



Corticosterone mitigates the stress response in an animal model of PTSD



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ABSTRACT

Activation of glucocorticoid receptor signaling in the stress response to traumatic events has been implicated in the pathogenesis of stress-associated psychiatric disorders such as post-traumatic stress disorder (PTSD). Elevated startle response and hyperarousal are hallmarks of PTSD, and are generally considered to evince fear (DSM V). To further examine the efficacy of corticosterone in treating hyperarousal and elevated fear, the present study utilized a learned helplessness stress model in which rats are restrained and subjected to tail shock for three days. These stressed rats develop a delayed long-lasting exaggeration of the acoustic startle response (ASR) and retarded body weight growth, similar to symptoms of PTSD patients (Myers et al., 2005; Speed et al., 1989). We demonstrate that both pre-stress and post-stress administration of corticosterone (3 mg/kg/day) mitigates a subsequent exaggeration of the ASR measured 14 days after cessation of the stress protocol. Furthermore, the mitigating efficacy of pre-stress administration of corticosterone (3 mg/kg/day for three days) appeared to last significantly longer, up to 21 days after the cessation of the stress protocol, in comparison to that of post-stress administration of corticosterone. However, pre-stress administration of corticosterone at 0.3 mg/kg/day for three days did not mitigate stress-induced exaggeration of the ASR measured at both 14 and 21 days after the cessation of the stress protocol. In addition, pre-stress administration of corticosterone (3 mg/kg/day for three days) mitigates the retardation of body weight growth otherwise resulting from the stress protocol. Congruently, co-administration of the corticosterone antagonist RU486 (40 mg/kg/day for three days) with corticosterone (3 mg/kg/day) prior to stress diminished the mitigating efficacy of the exogenous corticosterone on exaggerated ASR and stress-retarded body weight. The relative efficacy of pre versus post administration of corticosterone and high versus low dose of corticosterone on stress-induced exaggeration of innate fear response and stress-retarded body weight growth indicate that exogenous corticosterone administration within an appropriate time window and dosage are efficacious in diminishing traumatic stress induced pathophysiological processes. Clinical implications associated with the efficacy of prophylactic and therapeutic corticosterone therapy for mitigating symptoms of PTSD are discussed, particularly in relation to diminishing hyperarousal and exaggerated innate fear response.

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1. Objectives

Exposure to traumatic events alters the function of neuronal circuitry in the prefrontal cortex, amygdala, hippocampus, and, particularly, the hypothalamic-pituitary-adrenal axis (HPA) (Adamec et al., 2005; Belda et al., 2008; Osterlund and Spencer, 2011; Weiss, 2007; Yehuda, 1997). Enhanced plasma

glucocorticoid concentrations have been observed in human subjects exposed to traumatic events (Resnick et al., 1997; Yehuda, 2009). The extent and time course of plasma glucocorticoid elevation is dependent on the intensity and duration of the traumatic stressor (Servatius et al., 1995, 2001). The elevation of plasma glucocorticoid concentration may be salutary since lower baseline cortisol levels have been associated with a higher incidence of PTSD (Hauer et al., 2009).

In fact, several studies of PTSD patients do suggest that exogenously administered glucocorticoids diminish fear memory retrieval and other traumatic stress associated behaviors and

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symptoms (Aerni et al., 2004; Schelling et al., 2001; Zohar et al., 2011; Miller et al., 2011) and in animal models of PTSD (Cohen et al., 2008; de Quervain et al., 1998). The beneficial effects of glucocorticoids in reducing PTSD associated symptoms have been observed in patients who received high doses of hydrocortisone following treatment for septic shock and major surgery (Schelling et al., 2003, 2006). The efficacy of glucocorticoids in psychiatric conditions has been further observed in clinic trials (Aerni et al., 2004; Schelling et al., 2006; Weis et al., 2006). Further studies demonstrate that exogenous glucocorticoids can interfere with the retrieval of traumatic memories (de Quervain et al., 1998; de Quervain, 2008). In two double-blind, placebo-controlled studies, pre-administered glucocorticoids reduced phobic fear in subjects with social phobia and spider phobia (Soravia et al., 2006). Furthermore, administration of hydrocortisone has been reported in some studies to decrease re-experiencing and avoidance symptoms in patients with PTSD or impaired retrieval of declarative memory (Aerni et al., 2004; de Quervain et al., 2000; de Quervain et al., 2003). Likewise, memory retrieval is diminished in a water-maze spatial task in corticosterone treated rats (de Quervain et al., 1998).

Patients with PTSD are a heterogeneous population with different levels of trauma. PTSD symptoms may develop during various time frames post exposure and patients may present for treatment in various time frames after symptoms develop. To determine the efficacy of glucocorticoid in PTSD requires a population that is similar in its time prior to or post exposure and in the same stage of disease development.

Experimentally, such a population can be found in the restraint and tail shock animal stress model which demonstrates both an exaggerated fear response – hyperarousal – one of the most prominent symptoms of PTSD (Tomb, 1994) and HPA-axis dysfunction. Hyperarousal and HPA-axis dysfunction together comprise the closest model we have for simulating PTSD (Servatius et al., 1995). In this animal model of PTSD, the onset of enhanced ASR is not immediately observed but is delayed two weeks from the stressor, similar to the delay of onset of some symptoms of PTSD (Andrews et al., 2007; Jia et al., 2012; Solomon et al., 1989). In prior studies we addressed pharmacotherapy for PTSD in this stress model by examining the efficacy of α 1-adrenoceptor and 5-HT_{2A} receptor antagonists in mitigating exaggeration of the ASR (Jiang et al., 2009; Manion et al., 2007; Zhang et al., 2005). In the present study we continue along this line by evaluating the efficacy of corticosterone before and immediately after exposure to restraint and tail-shock. As before, exaggeration of the ASR is monitored. In comparison with non-stressed control or stress-alone subjects, current results from this study demonstrate a differential efficacy of corticosterone (3 mg/kg/day and 0.3 mg/kg/day) administration before versus immediately after three stress-exposures on the measurements of innate fear (acoustic startle) response and gain of body weight 14 and 21 days after the stress protocol.

The neuronal mechanisms associated with the differential effects of corticosterone administration pre and post-stress on delayed, exaggerated fear response and body weight gain, as well as the potential clinical implications for diminishing symptoms of PTSD, are discussed.

2. Materials and methods

2.1. Experimental animals

Male Sprague-Dawley rats initially weighing between 80 and 100 g (Taconic Farms, Derwood, MD, USA) were used. The animals were equally assigned to each group based on their body weight and baseline startle response. Animals were housed two per cage in

a climate controlled environment with free access to food and water, and were maintained on a 12 h reverse light/dark cycle (lights on 18:00) at 22 °C. All experimental procedures were approved by the Institutional Animal Care and Use Committee of the Uniformed Services University of the Health Sciences and conducted in accordance with their Guidelines and Regulations.

2.2. Acclimation

Animals were acclimated for three days to both the animal facility and to the acoustic startle chamber. Three consecutive days prior to the initial measurements animals were briefly handled in the acoustic startle chamber for 5 min each day to acclimate them.

2.3. A baseline measurement

Body weight and acoustic startle response measurements were taken one day before stress and/or other procedures as baseline measurements. Baseline body weights were 138 ± 7.3 g on average. Daily food consumption was measured. Since body weights between control group and stress group were significantly different after stress, to exclude the effect of body mass on food consumption results were expressed as food consumption (in mg) per gram of body mass.

2.4. Acoustic startle measurement

Acoustic startle response (ASR) measurement (Błaszczuk, 2003) was conducted with a Startle Response Acoustic Test System (Coulbourn Instruments, Columbus, Ohio, USA). This system consists of weight-sensitive platforms in a sound-attenuated chamber. The pressure against the platform due to the animal's movement in response to sound stimuli was measured as a voltage change by a strain gauge inside each platform and recorded as the maximum response occurring within 200 ms of the onset of the startle-eliciting stimulus (Jiang et al., 2011a). There were six types of stimulus trials: 100 dB alone, 100 dB with pre-pulse, 110 dB alone, 110 dB with pre-pulse, pre-pulse alone and no stimulus control. Each trial type was presented eight times. Trial types were presented in random order to avoid order effects and habituation. Inter-trial intervals ranged randomly from 15 to 25 s. In the current study the responses to 100 dB sound stimuli are presented. Among the eight trials only the maximum values were collected in the results and finally adjusted with the animal body weight of the same day to avoid the force difference due to different animal body weights on the platform, and adjusted with baseline. Animals were tested one day before stress or corticosterone as baseline reading and 0, 7, 14 and 21 days following the final day of the consecutive 3 days of the stress or corticosterone.

2.5. Stress

Stress exposure consisted of a 2-h per day session of immobilization and tail-shocks for three consecutive days. Stressing was done in the morning (between 0800 and 1200). Animals were restrained by being immobilized in a ventilated plexiglass tube. Forty electric shocks (2–3 mA, 3s duration; Animal Shocker, Coulbourn Instruments, USA) were delivered to their tails at semi-random intervals of 150–210 s (Graphic State Notation software, Habitest Universal Link, Coulbourn Instruments, USA) (Jiang et al., 2011a).

2.6. Chemicals

Corticosterone (Sigma) dissolved in 10% ethanol (3 mg/kg/day or 0.3 mg/kg/day) 30 min before or after stress was injected intra-

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