Psychoneuroendocrinology (2011) 36, 109—114

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Cortisol rapidly disrupts prepulse inhibition in healthy men

Steffen Richter [a,*], André Schulz [a], Carina M. Zech [a], Melly S. Oitzl [b], Nikolaos P. Daskalakis [b], Terry D. Blumenthal [c], Hartmut Schächinger [a]

[a] Division of Clinical Physiology, Institute of Psychobiology, University of Trier, Johanniterufer 15, D-54290 Trier, Germany
[b] Division of Medical Pharmacology, Leiden/Amsterdam Center for Drug Research, University of Leiden, Leiden, The Netherlands
[c] Department of Psychology, Wake Forest University, Winston-Salem, NC, USA

Received 13 December 2009; received in revised form 6 June 2010; accepted 5 July 2010

KEYWORDS
Non-genomic cortisol effects;
Prepulse inhibition;
Sensorimotor gating;
Startle;
Stress

Summary Stress is known to affect sensorimotor gating (measured with prepulse inhibition of startle, or PPI), possibly improving perception of threat signals at the expense of other input during states of arousal. Stress also induces a variety of autonomic nervous system and endocrine responses, such as an activation of the hypothalamic—pituitary—adrenal axis. The latter will result in the release of the stress hormone cortisol which is known to exert rapid and sustained action on several CNS processes. Since previous studies have not clarified whether and which stress response components may mediate effects on sensorimotor gating, this study asked whether a link may exist between cortisol and sensorimotor gating. We tested whether cortisol may affect PPI by assessing PPI before, during, and after non-stressful, covert 1 mg IV cortisol infusions in 27 healthy men in a single-blind and placebo-controlled within-subject design.

Cortisol induced a rapid reduction of PPI, with its maximum at 20 min after administration, and PPI returned to baseline after another 20 min. Startle magnitude in the absence of a prepulse was not affected. This rapid effect of the IV cortisol infusions is probably mediated by a non-genomic mechanism. We conclude that stress effects on sensorimotor gating may be mediated by glucocorticoids. The disruption of sensorimotor gating by the stress hormone cortisol may serve the processing of intense and potentially dangerous startling stimuli.

1. Introduction

Stress profoundly impacts on stimulus processing. It is known to reduce prepulse inhibition of startle (PPI), a measure of sensorimotor gating. The PPI paradigm involves a weaker prepulse stimulus preceding a louder startle eliciting stimulus activating an inhibitory function to protect processing of the prepulse (Graham, 1975). Disrupted PPI has been reported in response to acute stress in healthy individuals (Grillon and Davis, 1997), and in adults (Grillon et al., 1996) and children (Ornitz and Pynoos, 1989) with posttraumatic stress disorder (PTSD). Disrupted PPI can also be observed in animals after stress (Leitner, 1986). A disrupted PPI during states of stress and arousal may indicate improved threat and

* Corresponding author. Tel.: +49 6512013735; fax: +49 6512013737.
E-mail address: richters@uni-trier.de (S. Richter).

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doi:10.1016/j.psyneuen.2010.07.002

startle signal perception. Thereby, a disrupted PPI would support stronger reflexive motor responses, such as the eye-lid closure, and contribute to enhanced automatic defensive behaviour protecting against the impact of potentially harmful stimuli.

Stress is known to induce a variety of responses, such as activation of the autonomic nervous system and the hypothalamic—pituitary—adrenal (HPA) axis, the latter resulting in an increased level of circulating glucocorticoids (cortisol in humans, corticosterone in mice and rats). Glucocorticoids have been identified as modulators of PPI in animal studies: chronic exposure to high levels of corticosterone significantly reduces PPI in mice (Ingram et al., 2005). Acute intracerebroventricular infusions of corticotropin-releasing factor, sufficient to induce endogenous adrenal corticosterone release (Campbell et al., 2004), significantly reduce PPI in rats (Conti et al., 2002).

Recently, *in vitro* studies reported rapid non-genomic effects of the brain mineralocorticoid receptor, one of the two receptors mediating corticosteroid responses in the brain (de Kloet et al., 2008). Corticosteroids were found to non-genomically decrease the activity of hippocampal GABAergic neurons (Stromberg et al., 2005) which are crucial for successful sensorimotor gating (Adler et al., 1998) and counteract GABAergic inhibitory control by rapidly increasing glutamate release from the synapses (Venero and Borrell, 1999; Karst et al., 2005; Olijslagers et al., 2008), potentially contributing to reduced PPI.

Based on the recently described non-genomic effects of cortisol on neurotransmission, we hypothesized that cortisol would rapidly disrupt PPI in healthy humans. Cortisol was administered in a concentration that resembles the endogenous cortisol secretion in response to a moderate stress event. We employed a single-blind placebo-controlled within-subject design, and assessed PPI before, during, and after intravenous (IV) infusions of cortisol or placebo.

2. Methods and materials

2.1. Participants

Participants were recruited via the campus newsletter and offered a monetary incentive for participation. After routine medical examination on a separate day, 30 male volunteers were randomly assigned to receive either cortisol first, then placebo, or vice versa. Exclusion criteria were any acute or chronic illness, substance abuse (including nicotine at any dose), age below 18 or above 40, a body mass index below 18 or above 30, habitual listening to loud music, exposure to industrial noise (without proper ear protection) during the last 3 weeks, usage of contact lenses, or complete absence of startle eyeblinks (non-responders). Three participants were startle non-responders and thus were not included in the analysis. Of the remaining 27 participants (age: 26.0 years, SEM = 0.75; BMI: 24.3 kg/m^2, SEM = 0.57), 13 received cortisol first. All participants were asked to refrain from caffeine for 24 h before the experiment, to sleep sufficiently, and not to perform sports or eat heavy meals on the day of the experiment.

All participants gave their written informed consent. The study was approved by a community-based ethical committee (Landesärztekammer Rheinland-Pfalz).

2.2. Procedure

Experiments took place between 2 pm and 5 pm. Participants were seated in a quiet room with dim light. After cannulation of a cubital vein (18 G venflon, vasofix-safety, B.Braun Melsungen Co., Melsungen, Germany), participants were allowed to rest for 45 min. After the resting period, electrodes and headphones were attached and the experiment was started. The experiment consisted of two parts (28 min each, part 2 following part 1 immediately) with four blocks of 7 min duration ('baseline', 'infusion', 'post 1', and 'post 2'). PPI tests were run during the last 5 min of each block (minute 3—7). After the experiment, participants were decannulated and received their monetary reward.

2.3. Intravenous (IV) drug administration

We employed a constant background sodium-chloride (NaCl 0.9%, B.Braun Melsungen Co., Melsungen, Germany) infusion (120 ml/h) that was reduced for the cortisol (Hydrocortison 100, Rotexmedica, Trittau, Germany) and placebo (NaCl 0.9%) target infusions to keep flow constant at any time. Infusions were controlled by a CPU-operated modular Fluid-Management System (B.Braun Melsungen Co., Melsungen, Germany) located in an adjacent room. Because of absence of visual or auditory infusion-related cues, participants were not able to detect infusion onset or offset.

During the second block ('infusion') of each part, 1 mg cortisol or placebo was infused over the 7 min duration in a single-blind design. Thus, every participant received cortisol and placebo, while the order of application was counterbalanced across the participants.

2.4. Stimulus presentation

PPI tests were run during the last 5 min of each block (minute 3—7). Twenty startle probes (50 ms, white noise, 105 dB(A), instantaneous rise time), half of which were preceded by a weak prepulse-tone (50 ms, 440 Hz, 60 dB(A), 10 ms rise/fall time, SOA 120 ms) were presented in counterbalanced order with a randomized inter-startle interval of 10—14 s (mean: 12 s) during each block. A constant background noise of 50 dB(A) was employed to reduce the influence of ambient noise. The experimental room was sound attenuated. All stimuli were delivered by E-Prime 1.2 software (Psychology Software Tools Inc., Pittsburgh, PA, USA) via headphones for binaural stimulation (Sennheiser Electronic GmbH & Co. KG, Wedemark, Germany). The headphones for binaural stimulation covered the entire ear and further reduced ambient noise (passive noise reduction >10—40 dB(A), according to Sennheiser product information).

2.5. Cortisol concentrations in blood plasma

In a pilot study (healthy male participants; same exclusion criteria as described in Section 2.1; $n = 8$), we measured the amount of circulating cortisol in blood plasma in response to the 7 min infusion of 1 mg cortisol. Data revealed an increase in serum cortisol by 21.23 ± 3.60 ng/ml from 73.51 ± 7.46 ng/ml (before cortisol infusion) to 94.74 ± 9.32 ng/ml (after cortisol infusion). This is in the