Role of Norepinephrine in the Pathophysiology and Treatment of Posttraumatic Stress Disorder

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This review focuses on the role of norepinephrine (NE) in traumatic stress. The review is divided into three sections. The first section, "Norepinephrine and Arousal," describes preclinical studies related to norepinephrine's role in arousal, orienting to novel stimuli, selective attention and vigilance. It also contains a brief discussion of NE and its relationship to fear-provoking stimuli followed by preclinical and clinical studies that demonstrate heightened noradrenergic neuronal reactivity, increased α_2 receptor sensitivity and exaggerated arousal in organisms that have been exposed to chronic uncontrollable stress. The second section, "Norepinephrine and Memory," describes preclinical and clinical studies related to norepinephrine's role in enhanced encoding of memory for arousing and aversive events and in subsequent re-experiencing symptoms such as, intrusive memories and nightmares. The third section, "Norepinephrine and Pharmacologic Treatment," briefly discusses the use of adrenergic blockers, clonidine and propranol, as well as tricyclic and MAO inhibitors, for the treatment of PTSD. Finally, we attempt to synthesize trauma-related preclinical and clinical studies of norepinephrine. We do this, in part, by focusing on a series of yohimbine studies in subjects with PTSD because data from these studies allow for a discussion that brings together preclinical and clinical findings relevant to trauma-related alterations in arousal and memory. Biol Psychiatry 1999;46: 1192–1204 © *1999 Society of Biological Psychiatry*

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Introduction

A growing body of psychophysiological, neuroendocrine, receptor binding, pharmacologic challenge, brain imaging, and pharmacologic treatment studies have provided compelling evidence for increased noradrenergic activity in traumatized humans with posttraumatic stress disorder (PTSD) (Friedman and Southwick 1995; Southwick et al 1997). This increased activity generally is not observed under baseline or resting conditions but rather in response to a variety of stressors. It has been suggested that altered reactivity of noradrenergic neurons is associated with a variety of hyperarousal and reexperiencing symptoms characteristic of PTSD (Southwick et al 1997).

In this review, we begin by briefly describing preclinical studies related to norepinephrine's role in arousal, orienting, selective attention, vigilance and the organism's response to acute stress and fear-provoking stimuli. This is followed by preclinical and clinical studies that demonstrate heightened noradrenergic neuronal reactivity, increased α_2 receptor sensitivity and exaggerated arousal in organisms that have been exposed to chronic uncontrollable stress. Next we review preclinical and clinical studies related to norepinephrine's role in the enhanced encoding of memory for arousing and aversive events and speculate about the relationship between stress-related elevations in norepinephrine and subsequent symptoms of reexperiencing, such as intrusive memories and nightmares. Finally, we attempt to summarize and synthesize trauma-related preclinical and clinical studies involving norepinephrine.

Although the current review focuses on norepinephrine and PTSD, it is important to emphasize that numerous neurobiological systems are involved in acute and chronic responses to stress. In preclinical and clinical traumatic stress studies, alterations have been reported in noradrenergic, dopaminergic, adrenergic, opiate, γ-aminobutyric acid (GABA) benzodiazepine, and serotonergic systems as well as the thyroid and hypothalamic-pituitary-adrenal axes. Hormones, neurotransmitters, and neuropeptides are known to interact with one another in complex fashion so that alteration in one system often affects functioning in other systems. For example, the locus coeruleus is regulated by a variety of neurotransmitters and neuropeptides, with inhibitory effects from norepinephrine, epinephrine, endogenous opiates, benzodiazepines, and serotonin, and stimulatory effects from

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corticotropin releasing factor and glutamate. Alterations in any of these systems can affect noradrenergic activity.

Even more complex is the relationship between neurotransmitters and behavior. For example, hyperarousal and hypervigilance are commonly experienced by trauma survivors suffering from PTSD. Arousal is influenced by multiple neurotransmitters (e.g., norepinephrine, dopamine, acetylcholine, serotonin) that are simultaneously active in varying degrees and in various brain regions. Chronic alterations in arousal systems are likely to be very complex and involve long-term changes in neural function. Thus, in this review, descriptions of a potential relationship between norepinephrine and one or more symptoms of PTSD are highly simplistic. The distinct contribution of norepinephrine to symptoms and behavior simply is not known.

Norepinephrine and Arousal: Preclinical Studies

Preclinical Studies of Norepinephrine and Attention

Central noradrenergic neurons serve as elements within a diffuse modulatory system (Zigmond et al 1995) that detects and responds to meaningful internal and external stimuli. The cell bodies of most noradrenergic neurons in the brain are located within a discrete group of hindbrain nuclei, the most prominent of which is the locus coeruleus (LC). It has been suggested that these noradrenergic nuclei are critical in determining the organism's overall state of arousal and attention (Abercrombie and Zigmond 1995; Robbins and Everitt 1995).

In rats, cats and monkeys, an increase in LC neuronal firing rate is associated with alertness, whereas a decrease in rate is associated with drowsiness (Berridge 1991; Foote et al 1980; Jacobs et al 1995). For example, LC neuronal firing rate is dramatically reduced during slow-wave sleep and abruptly increases just before or at the time of transition from slow-wave sleep to waking. During waking states, LC neurons consistently respond to a wide variety of intense sensory stimuli, particularly if these stimuli interrupt ongoing nonvigilant behaviors, such as grooming and eating, and cause the animal to reorient its attention.

Norepinephrine (NE) also is involved in the organism's ability to selectively attend to meaningful stimuli. In sensory cortical neurons it repeatedly has been shown that NE increases responsivity to phasic sensory stimulation while decreasing or not altering tonic spontaneous discharge patterns in the same neuron, a phenomenon referred to as increased "signal to noise ratio" (Aston-Jones et al 1994). By selectively enhancing strong excitatory or inhibitory input, NE facilitates the processing of relevant stimuli. In related work by Waterhouse and others, NE has been shown to "gate" postsynaptic activity in target neurons (Waterhouse et al 1988). Thus, target neurons that fail to respond to a particular stimulus, become responsive to that same stimulus if sufficient NE is present. Norepinephrine enhanced responsivity to both excitatory and inhibitory inputs has been reported in the same neocortical target cells.

Preclinical Studies of Norepinephrine, Acute Stress and Fear

As part of its role in determining level of arousal, the LC seems to serve as a critical component of the brain's alerting or vigilance system (Aston-Jones et al 1994; Aston-Jones 1998). Thus acute stress and fear activate the LC/NE system (Redmond 1987). Similarly, activation of the locus coeruleus by direct electrical stimulation or by pharmacologic agents, such as yohimbine or piperoxan, elicits alerting and fear responses in primates. In contrast, such behaviors are reduced by pharmacologic agents that decrease LC firing. Further, fear-related behaviors to threatening and social group situations are reduced in monkeys after bilateral lesions of the LC (Charney et al 1995; Redmond 1987).

The meaning, as well as intensity of stimuli, seems to be an important factor in LC responding. For example, in freely moving cats, it has been shown that confrontation with a nonthreatening novel stimulus, such as a mouse, does not cause a specific increase in LC firing, whereas confrontation with a threatening stimulus, such as a dog or an aggressive cat, does cause a marked increase in firing. These data suggest that novelty, by itself, is not necessarily "meaningful" to the LC and does not always stimulate its firing. Stimuli that signal reward, like those that signal danger, also can activate LC firing (Jacobs et al 1995).

Stress and fear-related activation of the LC results in increased release of NE in multiple brain regions that are involved in perceiving, evaluating and responding to potentially threatening stimuli. Acute stress-related increases in NE have been found in the amygdala, hippocampus, striatum and prefrontal cortex. Rapid activation of the LC/NE system facilitates the organisms ability to respond effectively in dangerous situations (Charney et al 1995).

Preclinical Studies of Norepinephrine and Chronic Stress

Catecholaminergic neurons are capable of adjusting level of transmitter synthesis and release depending on current demands and past history (Abercrombie and Zigmond 1995; Zigmond et al 1995). A host of catecholamine-related adaptive responses also are observed under conditions of chronic stress, particularly when stress is

uncontrollable in nature. For example, prolonged stress can enhance synthesis of tyrosine hydroxylase resulting in an increased number of active tyrosine hydroxylase molecules (Melia et al 1992; Nisenbaum et al 1991).

Chronic uncontrollable stress also has been shown to increase responsivity of LC neurons to an excitatory stimulus (Simson and Weiss 1994). As a result of these and other adaptations, chronically stressed animals may respond to future stressors with exaggerated catecholamine reactivity. These increased responses have most commonly been observed after exposure to novel and potentially threatening stressors (Zigmond et al 1995). It has been hypothesized that enhanced catecholamine synthesis and release may help to protect the organism from depletion of neurotransmitter stores and allow the organism to respond more rapidly and robustly to future stressors; however, in some cases this over-responsiveness may prove to be maladaptive.

Noradrenergic neuron responsivity is, in part, regulated by presynaptic α_2 receptors. Preclinical investigations have demonstrated a high density of α_2 adrenergic receptors in the LC. Activation of α_2 receptors exerts a strong inhibitory influence on LC firing, whereas antagonism of these receptors, with agents such as yohimbine and piperoxan, increases LC firing rate and norepinephrine release in target brain regions. The increased responsiveness of LC neurons to excitatory stimulation has been observed after blockade of α_2 adrenergic receptors, but not after blockade of GABA, 5-HT, and opiate receptors (Simson and Weiss 1994).

Evidence from Nisenbaum and Abercrombie (1992) suggest that chronic stress-induced biochemical sensitization of NE release may be related, in part, to altered sensitivity of presynaptic α_2 receptors. Local infusion of clonidine into the hippocampus produced significantly greater reductions in NE whereas local infusions of idazoxan produced significantly greater elevations of NE in chronically stressed rats compared to naive control rats. These data suggest that α_2 receptor modulation of NE release is increased as a result of chronic uncontrollable stress.

Preclinical Studies of Norepinephrine and Prefrontal Cortex (PFC)

The prefrontal cortex (PFC) plays an important role in planning, guiding and organizing behavior through working memory. Lesions of the PFC can result in disinhibited behavior, increased motor activity, impaired attention and diminished ability to inhibit distracting stimuli. Noradrenergic projections from the LC modulate PFC functioning through postsynaptic α_1 and α_2 receptors. Preclinical research in rodents and primates suggests that moderate basal release of norepinephrine improves PFC cognitive functioning through preferential binding to postsynaptic α_{2A} receptors. Arnsten (1998a, 1998b) has proposed that postsynaptic α_{2A} receptor stimulation inhibits irrelevant and distracting sensory processing through effects on pyramidal cells that project to sensory association cortices. Inhibition or gating of irrelevant sensory stimuli allows the organism to concentrate on the contents of working memory.

Alpha-2 agonists improve PFC function in monkeys whose norepinephrine has been depleted naturally or experimentally. For example, clonidine and guanfacine have been shown to improve performance on tasks that assess prefrontal function such as the delayed response task (linked to the dorsolateral prefrontal cortex) and reversal of a visual object discrimination task (particularly sensitive to ventromedial-orbital PFC lesions), whereas the α_2 antagonist yohimbine impairs performance. In addition to its beneficial effects on working memory, guanfacine has been shown to produce behavioral calming (without sedation). At higher doses of guanfacine, aged monkeys have been described as less agitated, less disinhibited and less aggressive (Arnsten 1998b).

Under stressful conditions (especially uncontrollable stress) when NE release is increased above basal levels in the PFC, postsynaptic α_1 receptors become activated causing a decline in PFC functioning. It has been proposed that this inhibition of PFC functioning during stressful or dangerous situations has value for survival by allowing the organism to employ rapid habitual subcortical modes of responding (Arnsten 1998a; Birnbaum et al 1999).

Norepinephrine and Arousal: Clinical Studies

Clinical Studies of Psychophysiology and Arousal

For centuries symptomatic trauma survivors have been described as emotionally and physiologically aroused, anxious, vigilant, easily startled, restless, irritable and angry. In the 1940s, Kardiner (1941) coined the term *physioneurosis* to depict the physiologic hyperarousal that resulted from overwhelming combat stress. The central importance of disturbed arousal in patients with PTSD has been noted in victims of industrial accidents, brush fires and combat. In fact, McFarlane (1993) found that symptoms of attention and arousal were better at discriminating between brush fire victims with and without PTSD than were other PTSD symptoms.

Since WWII, researchers have conducted a large number of psychophysiologic studies in survivors of overwhelming psychological trauma. These studies typically have measured biological parameters, such as blood pressure, heart rate, skin conductance, and electromyographic (EMG) activity of facial muscles at baseline and

BIOL PSYCHIATRY 1999;46:1192–1204

in response to various trauma-related and generic stressors. Most studies have reported similar levels of baseline physiologic arousal in patients with PTSD compared to control subjects. Studies finding differences in baseline heart rate may have been confounded by greater anticipatory anxiety in subjects with PTSD as they waited for presentation of trauma-related cues (Prins et al 1995).

On the other hand, approximately two thirds of PTSD subjects in all published psychophysiology studies have demonstrated exaggerated reactivity to internal or external trauma-associated cues. The percent seems even higher among subjects with severe PTSD (Orr 1997a; Orr et al 1997b). Comparison groups of healthy nontraumatized control subjects, traumatized individuals with anxiety disorders other than PTSD, and traumatized combat veterans without either PTSD or other anxiety disorders have generally shown less physiological reactivity to reminders of personally experienced traumas than subjects with PTSD. Exaggerated psychophysiologic reactivity in response to generic stressors has not been found in most PTSD studies. In general normal baseline arousal in conjunction with exaggerated psychophysiologic reactivity to trauma-relevant but not generic stressors has been reported in survivors of both combat trauma and civilian trauma (Orr 1997a).

Clinical Studies of Baseline Catecholamines

To investigate the biological underpinnings of exaggerated psychophysiological reactivity, researchers have compared baseline indices of epinephrine and norepinephrine in subjects with PTSD and healthy controls. To date, at least three studies involving combat veterans have found similar plasma NE levels in subjects with PTSD and healthy controls and one study has reported comparable levels of MHPG (Southwick et al 1995). In contrast, Yehuda et al (1998) sampled plasma NE and MHPG concentrations under unstimulated conditions over a 24-hour period and found significantly higher mean NE levels in combat veterans with PTSD alone ($n = 7$) compared to combat veterans with PTSD and comorbid depression ($n = 8$), patients with MDD alone ($n = 12$) and healthy control subjects ($n = 13$). MHPG values did not differ significantly among the four subject groups.

Twenty-four hour urine investigations of catecholamine excretion generally have found elevated values in subjects with PTSD compared to controls. Two published reports have found elevated urine values for both norepinephrine and epinephrine in combat veterans with PTSD. Higher urine norepinephrine excretion in combat veterans with PTSD compared to patients with schizophrenia or major depression was first reported by Kosten et al (1987). Norepinephrine remained elevated in the PTSD group throughout several months of hospitalization. In a study comparing healthy controls to combat veterans with PTSD, Yehuda et al (1992) found significantly elevated 24-hour NE and epinephrine (E) excretion among inpatient veterans with PTSD compared to control subjects. Outpatient veterans with PTSD had higher NE but not E values. In contrast, Pitman et al (1990) reported comparable NE values for combat veterans with and without PTSD and Mellman (1995) found no differences in 24-hour urine norepinephrine and MHPG excretion between healthy controls and veterans with PTSD. Of note, the NE values that Pitman reported for combat veterans with and without PTSD were similar to the values reported by Yehuda for combat veterans with PTSD. Further, whereas Mellman reported no differences in 24-hour urine excretion of NE and MHPG, PTSD subjects and healthy controls, did differ in their nocturnal versus daytime MHPG excretion supporting a possible relationship between disturbances in sleep and nondiminished central noradrenergic activity at night.

In a study comparing 19 women with histories of childhood sexual abuse (11 with PTSD and 8 without PTSD) to nine nonabused control subjects, Lemieux and Coe (1996) reported significantly higher NE and E levels in the PTSD group compared to the nonabused control group. The non-PTSD sexual abuse group did not differ significantly from either the PTSD or the nonabused control group. A significant positive correlation was found between E and the intrusive, avoidance and arousal subscales of the Impact of Events Scale and between NE and the intrusive subscale. Elevated 24-hour catecholamines also have been reported in sexually abused girls (Debellis et al 1997) and in children with PTSD (Debellis et al 1992).

The neurochemical message of NE is translated, in part, by α_2 adrenergic receptors. Fewer total α_2-adrenergic receptor binding sites per platelet have been reported in adults (Perry et al 1990) and children (Perry 1994) with PTSD compared to healthy controls. It has been hypothesized that chronic elevation of circulating catecholamines causes a downregulation or reduced number of available receptor sites and that this downregulation protects against overstimulation by agonist (Perry 1994). Reduced platelet α_2 adrenergic receptor number has been found in other conditions characterized by chronic and excessive catecholamine activity such as congestive heart failure and hypertension. Studies focused on baseline beta-adrenergic receptor mediated adenylate cyclase levels have been mixed (Southwick et al 1995).

Clinical Studies that Challenge the Norepinephrine System

A number of challenge paradigms have been used to test noradrenergic reactivity in subjects with PTSD. These

have included in vitro paradigms with platelets and lymphocytes and in vivo paradigms with auditory reminders of trauma and with pharmacologic probes such as lactate, desipramine, and yohimbine.

Using an in vitro approach to assess dynamic functioning and regulation of α_2 adrenergic receptors, Perry et al (1990) incubated intact platelets with high levels of E and found a greater and more rapid loss in receptor number among combat veterans with PTSD compared to controls. These findings suggested that α_2 receptors in this population of chronically stressed veterans were unusually sensitive and responsive to agonist stimulation. Mixed results have been reported using in vitro challenges of the lymphocyte β-adrenergic receptor mediated cyclic 3′,5′-monophosphate system in patients with PTSD (Southwick et al 1995).

Auditory reminders of trauma have been used as in vivo nonpharmacologic probes of noradrenergic responsivity in combat veterans with PTSD. In a study of 15 combat veterans with PTSD compared to six combat veterans without mental disorder, Blanchard et al (1991) sampled plasma NE before and after exposure to auditory stimuli reminiscent of combat. The PTSD group showed a 30% increase in plasma NE compared to no change in the combat control comparison group. The PTSD group also showed a concomitant increase in heart rate.

In vivo pharmacologic challenge studies generally have reported exaggerated noradrenergic reactivity in subjects with PTSD. Although Dinan et al (1990) found no difference in growth hormone response to desipramine (a marker of postsynaptic α_2 adrenergic receptor sensitivity) between eight traumatized women with PTSD and a group of healthy control subjects, Rainey et al (1987) and Jenson et al (1997) reported that lactate infusion caused panic attacks and flashbacks in subjects with PTSD but not in control subjects. Although the precise mechanism of lactate-induced anxiety and panic is unknown, central noradrenergic stimulation has been implicated.

We now focus on a series of yohimbine challenge studies that have been conducted in combat veterans with PTSD. Yohimbine is an α_2-adrenergic antagonist that activates noradrenergic neurons by blocking the α_2 autoreceptor, thereby increasing presynaptic noradrenergic activity. Although yohimbine has effects on multiple neurotransmitter systems, its primary action is on the noradrenergic system. In preclinical studies yohimbine has been shown to readily cross the blood–brain barrier (Goldberg and Robertson 1983). Support for the use of yohimbine as a probe of central noradrenergic function in humans comes from a study of healthy controls where yohimbine administration resulted in increased levels of cerebrospinal fluid NE (Peskind et al 1989). Plasma MHPG is believed to represent a combination of MHPG that has been derived from peripheral sympathetic neurons and MHPG that has crossed the blood–brain barrier from the brain (Cooper et al 1982).

YOHIMBINE VERSUS PLACEBO. Twenty combat veterans with PTSD and 18 healthy control subjects received either yohimbine hydrochloride (0.4 mg/kg) or saline solution on two separate test days in double-blind fashion and in randomized balanced order (Southwick et al 1993). In the PTSD group yohimbine caused panic attacks in 70% and flashbacks in 40% of subjects. There were no panic attacks and one flashback in response to placebo. In the healthy control group there were no panic attacks or flashbacks on either the yohimbine or the placebo day. The subgroup of PTSD patients with yohimbine-induced panic attacks also had significantly greater increases in heart rate, sitting systolic blood pressure, and plasma MHPG than controls. Multiple anxiety and PTSD-related symptoms (reexperiencing, arousal, and avoidance symptoms) also increased to a significantly greater degree in the PTSD patients compared to control subjects. Many subjects reported distortions of sensory experiences and a variety of dissociative symptoms, including derealization and depersonalization. For example, shortly after yohimbine infusion one patient experienced intense fear, anxiety, tremulousness, diaphoresis, and memories of combat. A second patient had a flashback in which he saw, heard, and smelled the crashing of a helicopter. In many cases the intrusive thoughts were described as being extremely clear and vivid as if the events had happened "just the other day."

YOHIMBINE AND NEUROPEPTIDE Y (NPY). Neuropeptide Y (NPY) is a 36 amino acid peptide neurotransmitter that is co-localized with NE in most sympathetic nerve terminals and has been found in multiple brain regions that respond to stress including the LC, amygdala, hippocampus, periaquaductal gray and PFC (Helig and Widerlov 1995). One of NPY's central and peripheral actions is to inhibit release of the neurotransmitter with which it is co-localized. In numerous preclinical studies, NPY has been shown to inhibit the firing rate of LC neurons and to inhibit release of NE through actions at the presynaptic Y2 receptor.

Release of NPY is related to the intensity and duration of stress (Zukowska-Grojec 1995). Thus, animal and human studies have found that plasma NPY does not increase in response to mild or brief stress but does increase with moderate or intense stress. Although intense acute stress increases plasma NPY, chronic stress has been shown to decrease plasma NPY and to enhance the noradrenergic response to a novel stressor. In a study by Corder et al (1992), rats exposed to 12 consecutive days of

restraint stress and then one episode of footshock, had significantly lower plasma NPY but significantly greater elevations of plasma NE compared to naive rats that were exposed to footshock alone.

In a study investigating the effects of yohimbine on plasma NPY, Rasmusson and colleagues (in press) found significantly lower baseline plasma NPY and an increase in plasma NPY after yohimbine infusion that was significantly blunted in a group of 18 combat veterans with PTSD compared to eight healthy controls. There also was a negative correlation between baseline plasma NPY and yohimbine-induced increases in MHPG. Finally, in the PTSD group, degree of combat exposure was negatively correlated with baseline plasma NPY and postyohimbine plasma NPY.

PET YOHIMBINE VERSUS PLACEBO CHALLENGE. To more directly study CNS noradrenergic systems in combat veterans with PTSD, Bremner et al (1997a) administered a single bolus of [F-18]2-fluoro-2-deoxyglucose to 10 combat veterans with PTSD and 10 healthy age-matched control subjects. This was followed immediately by either IV yohimbine (0.4 mg/kg) or placebo infusion. All subjects received both yohimbine and placebo on two separate test days under double-blind conditions and in randomized balanced order. After completion of the yohimbine or placebo infusion, subjects underwent PET scanning for 60 min. To determine brain metabolic activity a PET image was reconstructed 30–50 min after infusion.

Preclinical pharmacologic and blood flow studies suggest a dose-response relation for the effects of NE on neuronal activity, brain metabolism, and blood flow with low levels of NE causing no effect or an increase in activity and high levels causing a decrease or inhibition of activity (Bremner et al 1997a). For example, large doses of yohimbine cause a decrease in blood flow and metabolism in brain areas that receive noradrenergic innervation including the frontal, parietal, temporal, postcentral, and occipital cortex. Based on the foregoing preclinical studies and on the earlier reviewed evidence for increased responsivity of noradrenergic systems in patients with PTSD, it was hypothesized that yohimbine administration would result in a relative decrease in brain metabolism in neocortical areas among combat veterans with PTSD compared with controls.

Six of the ten patients with PTSD had a yohimbine-induced panic attack and three of ten a flashback. None of the control subjects had either a panic attack or a flashback. These behavioral responses were similar to those observed in the aforementioned yohimbine PTSD studies. The metabolic response to yohimbine significantly differed between patients and controls. In neocortical brain regions (orbitofrontal cortex, temporal cortex, prefrontal cortex, parietal cortex) healthy control subjects had a significant increase and PTSD subjects a significant decrease in metabolism with yohimbine compared to placebo.

The results were consistent with the notion that PTSD patients as a group released more NE than did control subjects in response to yohimbine. This increase in NE resulted in a relative decrease in brain metabolism. It was speculated that the degree of decrease in metabolism may be related to the degree of yohimbine-induced anxiety/panic symptoms and PTSD-specific symptoms including impairment of attention and vigilance. It is possible that high levels of NE cause a net decrease in neuronal activity with an increase in signal-to-noise ratio that has the functional effect of potentiating recognition of relevant stimuli while dampening or suppressing background neuronal activity or "noise." It is possible that increasing signal to noise contributes to chronic hyperarousal and vigilance in individuals with PTSD. It is of interest that the greatest magnitude of difference between PTSD and controls was in the orbitofrontal portion of prefrontal cortex. Dysfunction of prefrontal cortex during noradrenergic stimulation may be relevant to the failure of inhibition of intrusive memories and cognitions that are characteristic of PTSD. Such failures of inhibition are often apparent clinically during times of stress or presentation of traumatic cues that are associated with excessive activation of noradrenergic systems in PTSD.

YOHIMBINE FAMILY HISTORY STUDY. To determine whether a family history of panic disorder predisposed combat veterans with PTSD to experience yohimbine-induced panic attacks, Nagy et al (1999) conducted a family history study of Axis I disorders in 24 combat veterans and their first degree relatives. All 24 probands participated in one of two yohimbine studies. Results indicated a 3.2% rate of panic disorder in 63 first degree relatives of probands who did not have yohimbine-induced panic attacks and a 2.4% rate of panic disorder in 85 first degree relatives of probands who did have yohimbine-induced panic attacks. The data suggest that family history of panic disorder is not a predisposing vulnerability for the development of yohimbine-induced panic attacks. The data also support the possibility that panic symptoms seen in patients with PTSD result from non-genetic factors such as traumatic exposure.

ACOUSTIC STARTLE: YOHIMBINE VERSUS PLACEBO CHALLENGE. Acoustic startle is a cardinal symptom of PTSD that is thought to represent an objective index of central nervous system dysregulation in many traumatized individuals with PTSD. Preclinical studies have shown that fear potentiated startle is increased by α_2 receptor

antagonists, such as yohimbine and piperoxan, and reduced by the α_2 receptor agonist clonidine. In a study of 18 combat veterans with PTSD (Morgan et al 1994), yohimbine caused significantly greater increases in acoustic startle amplitude than placebo at 90, 96, 102, 108, and 114 db. Differences in the effects of yohimbine compared to placebo were not seen in a comparison group of 11 combat veterans without PTSD. The data suggest that the exaggerated startle reflex seen in patients with PTSD is, at least in part, mediated by hyperresponsive noradrenergic systems.

Catecholamines and Memory

PTSD is characterized by repetitive re-experiencing of trauma in the form of intrusive daytime memories, nightmares, and flashbacks. These intrusive recollections often remain vivid for the lifetime of the individual and at times are experienced as if they are occurring in the present rather than the past. A large body of evidence suggests that arousing, fearful or emotionally exciting events are remembered better and for longer periods of time than emotionally neutral events. Most trauma survivors find these intrusive memories to be distressing and tormenting.

Preclinical Studies of Norepinephrine and Memory

Catecholamines play a central role in the encoding of memory for events and stimuli that are arousing, stressful or fear provoking. For example, it is well known that consolidation of recently formed memories can be enhanced by posttraining administration of epinephrine or norepinephrine. In 1975, Gold and Van Buskirk (1975) were the first to demonstrate that posttrial injections of epinephrine facilitated retention of inhibitory avoidance training and that the effects were dose and time dependant. The relationship between dose and degree of retention was described as an inverted "u," where intermediate (but not low or high) doses of epinephrine enhanced retention. Further, as the time between training and epinephrine administration increased, the memory enhancing effects of epinephrine decreased. Posttrial administration of epinephrine has similar effects on other aversive and nonaversive but arousing training tasks (Introini-Collison 1981; Sternberg 1985).

A number of observations support a relationship between elevated plasma E and enhanced retention. Memory for an inhibitory avoidance task is impaired by removal of the adrenal glands. Immediate posttrial injections of epinephrine cause a dose-related restoration in retention (Borrell et al 1983). Additionally, exogenous injections of epinephrine, at doses that enhance memory retention, result in plasma levels of epinephrine that are similar to levels obtained in response to high footshock (McCarthy and Gold 1981).

A similar relationship between enhanced memory and increased release of NE in the amygdala is supported by the finding that retention for an inhibitory avoidance task is enhanced by intra-amygdala infusion of NE immediately after training (Liang et al 1990). Evidence suggests that multiple neuromodulators such as opioid peptides, GABA, and glucocorticoids influence memory consolidation by activation of NE in the amygdala (Intrioni-Collison 1989; McGaugh 1988; McGaugh 1990).

Epinephrine seems to influence learning through effects on norepinephrine release in limbic structures including the amygdala and the LC. The memory enhancing effects of peripherally administered epinephrine are blocked by posttrial administration of the peripherally acting B-antagonist sotalol and by intra-amygdala infusion of propranolol (Liang et al 1990). It is thought that epinephrine, that does not readily cross the blood brain barrier, affects memory storage by first activating peripheral βadrenergic receptors on afferent fibers of the vagus nerve that project to the nucleus of the solitary tract. Projections from the nucleus solitary tract then release NE in the amygdala (Introini-Collison 1992; Packard 1995; Schreurs 1986). There also is evidence suggesting that E enhances memory by increasing circulating levels of glucose that readily crossed the blood brain barrier (Gold and McCarty 1995).

In addition to their effects on consolidation of memory at or around the time of training, E and NE have been shown to enhance memory retrieval when administered at the time of memory testing. Stone et al (1990) found that E, amphetamine, and glucose administered 30 min before retention testing each significantly enhanced memory for a one trial inhibitory avoidance task. Sara (1985) and Sara and Devauges (1989) reported that yohimbine and idazoxan, both of which increase central NE, effectively alleviated forgetting. Sara and Devauges (1989) have argued that effectiveness of retrieval appears dependent on an intact central noradrenergic system. It repeatedly has been shown in a variety of forgetting paradigms that cues related to the context in which the original learning took place play an important role in the facilitation of memory retrieval.

Clinical Studies of Norepinephrine and Memory

It has been hypothesized that traumatic events stimulate the release of epinephrine and norepinephrine and that these neurotransmitters cause an over consolidation of memory for the stressful event (McGaugh 1989; Roozendal 1997). The result would be a deeply engraved traumatic memory that is clinically expressed in the form of

intrusive recollections, flashbacks, repetitive nightmares and perhaps conditioned emotional responses (Pitman 1989). A positive feedback loop might be formed when the already consolidated traumatic memory was reexperienced with its attendant release of E and NE that further strengthened the memory trace and caused an even greater likelihood of subsequent intrusive recollections. Strengthening of the memory trace would be especially pronounced for those trauma survivors with a hyperresponsive sympathetic nervous system that releases excess catecholamines in response to stressors such as intrusive memories (Southwick et al 1997). Although remembering dangerous situations may protect one from similar potentially dangerous situations in the future, these traumatic memories are usually very painful.

The relationship between catecholamines and memory for emotional events recently has been studied in humans. Cahill et al (1994) examined the effect of propranolol on long-term memory for an arousing story in comparison to a closely matched emotionally neutral story among healthy subjects. In randomized double-blind fashion, subjects received either propranolol or placebo one hour before viewing a series of slides that depicted either neutral scenes or emotionally stressful scenes. One week after viewing the slides subjects returned for surprise memory testing. Subjects who received placebo had significantly better memory for emotional slides than neutral slides. On the other hand, subjects in the propranolol condition did not remember emotional slides any better than neutral slides suggesting that beta-activation is involved in the enhanced memory associated with arousing or emotional experiences. The results could not be explained by potential effects of propranolol on attention and sedation.

Because propranolol is lipid soluble and readily crosses the blood brain barrier, its effects on emotional memory could be mediated by central or peripheral actions of the drug. Nadolol, on the other hand, is a beta blocking drug that does not easily cross the blood brain barrier and thus primarily blocks beta receptors at peripheral sites. To clarify the role of central vs. peripheral beta receptors in the enhanced encoding of memory for emotional stimuli, Van Stegren (1998) administered either propranolol, nadolol or placebo to subjects 1–3 hours before viewing the same emotional and neutral slides used in the above study by Cahill et al (1994). Supporting the notion that central but not necessarily peripheral beta receptor activation is involved in enhanced memory for emotional events, propranolol but not nadolol impaired memory (compared to placebo) in subjects who viewed the emotional slide show. Of note, the emotional impact of the slides used in this study was relatively mild. It is possible that peripheral beta stimulation could have an effect on memory under more emotionally stressful conditions, such as real life traumas.

In a recent study designed to extend the work of Cahill et al (1994), we recently tested the effects of IV yohimbine (Southwick et al 1999) compared to placebo on memory for the same emotionally arousing and neutral slides used by Cahill. We predicted that yohimbine would have the opposite effect of propranolol and would enhance memory for the slides by increasing rather than blocking norepinephrine at the time of memory encoding. The results tended to support our hypothesis. For the group as a whole (yohimbine subjects plus placebo subjects) there was a positive correlation between peak change in plasma MHPG at the time of memory encoding and recall one week later for the slides. The results suggest that noradrenergic effects on memory are not limited to aversive or emotional stimuli but also include neutral stimuli. The level of norepinephrine, independent of the emotional valence of a stimulus, seems to be an important factor in memory encoding.

At least three human investigations have reported a relationship between NE and intrusive memories of past traumas. In studies of combat veterans with PTSD (Yehuda et al 1992) and women with child abuse-related PTSD (Lemieux 1990), 24-hour urinary excretion of NE has been positively correlated with intrusive traumatic memories as measured by the IES. Further, in an earlier mentioned challenge study (Southwick et al 1993), combat veterans with PTSD experienced intrusive memories and flashbacks in response to IV yohimbine. Although the mechanism by which yohimbine elicited intrusive memories and flashbacks is not known, it is possible that yohimbine, by increasing NE in specific brain regions, recreated a neurobiologic state resembling the one that existed at the time of memory encoding. It is well known that memory retrieval can be facilitated by reexposure to the external or internal context (environment) in which the original learning took place (state dependent recall). Thus, yohimbine may have caused increased NE release and thereby produced an internal hypercatecholaminergic state resembling the state that was present when traumatic memories were originally encoded. Accompanying subjective experiences likely included fear, anxiety, and heightened arousal.

It is also possible that a hypercatecholaminergic state may have facilitated the intrusion of traumatic memories by releasing inhibition normally provided by the prefrontal cortex. Yohimbine powerfully impairs prefrontal cortical function by blocking the beneficial effects of NE at postsynaptic α_2 receptors in the prefrontal cortex and by increasing norepinephrine release that promotes NE's detrimental effects at α_1 receptors (Arnsten 1998a). Similarly, exposure to high levels of stress increases endogenous catecholamine release and impairs prefrontal cortical function (Birnbaum et al 1999). The prefrontal cortex normally serves to inhibit processing of inappropriate

stimuli and responses (Arnsten et al 1996). It is possible that the prefrontal cortex similarly inhibits recall of traumatic memories and that loss of this inhibition during stress or yohimbine administration contributes to the increased intrusion of painful memories. In contrast, among normal subjects, stress likely causes smaller increases in NE with the result that postsynaptic α_2 receptors are activated and cognition potentially improved.

Norephinephrine and Pharmacologic Treatment

Although many pharmacologic strategies have been used to treat PTSD, currently there is no definitive treatment of choice (Friedman and Southwick 1995). To date most pharmacologic agents have been chosen for their efficacy in the management of adjunctive symptoms related to PTSD, such as depression and impulsivity, rather than for their effects on PTSD-specific symptoms such as intrusive memories, hypervigilance and increased startle. The above review of noradrenergic alterations in PTSD suggests that pharmacologic agents that specifically target noradrenergic hyperreactivity might be useful in the treatment of symptomatic trauma survivors.

Clonidine, an α_2 adrenergic receptor agonist that has peripheral and central effects, suppresses release of NE through actions at the presynaptic α_2 autoreceptor. It also has actions at the postsynaptic α_2 receptor. Clonidine has been reported as helpful for symptoms of hyperarousal, hypervigilance, sleep disruption, exaggerated startle response, nightmares, behavioral irritability, and aggression in open trials of combat veterans (Kolb et al 1987), cambodian refugees (Kinsea 1989) and children with PTSD (Perry 1994).

Propranolol is a nonselective beta-adrenergic blocking agent that affects both B1 and B2 receptors. With psychiatric patients it has been used to treat social phobia, disorders of aggression and violence, resistant mania and akasthesia. Open treatment trials of propranol also have been conducted in children (Famularo et al 1990) and combat veterans with PTSD (Kolb et al 1987). These trials have reported a decrease in nightmares, explosiveness, exaggerated startle, insomnia, and hyperalertness. Of note, results from studies involving clonidine and propranolol for the treatment of PTSD must be viewed with caution as none have been double blind and placebo controlled.

It is possible that propranolol, if administered before or immediately after a traumatic event, could prevent or diminish the sensitization of catecholamine systems and associated PTSD symptoms. It is also possible that early administration of propranolol might prevent the overencoding of traumatic memories that results from stress-related increases in E and NE. In the future it will be important for pharmacologic studies that are directed toward alterations in NE to be targeted at prevention and early intervention as well as treatment of chronic symptoms.

Other psychotropic medications with prominent actions on NE that have been used for the treatment of PTSD include tricyclic antidepressants and MAO inhibitors. Three randomized placebo controlled trials involving imipramine, amitriptyline and desipramine, in addition to numerous open trials and case studies, have shown TCAs to be of moderate efficacy for the treatment of re-experiencing and arousal symptoms. In general, phenelzine has seemed somewhat more effective than TCAs in treating PTSD-specific symptoms (Southwick et al 1994). Like TCAs symptom reduction has been greatest for re-experiencing and hyperarousal symptoms; however, to date there have only been two randomized placebo-controlled and two open trials of phenelzine for the treatment of PTSD.

Symptoms of PTSD also seem to respond to SSRI's. In a randomized placebo controlled trial of fluoxetine, civilians with PTSD showed significant reduction in overall PTSD symptoms, especially those in the hyperarousal and avoidance clusters (van der Kolk et al 1994). A number of open trials and case reports using SSRI's also have reported positive results (Friedman 1998). The fact that various symptoms and symptom clusters respond to different pharmacologic agents with separate mechanisms of action, suggests that PTSD represents a multi-system neurobiologic disorder.

Summary

In the aggregate, the studies reviewed in this manuscript provide evidence for increased responsivity of noradrenergic neurons that is detectable under conditions of stress in adults and children with PTSD (Bremner et al 1999; Southwick et al 1997). Consistent elevations of heart rate, blood pressure, plasma NE, and plasma MHPG have not been reported at baseline in this population but generally have been reported in response to neuroendocrine and psychological challenges. Increased responsivity of noradrenergic systems is consistent with a sensitization model of PTSD where biochemical, physiological and behavioral responses to subsequent stressors increase over time. It has been suggested that sensitization of noradrenergic systems contributes to arousal symptoms in PTSD including hypervigilance, exaggerated startle, anger and insomnia.

The yohimbine studies described in this review provide a body of research that may help to delineate possible mechanisms involved in noradrenergic hyperreactivity among individuals with PTSD. In these studies, equivalent doses of yohimbine caused significantly

greater behavioral, cardiovascular and biochemical (MHPG) responses among subjects with PTSD compared to controls. It has been suggested that this increased responsivity may have been due to increased synthesis and subsequent release of NE or altered sensitivity of α_2 adrenergic receptors (Bremner et al 1999; Southwick et al 1993); however, at least two other factors, in addition to sensitization, may have contributed to the robust yohimbine response observed in this population. These include decreased NPY and hypersecretion of CRF.

As noted earlier, baseline NPY was significantly lower in combat veterans with PTSD compared to controls and negatively correlated with degree of combat exposure and peak yohimbine-induced plasma MHPG. Further, yohimbine-induced increases in NPY were significantly blunted in the PTSD group (Rasmusson et al, in press). These results suggest that the increased noradrenergic response to yohimbine observed in patients with PTSD may, in part, have been caused by combat-induced decreases in NPY. Lower NPY would mean reduced capacity to restrain noradrenergic system reactivity to yohimbine with a resultant exaggerated release in NE and a corresponding elevation of plasma MHPG in the PTSD group. In day to day life, decreased NPY might contribute to hypersensitive alarm or anxiety reactions to current stressors.

A second potential modulating factor is CRF. Multiple sources of evidence have shown that CRF and norepinephrine participate in a mutually reinforcing feedback loop under stressful conditions. For example, intracerebroventricular infusion of CRF increases norepinephrine turnover in several forebrain areas (Dunn and Berridge 1987); CRF increases firing rate of NE/LC neurons in a dose dependent fashion (Valentino and Foote 1988); stress that activates norepinephrine neurons markedly increases CRF concentrations in the LC (Chappel et al 1990); CRF infusion into the LC is anxiogenic and produces significant increases in MHPG in brain areas such as the amygdala and hypothalamus (Butler et al 1990). Moreover, preclinical studies have demonstrated that chronic stress can cause hypersecretion of CRF (Coplan et al 1996) and Bremner and colleagues (1997b) recently reported higher resting CSF levels of CRF in combat veterans with PTSD compared to controls. The above evidence suggests that hypersecretion of CRF in individuals with PTSD may serve as a modulating factor that enhances stress-related release of NE.

Thus, increased synthesis of norepinephrine, altered sensitivity of pre-synaptic α_2 receptors, hypersecretion of CRF and decreased NPY may each have been factors that contributed to the exaggerated release of NE seen in PTSD subjects who received yohimbine. This increased noradrenergic response may have contributed to anxiety and fear related behaviors through effects on multiple brain regions including the amygdala, hippocampus, cortex, and striatum. Increases in cardiovascular function may have been coordinated through the PGI and the hypothalamus. Retrieval of overencoded traumatic memories may have been facilitated by elevated NE levels in the amygdala and hippocampus.

In approximately 30–40% of PTSD subjects, intrusive memories that followed yohimbine infusion were experienced as flashbacks. In these subjects, PFC functioning may have been compromised by yohimbine induced increases in NE that engaged postsynaptic alpha-1 receptors and blocked postsynaptic α_2 receptors. The result may have been impairment in executive functions such as simulation and reality testing. Simulation involves the generation of internal models of external reality, including models of the past. Reality testing includes the monitoring of information sources. Thus, elevated NE in the amygdala and hippocampus may have facilitated retrieval of past traumatic memories (state dependent recall) but deficits in reality testing may have made it difficult to discriminate between the current external world and the internally generated memory of the past. The result would be a flashback where the past memory is experienced as if it were occurring in the present. This model is consistent with results from the earlier mentioned yohimbine PET study (Bremner 1997) where the PTSD group, compared to controls, showed decreased metabolism in neocortical brain regions, including the PFC.

Currently double-blind placebo controlled treatment trials are being conducted with both propranolol and clonidine. These studies involve combat veterans with chronic PTSD, children with PTSD and civilian women who have been sexually violated. It is hoped that these adrenergic blocking agents will help to prevent symptoms of PTSD and to treat symptoms in individuals who already have developed PTSD.

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