeroff, 2001; for review see Southwick et al., 1999]. Clinical studies indicate that patients with PTSD have tonically elevated central nervous system (CNS) norepinephrine concentrations [Geracioti et al., 2001], exaggerated CNS responses to noradrenergic activation by means of antagonism of the

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presynaptic α_2 autoreceptor [Bremner et al., 1997a,b; Southwick et al., 1993, 1997] and noradrenergic hyperresponsiveness to a variety of stimuli [Blanchard et al., 1991; Liberzon et al., 1999a; McFall et al., 1992; Murburg et al., 1995; Pitman et al., 1987] including traumatic stimuli [Geracioti et al., 2006]. In addition, autonomic hyperactivity, as assessed by heart rate, blood pressure, and electroencephalographic activity, has been documented in patients with "traumatic war neuroses" and PTSD for nearly 50 years [Blanchard et al., 1982; Dobbs and Wilson, 1960] and autonomic elements such as blood pressure, which are normally be tightly regulated by central norepinephrine, are dissociated from normal central noradrenergic control [Strawn et al., 2004].

In this article, we review studies of central and peripheral noreadrenergic hyperactivity under both basal and challenge conditions and explore these derangements as potential psychopharmacologic targets in patients with PTSD. The source of this review is the published literature published between 1956 (January) and 2006 (July) obtained through a selective, manualized search of the National Library of Medicine using the search terms (stress, PTSD, or posttraumatic stress disorder) and (norepinephrine, NE, catecholamine, adrenalin, noradrenalin, doxazosin, prazosin, clonidine, guanfacine, propranolol, metoprolol, atenolol, alpha antagonist, alpha agonist, or beta blocker). Additionally, the bibliographies of included articles were reviewed.

BIOCHEMISTRY AND THE ANATOMY OF THE MAMMALIAN NORADRENERGIC SYSTEM

The catecholamines norepinephrine and epinephrine are both derived from the amino acid tyrosine. The

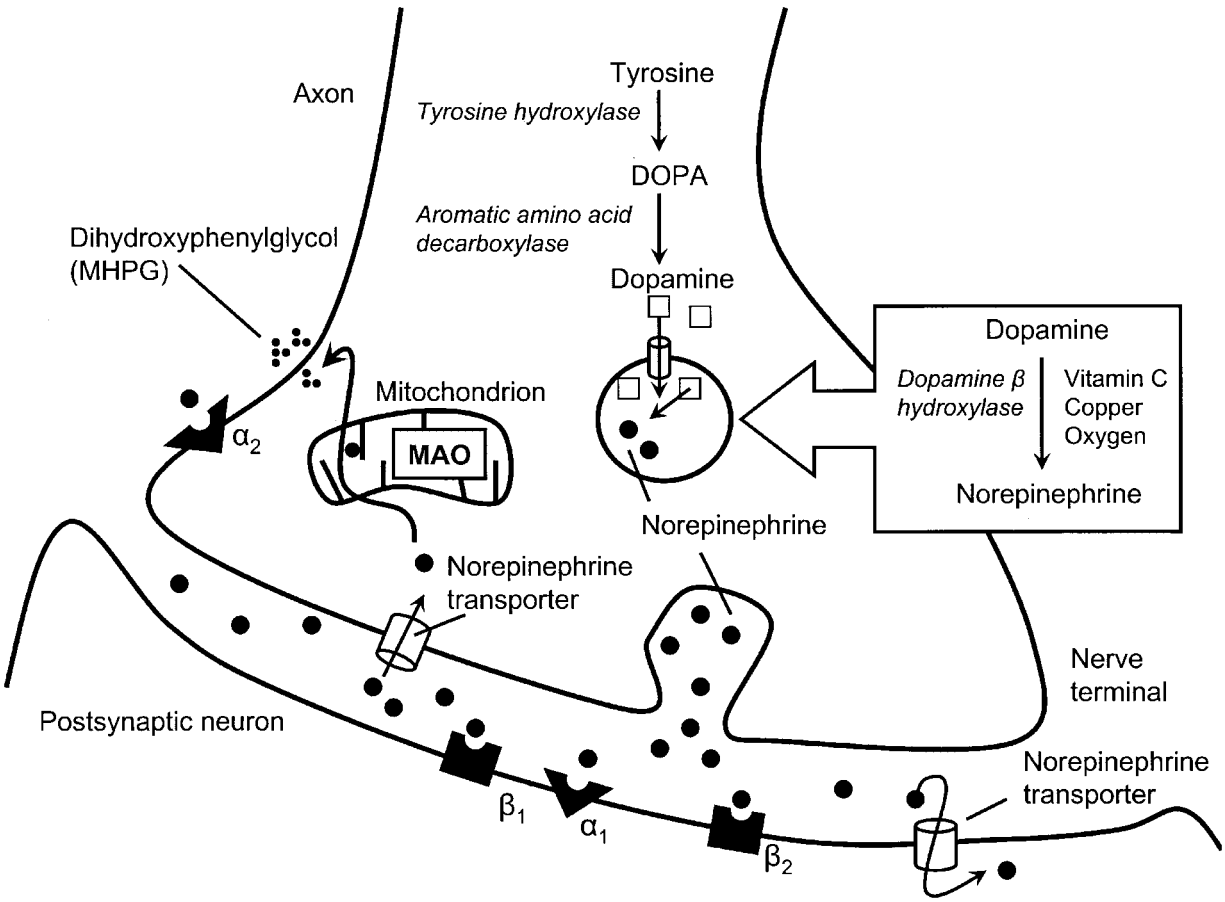

Figure 1. Schematic of norepinephrine metabolism in the central nervous system. The catecholamine norepinephrine is derived from the amino acid tyrosine, which is converted by tyrosine hydroxylase to the intermediate DOPA. From this intermediate compound, dopamine is synthesized and pumped into synaptic vesicles where it is converted to norepinephrine by dopamine β hydroxylase using oxygen, vitamin C, and copper as cofactors. As shown schematically, the synaptic vesicles containing norepinephrine are released from the nerve terminal and—depending on the local cellular environment—bind to a number of adrenergic receptors (subtypes not shown). Among these adrenergic receptors are the postsynaptic α_1 β_1, β_2, and β_3 receptors and the presynaptic α_2 receptors. Subsequently, norepinephrine is taken up by the neuron by way of the norepinephrine transporter and enters the mitochondrion where it is degraded to dihydroxyphenylglycol (MHPG) by monoamine oxidase (MAO).

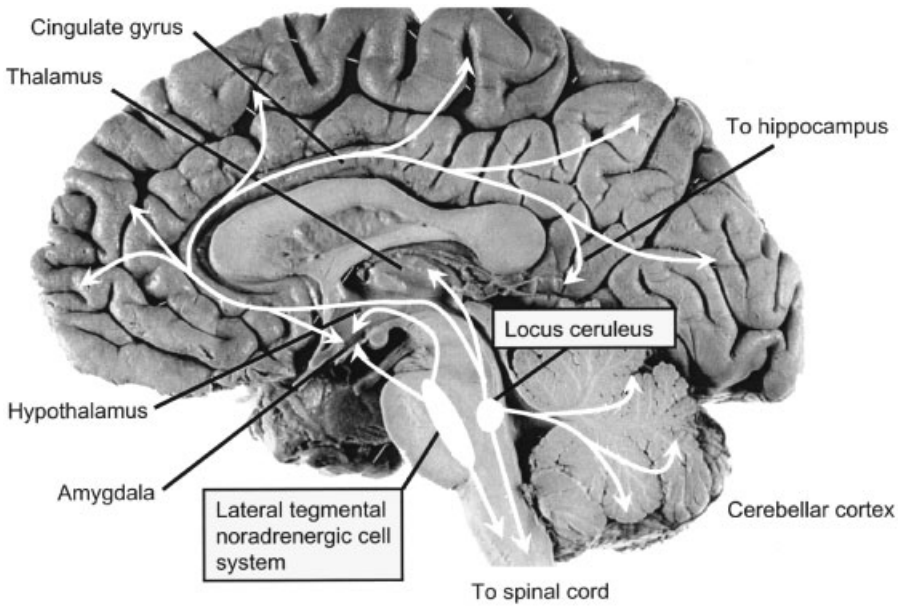

Figure 2. Noradrenergic projections in the human central nervous system. Norepinephrine is primarily derived from neurons whose cell bodies reside in the locus coeruleus, located below the floor of the fourth ventricle, and in the lateral tegmental noradrenergic cell system. These pontine collections of neurons project to a constellation of structures that are altered or implicated in the pathophysiology of PTSD, including the prefrontal cortex, amygdala, hippocampus, hypothalamus, periaqueductal gray matter and the thalamus. (Photograph courtesy of Patricia Brown, Ph.D., University of Cincinnati, Department of Cell Biology, Neurobiology and Anatomy.)

rate-limiting enzyme for the biosynthesis of both amines is tyrosine hydroxylase in the periphery and the CNS (Fig. 1). The predominant peripheral sympathetic transmitter is epinephrine, derived from the adrenal cortex, while the major central catecholamine is norepinephrine, derived from neurons whose cell bodies reside in the locus coeruleus. This latter pontine collection of neurons projects to a constellation of structures which are altered or implicated in the pathophysiology of PTSD (Fig. 2), including the prefrontal cortex, amygdala, hippocampus, hypothalamus, periaqueductal gray matter and the thalamus [Liberzon et al., 1999b; Phan et al., 2006; Pissiota et al., 2002]. The relationship between norepinephrine and neuronal factors affecting synaptic release and firing frequency is complex. Within the mammalian CNS, norepinephrine release from the locus coeruleus is related to firing frequency with low and high frequencies associated with decreased norepinephrine release and middle-ranging firing frequencies associated with increased release [for a review, see Ressler and Nemeroff, 2001]. In addition, studies in lower animals demonstrate oscillation in response to post-operative stress [Akaike, 1982]. Central noradrenergic activity is also regulated by the cAMP system (including adenylyl cyclase and protein kinase A) and expression of tyrosine hydroxylase [Melia et al., 1992a].

The adrenergic receptors to which norepinephrine (and epinephrine) bind are divided into two major types, α and β adrenoreceptors (Fig. 1). These are further divided into heterogeneous subclasses: α_1 and α_2 as well as β_1, β_2, and β_3 receptors. β receptors are linked to G-protein systems and, through activation of the G_s subunit, increase the second messenger adenylyl cyclase [Brandt et al., 1983]. By the contrast, α receptors are associated with a myriad of biochemical effectors, although, like the β receptors, their effects are transduced through G-protein systems. α_1 receptors primarily activate G_q proteins to increase phospholipase C, D, and A_2 activity (with contribution from G_i/G_o in the case of phospholipase A_2), leading to mobilization of intracellular calcium. CNS α_2 receptors largely function as presynaptic autoreceptors and, through activation of the inhibitory subunit of the G-protein system (G_i), decrease adenylyl cyclase and, in some neurons, increase potassium channel activity [Repaske et al., 1987]. Further the G_i systems linked to the α_2 receptors may decrease presynaptic L- and N-type calcium channel currents [Bhave et al., 1990; Hirning et al., 1988].

Not surprisingly, norepinephrine dynamics are affected by phenomena linked to and treatments directed at PTSD symptoms. In feline models, acute stress (e.g. restraint or loud white noise) increases the firing frequency of neurons in the locus coeruleus compared with behaviorally activating but non-stressful stimuli [Abercrombie and Jacobs, 1987a]. Chronic stress, which increases activity within the cAMP pathway [Nestler et al., 1999], upregulates tyrosine hydroxylase [Graham-Jones et al., 1983; Melia et al., 1992] and exaggerates locus coeruleus firing in response to challenges. In addition, firing of these neurons in rats is strongly inhibited by the iontophoretic application of morphine, noradrenaline, clonidine and the inhibitory

neurotransmitter γ-aminobutyric acid [Abercrombie and Jacobs, 1987b; Abercrombie et al., 1988; Guyenet, 1980]. Acute treatment with desipramine and other tricyclic antidepressants decreases the firing frequencies of these neurons in rats [Scuvee-Moreau and Dresse, 1979] while chronic antidepressant treatment decreases activity within the cAMP pathway [Melia et al., 1992b] and down regulates tyrosine hydroxylase expression [for review, see Nestler et al., 1999].

Regarding these preclinical data, it should be noted that various limitations and complexities are involved in translating stress/PTSD data from lower animal models to human PTSD; this topic has been recently reviewed [Cohen et al., 2006; Siegmund and Wotjak, 2006] and is beyond the scope of this work.

PERIPHERAL NOREPINEPHRINE IN PTSD

Evaluation of urinary norepinephrine in patients with PTSD has yielded conflicting results. Only a few studies have examined urinary catecholamine excretion in combat veterans with PTSD and one study has examined urinary catecholamines in civilian PTSD. In sexually abused girls, 24-hr excretion of catecholamines is increased compared with a non-traumatized cohort [De Bellis et al., 1994] and this increased norepinephrine excretion appears to persist into adulthood in individuals who go on to develop PTSD related to childhood sexual abuse [Lemieux and Coe, 1995]. Similarly, 24-hr urinary epinephrine and norepinephrine excretion in combat-veterans with PTSD is increased compared with patients with major depression, bipolar mania, paranoid schizophrenia, undifferentiated schizophrenia, and healthy control subjects [Kosten et al., 1987; Yehuda et al., 1992]. Mellman et al. [1995] evaluated noradrenergic production via urinary excretion of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in relation to sleep/wake activity in patients with chronic, combat-related PTSD and observed that nocturnal noradrenergic activity does not decrease as would normally be expected but rather continues throughout the night and is associated with dyssomnia. In a more recent study of young adults from a health maintenance organization, PTSD was associated with increased 24-hr urinary epinephrine and norepinephrine excretion compared with both a traumatized cohort without PTSD symptoms and a cohort that had not been traumatized [Young and Breslau, 2004]. However, not all studies observed increased catecholamine excretion in patients with PTSD [Glover and Poland, 2002]. Interestingly, a recent study of 12-hr urinary cortisol and epinephrine in children and adolescents (aged 8–18 years) immediately following admission to a trauma center demonstrates that increased cortisol and epinephrine excretion immediately following a traumatic event is associated with an increased risk for the development of acute PTSD symptoms, especially in boys [Delahanty et al., 2005].

Plasma norepinephrine concentrations (or levels of MHPG) are most often within normal limits or even reduced at baseline in patients with PTSD [Blanchard et al., 1991; Jensen et al., 1997; Liberzon et al., 1999a, b; McFall et al., 1992; Murburg et al., 1995; Pitmann and Orr, 1990; Southwick et al., 1993; Yehuda et al., 1998] although peripheral noradrenergic activity ap-

TABLE 1. Studies of plasma norepinephrine concentrations and urinary norepinephrine excretion in patients with PTSD

	Plasma norepinephrine		Urinary norepinephrine
Study	Basal	Provocation	Basal
Young and Breslau [2004]			↑ NE and epinephrine
Marshall et al. [2002]	↓ MHPG		
Glover and Poland [2002]			↑ NE (trend), normal epinephrine
Liberzon et al. [1999a,b]		↑ Catecholamines (symptom provocation)	
Yehuda et al. [1998]	↑ NE		
Yatham et al. [1996]	↑ NE	↓NE (orthostatic challenge)	
Murburg et al. [1995]	↓ NE		
Mellman et al. [1995b]			↑ MHPG (nocturnal) Normal 24-hr NE and MHPG
Lemieux and Coe [1995]			↑ NE, Epi, DA
McFall et al. [1992]	Normal		
Yehuda et al. [1992]			↑ NE, epinephrine
Blanchard et al. [1991]	↑ NE	↑NE (combat auditory stimuli)	

MHPG, 3-methoxy-4-hydroxyphenylglycol; NE, norepinephrine; PTSD, posttraumatic stress disorder; ↑, increased; ↓, decreased.

pears to be hyperresponsive to stressful stimuli like combat sounds [Liberzon et al., 1999a, b].

Though relatively few studies have assessed salivary noradrenergic indices, several studies have demonstrated abnormalities in MHPG in traumatized individuals [Goenjian et al., 1996; Otte et al., 2005]. In police academy recruits with childhood trauma histories, salivary concentrations of MHPG were increased in response to acute psychological stress [Otte et al., 2005]. In addition, adolescent earthquake survivors who lived close to the epicenter exhibited a more rapid decline in salivary MHPG levels following dexamethasone administration compared with individuals who had lived farther from the epicenter [Goenjian et al., 1996].

Regardless of what these peripheral data show (Table 1), they provide limited information regarding CNS norepinephrine. Whether secondary to disparate origins or to the relative inability of norepinephrine to cross the blood brain barrier, peripheral norepinephrine concentrations do not well reflect CNS norepinephrine concentrations.

CENTRAL NERVOUS SYSTEM NOREPINEPHRINE IN PTSD

CNS norepinephrine dynamics differ substantially from peripheral noradrenergic dynamics [Peskind et al., 1986]. For example, norepinephrine in plasma and in cerebrospinal fluid (CSF) are derived from largely, but not completely [Goldstein et al., 1987] disparate sources; therefore, dissociation between peripheral and CNS norepinephrine concentrations can take place. Results of serial CSF and plasma sampling studies in humans indicate that plasma concentrations of norepinephrine predict only about 20% of the cerebrospinal fluid (i.e. CNS) norepinephrine concentrations [Geracioti et al., 1993].

The results of studies of CNS norepinephrine in PTSD suggest a pathophysiologic role for excessive norepinephrine and indicate that CNS norepinephrine is robustly secreted in response to acute psychological stress. Using continuous CSF sampling in male combat veterans with chronic PTSD and healthy veterans without PTSD, our group found tonic CSF norepinephrine concentrations to be significantly higher in the men with PTSD than in the healthy men and observed that CSF norepinephrine levels strongly and positively correlated with the severity of PTSD symptoms [Geracioti et al., 2001]. However, we found no significant relationship between the severity of PTSD symptoms and plasma norepinephrine concentrations. Recently, in a within-subject, crossover, randomized continuous CSF sampling study of different patients with chronic, combat-related PTSD wherein CSF was withdrawn before, during and after a traumatic or neutral video shown on separate occasions 6–9 weeks apart in each subject, we observed that CSF norepinephrine concentrations significantly increase in response to a symptom-provoking psychological stimulus, indicating that norepinephrine is secreted acutely in response to psychological stress and symptom-provocation in PTSD patients [Geracioti et al., in review].

TARGETING NORADRENERGIC DYSREGULATION IN PTSD

The noradrenergic system can be pharmacologically adjusted in a variety of ways by a number of agonists or antagonists of the α and β adrenergic receptors as well as by inhibition of the neuronal norepinephrine transporter. The targets of centrally active noradrenergic compounds discussed in this review are shown in Table 2.

TABLE 2. Emerging pharmacology of the central noradrenergic system in PTSD

Receptor/target	Drug	Dose (mg/day)	Half-life (hr)	Common adverse effects
α_1 antagonist (postsynaptic)	Prazosin	6–10	2–3	Reflex tachycardia, orthostatic hypotension (may have first dose hypotension)
α_2 agonist (pre/postsynaptic)	Clonidine	0.2–0.6	6–24	Dry mouth, sedation, sexual dysfunction (delayed ejaculation, decreased libido), bradycardia, rebound hypertension
	Guanfacine	1–3	12–24	Dry mouth, sedation, dizziness, sexual dysfunction
β_1/β_2	Propranolol	40–60	3–5	Bradycardia, sedation, possible depressive symptoms, psychomotor slowing. Serious adverse effects include bronchospasm, AV block and thrombocytopenic purpura. Use with caution in asthmatics.

PTSD, posttraumatic stress disorder.

Several studies have examined the effects of antinoradrenergic agents on PTSD symptoms using drugs that reduce norepinephrine release (e.g. using centrally acting α_2 agonists such as clonidine) or by a postsynaptic receptor blockade (e.g. using centrally acting α_1 or β receptor antagonists such as prazosin [Vaiva et al., 2003]) or propranolol, respectively [Kolb et al., 1985; Pitman et al., 2002; Raskind et al., 2000, 2002, 2003]. Although there are a paucity of double-blind randomized, controlled trials examining the antiadrenergic agents in the treatment of PTSD, a number of case reports and open-label trials strongly suggest efficacy for these agents in the treatment of PTSD symptoms. These studies and reports are reviewed below and detailed in Table 3.

α_1 ANTAGONISTS

Of the α_1 antagonists, the quinazoline derivative prazosin is perhaps the best studied with respect to PTSD symptoms. Prazosin, which is approved in the United States for the treatment of hypertension, is highly protein-bound with peak concentrations occurring within 3 hr of ingestion and a disappearance half-life ($t_{1/2}$) of approximately 3 hr. Of note, prazosin is unique among the α-adrenergic receptor blockers in that it is associated with a relatively low incidence of reflex tachycardia.

Multiple case series and case reports [Griffith, 2005; Peskind et al., 2003; Raskind et al., 2000, 2002; Taylor and Raskind, 2002] and at least one double-blind, placebo-controlled crossover study of prazosin [Raskind et al., 2003] have demonstrated prazosin-related reductions in combat-related nightmares in combat veterans as well as improvement in total scores and core symptom cluster scores for re-experiencing, avoidance/numbing, and hyperarousal on the Clinician-Administered PTSD Scale (CAPS) [Raskind et al., 2003]. In a double-blind, placebo-controlled trial, 10 male patients with chronic, combat-related PTSD were randomized to a within-subject crossover study over a period of 20 weeks. In this study, prazosin was found to be well tolerated in all patients and significant improvements in recurrent distressing dreams, initial insomnia/sleep maintenance, re-experiencing/intrusive symptoms, avoidance and numbing were noted [Raskind et al., 2003]. Dosages of prazosin in these studies averaged 9.6 mg/day (1 mg/day for 3 days, followed by 2 mg/day for 4 days, followed by 4 mg/day for 7 days, then 6 mg/day with an additional 4 mg/day administered daily at 15:00 h thereafter). In this study, the most commonly reported adverse effects were orthostatic hypotension and initial dizziness, both of which improved with upward dose titration [Raskind et al., 2003]. However because of the relatively short half-life of prazosin (approximately 3 hr), many of the patients who had demonstrated improvement with nightly PTSD continued to have PTSD symptoms during the day [Raskind et al., 2003; Taylor and Raskind, 2002]. Recently, 11 patients with civilian PTSD who had responded to nighttime prazosin but who experienced residual daytime symptoms were randomized to receive daytime prazosin (3.2 ± 1.3 mg) or placebo augmentation [Taylor et al., 2006]. Those who received daytime prazosin had significantly reduced psychological distress compared to placebo in response to verbal trauma cues and reduced global severity of PTSD symptoms [Taylor et al., 2006].

CENTRALLY ACTING α_2 AGONISTS

Clonidine has inhibitory action primarily at the adrenergic α_2 autoreceptor of the locus coeruleus and is possibly the most extensively studied of the antiadrenergic medications in psychiatry. Clonidine is effective in controlling hyperarousal, hypervigilance, sleep disruption, exaggerated startle responses, and nightmares in open label trials in war veterans with PTSD [Kolb et al., 1985] and was effective when openly coadministered with tricyclic antidepressants to refugees with PTSD [Kinzie and Leung, 1989]. Clonidine monotherapy decreases reenactment symptoms in pediatric patients with abuse-related PTSD [Harmon and Riggs, 1996; Porter and Bell, 1999] and several case reports suggest that guanfacine, another centrally acting α_2 agonist may reduce nightmares in children with PTSD [Horrigan and Barnhill, 1996; Horrigan, 1996].

Common adverse effects of α_2 agonists include dry mouth and sedation, both of which decrease with time. At high doses, in patients with hypertension, abrupt discontinuation can be associated with rebound hypertension. The α_2 agonist clonidine has a high bioavailability, reaches peak concentrations in 1–3 hr and has a disappearance half-life of approximately 6–24 hr [Lowenthal et al., 1988]. The α_2 agonist guanfacine also rapidly penetrates the CNS and has a similar half-life (12–24 hr), but is substantially more selective for the α_2 receptor than clonidine and may have fewer adverse effects than clonidine in the clinical situation.

CENTRALLY ACTING β-BLOCKERS

The centrally acting, long-chain β-blocker propranolol is receiving increasing attention as a means to both ameliorate and prevent PTSD. This non-selective β-receptor antagonist is highly protein bound and almost completely absorbed from the gastrointestinal tract with peak concentrations occurring in 1–1 1/2 hr and a $t_{1/2}$ of approximately 4 hr. Preclinical studies have demonstrated that propranolol-induced β-blockade in the rat amygdala blocks memory reconsolidation, suggesting that treatment with propranolol following consolidation of a traumatic event might interfere with amygdalar retrieval of this event and may thereby

TABLE 3. Studies antiadrenergic agents in PTSD (excluding single case reports)

Study	Drug	Population	Design	*N*	Effect
Taylor et al. [2006]	Prazosin	Civilian PTSD	Open-label addition of daytime prazosin to bedtime prazosin responders	11	↓ "Psychological distress" in response to traumatic cues using the emotional Stroop paradigm
Peskind et al. [2003]	Prazosin (2–4 mg QHS)	Elderly men with military/ Holocaust trauma	Open-label	9	Substantially↓nightmares overall PTSD severity in eight/nine patients
Raskind et al. [2003]*	Prazosin (9.5 mg/day)	Vietnam combat veterans with chronic PTSD crossover	20-week double-blind placebo-controlled	10	Significant improvement in sleep disturbance, nightmares, and other PTSD symptoms
Raskind et al. [2002]*	Prazosin (9.6 ± 0.9 mg)	Treatment-resistant chronic PTSD	Retrospective chart review	51	↑ CGI and ↓ CAPS recurrent, distressing nightmare score
Taylor and Raskind [2002]*	Prazosin (1–4 mg/day)	Outpatients with non-combat related PTSD	6-week, open-label	5	All patients improved on the CGIC and exhibited >4 point ↓ in CAPS PTSD and sleep categories
Famularo et al. [1988]	Propranolol	Children with PTSD from physical and or sexual abuse	Case series	11	"Significant clinical improvement"
Vaiva et al. [2003]	Propranolol (40 mg tid)	Adult outpatient, status post acute traumatization	Prospective, secondary prevention	11	Three/eight patients developed PTSD in non-propranolol group, whereas 1/11 patients in the propranolol group developed PTSD
Pitman et al. [2002]	Propranolol (40 mg bid)	Adult outpatient, status post acute traumatization placebo controlled	Prospective, secondary prevention, double-blind	41	1-month CAPS PTSD scores averaged 27 in propranolol treated patients and 35 in patients who had received placebo

*Studies in which the antiadrenergic was used as an adjunctive agent. Concomitant psychotropic medication could not be determined from review of Taylor et al. [2006]. PTSD, posttraumatic stress disorder; ↓ indicates decreased; ↑ indicates increased; CAPS, Clinician-Administered PTSD Scale; CGI, Clinical Global Impression.

ameliorate intrusive symptoms associated with PTSD [Debiec and Ledoux, 2004]. Clinical studies have demonstrated that when pretreated with 40 mg of propranolol, PTSD patients and healthy volunteers demonstrate poorer recall of an emotionally arousing, narrated slide show compared with individuals receiving placebo [Reist et al., 2001]. Subsequent studies of traumatized individuals treated with 40 mg of propranolol immediately following the traumatic event demonstrated that fewer individuals in the propranolol group developed PTSD compared with those receiving placebo [Pitman et al., 2002].

A report by Kolb et al. [1985] suggested that propranolol may be of some benefit in the treatment of hyperarousal symptoms of PTSD and a number of case reports suggest that propranolol may ameliorate PTSD symptoms in patients who have had only partial responses to other therapies. Taylor and Cahill [2002] treated a 44-year-old woman with "severe PTSD despite multiple pharmacotherapies" with 60 mg of propranolol twice daily and observed significant improvement in her symptoms within 48 hr and observed an improvement in CAPS score from 86 to 56. In a pediatric case series of 11 children with PTSD related to physical and/or sexual abuse, children were treated in an on-off-on design with propranolol and were noted to have had significantly fewer symptoms while receiving propranolol [Famularo et al., 1988].

Propranolol has also been studied as a possible means of secondary prevention of PTSD. Pitman and Delahanty [2005] have explained the link between propranolol pre-treatment and secondary prevention in terms of classical conditioning in which the release of "stress hormones" represents an unconditioned response which is paired with a traumatic reminder (the unconditioned stimulus) to generate the conditioned response, trauma-induced release of "stress hormones." There are two published double-blind controlled trials of propranolol in the secondary prevention of PTSD. In the first double-blind, placebo-controlled trial, Pitman and colleagues treated 18 patients within 6 hr of traumatization with a 10-day course of propranolol (40 mg, four times daily) and 23 traumatized control patients with placebo and observed that CAPS scores were significantly lower in the propranolol-treated patients at 1 month. Also the authors of this study observed that PTSD prevalence in the placebo group was 30 and 10% in the propranolol-treated group at 1 month (following the exclusion of one outlying patient), whereas at 3-month follow-up, the PTSD prevalence was 11% in the placebo group and 13% in the propranolol group [Pitman et al., 2002]. The authors raised concern based on the lack of significant difference in heart rate between the placebo and propranolol groups after the administration of propranolol and suggested that the 40 mg dose was "insufficient to fully attenuate patients' acute posttraumatic hyperadrenergic states" and speculated that this may have accounted for the lack of a significant longer-term preventive effect on PTSD development [Pitman et al., 2002]. Vaiva and colleagues in a study of motor-vehicle accident survivors treated 11 patients with 40 mg of propranolol three times daily for 7 days, followed by a taper period of 8–12 days and noted that, when compared with eight traumatized patients who did not receive propranolol, only one in the 11 treated patients developed PTSD 2 months after the trauma, whereas PTSD developed in three of the eight untreated patients [Vaiva et al., 2003].

DISCUSSION

A number of mechanisms may underlie the putative efficacy of α_1 adrenergic receptor antagonists in PTSD, particularly with respect to hyperarousal and intrusive symptoms. Therapeutic effects may be mediated through the hypothalamic-pituitary-adrenocortical (HPA) system which is centrally hyperactivated in chronic, combat-related PTSD [Baker et al., 1999; Bremner et al., 1997a,b] and tightly linked with the central noradrenergic system [Valentino et al., 1992]. In fact, corticotropin-releasing hormone (CRH) serves as the excitatory neurotransmitter in the locus coeruleus and causes dose-dependent increases in firing frequency and increases norepinephrine release [Curtis et al., 1997]. In lower animals, photic stimulation-induced release of CRH from the hypothalamus can be blocked when the α_1 antagonist prazosin, but not the β_1 receptor antagonist atenolol, is injected into the amygdala, a locus which is known to be hyperresponsive to fearful stimuli in men with PTSD [Feldman and Weidenfeld 1996; Shin et al., 2005]. These findings suggest, at least in lower animals, that amygdalar norepinephrine plays a role in the activation of the HPA axis following neural stimuli and that this effect is mediated by α_1 adrenoceptors in the central amygdala. Similarly, using a rat hypothalamic organ culture, Gold's group observed that the norepinephrine-induced release of CRH was antagonized by the non-selective α antagonist phentolamine, prazosin, and the α_2 antagonist yohimbine, but not by the β-blocker propanolol. Also in this preparation, CRH secretion was noted to be increased by the α_1 agonist phenylephrine in a dose-dependent fashion [Calogero et al., 1988]. In humans, CSF levels of CRH significantly correlate with urinary norepinephrine excretion and with CSF and plasma levels of norepinephrine [Roy et al., 1987]. Subsequent studies in humans have suggested that the link between central (i.e. CSF) norepinephrine and CRH is "mutually reinforcing" [Wong et al., 2000]. Accordingly, we have found both norepinephrine and CRH levels to be increased in the CSF of PTSD patients [Baker et al., 1999; Geracioti et al., 2001]. This intra-CNS link is further supported by the observation that blockade of the α_2 receptor by administration of yohimbine produces significant increases in serially sampled CSF concentrations of both CRH and norepinephrine [Vythilingam et al.,

2000]. Finally, although it has been proposed that hypocortisolemia may be mechanistically involved in PTSD-related hypernoradrenergia, we have recently observed elevated—not low—cortisol concentrations in the CSF of PTSD patients [Baker et al., 2005].

Given the relative heterogeneity of the α-receptor-linked post-receptor signal transduction systems in comparison with β receptors, multiple mechanisms may underlie the putative efficacy of α-active drugs in ameliorating PTSD symptoms. Clinical data concerning one potential mechanism of α_2 agonist effects for which there are supportive data is the modification of the HPA axis. For example, Marshall et al. [2002] examined the functional responsivity of cortisol and the major norepinephrine metabolite, MHPG, to clonidine challenge in seven patients with PTSD in comparison with patients with panic disorder and healthy controls. Following administration of clonidine (0.15 mg), plasma cortisol and plasma MHPG were found to be significantly reduced in the PTSD patients relative to panic disorder patients and healthy comparison subjects [Marshall et al., 2002]. Hansenne and colleagues noted blunting of growth hormone secretion following clonidine challenge in a 20-year-old with motor-vehicle accident-related PTSD, suggesting decreased sensitivity of central, postsynaptic α_2 receptors [Hansenne et al., 1991]. Finally, in a pediatric case report, a maltreated child with PTSD when treated with clonidine was noted on SPECT scan to have increased anterior cingulate N-acetylaspartate/creatine ratios, a marker of neural integrity, as well as an improvement in sleep measures [De Bellis et al., 2001].

Although direct antagonism of norepinephrine signaling may directly ameliorate PTSD symptoms, it is possible that β-blockers may exert their therapeutic effect in PTSD by modulating the substance P system. Like norepinephrine, the pain-transmitting neuropeptide substance P is tonically elevated and robustly secreted in response to acute psychological stress in PTSD patients [Geracioti et al., 2006]. Preclinical data suggest that substance P responses can be attenuated by the β-antagonist, practolol, but not by prazosin [Jones and Olpe, 1986]. Interestingly, intrathecal administration of substance P to anesthetized rats induces an increased heart rate that can be blocked by propranolol [Yashpal and Henry, 1993]. It will be of great interest to determine if neurokinin-1 receptor antagonists (substance P antagonists) prove to be of clinical benefit to PTSD patients. Currently a phase II, 10-week, double-blind, placebo-controlled trial of one such agent is ongoing in patients with PTSD [Charney, 2006].

The preference of many PTSD patients for opiates [Bremner et al., 1996b] may be related to the effects of opiates on the noradrenergic system. In this regard, the ability of opiates to dampen central noradrenergic hyperactivity may represent a means by which patients intuitively treat their own CNS noradrenergic hyperactivity. Further, this effect may explain the increased CNS opioid activity (i.e. β-endorphin secretion) observed in chronic PTSD which is known to be negatively correlated with avoidant/intrusive symptoms, possibly in an adaptive manner [Baker et al., 1997]. Case series report lifetime opiate dependence diagnoses in 26% of PTSD patients [Bremner et al., 1996b]. In lower animals tyrosine hydroxylase expression is increased during withdrawal from morphine [Gonzalez-Cuello et al., 2004] and firing of these noradrenergic neurons within the locus coeruleus is strongly inhibited by the iontophoretic application of morphine [Guyenet, 1980]. In neonates, Simons et al. [2005] observed that continuous infusion of morphine significantly decreased plasma noradrenaline concentrations compared with placebo. Indeed, modification of the opioid system is an intriguing line of investigation in the treatment of PTSD; in this regard, the authors have seen patients with PTSD who showed clinical improvement from heroin (illicit use), methadone or tramadol—controlled clinical trial data remain to be obtained.

CONCLUSION

Given the significant involvement of the CNS noradrenergic hyperactivity in PTSD and its link to intrusive and hyperarousal symptoms, it is not surprising that treatments directed at this system have therapeutic potential in PTSD. In addition, agents selective for specific subtypes of adrenergic receptors may be used as probes to further elucidate the noradrenergic involvement of specific subsystems in the pathophysiology of PTSD. Although the specific role of anti-adrenergics in the clinical treatment of PTSD remains to be determined, it is possible that these drugs may gain primary or, perhaps more likely, adjunctive roles in a disorder that is only modestly responsive to traditional psychological [Bisson and Andrew, 2005] and pharmacologic [Stein et al., 2006] treatments.

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