SYNAPSE 23:39–51 (1996)

Noradrenergic Mechanisms in Stress and Anxiety: II. Clinical Studies

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KEY WORDS Anxiety, Noradrenergic function, Posttraumatic stress disorder, Panic disorder, Generalized anxiety disorder, Obsessive-compulsive disorder

ABSTRACT Studies in animals have shown a relationship between alterations in noradrenergic brain system function and behaviors of anxiety and fear. These findings have generated the hypothesis that the symptoms seen in patients with anxiety disorders may be related to alterations in noradrenergic function. A number of clinical studies have tested this hypothesis, utilizing measures of catecholaminergic function such as heart rate and blood pressure, measurement of norepinephrine and its metabolites in urine and plasma and adrenergic receptor binding in platelets, as well as pharmacological challenge to the noradrenergic system. Acute stressors, such as public speaking, have been associated with an increase in heart rate, blood pressure, and norepinephrine and its metabolites in urine and plasma. Findings in patients with panic disorder at baseline related to heart rate, blood pressure, baseline norepinephrine and its metabolites, and platelet adrenergic receptors have been mixed, while the most consistent findings have been blunted growth hormone response to clonidine and increased 3-methoxy-4-hydroxyphenylethylene-glucol (MHPG) and anxiety following stimulation of the noradrenergic system with yohimbine. Baseline measures of noradrenergic function in patients with posttraumatic stress disorder (PTSD) have also been mixed, while an increased heart, blood pressure and norepinephrine response to traumatic reminders, as well as increased behavioral (as well as different brain metabolic) response to yohimbine, have been found in PTSD. There are fewer studies of noradrenergic function in the other anxiety disorders, and the findings there have not been consistent. These studies provide evidence for increased noradrenergic responsiveness in panic disorder and PTSD, although there does not appear to be an alteration in baseline noradrenergic function in these patients.
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INTRODUCTION

Considerable interest has been focused on the relationship between norepinephrine and anxiety. We have reviewed in a previous paper the evidence from animal studies for a relationship between norepinephrine and behaviors related to anxiety and stress. In this current paper we review evidence from clinical studies which have examined the relationship between norepinephrine and behaviors of anxiety and fear in human subjects, as well as alterations in noradrenergic function in patients with psychiatric disorders related to anxiety and stress, panic disorder, and posttraumatic stress disorder (PTSD).

The interest in the relationship between norepinephrine and anxiety and stress is partially related to the observation that there is a similarity between behavioral states associated with increases in catecholaminergic function and those associated with anxiety and fear. For instance, one of the authors treated a female patient with panic disorder who had panic attacks about once a week, characterized by the sudden onset of an increase in heart rate, with flushing and trembling, sweating, dry mouth, and dizziness. She had the feeling that she could not swallow, and became restless and short of breath. Thoughts began rushing into her head, like "this is the big one," "I'm going to die of a heart attack." This was followed by a further increase in heart rate and blood pressure. At this point the patient typically lost complete control and had an overwhelming panic attack, which she described as one of the worst things that could happen to her, something that she

Received May 8, 1995; accepted July 9, 1995.

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TABLE I. Evidence for noradrenergic contributions to anxiety and fear in healthy human subjects

Symptom	Supporting	Refuting
Increased heart rate with fear	Fenz and Epstein, 1967; Fenz and Jones, 1972; Schwartz et al., 1981;	
Increase in urinary epinephrine and norepinephrine during situations of fear	von Euler and Lundberg, 1954;	
Increase in plasma epinephrine and norepinephrine during stress and situations of fear	Ward et al., 1983; Dimsdale and Moss, 1980; Taggart et al., 1971, 1973;	
Increase in urinary MHPG during stress and anxiety	Lader, 1974; Buchsbaum et al., 1981; Rubin et al., 1970;	
Increase in plasma MHPG during stress and anxiety	Uhde et al., 1982, 1984	

would go to great lengths to avoid. These symptoms, which are typical of panic disorder, can also be elicited by administration of the catecholamines, including epinephrine and norepinephrine, and are associated with pheochromocytomas, which are tumors producing increased levels of the catecholamines (Goodman and Gilman, 1985).

Similar symptoms are also seen in patients with a history of exposure to psychological trauma and the diagnosis of PTSD. These patients suffer from chronic symptoms of increased arousal, irritability, exaggerated startle, decreased sleep and feeling on guard, all of which could potentially be related to increases in catecholaminergic function. Increases in heart rate and blood pressure with exposure to traumatic reminders, one of the most replicated findings in PTSD, may also be a result of abnormal noradrenergic function. The fact that increased release of catecholamines occurs during exposure to stress, in addition to the similarity between many symptoms of PTSD and behavioral effects of catecholamine administration, has led to the idea that alterations in catecholaminergic function may be associated with PTSD. Evidence based on clinical studies, which is reviewed below, supports this idea.

NORADRENERGIC CONTRIBUTIONS TO ANXIETY IN HEALTHY HUMAN SUBJECTS

Accumulated evidence suggests that noradrenergic brain systems play a role in mediating normal state anxiety and the response to stress in healthy human subjects (Table I). Administration of norepinephrine to healthy subjects results in an increase in blood pressure, respiratory rate, and subjective sensations of anxiety. Administration of epinephrine results in an increase in blood pressure, heart rate, cardiac output, respiratory rate, and subjective sensations of anxiety (Goodman and Gilman, 1985). States of anxiety or fear appear to be associated with an increase in norepinephrine release in healthy subjects (reviewed in Weiner, 1984). The situation of an approaching parachute jump is associated with an increase in subjective fear and a steady increase in heart rate (Fenz and Epstein, 1967; Fenz and Jones, 1972). With experimental induction of a variety of emotions in healthy subjects, anger produces the greatest increase in diastolic blood pressure and heart rate, with increases in heart rate and blood pressure also seen during states of fear. These changes in heart rate and blood pressure with anger and fear are distinct from situations of relaxation (Schwartz et al., 1981). Increases in heart rate and blood pressure during situations of anxiety or fear are consistent with increases in peripheral catecholamines. Considering the linkage between peripheral and central catecholamine responses which is reviewed above, these studies support a relationship between norepinephrine and stress and anxiety in healthy human subjects.

Several studies in healthy subjects are consistent with a relationship between anxiety and fear and increases in circulating catecholamines (Table I). Unexperienced privates in the Air Force have an increase in urinary epinephrine during flight in transport planes in comparison to ground activity. Pilots of the airplane have an increase in both urinary norepinephrine an epinephrine during flight in comparison to ground activity (von Euler and Lundberg, 1954). Increases in plasma norepinephrine and epinephrine have also been associated with situations of anxiety and fear. During public speaking, epinephrine levels increase twofold, while during physical exercise, norepinephrine levels increase threefold (Dimsdale and Moss, 1980). Plasma epinephrine and norepinephrine levels increase over baseline in healthy subjects during cognitive stressors (mental arithmetic), physical stressors (knee bends), and pain stressors (cold pressor and venipuncture). Epinephrine levels were greatest during cognitive stressors in this study, while painful stressors evoked the greatest norepinephrine response (Ward et al., 1983). Among young physicians making a presentation at ground rounds, epinephrine levels rose sharply before and at the onset of the talk, while norepinephrine levels increased gradually and remained elevated throughout the duration of the talk. The bulk of the total increase in catecholamines was almost totally secondary to the increase in norepinephrine. These increases in catecholamines were associated with increases in heart rate and electrocardiographic abnormalities and were blocked by administration of a β-antagonist (Taggart et al., 1973). In race car drivers assessed during the emotional stress of race car driving, there was a gross elevation of catecholamines, which was highest near the start of the

race, and which was largely due to norepinephrine (Taggart et al., 1971). Studies have not consistently found, however, a relationship between subjective anxiety and plasma norepinephrine and epinephrine (Morrow and Labrum, 1978).

The norepinephrine metabolite 3-methoxy-4-hydroxy-phenylethylene-glycol (MHPG) has also been found to increase in healthy subjects during emotional stress (Buchsbaum et al., 1981; Lader, 1974). Urinary MHPG increased in naval aviators after landings of aircraft on aircraft carriers, an extremely dangerous and potentially stressful undertaking, in comparison to a nonflying control day (Rubin et al., 1970). Plasma MHPG was correlated with state anxiety in healthy subjects exposed to the anticipatory stress of receiving an electric shock, while there was no such correlation in the absence of the electric shock threat (Uhde et al., 1982, 1984). Significant within-individual correlations between changes in urinary MHPG and changes in state anxiety have been found in healthy human subjects (Sweeney et al., 1978). These studies are consistent with a relationship between norepinephrine and anxiety in healthy human subjects.

NORADRENERGIC CONTRIBUTIONS TO PANIC DISORDER

Extensive research has focused on the role of noradrenergic brain system function in panic disorder (Table II). Patients with panic disorder experience discrete episodes of panic or severe anxiety associated with physical symptoms which are also seen with norepinephrine administration, including shortness of breath, dizziness, trembling, sweating, choking, nausea, numbness, muscle tension, restlessness, palpitations or rapid heart rate, dry mouth, hot flushes, and trouble swallowing. As can be seen in Table II, an increase in resting heart rate and blood pressure in comparison to controls has been shown in some studies, but not others. One study showed significantly higher resting heart rate in panic disorder patients with yohimbine-induced panic attacks than healthy subjects (Charney et al., 1987a), although the same was not found for patients with lactate-induced panic attacks (Freedman et al., 1984). Resting heart rate was often measured during a period when the patients were anticipating a pharmacological challenge, which suggests that they may have been experiencing anticipatory anxiety. One study showed significantly greater heart rate response to orthostatic challenge in panic disorder patients in comparison to controls (Stein et al., 1992). Increases in heart rate have been fairly consistently seen during panic attacks in patients with panic disorder, while conflicting results have been obtained for blood pressure response during spontaneous and situational panic attacks.

Several studies have investigated circulating epinephrine and norepinephrine in patients with panic disorder. Conflicting results have been obtained for resting urinary norepinephrine and epinephrine. An increase in plasma epinephrine has been found in panic disorder in comparison to controls (Nesse et al., 1984; Villacres et al., 1987), with one study showing a correlation between rated anxiety and epinephrine (Villacres et al., 1987). Conflicting results have been obtained for plasma norepinephrine at baseline in panic disorder patients in comparison to controls (Table II). Urinary MHPG has been found to be increased in patients with depression and panic disorder in comparison to patients with depression without panic disorder (Garvey et al., 1987). Plasma MHPG has not been found to be increased in patients with panic disorder at baseline in comparison to controls, and conflicting results have been found for the relationship between MHPG and anxiety during panic attacks (Table II). Panic attacks associated with inhalation of CO_2 in patients with panic disorder have been associated with an increase in plasma norepinephrine, as well as diastolic blood pressure (Gorman et al., 1988). Spontaneous attacks have not been associated with an increase in plasma norepinephrine, epinephrine, or MHPG (Cameron et al., 1987). Cerebrospinal fluid MHPG has been found to correlate with self-rated anxiety in affective disorder patients with associated symptoms of anxiety (Post et al., 1980). In summary, evidence from measures of heart rate and blood pressure as well as studies of peripheral catecholamines do not support an increase in norepinephrine at baseline. However, there is evidence to support an increased release of norepinephrine during panic attacks.

Early studies attempted to clarify mechanisms of alterations in adrenergic function in panic disorder at the level of the β-adrenergic receptor. In fact, some, but not all, early investigators called patients with what would be classified today as panic disorder "hyperdynamic β-adrenergic circulatory state" (Frohlich et al., 1966, 1969). Subsequently there has not been evidence to support an increase in β-adrenergic receptor activity in panic disorder. Infusion of the β-agonist, isoproterenol, has been shown to result in both increases or no change in heart rate in patients with panic disorder in comparison to controls (Nesse et al., 1984). Administration of the β-antagonist, propranolol, has been found to be mildly beneficial in the treatment of patients with panic anxiety (Kathol et al., 1980), including patients sensitive to the effects of isoproterenol infusion (Easton and Sherman, 1976), although not effective when administered i.v. in blocking lactate-induced panic attacks in lactate-sensitive patients (Gorman et al., 1983). Administration of imipramine, however, blocks lactate-induced panic attacks in these patients (Pitts et al., 1967). Patients with panic disorder have been found to have a decrease in peripheral lymphocyte β-adrenergic binding sites (B_{max}) and in increase in affinity (K_D) (Brown et al., 1988), as well as a decrease in basal activity of cyclic adenosine monophosphate (cAMP), a second

TABLE II. Evidence for noradrenergic contributions to panic disorder

Symptom	Supporting	Refuting
Increased resting heart rate	Nesse et al., 1984, 1985b; Cameron and Nesse, 1988; Gorman et al., 1988; Freedman et al., 1984	Freedman et al., 1985; Cameron et al., 1987; Villacres et al., 1987; Stein et al., 1992
Increased resting blood pressure	Gorman et al., 1988	Villacres et al., 1987; Cameron et al., 1987; Nesse et al., 1984
Increased resting heart rate in panic-prone patients	Charney et al., 1987a	Freedman et al., 1984
Increased heart rate response to orthostatic challenge	Stein et al., 1992	
Increased heart rate during panic attacks	Woods et al., 1987; Freedman et al., 1985; Taylor et al., 1986; Shear et al., 1987; Balon et al., 1988	Freedman et al., 1984; Cameron et al., 1987
Increased blood pressure during panic attacks	Balon et al., 1988; White and Baker, 1986	Woods et al., 1987; Cameron et al., 1987
Increased plasma norepinephrine	Nesse et al., 1985b	Stein et al., 1992; Woods et al., 1987; Cameron et al., 1987; Villacres et al., 1987; Nesse et al., 1984
Increased plasma epinephrine	Nesse et al., 1984; Villacres et al., 1987	
Increased resting urinary epinephrine and norepinephrine	Cameron et al., 1984b; Nesse et al., 1985a	Cameron et al., 1987
Increased plasma MHPG at baseline		Uhde et al., 1988; Edlund et al., 1987; Cameron et al., 1987
Increased plasma MHPG during panic attacks	Ko et al., 1983	Woods et al., 1987; Cameron et al., 1987
Decrease in lymphocyte β-adrenergic binding sites	Brown et al., 1988	
Decrease in basal activity of cAMP	Charney et al., 1990	
Decreased platelet alpha$_2$ binding sites (B_{max}) for clonidine	Cameron et al., 1990	Cameron et al., 1984
Decreased platelet alpha$_2$ binding sites (B_{max}) for yohimbine	Cameron et al., 1984, 1990; Albus et al., 1986	Charney et al., 1990; Nutt et al., 1987
Decreased platelet alpha$_2$ receptor affinity (K_D) for clonidine		Cameron et al., 1984
Decreased platelet alpha$_2$ receptor affinity (K_D) for yohimbine	Charney et al., 1990a	
Decreased platelet alpha$_2$ (B_{max}) and (K_D) for [^{3}H]rauwolscine		Norman et al., 1987
Reduction in panic anxiety with clonidine	Uhde et al., 1984, 1989; Liebowitz et al., 1981; Hoehn-Saric et al., 1981	Charney and Heninger, 1986
Blunted growth hormone response to clonidine	Uhde et al., 1986; Charney and Heninger, 1986; Curtis et al., 1989; Charney et al., 1992	
Increase in panic and plasma MHPG with yohimbine	Charney et al., 1984a, 1987a, 1992; Uhde et al., 1984; Gurguis and Uhde, 1990	

messenger coupled to β-adrenergic receptors (Charney et al., 1990) in comparison to controls. In addition, patients with "incapacitating anxiety" have been shown to have decreased in vitro isoproterenol-stimulated production of cAMP in comparison to controls, which increases after 4 weeks of treatment with propranolol (Lima et al., 1983). In summary, the evidence does not support an increased sensitivity of β-adrenergic receptors in panic disorder as was originally hypothesized. In fact, several studies support a decrease in β-receptor sensitivity, which could result from chronic increases in circulating catecholamines.

Mixed results have been obtained for alterations in alpha$_2$ adrenergic receptor binding in panic disorder. Some studies have found decreases and others have found no change in alpha$_2$ adrenergic receptor binding sites (B_{max}) on platelet membranes, as measured with tritiated yohimbine, clonidine, and rauwolscine, in patients with panic disorder in comparison to controls (Table II). Alpha$_2$ adrenergic receptor affinity (K_D) has been found to be either not different or lower (higher K_D) as measured by tritiated yohimbine, clonidine, and rauwolscine. A reduced EC_{50} for the epinephrine inhibition of adenylate cyclase activity, and a decreased stimulation of adenylate cyclase activity by prostaglandin E_1 and sodium fluoride, has been associated with panic disorder patients in comparison to controls (Charney et al., 1990). These findings suggest that panic disorder is associated with a decrease or no change in alpha$_2$ receptor number, and a decrease or no change in alpha$_2$ receptor affinity. In addition, our groups results are consistent with a dysfunction at the level of the stimulatory GTP binding regulatory protein G_s, or the adenylate cyclase catalytic unit. This could be secondary to a down-regulation in response to high levels of circulating norepinephrine, and/or a primary alteration in alpha$_2$ receptor morphology or function. An important function of presynaptic alpha$_2$ receptors is to act as an autoreceptor to decrease release of norepinephrine from the terminal in response to binding of norepinephrine to the alpha$_2$ receptor. A decrease in alpha$_2$ receptor number or affinity may result in increased release of norepinephrine into the synapse in patients with panic disorder.

Administration of the alpha$_2$ agonist, clonidine, has been utilized in the study of noradrenergic contribu-

tions to panic disorder. Some studies, but not all, have found clonidine to be effective in the reduction of anxiety and panic symptomatology in patients with panic disorder (Table II). Administration of clonidine to patients with panic disorder has been shown to result in a decrease in plasma MHPG (Charney et al., 1992; Ko et al., 1983). In one study, subjects with the highest baseline plasma MHPG had the greatest improvement in anxiety symptoms with clonidine (Uhde et al., 1984). Stimulation of central alpha$_2$ receptors appears to result in an increase in peripheral release of growth hormone; therefore, the growth hormone response to clonidine has been advocated as a test of central alpha$_2$ adrenergic receptor function (Siever et al., 1983). Patients with panic disorder have been found to have a blunted growth hormone response to clonidine in comparison to healthy controls, which is similar to the response seen in patients with major depression (Charney and Heninger, 1986; Charney et al., 1992; Curtis et al., 1989; Uhde et al., 1986). These findings are consistent with a subsensitivity of central alpha$_2$ adrenergic receptors in panic disorder.

Administration of the alpha$_2$ antagonist, yohimbine, which increases release of norepinephrine in the hippocampus and other central target brain structures through increased firing of the locus coeruleus (reviewed in Goldberg and Robertson, 1983), results in an increase in behavioral and biological correlates of anxiety in patients with panic disorder. An increase in panic attacks, self-rated anxiety, palpitations, restlessness, tremors, and systolic blood pressure has been found in panic disorder patients following administration of yohimbine in comparison to controls. In addition, panic disorder patients with greater than 2.5 panic attacks per week had a greater plasma MHPG response to yohimbine than controls and panic disorder patients with less frequent panic attacks. Rise in MHPG following yohimbine was correlated with self-rated anxiety in patients with panic disorder (Charney et al., 1984a, 1987a). Patients with yohimbine-induced panic attacks have also been found to have greater increases in MHPG following yohimbine than healthy subjects and other panic disorder patients without yohimbine-induced panic attacks (Charney et al., 1992). Other groups have also found an increase in anxiety symptoms, panic attacks, heart rate, and blood pressure in panic disorder patients in comparison to controls and positive correlations between yohimbine-induced increases in MHPG and increases in self-rated anxiety in patients with panic disorder (Gurguis and Uhde, 1990; Uhde et al., 1984). These findings are consistent with an increased responsivity of noradrenergic brain systems in patients with panic disorder, possibly secondary to a decreased sensitivity of the alpha$_2$ adrenergic autoreceptor, which is less sensitive to the inhibitory feedback of norepinephrine in the synapse.

Medications which act at the level of noradrenergic brain systems have been found to be effective in the treatment of panic disorder. As noted above, clonidine, which decreases firing in the locus coeruleus, has been shown in some studies to result in an improvement in symptoms of anxiety in patients with panic disorder. Most of the tricyclic medications are efficacious in the treatment of panic disorder, including imipramine (Tofranil) (Ko et al., 1983), desipramine (Norpramin), and clomipramine (Anafranil) (reviewed in Bremner and Charney, 1994). These medications act by blocking the re-uptake of norepinephrine into the neuron at the level of the synapse. Tricyclics also down-regulate β-adrenergic receptors and decrease β-adrenergic agonist-induced cAMP production, which has been hypothesized to represent their mechanism of therapeutic action. Imipramine has been shown to decrease MHPG in conjunction with its anxiolytic effect in patients with panic disorder (Ko et al., 1983). Treatment with imipramine decreases the number of alpha$_2$ receptor binding sites measured with tritiated yohimbine and increases catecholamine levels in patients with panic disorder, with a significant correlation between reduction of self-rated anxiety with treatment and reduction of tritiated yohimbine binding sites (Cameron et al., 1984a).

Few studies have examined genetic contributions to panic disorder. Some studies suggest a familial contribution to panic disorder (Noyes et al., 1978). In a study examining genetic loci in patients with panic disorder, no evidence were found for genetic mutation at the loci for adrenergic receptors (Wang et al., 1992). Future studies are indicated to examine potential genetic contributions to alterations in noradrenergic function in patients with panic disorder.

NORADRENERGIC CONTRIBUTIONS TO POSTTRAUMATIC STRESS DISORDER

PTSD is characterized by a constellation of symptoms which occur following exposure to an extremely stressful or traumatic event, such as exposure to combat, life-threatening natural disasters, being held hostage, train wrecks, rape, or physical abuse. Symptoms of PTSD include flashbacks, nightmares, feeling worse with reminders of the trauma, sleep disturbance, avoidance of the trauma, physiological arousal, exaggerated startle response, guilt, emotional numbing, and feeling cut off from other people. Kardiner noted in 1941 that veterans with psychiatric conditions related to their war experiences exhibited what appeared to be a hyper-responsiveness of the sympathetic system, manifested by increases in heart rate, blood pressure, sweatiness, irritability, palpitations, vertigo, dizziness, nausea, and syncope. Kolb hypothesized that the central disturbance of PTSD consisted of the "conditioned emotional response" to the original traumatic event which resulted in a heightened phsyiological response, mediated through adrenergic systems, to subsequent events

which were reminiscent of the original trauma. Since the time of Kardiner the psychophysiology technique has been used extensively to study conditioned emotional responding and sympathetic correlates of exposure to traumatic reminders in PTSD. Physiological variables which are recorded typically include heart rate, systolic and diastolic blood pressure, skin conductance, electromyographic (EMG) activity of the frontalis, corrugator, zygomaticus or orbicularis oculi muscles, and skin temperature. These variables reflect in part activity of the peripheral sympathetic nervous system. Exposure to traumatic reminders and neutral scenes utilized in the psychophysiology paradigm include slides (with or without accompanying sounds) of scenes similar to the original trauma or reading scripts which are descriptions of what actually happened during the original trauma. Comparisons are then made between exposure to trauma-related material and both the baseline and/or the neutral exposures.

The use of the psychophysiology technique has been in use since the time of the Second World War. Wenger (1948) noted that veterans of the Second World War with stress-related symptoms had increased heart rate and skin conductance at baseline in comparison to patients with other psychiatric disorders and healthy control subjects. Dobbs and Wilson (1960) first described increased heart rate and blood pressure responses in combat veterans with and without stress-related pathology who were exposed to combat slides and sounds in comparison to healthy controls. They also found increased heart rate at baseline in both the combat veterans with stress-related pathology and combat veterans without pathology in comparison to the healthy controls.

A number of investigators have utilized the psychophysiology paradigm since the time of these original studies (reviewed in Prins et al., 1995). Conflicting results have been obtained with regard to baseline heart rate and blood pressure in patients with PTSD (Table III). In the studies which have found increases at baseline, this may be attributed to the fact that the patients had anticipatory anxiety related to aspects of the testing situation, such as the fact that they would later be exposed to trauma-related material. An increase in reactivity to traumatic reminders has been a consistent finding in patients with PTSD. An increase in heart rate in response to auditory reminders of trauma (such as tapes of the sound of gunfire) has been found in Vietnam combat veterans with PTSD in comparison to healthy nonveteran controls (Blanchard et al., 1982) and Vietnam combat veterans without PTSD (Blanchard et al., 1986, 1989). No increase in heart rate in response to the stressor of mental arithmetic was found in any of these studies. An increase in heart rate following exposure to combined combat slides and sounds has been found in Vietnam combat veterans with PTSD in comparison to Vietnam combat veterans without PTSD (Malloy et al.,1983; McFall et al., 1990). Hearing scripts of the individual's traumatic experiences resulted in an increase in heart rate in Vietnam combat veterans with PTSD in comparison to Vietnam combat veterans without PTSD (Pitman et al., 1987, 1990b). An increase in heart rate with traumatic scripts has also been found in WWII and Korean veterans with PTSD in comparison to those without PTSD (Orr et al., 1993) and in patients with civilian trauma-related PTSD in comparison to controls (Shalev et al., 1992).

Studies have found abnormalities of the startle response in patients with PTSD. Increased startle magnitude has been found in Vietnam combat veterans with PTSD in comparison to Vietnam combat veterans without PTSD in some studies (for 80 dB bursts of white noise (for 95 and 100 dB noise—Butler et al., 1990) but not others (Paige et al., 1990). Other studies have shown no difference in trials to habituation of startle response (Ross et al., 1989). An increase in heart rate and skin conductance during the startle paradigm has been reported in patients with civilian PTSD in comparison to controls (Shalev et al., 1992).

Several groups have examined peripheral measures of noradrenergic function in PTSD. An increase in norepinephrine and epinephrine has been found in 24-h urines of PTSD patients in comparison to patients with major depressive disorder, paranoid schizophrenia, undifferentiated schizophrenia, and healthy controls, and an increase in norepinephrine in PTSD compared to patients with bipolar (manic-depressive) disorder (Kosten et al., 1987). An increase in the norepinephrine/cortisol ratio has been found to more specifically differentiate patients with PTSD from these patient groups (Mason et al., 1988). Other investigators, however, have found no difference in urinary levels of norepinephrine or cortisol in patients with PTSD in comparison to Vietnam veterans without PTSD (Pitman et al., 1990), or in plasma levels of norepinephrine at baseline in Vietnam veterans with PTSD in comparison to healthy controls (Blanchard et al., 1991; McFall et al., 1992). An increase in plasma epinephrine (McFall et al., 1990) and norepinephrine (Blanchard et al., 1991) has been shown following exposure to traumatic reminders in Vietnam veterans with PTSD in comparison to healthy subjects. Although these studies do not consistently support an increase in basal sympathetic function in PTSD, they do suggest that patients with PTSD may have an increased responsiveness of the sympathoadrenal system.

Studies of peripheral norepinephrine receptor function have also shown alterations in $alpha_2$ receptor and AMP function in patients with PTSD which are similar to those in panic disorder. A decrease in platelet adrenergic $alpha_2$ receptor number as measured by total binding sites for the $alpha_2$ antagonist [^{3}H]rauwolscine (Perry et al., 1987), and a significantly greater reduction in number of platelet $alpha_2$ receptors after exposure to agonist (epinephrine), has been observed in PTSD

TABLE III. Evidence for noradrenergic contributions to posttraumatic stress disorder

Symptom	Supporting	Refuting
Increased resting heart rate	Wenger, 1948; Blanchard et al., 1982; Kolb et al., 1984; Blanchard et al., 1986; Pitman et al., 1987	Malloy et al., 1983; McFall et al., 1990; Pitman et al., 1990b; Orr et al., 1993; Shalev et al., 1992
Increased heart rate and blood pressure response to traumatic slides and sounds	Dobbs and Wilson, 1960; Blanchard et al., 1982, 1986; Malloy et al., 1983; McFall et al., 1990	
Increased heart rate and blood pressure response to traumatic scripts	Pitman et al., 1987, 1990; Orr et al., 1993; Shalev et al., 1992	
Increased resting urinary norepinephrine	Kosten et al., 1987; Mason et al., 1988	Pitman et al., 1990a
Increased resting plasma norepinephrine		
Increased plasma norepinephrine in response to traumatic reminders	Blanchard et al., 1991	McFall et al., 1992; Blanchard et al., 1991
Increased plasma epinephrine in response to traumatic reminders	McFall et al., 1990	
Increased startle reaction	Butler et al., 1990	
Decreased binding to platelet alpha$_2$ receptors	Perry et al., 1987	Paige et al., 1990
Decrease in activity of cAMP	Lerer et al., 1987	
Decrease in platelet monoamine oxidase activity	Davidson et al., 1985	
Increase in PTSD and plasma MHPG with yohimbine	Southwick et al., 1993	
Differential effect of yohimbine on brain metabolism	Bremner et al., 1993	

patients in comparison to healthy controls (Perry et al., 1991). A decrease in basal adenosine 3′,5′-monophosphate (cAMP) signal transduction as well as isoproterenol and forskolin-stimulated cyclic adenosine 3′,5′-monophosphate (cAMP) signal transduction was noted in PTSD patients in comparison to healthy controls (Lerer et al., 1987). In addition, a decrease in platelet monoamine oxidase activity has been found in 23 PTSD patients in comparison to 19 age-matched controls (Davidson et al., 1985). These findings are consistent with alterations in noradrenergic function, possibly reflecting chronic high levels of norepinephrine release which lead to compensatory receptor downregulation and decreased responsiveness.

Pharmacological studies are also consistent with alterations in noradrenergic function in patients with PTSD. Administration of the alpha$_2$ antagonist, yohimbine, which results in an increase of release of norepinephrine in the brain, results in flashbacks in 40% and panic attacks in 70% of Vietnam veterans with combat-related PTSD. PTSD patients report an increase in PTSD-specific symptomatology, including intrusive memories, emotional numbing, and hyperarousal with yohimbine. Yohimbine administration also results in increased MHPG, blood pressure, and heart rate response in patients with PTSD in comparison to normal healthy controls (Southwick et al., 1993).

Alterations in noradrenergic function may be associated with changes in central brain function in patients with PTSD. Preclinical studies have shown that high-dose yohimbine administration results in a decrease in brain metabolism in neocortical areas, including temporal, parietal, prefrontal, and orbitofrontal cortex, as well as caudate (Inoue et al., 1991). Other pharmacological studies suggest that norepinephrine has a dose-response effect on neuronal activity (which is associated with metabolism), so that while high levels of norepinephrine release result in a decrease in neuronal activity, low levels of norepinephrine release are associated with an increase in neuronal activity (McCullouch and Harper, 1979; Raichle et al., 1975). Using positron emission tomography with [^{18}F]2-fluoro-2-deoxyglucose we have examined brain metabolic response in patients with combat-related PTSD (N = 10) and controls (N = 10) following administration of yohimbine and placebo. Yohimbine was associated with a differential effect on brain metabolism in neocortical areas, including orbitofrontal, temporal, prefrontal, and parietal cortex, with metabolism having a tendency to increase in the controls and decrease in the patients. One possible interpretation of these findings is that yohimbine administration results in higher levels of norepinephrine release in the PTSD patients compared to controls, secondary to an increase in noradrenergic reactivity to following yohimbine challenge (Bremner et al., 1993). This would be consistent with the preclinical and clinical studies outlined above. These studies also suggest that common alterations in norepinephrine function may occur in PTSD and panic disorder.

NORADRENERGIC CONTRIBUTIONS TO GENERALIZED ANXIETY DISORDER (GAD)

Although the evidence is less consistent in generalized anxiety disorder (GAD) than for panic disorder or PTSD, some studies are consistent with alterations in norepinephrine function in patients with GAD (Table IV). GAD is characterized by an excessive worry or preoccupation with life circumstances. This can take the form, for instance, of worrying about one's finances, misfortune to one's children when there is no danger present, or problems with one's health when there is no cause for concern. Plasma MHPG levels have been

1990). It appears that noradrenergic brain systems may play a limited role, if any, in conjunction with alterations in serotonergic brain systems, in patients with OCD.

NORADRENERGIC CONTRIBUTIONS TO PHOBIC DISORDERS

Few studies have examined noradrenergic function in patients with phobic disorders. Simple phobia is defined as the persistent fear of a specific stimulus, such as animals, closed spaces, or heights. In patients with simple phobias, increases in subjective anxiety and increased heart rate, blood pressure, plasma norepinephrine, and epinephrine have been associated with exposure to the phobic stimulus (Nesse et al., 1985b). This finding may be of interest from the standpoint of the model of conditioned fear, reviewed above, in which a potentiated release of norepinephrine occurs in response to a re-exposure to the original stressful stimulus.

Social phobia is the fear of being in public situations in which the person would come under scrutiny or be the subject of humiliation. Examples include the fear of eating in public, with the specific fear that something would happen which would be the source of embarrassment. Patients with social phobia have been found to have increases in plasma norepinephrine in comparison to healthy controls and patients with panic disorder (Stein et al., 1992). Patients with social phobia have also been found to have a normal growth hormone response to clonidine in comparison to controls (Tancer and Uhde, 1989).

Recent studies of the construct of behavioral inhibition to the unfamiliar may support a relationship between alterations in norepinephrine and anxiety. There is considerable variation within species in the tendency to approach or avoid novelty (reviewed in Kagan et al., 1988). Avoidant kittens, which avoid novel objects and humans in infancy and as adults do not attack rats, show greater neural activity in the basomedial amygdala following exposure to a rat, as well as larger evoked potentials in the ventromedial hypothalamus following direct stimulation of the basomedial amygdala, than comparison cats that do not avoid novelty (Adamec and Stark-Adamec, 1986). Studies in rhesus monkeys show that animals who are slow to explore show higher heart rates in unfamiliar settings than animals who are not avoidant (Suomi, 1987). Behavioral inhibition appears to be associated with increased sympathetic activity in the periphery. The fact that behavioral inhibition is present in infancy and persists throughout life suggests that this behavior is inheritable.

Behavioral inhibition is also a phenomenon present in young children. Inhibited responses to novel situations have been found to be a consistent response in a minority of young children which appears to persist throughout life. Behavioral inhibition in children is correlated with levels of urinary norepinephrine, saliva cortisol, changes in heart rate with cognitive procedures and with postural changes, and mean sleeping heart rates. Unusual fears were highest in children with behavioral inhibition and increased heart rates, and lowest in children without inhibition and with low heart rates (Kagan et al., 1988). The authors concluded that increased sympathetic activity, possibly mediated by limbic brain structures such as the amygdala, may be associated with a subgroup of children exhibiting behavioral inhibition.

Behavioral inhibition has been associated with the anxiety disorders. Increased rates of behavioral inhibition have been reported in children who are the offspring of parents with panic disorder and agoraphobia (Rosenbaum et al., 1988). Inhibited children of parents with panic disorder and agoraphobia have been found to have increased rates of several anxiety disorders as well as social phobia (Biederman et al., 1990). Parents of behaviorally inhibited children have also been found to have increased rates of social phobia (Rosenbaum et al., 1991) and other anxiety disorders (Rosenbaum et al., 1992). These studies suggest that a subgroup of individuals may have an inherited increased tendency to inhibition and fearfulness, which may be associated with increased sympathetic activity and increased risk for social phobia, panic disorder, and other anxiety disorders. Behavioral inhibition may represent a useful model for the relationship between alterations in noradrenergic brain system function, alterations in brain structures such as the amygdala which are involved in the fear response, heredity, and the pathophysiology of the anxiety disorders.

PHARMACOLOGICAL STUDIES OF THE RELATIONSHIP BETWEEN NOREPINEPHRINE AND STRESS AND ANXIETY: IMPLICATIONS FOR TREATMENT

The literature reviewed in this paper on the relationship between noradrenergic function and stress and anxiety has implications for the treatment of psychiatric disorders such as PTSD and panic disorder (Bremner and Charney, 1994). A widely used form of psychotherapy with demonstrated efficacy for these disorders is desensitization (Keane et al., 1989; Solomon et al., 1992). This involves repeated exposure of the patient to a stress-inducing stimulus, with the objective of obtaining a decrease in responsiveness to that stimulus over time. Preclinical studies have shown that reexposure of a chronically stressed animal to a stressor results in a potentiated release of norepinephrine in brain structures involved in memory, such as the hippocampus, amygdala, and prefrontal cortex. A similar mechanism may exist in patients with PTSD, and panic disorder who are highly sensitized to stressful stimuli. One might speculate that repeated exposure of these patients to stressful stimuli through desensitization ther-

TABLE IV. Evidence for noradrenergic contributions to generalized anxiety disorder, the phobic disorders, and obsessive-compulsive disorder

Symptom	Supporting	Refuting
Generalized anxiety disorder		
Increased plasma norepinephrine	Sevy et al., 1989; Mathew et al., 1980, 1981	Munjack et al., 1990
Increased plasma epinephrine	Mathew et al., 1980, 1981	
Increased plasma MHPG	Sevy et al., 1989; Munjack et al., 1990	
Increased monoamine oxidase activity	Mathew et al., 1981	
Decreased platelet alpha$_2$ adrenergic binding sites (B_{max})	Sevy et al., 1989	Cameron et al., 1990
Blunted growth hormone response to clonidine	Curtis et al., 1989	
Behavioral and biological responses to yohimbine		Charney et al., 1987b
Phobic disorders		
Increases in heart rate, blood pressure, plasma norepinephrine and epinephrine with phobic stimulus in simple phobia	Nesse et al., 1985b	
Increased plasma norepinephrine in social phobia	Stein et al., 1992	
Blunted growth hormone response to clonidine in social phobia	Tancer and Uhde, 1989	
Obsessive-compulsive disorder		
Increased plasma norepinephrine	Siever et al., 1983	
Increased plasma MHPG	Siever et al., 1983	Lee et al., 1990
Blunted growth hormone response to clonidine	Siever et al., 1983	Curtis et al., 1989; Hollander et al., 1991; Lee et al., 1990
Behavioral and biological effects of yohimbine		

shown to be increased in GAD patients in comparison to normal controls (Munjack et al., 1990; Sevy et al., 1989), while conflicting results have been obtained for resting plasma norepinephrine (Table IV). Other studies have shown an increase in plasma epinephrine in comparison to controls (Mathew et al., 1980, 1981). Alpha$_2$ receptor number (B_{max}) as measured by specific binding of tritiated yohimbine on platelet membranes has been found to be reduced (Sevy et al., 1989) or unchanged (Cameron et al., 1990) in GAD patients in comparison to controls. Monoamine oxidase activity has been shown to be increased in GAD patients in comparison to controls (Mathew et al., 1981). In addition, growth hormone response to clonidine, a probe of post-synaptic alpha$_2$ receptor function, has been found to be blunted in GAD patients in comparison to controls (Curtis et al., 1989), and administration of clonidine results in a decrease in the symptom of anxiety in these patients (Hoehn-Saric et al., 1981). Patients with GAD have not been found to have behavioral or biological responses to the alpha$_2$ antagonist, yohimbine, which are significantly different from controls (Charney et al., 1987b). These findings are consistent with an increase in presynaptic norepinephrine which may be associated with a downregulation of pre-synaptic alpha$_2$ receptors. However, the increased reactivity of the norepinephrine system seen in patients with PTSD and panic disorder does not appear to be characteristic of GAD.

NORADRENERGIC CONTRIBUTIONS TO OBSESSIVE-COMPULSIVE DISORDER (OCD)

Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessive and compulsive symptoms which cause marked distress, are time consuming (take up more than 1 hour of the day), or cause significant impairment in one's work or relationships with people. Obsessions are recurrent ideas, thoughts, or impulses which the individual experiences as intrusive or senseless, and which the individual attempts to ignore or suppress. Compulsions are repetitive behaviors, such as washing one's hands, which are designed to neutralize or prevent some discomfort or dreaded situation, such as perpetually having dirt on one's hands.

Limited evidence supports a role for noradrenergic systems in the pathophysiology of OCD. Patients with OCD have been found to have an increase in plasma norepinephrine in comparison to controls (Siever et al., 1983). Some studies have shown an increase in baseline plasma MHPG in OCD (Siever et al., 1983) while others have found no difference in comparison to controls (Lee et al., 1990). Some studies (Hollander et al., 1991; Knesevich et al., 1982) but not others (Lee et al., 1990) have found a reduction in the symptoms of obsessions and compulsions following administration of the alpha$_2$ agonist, clonidine, which results in a decrease in noradrenergic activity. One study found a blunted growth hormone response to 2 μg/kg clonidine in patients with OCD (Siever et al., 1983), while other groups have been unable to replicate this finding (Curtis et al., 1989; Hollander et al., 1991; Lee et al., 1990). In addition, no difference in response of plasma cortisol, blood pressure, pulse, or MHPG has been found following administration of clonidine in OCD patients in comparison to controls (Hollander et al., 1991; Lee et al., 1990). Administration of the alpha$_2$ antagonist, yohimbine, does not result in a significant difference in MHPG or behavioral responses between OCD patients and controls, although there is a significantly greater cortisol response in the patients. An increase in the number of binding sites (B_{max}) for tritiated clonidine in platelets has been shown in OCD patients in comparison to controls (Lee et al.,

apy may result in a decrease in norepinephrine release in these brain regions over time.

Tricyclic antidepressants have been shown to be efficacious in the treatment of panic disorder, and to a lesser degree PTSD. These medications reduce firing of locus coeruleus neurons and result in a down-regulation of post-synaptic β-receptors. Removal of tricyclics results in a rebound increase in noradrenergic activity (Charney et al., 1982). This is relevant to the clinical treatment of panic disorder, in that patients experience an increase in panic attacks upon tapering off of tricyclic antidepressants, which may be a result of the increase in noradrenergic activity which has been associated with removal of these mediations. Preclinical studies have also shown that administration before exposure to stress of tricyclics, but not other medications, prevents the acquisition of stress-related behaviors (Petty and Sherman, 1979; Sherman et al., 1979). These findings provide a rational explanation for the efficacy of tricyclic antidepressants in the treatment of panic disorder and PTSD.

Based on findings of noradrenergic contributions to panic disorder and PTSD, one would predict that agents which result in a decrease in noradrenergic function would be beneficial for these disorders. The evidence reviewed above has shown some efficacy for the alpha$_2$ agonist, clonidine, which causes a decrease in norepinephrine release in the brain, in the treatment of panic disorder. Controlled trials are now being conducted with clonidine in PTSD. This medication does not result in a complete amelioration of symptoms in panic disorder or PTSD, however, probably due to the development of tolerance, or the fact that other brain systems besides norepinephrine contribute to the symptoms of anxiety.

COMMENT

Findings in animal studies relating locus coeruleus/noradrenergic function to stress and anxiety have been corroborated in human studies as well. Stressful situations which induce fear in healthy human subjects, such as parachute jumping, are associated with increases in heart rate and blood pressure, urinary and plasma norepinephrine and epinephrine, and urinary and plasma levels of MHPG. Some studies also support a relationship between alterations in norepinephrine and the symptomatology of patients with panic disorder. Increased heart rate and blood pressure at baseline have not been consistently found in patients with panic disorder, while increases in heart rate and blood pressure have been found during panic attacks, suggesting an increase in circulating catecholamines at these times. Studies have shown an increase in resting urinary norepinephrine and epinephrine, while studies of resting plasma norepinephrine and epinephrine have been more equivocal. Conflicting results have been obtained related to a decrease in alpha$_2$ receptors on platelets, which would be consistent with an increase in circulating catecholamines. Several studies have shown a blunted growth hormone response to clonidine, which could be secondary to a decrease in post-synaptic alpha$_2$ receptor function associated with chronic increases in catecholamines. Patients with panic disorder have been shown to have an increase in panic anxiety and MHPG following administration of the alpha$_2$ antagonist, yohimbine, which increases norepinephrine in the brain. Finally, the efficacy of medications such as the benzodiazepines and tricyclic antidepressants which decrease firing of the locus coeruleus is consistent with a role for norepinephrine in panic anxiety. These studies are consistent with alterations in noradrenergic function in patients with panic disorder, possibly an increased responsiveness of noradrenergic brain systems during panic attacks.

PTSD is associated with alterations in noradrenergic function which are similar to those seen in panic disorder. Although conflicting results have been found for increased resting heart rate and blood pressure, studies are more supportive of an increase in heart rate and blood pressure during exposure to reminders of the original trauma, such as showing slides of combat to Vietnam combat veterans with PTSD. Resting urinary and plasma norepinephrine and epinephrine have not been found to be increased, while one study found an increase in plasma norepinephrine in response to traumatic reminders. Decreases in platelet alpha$_2$ receptors have been found which are consistent with an increase in circulating catecholamines in PTSD. Administration of the alpha$_2$ antagonist, yohimbine, has been associated with an increase in PTSD symptoms, heart rate, and plasma MHPG in PTSD patients in comparison to controls. These studies are consistent with an increased reactivity of the noradrenergic system which suggest similarities between PTSD and panic disorder.

Studies in the other anxiety disorders have been less extensive and do not support a role for noradrenergic brain systems to the same degree as for panic disorder and PTSD. Increased resting plasma MHPG has been found in GAD, although studies on plasma norepinephrine and platelet alpha$_2$ receptors have been equivocal. Patients with GAD have not been found to have an increase in behavioral or biological responses to the alpha$_2$ antagonist, yohimbine. Patients with simple phobia have been found to have an increase in heart rate, blood pressure, plasma norepinephrine, and epinephrine following exposure to the phobic stimulus in one study. Social phobia has been associated with an increase in resting plasma norepinephrine in one study, but no alteration in post-synaptic alpha$_2$ receptors as measured by a blunted growth hormone response to clonidine. Patients with OCD have been found to have an increase in plasma norepinephrine, while equivocal results have been obtained relating to plasma MHPG, growth hormone response to clonidine, and behavioral effects of clonidine administration. Administration of

the alpha$_2$ antagonist, yohimbine, has not been associated with an increase in behavioral or biological responses in patients with OCD. These studies suggest that alterations in norepinephrine do not appear to play a major role in the symptomatology of patients with GAD and OCD, while further studies are indicated in patients with phobic disorders.

Alterations in norepinephrine, which are involved in the stress response, are therefore specific to two of the anxiety disorders which are related to stress, panic disorder, and PTSD. PTSD is obviously related to stress through the requirement of exposure to an event "beyond the range of normal human experience" for the diagnosis. Panic disorder is related to stress through the clinical observation that panic attacks are frequently exacerbated by stressors, and the phenomenological similarity between panic attacks and the fear response. Certainly, norepinephrine facilitates behaviors which could promote survival in the face of life-threatening situations. It could be argued that OCD, social phobia, and GAD do not have such a clear connection with stress in their etiologies. Certainly, other neurotransmitter systems (serotonin) and other animal models have been invoked with greater interest in the etiology of OCD, while relatively much less research has been conducted in GAD and social phobia. Future studies will provide more information about these disorders, and about the relationship between norepinephrine and other brain systems involved in the stress response in the etiology of panic disorder and PTSD. On the other hand, this response may represent one part of a multi-faceted stress response, which in part serves to regulate other components of the stress response.

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