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A pilot study of noradrenergic and HPA axis functioning in PTSD vs. panic disorder

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Abstract

The biological literature in the anxiety disorders has focused on comparisons between patient groups and normal volunteers, with relatively little comparative study of the anxiety disorders. We therefore conducted this pilot study to compare a group of patients with post-traumatic stress disorder (PTSD) ($n=7$) to a contiguously studied panic disorder group ($n=17$) and healthy control subjects ($n=16$) on baseline levels of cortisol and 3-methoxy-4-hydroxyphenylglycol (MHPG), and response to clonidine challenge. Despite the small sample size, highly significant differences were found on the following measures: PTSD patients had lower cortisol, lower MHPG, reduced MHPG volatility to clonidine challenge, and marginally reduced cortisol volatility compared to patients with panic disorder. These biological findings support existing clinical, epidemiologic, family study, and clinical trial findings that distinguish these two disorders as distinct syndromes.

Keywords: PTSD; Panic disorder; MHPG; Clonidine; Cortisol; Hypothalamic-pituitary-adrenal axis

1. Introduction

Study of pathological anxiety has primarily focused on differentiation of the various anxiety disorders from normal anxiety and fear states (Marshall and Klein, 1999). An equally important theoretical assumption of the current nosology, however, is that syndromal distinctions between the anxiety disorders have a biological basis.

Panic disorder and post-traumatic stress disorder (PTSD) differ on fundamental features such as age of onset, clinical presentation, course of illness, and treatment response. Nonetheless, they also share a number of common clinical and physiologic features (Kellner and Yehuda, 1999). In addition, panic disorder is commonly comorbid with PTSD in both epidemiologic and clinical samples (Kessler et al., 1995; Marshall et al., 1998; Davidson et al., 1990, 1985).

Aspects of noradrenergic function have been studied in both disorders, with distinctly discrepant

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findings. For example, in panic disorder, studies have found that baseline levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) are slightly elevated or no different from those of healthy control subjects (for review, see Sullivan et al., 1999). It is notable, however, that substantial variance has been observed within most samples, suggesting heterogeneity within the disorder (Garvey et al., 1990).

In contrast to panic disorder, baseline measures in PTSD of MHPG have been widely discrepant, and found to be elevated, lower, or equivalent to those of control groups without psychiatric disorder (for review, see Sullivan et al., 1999; Charney and Bremner, 1999; Murburg et al., 1995). Elevated urinary catecholamines have been found in sexually abused children (De Bellis et al., 1994) and in children with PTSD (De Bellis et al., 1999a,b). Since measures of urinary catecholamines reflect an average output over a period of time, they must be distinguished from baseline cross-sectional measures of catecholamines. Taken together, this literature suggests at least four distinct possibilities: (1) PTSD patients' noradrenergic systems may be more reactive but not necessarily have altered baseline functioning, which might explain discrepant findings on the basis of methodologic differences across studies; (2) there may be true biological heterogeneity within the diagnosis of PTSD; (3) physiologic manifestations of PTSD differ as a function of developmental stage; (4) contradictions in the literature primarily reflect methodologic inconsistencies across studies.

Challenge studies also suggest the existence of shared, though not identical, biological features in these two disorders. Panic disorder patients show increased sensitivity at the alpha-2 receptor in response to both agonists and antagonists (Charney and Heninger, 1986; Nutt, 1989). Challenge with yohimbine (an alpha-2 antagonist) consistently provokes panic attacks in patients with panic disorder (see Charney and Bremner, 1999), although these differ from lactate-induced attacks in that they cannot be blocked by imipramine and do activate the hypothalamic-pituitary-adrenal (HPA) axis (Klein, 1993). Similarly, both yohimbine and lactate challenge produce panic attacks with re-experiencing symptoms in a subgroup of patients with PTSD (Southwick et al., 1993; Mellman et al., 1995; Rainey et al., 1987; Jensen et al., 1997, 1998).

On measures of the HPA axis, distinctly different findings have been reported in panic disorder as compared to PTSD, although there are no direct comparisons to date. Most studies have found normative or slightly elevated baseline levels of plasma cortisol in panic patients (see Charney and Bremner, 1999). Cortisol is elevated in anticipation of panic attacks in the laboratory, but not during the attack (Coplan et al., 1998), which distinguishes panic attacks from normal fear reactions.

In contrast, studies of adults with chronic PTSD have been inconsistent with respect to both baseline serum cortisol levels, and 24-h urinary cortisol levels (for review, see Heim et al., 2000; Yehuda et al., 2000). Problems in interpreting this literature include differences in subject population (veterans vs. civilians, adults vs. children); differences in measurement (single time point vs. serial assessment; serum vs. urinary measures) and variations in experiment paradigm (measurement only vs. pre-behavioral challenge). To date, more studies have found cortisol levels to be higher than or equivalent to normal values than to be lower than normal values. A complete review of this complex literature is beyond the scope of this article (for review, see Heim et al., 2000; Yehuda et al., 2000).

In contrast to the variability in baseline cortisol among PTSD patients, the finding of super-suppression of cortisol following a low-dose dexamethasone test in chronic PTSD has been replicated in several studies and populations (for review, see Yehuda et al., 2000; Heim et al., 2000).

Surprisingly, the biological characteristics of these two disorders have rarely been studied in direct comparison (Jensen et al., 1997; Shalev et al., 1998). We therefore conducted this pilot study to compare noradrenergic functioning and HPA axis functioning in PTSD, panic disorder, and normal control subjects, assessing both baseline levels and response to clonidine challenge. Clonidine is an alpha-2 agonist that stimulates postsynaptic and presynaptic inhibitory receptors, and produces a reduction of neuronal firing from the locus coeruleus and a consequent reduction in