Catecholamine Function in Posttraumatic Stress Disorder: Emerging Concepts

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Note: The authors have worked to ensure that all information in this book concerning drug dosages, schedules, and routes of administration is accurate as of the time of publication and consistent with standards set by the U.S. Food and Drug Administration and the general medical community. As medical research and practice advance, however, therapeutic standards may change. For this reason and because human and mechanical errors sometimes occur, we recommend that readers follow the advice of a physician who is directly involved in their care or in the care of a member of their family.

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Chapter 8

Basal Sympathoadrenal Function in Patients With PTSD and Depression

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Clinical evidence suggests that central and peripheral noradrenergic function, including activity of the sympathetic nervous system (SNS), may be altered in posttraumatic stress disorder (PTSD). Historically, symptoms of anxiety and autonomic instability, including tremor, tachycardia, and elevated blood pressure, have been observed clinically in the veterans of a number of wars (DaCosta 1871; Hartshorne 1863; Wenger 1948). Currently, hypervigilance, exaggerated startle response, difficulty concentrating, irritability, and physiological reactivity to stimuli resembling the trauma are among the DSM-III-R criteria for diagnosing PTSD (American Psychiatric Association 1987).

A number of laboratory findings suggest that SNS activity may be altered in PTSD. Psychophysiological studies have reported increased resting heart rate in patients with PTSD compared with control subjects (Blanchard et al. 1982, 1986; Gerardi

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et al. 1989; Pallmeyer et al. 1986; Pitman et al. 1987) and other patient groups (Pallmeyer et al. 1986). In addition, neuroendocrine studies of traumatized populations and of PTSD patients have found increased catecholamine levels in 24-hour urine collections from these groups (Davidson and Baum 1986; Kosten et al. 1987). Perry et al. (1987) reported a decreased number of alpha$_2$ (α_2)–adrenergic receptor binding sites on platelets of PTSD patients, suggesting increased circulating levels of norepinephrine and/or epinephrine in patients with this disorder. Our group has described a greater release of epinephrine in response to trauma-relevant stressful stimuli than to trauma-irrelevant stressful stimuli in PTSD, and greater and longer-lasting increases in arterialized plasma epinephrine levels after exposure to trauma-relevant stressful stimuli in PTSD patients than in control subjects (McFall et al. 1990; see also Murburg et al., Chapter 9, this volume).

A number of basic neurobiological studies relevant to PTSD also suggest that SNS function may be altered by stress (see Murburg et al. 1990 for review). Animal studies show that acute inescapable stress may increase activity in some central norepinephrine nuclei, including the locus coeruleus (LC), with subsequent norepinephrine depletion, and may produce behaviors similar to those seen in depression (Anisman 1978; Kvetnansky et al. 1977; Lehnert et al. 1984; Nakagawa et al. 1981; Palkovits et al. 1975; Stone 1975; Weiss et al. 1970, 1980; see also Simson and Weiss, Chapter 3, this volume). Similar changes also occur in some central epinephrine nuclei (Kvetnansky et al. 1978; Saavedra et al. 1984). With chronic inescapable stress, synthesis and release of central norepinephrine and epinephrine in many brain areas appear to increase, and the number of ß-adrenergic receptors decreases (Axelrod et al. 1970; Kvetnansky et al. 1977; Musacchio et al. 1969). Peripheral epinephrine and norepinephrine are also released in response to acute stress (Kvetnansky and Mikulaj 1970; Kvetnansky et al. 1977, 1984). With chronic stress, arterial plasma catecholamine levels are high (Kvetnansky et al. 1984), and peripheral norepinephrine turnover rate remains elevated, while norepinephrine reuptake is decreased (see Stone 1975 for review).

Although many of these studies describe alterations in central,

as opposed to peripheral, catecholaminergic systems following different types of stress, it has recently been discovered that central and peripheral norepinephrine effector systems may be activated in parallel (see Aston-Jones et al., Chapter 2, this volume). Central (i.e., LC) and peripheral (i.e., SNS) stress-responsive norepinephrine effector systems are coordinately controlled by the nucleus paragigantocellularis (PGi) in the rostral ventral medulla (Aston-Jones and Ennis 1988; Aston-Jones et al. 1990; Chiang and Aston-Jones 1989; Elam et al. 1985, 1986; Reiner 1986; see also Aston-Jones et al., Chapter 2, this volume). Among the neurochemical mediators of this parallel activation may be corticotropin-releasing factor (CRF), a neuropeptide produced by the hypothalamus and other areas of the CNS that is released in response to stress. When centrally applied, CRF increases SNS activity (Brown et al. 1985; Swanson et al. 1983) and increases neuronal firing in the LC (Valentino 1989).

Interpretation of the above-mentioned studies is complicated by a number of factors. First, the applicability of many animal models of stress response to human PTSD is far from straightforward (see Zacharko, Chapter 5; Yehuda and Antelman, Comment, this volume). Second, not all human studies suggest that basal SNS function is altered in PTSD. Some studies have reported no differences in resting heart rate between PTSD patients and control subjects (Dobbs and Wilson 1960; Malloy et al. 1983), and other studies have reported no differences in resting heart rate between PTSD patients and other groups of psychiatric patients (Malloy et al. 1983; Pitman et al. 1990). Neuroendocrine studies of PTSD patients have also included mixed findings: one group of investigators has reported that 24-hour urine levels of catecholamines in PTSD patients were not different from those in combat-exposed control subjects (Pitman and Orr 1990). Third, the measures used in the human studies cited above have some methodological features that limit their interpretation (see Veith and Murburg, Chapter 16, this volume). Heart rate is an indirect indicator of SNS function, because it is influenced so prominently by parasympathetic input. Neuroendocrine studies investigating SNS function in PTSD by measuring urinary catecholamine output (Kosten et al. 1987; Pitman and Orr 1990) have not been specifically designed to detect tonic as opposed to phasic in-

creases in sympathoadrenal activity. Studies that have included patients with comorbid psychiatric conditions in the PTSD group may be confounded by the presence of disorders, such as major depressive disorder, that are known to alter SNS function (Barnes et al. 1983; Louis et al. 1975; Rudorfer et al. 1985; Veith et al. 1988, in press). Thus, the question of whether patients with PTSD have tonically increased levels of sympathoadrenal activity remains unanswered.

The goal of the present study was to evaluate basal sympathoadrenal function in PTSD patients by measuring levels of norepinephrine and epinephrine in arterialized plasma, as well as heart rate and blood pressure, to determine whether basal sympathoadrenal activity in this population differs from that expected of healthy, asymptomatic control subjects. Our hypothesis was that PTSD patients would have increased resting levels of SNS activity, resulting in increased resting pulse rate and blood pressure, as well as increased release of norepinephrine and epinephrine into plasma by sympathetic nerves and the adrenal medulla. As a result, basal plasma levels of norepinephrine and epinephrine were expected to be increased in PTSD patients compared with normal control subjects. Because major depression is a frequent comorbid condition in PTSD, and because increased SNS activity occurs in patients with major depression, particularly in those who are dexamethasone-resistant (presumably those with hyperactivity of the hypothalamic-pituitary-adrenal [HPA] axis) (Barnes et al. 1983; Louis et al. 1975; Rudorfer et al. 1985; Veith et al. 1988, in press), we segregated our patients in this study according to the presence or absence of major depression.

METHODS

Subjects

The sample consisted of 18 Vietnam veterans undergoing treatment for PTSD at the VA Medical Center or the Vietnam Veterans Outreach Center in Seattle. Nine patients were recruited from the Inpatient Psychiatry Service, and the remaining nine were outpa-

tients. Fifteen subjects were white, one was Mexican-American, one was Native American, and one was mixed Eskimo-American. The mean age for the sample was 41.1 years. Control subjects ($n = 16$) were asymptomatic nonpatient volunteers who responded to an advertisement. Fifteen subjects were white, and one was black. Control subjects had an average age of 40.1 years. PTSD subjects and control subjects averaged 116% and 106%, respectively, of ideal body weight, as defined by the 1983 Metropolitan Life Insurance Tables. All subjects were physically healthy, having no diagnosable medical conditions. Participants abstained from alcohol and illicit drug use for at least 2 weeks, and had not taken psychotropic medications or other medications known to alter plasma catecholamine levels for at least 4 weeks prior to the study. Finally, subjects habitually used three or fewer cups of caffeinated beverages per day and abstained entirely from caffeine, nicotine, and food ingestion for 12 hours before the procedure began.

All subjects were screened using the Structured Clinical Interview for DSM-III-R (Patient Version) (SCID; Spitzer et al. 1987). PTSD patients also exceeded published cutoff scores for combat veterans diagnosed with PTSD on the Revised Combat Scale (Gallops et al. 1981), the Mississippi Scale for Combat-Related PTSD (Keane et al. 1988), and the Impact of Event Scale (Zilberg et al. 1982). In order to be included in the study, PTSD subjects had to meet DSM-III-R criteria for PTSD by the SCID, while control subjects could not meet criteria for PTSD or other mental disorder by SCID. Current comorbid diagnoses for the PTSD sample were as follows: major depression ($n = 9$); major depression in partial remission ($n = 3$); dysthymia ($n = 3$); bipolar disorder, depressed ($n = 1$); generalized anxiety disorder ($n = 2$); obsessive-compulsive disorder ($n = 1$); social phobia ($n = 2$); and adjustment disorder ($n = 1$). Ten subjects also had a history of substance use disorder that had been in remission for at least 4 weeks prior to the study.

Procedure

All patients gave written informed consent. Participants remained supine throughout the study. An 18- or 19-gauge intrave-

nous catheter was inserted into a superficial vein on the dorsum of one hand, which was placed in a warming box at 60°C to arterialize the venous blood. Normal saline containing 1,000 U sodium heparin per 500 cc was infused at a rate sufficient to maintain patency of the catheter and to replace blood volume removed.

Subjects rested for 30 minutes after the intravenous catheter was properly operating. After this initial rest period, blood samples were drawn via the catheter, and assessments of vital signs were made at 10-minute intervals over a 30-minute baseline period (at 0, 10, 20, and 30 minutes), beginning at 1:00 P.M. Plasma samples for norepinephrine and epinephrine were collected in prechilled glass tubes containing EGTA and reduced glutathione, and placed on ice until prompt centrifugation at 4°C. Plasma was then stored at –70°C until assay. Heart rate and blood pressure were measured using an automated ultrasonic detector (Dinamap, Critikon, Tampa, Florida).

Circulating levels of norepinephrine and epinephrine were measured in arterialized forearm venous plasma (see Veith and Murburg, Chapter 16, this volume, for a more in-depth discussion of this technique). We have demonstrated in previous studies that forearm venous plasma arterialized by our method contains norepinephrine concentrations that are 94% of simultaneous peripheral arterial concentrations (Veith et al. 1984), thus providing a better indicator of systemic SNS activity than would venous blood, which is more prominently influenced by local factors (Best and Halter 1982, 1985). At each sampling time, a 10-ml sample of arterialized blood was collected in a prechilled glass tube containing EGTA and reduced glutathione, and placed on ice until centrifugation at 4°C. Plasma was then stored at –70°C until assay. Plasma norepinephrine and epinephrine concentrations were measured using a single-isotope enzymatic assay (Evans et al. 1978), and duplicate determinations were made for each sample. The interassay coefficient of variation for the plasma catecholamine assay in this laboratory is 6.5% in the >300 pg/ml range, and 12% in the 100 pg/ml range. The intra assay coefficient of variation is less than 5%. Statistical evaluations were performed using the Kruskal-Wallis one-way analysis of variance.

RESULTS

As shown in Table 8–1, PTSD patients with and without current full-syndrome major depression did not differ significantly from each other or from control subjects in measures of SNS function. Although the number of subjects was small, the expected increases in basal heart rate, blood pressure, and plasma catecholamine levels in patients with PTSD, particularly those with comorbid major depressive disorder, were clearly not found in this study.

DISCUSSION

The results of this study do not provide obvious support for the hypothesis that combat veterans with PTSD have higher basal levels of sympathoadrenal activity than do normal control subjects. Our finding that resting heart rate and blood pressure were equivalent for the three groups is in apparent conflict with the findings of five studies to date that did report higher heart rates and blood pressure in PTSD patients than in other groups. How-

Table 8–1. Means/standard deviations and probability values for physiological variables

Measure	PTSD alone ($n = 9$) mean	PTSD + MDD ($n = 9$) mean	Control ($n = 16$) mean	P^a
Heart rate (beats per minute)	63.3 ± 8.2	63.2 ± 8.0	61.4 ± 8.7	NS
Systolic BP (mmHg)	121.2 ± 5.8	124.4 ± 11.6	118.5 ± 8.1	NS
Diastolic BP (mmHg)	77.9 ± 7.8	79.9 ± 6.1	73.8 ± 7.0	NS
Norepinephrine (pg/ml)	231.6 ± 44.4	196.8 ± 67.8	249.2 ± 86.1	NS
Epinephrine (pg/ml)	66.5 ± 37.2	54.2 ± 29.0	76.4 ± 33.8	NS

Note. MDD = major depressive disorder; BP = blood pressure.
[a]Two-tailed *P*; NS = not significant.

ever, our finding is consistent with the findings of two other studies that reported no significant group differences (see McFall et al. 1989 for review). It is possible that an explanation for the differences in findings among these studies may be found in the different waiting periods used to allow subjects to achieve a true baseline.

Studies reporting predicted differences in vital signs between PTSD patients and normal control subjects typically allowed subjects to rest for between 3 and 12 minutes before heart rate and blood pressure were measured. Such a brief rest period may not have been long enough to allow patients to reach their true basal levels. Indeed, our previous study indicated that Vietnam combat veterans with PTSD continued to display elevations in heart rate, blood pressure, and plasma epinephrine levels 30 minutes after they finished viewing a film of scenes of the Vietnam War (McFall et al. 1990; see also Murburg et al., Chapter 9, this volume). In the present study, patients were allowed to rest for 30 minutes prior to baseline measurements being taken. This longer waiting period may have allowed our PTSD patients to arrive at a level of SNS functioning that more accurately reflected their true basal state.

The lack of significant differences between basal epinephrine and norepinephrine plasma levels in PTSD patients and normal control subjects in the present study may be consistent with Pitman and Orr's (1990) negative findings for urinary epinephrine and norepinephrine, although their group used asymptomatic combat veterans as control subjects, whereas our control group consisted of combat-naive normal subjects. Our findings are in apparent conflict with those of Kosten et al. (1987), who found higher urinary output of norepinephrine and epinephrine in PTSD patients than in other groups of psychiatric patients. However, plasma and urinary measurements of catecholamines obviously represent different physiological processes. A measurement of norepinephrine and epinephrine in a 24-hour urine collection provides an index of the amount of unmetabolized catecholamines cleared by the kidney following both tonic and phasic release by the sympathoadrenal system over a full day. Many variables, including current and recent administration of a variety of drugs, posture, physical activity level, dietary status,

smoking, and affective state throughout the sampling period, can influence the net measurement. In contrast, measurement of catecholamines in arterialized plasma taken from calm, resting subjects whose diet, physical activity, and pharmacological status have been controlled represents a net balance, at a particular point in time, between the rate of release of catecholamines into plasma by sympathetic nerves and the adrenal, and the rate of removal of catecholamines from plasma by neuronal reuptake and metabolism and by the kidneys. It has previously been shown that resting plasma norepinephrine levels correlate closely with direct measurements of peripheral sympathetic nerve activity in humans and that these measures are reproducible within individuals over periods of months to years (Wallin 1981).

Research to date consistently shows that PTSD patients experience phasic increases in sympathoadrenal activity that distinguish them from asymptomatic control subjects and from other psychiatric patient groups. These phasic increases may be provoked by exposure of the patients to trauma-related stimuli. In contrast, the present study, together with some of the research cited earlier in this chapter, suggests that levels of tonic or basal SNS activity in PTSD patients may not differ from levels found in control subjects. Even in the presence of a syndrome meeting criteria for the diagnosis of comorbid major depression, PTSD patients in this study showed no evidence of basal SNS hyperactivity. Our data further suggest that the syndrome of major depression seen as a comorbid complication of PTSD may differ in important biological aspects from primary major depression. Further clarification of the biological differences between the syndromal depression complicating PTSD and primary major depression is critical to increasing our understanding of the pathophysiology and treatment of both disorders.

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