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Abnormalities in response to vasopressin infusion in chronic fatigue syndrome

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Abstract

Several neuroendocrine studies have suggested hypoactivation of the hypothalamic–pituitary–adrenal axis in chronic fatigue syndrome. One possible determinant of this neuroendocrine abnormality, as well as the primary symptom of fatigue, is reduced hypothalamic secretion of corticotropin-releasing hormone (CRH). Because CRH and vasopressin secreted from the hypothalamus act synergistically at the pituitary to activate ACTH secretion, the ACTH response to peripheral infusion of vasopressin can provide an indirect measure of hypothalamic CRH secretion. We measured the ACTH and cortisol response to a one hour infusion of arginine vasopressin in 19 patients with chronic fatigue syndrome and 19 age and sex matched healthy volunteers. Patients with chronic fatigue syndrome had a reduced ACTH response to the vasopressin infusion and a more rapid cortisol response to the infusion. These results provide further evidence of reduced hypothalamic CRH secretion in patients with chronic fatigue syndrome.

Keywords: Vasopressin; ACTH; CRH; Chronic fatigue syndrome; Cortisol; HPA axis

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1. Introduction

Chronic fatigue syndrome is a clinical disorder of unknown and probably heterogeneous etiology. The syndrome is currently defined as continuous or relapsing, debilitating fatigue, which, together with at least 4 of 8 other signs and symptoms, has persisted for at least six months in the absence of any other fatigue associated medical condition (Fukuda et al., 1994; Holmes et al., 1988). Although many cases of chronic fatigue syndrome develop following an acute infectious illness, some cases seem to occur independent of infection and onset may be associated with other types of physical or emotional stress (Demitrack, 1994). It is postulated that the chronic fatigue syndrome is perpetuated by a persisting, pathological response to the onset stress which includes symptoms of fatigue and low-grade inflammation (Demitrack, 1994; Strober, 1994). It is unclear whether the syndrome arises from a central nervous system dysfunction or a more peripheral abnormality at the neuromuscular junction, in muscle, or in immunologic activity. Although several investigators have failed to detect abnormalities in peripheral neuromuscular function in patients with chronic fatigue syndrome (Edwards et al., 1993; Gibson et al., 1993; Kent-Braun et al., 1993; Lloyd et al., 1991; Riley et al., 1990; Rutherford and White, 1991), a recent study found an increase in central motor fatigue (Samii et al., 1996). The pervasive symptoms of impaired concentration and memory in patients with chronic fatigue syndrome also point to central nervous system involvement in the etiology of the fatigue symptoms.

Both the clinical symptomatology of chronic fatigue syndrome and previous neuroendocrine studies have suggested impaired activation of the hypothalamic–pituitary–adrenal axis in patients with the syndrome (Demitrack, 1994). Adrenal steroid deficiency and adrenal steroid withdrawal is associated with several symptoms characteristic of chronic fatigue syndrome including fatigue, arthralgias, myalgias, adenopathy, exacerbation of allergic responses, feverishness, and changes in mood, cognition, and sleep (Henneman et al., 1955). Because glucocorticoids play a major role in restraint of inflammatory processes (Munck et al., 1984), reduced activation of HPA axis could contribute to symptoms and signs of chronic mild inflammation in patients with chronic fatigue syndrome and reported subtle abnormalities in laboratory measures of cell mediated and humoral immunity (Kent et al., 1992; Mawle et al., 1997; Strober, 1994). In addition, there have been reports of varying degrees of symptom improvement during treatment with hydrocortisone (Cleare et al., 1999; McKenzie et al., 1998) and fludrocortisone, a mineralocorticoid (Bou-Holaigah et al., 1995).

Many neuroendocrine studies of chronic fatigue syndrome, but not all (Bearn et al., 1995; Wood et al., 1998; Young et al., 1998), have noted reduced HPA axis activity in chronic fatigue syndrome. Positive findings include reductions in urinary free cortisol (Demitrack et al., 1991; Scott and Dinan, 1998), reduced plasma (Demitrack et al., 1991; Poteliakhoff, 1981) and salivary (Strickland et al., 1998) cortisol levels, reduced adrenal cortisol and dehydroepiandrosterone (DHEA) responses to moderate and high dose adrenocorticotropin (ACTH) stimulation (DeBecker et al., 1998; Demitrack et al., 1991; Scott et al., 1998a), and reduced