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High dose hydrocortisone immediately after trauma may alter the trajectory of PTSD: Interplay between clinical and animal studies ☆

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Abstract

High-dose corticosteroids have been reported to reduce symptoms of acute stress and post-traumatic stress in polytrauma patients and in animal studies. The underlying mechanism of action remains largely unclear. These issues were addressed in parallel in the clinical and preclinical studies below. In this preliminary study, 25 patients with acute stress symptoms were administered a single intravenous bolus of high-dose hydrocortisone (100–140 mg) or placebo within 6 h of a traumatic event in a prospective, randomized, double-blind, placebo-controlled pilot study. Early single high-dose hydrocortisone intervention attenuated the core symptoms of both the acute stress and of subsequent PTSD in patients. High-dose hydrocortisone treatment given in the first few hours after a traumatic experience was associated with significant favorable changes in the trajectory of exposure to trauma, as expressed by the reduced risk of the development of PTSD post-trauma. In parallel, a comparative study of morphological arborization in dentate gyrus and its modulating molecules was performed in stress-exposed animals treated with high-dose hydrocortisone. Steroid-treated stressed animals displayed significantly increased dendritic growth and spine density, with increased levels of brain-derived neurotrophic factor (BDNF) and obtunded postsynaptic density-95 (PSD-95) levels. The animal study provided insights into the potential mechanism of this intervention, as it identified

☆ The trial name: Efficacy of Single Dose IV Hydrocortisone in Post Traumatic Stress Disorder (PTSD) Prevention.URL: www.clinicaltrials.gov. Registration number: NCT00855270.

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relevant morphological and biochemical associations to the clinical observations. Thus, evidence from clinical and animal studies suggests that there is a "window of opportunity" in the early aftermath of trauma to help those who are vulnerable to the development of chronic PTSD.

1. Introduction

Glucocorticoids (GCs) play a major role in orchestrating the complex physiological and behavioral reactions essential for the maintenance of homeostasis (McEwen, 2002). These compounds enable the organism to prepare for, respond to, and cope with the acute demands of physical and emotional stressors. The appropriate GC release, commensurate with stressor severity, enables the body to properly contain stress responses so as to promote recovery by rapidly restoring homeostasis (Yehuda et al., 1998). Indeed, inadequate GC release following stress not only delays recovery by disrupting biological homeostasis in the short run but can also interfere with the processing or interpretation of stressful information that results in long-term disruptions in memory integration (McEwen, 2002). A salient example of such an impaired post-traumatic process in the clinic is exemplified in post-traumatic stress disorder (PTSD) (DSM-IV-TR, American Psychiatric Association, 2000).

While conventional wisdom holds that people who develop PTSD following exposure to extreme trauma might have sustained elevations in GCs, several studies have reported that lower cortisol levels in the acute aftermath of trauma are predictors for subsequent PTSD symptoms (Delahanty et al., 2000; McFarlane et al., 1997; McFarlane, 2000; Witteveen et al., 2010). Therefore, it is possible that the administration of cortisol immediately after exposure to a trauma might alter the trajectory of trauma exposure by promoting recovery. To date, however, information on the effect of cortisol injection on trauma recovery is limited, although a series of naturalistic studies have demonstrated that administration of cortisol following septic shock reduced the incidence of PTSD (Schelling et al., 1999, 2001, 2003). Several studies have reported that exogenously administered cortisol reduces PTSD symptoms in patients with chronic PTSD (Aerni et al., 2004; Miller et al., 2011; Suris et al., 2010).

Our group has initiated a series of studies examining the role of GCs in susceptibility to "PTSD-like behaviors" in a well-validated animal model for PTSD (Cohen et al., 2003, 2005). In keeping with the little data that is available on traumatized people, these studies demonstrated a greater susceptibility to experimentally induced PTSD-like behavioral changes in rats with a hypoactive and hypo-reactive hypothalamic–pituitary–adrenal (HPA) axis, i.e., Lewis strain, compared to a rat strain with a hyper-responsive HPA-axis, i.e., Fischer rats. Exogenous administration of cortisol to Lewis rats prior to the stressor effectively decreased the prevalence of subsequent extreme behavioral disruption (Cohen et al., 2006a). Further animal studies examined the effect of a single intervention with high-dose corticosterone immediately after exposure to a stressor (Cohen et al., 2008b). A controlled prospective study showed a significant reduction in the incidence of PTSD-like behaviors and improved resilience to subsequent trauma (Cohen et al., 2008b). However, corticosterone administration 14 days following stress-exposure and immediately after memory reactivation had no effect on the behavior of the rats (unpublished data). These findings suggest that a disruption in the initial adaptive endogenous response of the HPA-axis unfavorably alters the trajectory of trauma exposure. To the extent that findings from animal models "translate" to humans, treatment with GCs could provide a possible avenue for early pharmacotherapeutic intervention in the acute phase, aimed at prevention of chronic stress-related disorders, such as PTSD.

The goal of this study was twofold: a) to evaluate the therapeutic effects of a single dose of hydrocortisone in acutely traumatized persons, and b) to explore the morphological and molecular changes in brain tissue of animals "treated" with hydrocortisone immediately after exposure to trauma. The first goal was accomplished in the context of a randomized, prospective, double-blind, placebo-controlled trial, and the second, by evaluating dendritic arborization in Golgi-impregnated neurons in dentate gyrus (DG) granule cells of stress-exposed animals and the impact of these changes on the expression of brain-derived neurotrophic factor (BDNF) and postsynaptic density-95 (PSD-95) in this region.

We hypothesized that trauma patients in a hospital emergency room (ER) treated with a single injection of hydrocortisone would have an altered trajectory of PTSD, as measured at one and three months, in a favorable way, as compared to those given a placebo. In parallel, we hypothesized that animals receiving a single high-dose of hydrocortisone immediately after exposure would exhibit increased synaptic plasticity, synaptic strength and dendritic complexity with a concomitant attenuation of behavioral stress responses (less prevalence of PTSD-like response).

2. Materials and methods

2.1. Clinical trial

2.1.1. Participants

Seventy consecutive patients who were exposed to a traumatic event, experienced either acute stress reaction or sub-threshold acute stress reaction, and met the DSM-IV PTSD A.1 (stressor) and A.2 (response) criteria (fulfilling criteria A, 2 of the symptoms in criteria B, 3 out of 4 of criteria C, D, E, and F, and meeting criterion H of the ASD criteria set out in DSM-IV) were recruited from the emergency department at the Chaim Sheba Medical Center. Exclusion criteria included serious physical injury (a score of 3 or above on the Abbreviated Injury Scale), brain trauma, substance abuse disorders, cardiac pacemaker implant, a history of epilepsy, neurosurgery, chronic medical conditions of any sort. Medication-specific exclusion criteria included hypersensitivity to hydrocortisone, pregnancy, or treatment for asthma. After receiving full explanation of the procedures, only subjects signing a written informed consent 25 out of 70 approved by the Helsinki Ethics Committee of The Chaim Sheba Medical Center were recruited. The subject group consisted of 14 men and 11 women, with a mean age of 35.16 (±S.D. 12.62) years, range 20–62. The types of trauma were: traffic accidents = 20, work accident = 4, and snake bite = 1.