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Effects of dexamethasone on declarative memory function in posttraumatic stress disorder

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Abstract

Alterations in the hypothalamic–pituitary–adrenal (HPA) axis and hippocampal-based memory have been associated with posttraumatic stress disorder (PTSD), and the administration of exogenous glucocorticoids has been shown to result in a transient verbal declarative memory impairment in healthy human subjects. The purpose of this study was to assess the effects of the glucocorticoid dexamethasone on verbal declarative memory function in patients with PTSD. Forty-two men and women with (n=14) and without (n=28) PTSD received placebo or dexamethasone (1 and 2 mg on two successive days) in a double-blind, randomized fashion. Declarative memory was assessed with paragraph recall at baseline (day 1) and day 3. There was a significant interaction between diagnosis and drug (dexamethasone vs. placebo) on paragraph recall related to a relative detrimental effect of dexamethasone on memory function in healthy subjects, but not those with PTSD. These findings are consistent with an altered sensitivity of declarative memory function in PTSD to regulation by glucocorticoids, possibly explainable by alterations in glucocorticoid receptors in the hippocampus or other brain regions mediating declarative memory.

Keywords: PTSD; Memory; Dexamethasone; Cortisol; Glucocorticoids; Hippocampus

1. Introduction

Alterations in cognition and memory are an important aspect of the clinical presentation of posttraumatic stress disorder (PTSD). Empirical stud-

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ies have shown problems with learning and memory in PTSD that are specific to verbal declarative memory functions, such as the learning of new words or paragraphs (Gil et al., 1990; Bremner et al., 1993; Uddo et al., 1993; Bremner et al., 1995a; Yehuda et al., 1995b; Barrett et al., 1996; Golier et al., 1997; Jenkins et al., 1998; Vasterling et al., 1998; Moradi et al., 1999; Sachinvala et al., 2000; Gilbertson et al., 2001; Roca and Freeman, 2001; Vasterling et al., 2002). Understanding the neurobiological basis of memory alterations in PTSD may promote the development of new treatment approaches for this disabling aspect of PTSD.

The hypothalamic–pituitary–adrenal (HPA) axis plays a critical role in the stress response as well as modulating memory function (Heffelfinger and Newcomer, 2001). Patients with PTSD were found to have increased levels of corticotropin releasing factor (CRF) (Bremner et al., 1997a; Baker et al., 1999), enhanced cortisol suppression with dexamethasone (Yehuda et al., 1993), increased lympocyte glucocorticoid receptors (Yehuda et al., 1991a), lower resting cortisol levels in some studies (Yehuda et al., 1991b; Yehuda et al., 1994; Yehuda et al., 1995a; Kanter et al., 2001) but not others (Pitman and Orr, 1990; Lemieux and Coe, 1995) and increased cortisol response to stressors (Heim et al., 2000; Elzinga et al., 2003; Bremner et al., 2003a). The hippocampus is involved in memory (Zola-Morgan and Squire, 1990) as well as regulation of the HPA axis. (Herman et al., 1989). Stress results in alterations in hippocampal structure, an effect hypothesized to be secondary, at least in part, to stress-induced release of glucocorticoids (Pavlides et al., 1995; Diamond et al., 1996; Sapolsky, 1996) with associated inhibition of new neuronal growth (Gould et al., 1998; Malberg et al., 2000) and deficits in memory (Arbel et al., 1994; Luine et al., 1994). Mechanisms that have been proposed for the negative effects of stress on the hippocampus include increased activation of the type 2 glucocorticoid receptors (Sapolsky et al., 1990; Newcomer et al., 1994; Sapolsky, 1996), stress-induced decreases in brain-derived neurotrophic factor (BDNF) (Nibuya et al., 1995; Smith et al., 1995; Malberg et al., 2000; Duman et al., 2001), increased levels of excitatory amino acids (Moghaddam et al., 1997) and alterations in serotonin (McEwen et al., 1997).

Elevations of glucocorticoids within the physiological range result in reversible deficits in memory function in animals (Oitzl and de Kloet, 1992; Bodnoff et al., 1995) as well as human subjects (Newcomer et al., 1994; Kirschbaum et al., 1996; Lupien et al., 1997; Lupien et al., 1999; Newcomer et al., 1999; de Quervain et al., 2000; Wolf et al., 2001; Lupien et al., 2002). Glucocorticoids released during stress, possibly acting through the hippocampus, may explain in part the acutely reversible as well as chronic effects that stress has on declarative memory (Kirschbaum et al., 1996; Porter and Landfield, 1998; de Kloet et al., 1999; Wolf, 2003). Greater deficits are seen in younger subjects in comparison to older subjects, hypothesized to be secondary to age-related decreases in glucocorticoid receptor density (Newcomer et al., 1995). Studies in other neuropsychiatric disorders associated with hippocampal dysfunction, including schizophrenia (Newcomer et al., 1998) and depression (Bremner et al., 2004), found a relative sparing of the effects of dexamethasone on declarative memory function relative to normal human subjects, hypothesized to be secondary to disease-related decreases in glucocorticoid receptor function. PTSD has been described as an "accelerated aging" (Bremner and Narayan, 1998) related to common theories of progressive hippocampal atrophy and dysfunction in both processes. Therefore, it might be expected that dexamethasone would have less of an effect on verbal declarative memory function in PTSD than in controls. The purpose of the present study was to assess the effects of dexamethasone on verbal declarative memory function in patients with PTSD. We hypothesized that glucocorticoids would have less of an effect on declarative memory function in PTSD than in controls.

2. Methods

2.1. Subjects

Forty-two male and female subjects who were 18 years of age or older participated in the study. Subjects were included with (n=14) and without PTSD (n=28). All subjects were recruited by advertisement and gave written informed consent for participation in the study. This study was approved by the Yale University Investigational Review Board. PTSD subjects were included with the diagnosis of