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Stress-induced enhancement of response inhibition depends on mineralocorticoid receptor activation

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Summary Stress is a well-known modulator of cognitive functions. These effects are, at least in part, mediated by glucocorticoid stress hormones which act via two receptor types in the brain, glucocorticoid receptors (GR) and mineralocorticoid receptors (MR). Here, we examined whether stress affects inhibitory control processes and, if so, whether these effects are mediated by the MR. To this end, healthy participants received 300 mg of the MR antagonist spironolactone or a placebo and underwent a stressor (socially evaluated cold pressor test) or a non-stressful control task 90 min later. Shortly after the stressor, participants performed a stop-signal task that required them to rapidly suppress a well-established response whenever a tone was presented. Results revealed that stress enhanced response inhibition in the stop-signal task and that this enhancement was abolished by spironolactone. Our results show that stress may facilitate inhibitory control and that these effects depend on MR functioning.

1. Introduction

The ability to inhibit automatic or natural responses that are inappropriate in the current context is a hallmark of adaptive behavior. Lack of inhibitory control may lead to interpersonal conflicts and has also been suggested to play an important role in attention-deficit hyperactivity disorder (ADHD) or substance abuse (Ersche et al., 2012; Sergeant et al., 2003). At the neural level, response inhibition is subserved by a fronto-thalamo-basal ganglia network that includes the inferior frontal cortex, the middle frontal gyrus, the medial frontal cortex, the insula, the pre-supplementary motor area, the basal ganglia and the thalamus (Aron and Poldrack, 2006; Chambers et al., 2009; Verbruggen and Logan, 2008; Wager et al., 2005).

In particular, prefrontal areas express receptors for glucocorticoid stress hormones (cortisol in humans) at a high density (McEwen et al., 1986; Reul and de Kloet, 1985) and stress and glucocorticoids are well-known modulators of prefrontal activity (Diamond et al., 2007; Qin et al., 2009; Schwabe et al., 2012b), thus suggesting that stress and stress hormones may alter prefrontal cortex-dependent behaviors. Indeed, there is ample evidence that stress affects working memory and executive functions that are supported by the

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prefrontal cortex. The direction of these effects, however, is not entirely clear as some studies showed impairing (Barsegyan et al., 2010; Plessow et al., 2011; Scholz et al., 2009) and others enhancing effects of stress (hormones) on working memory and executive functions (Henckens et al., 2011; Yuen et al., 2009). Because inhibitory control has been suggested to play a crucial role in substance abuse disorders (Ersche et al., 2012; Nigg et al., 2006) and the development of and relapse to substance abuse can be triggered by stress (Sinha, 2001), potential stress effects on inhibitory control would be of particular interest. There is already some evidence that cortisol, chronic or early life stress may affect inhibitory control (Lyons et al., 2001; Mika et al., 2012; Mueller et al., 2010; Tops and Boksem, 2011). However, whether and how acute stress affects response inhibition has not been systematically tested yet.

Glucocorticoids are a key modulator of stress effects on the brain (Roozendaal et al., 2009; Schwabe et al., 2012a). They exert their actions via two types of membrane-bound and intracellular receptors: glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs; de Kloet et al., 2005; Joëls and Baram, 2009). Evidence from rodent studies indicates that GRs are mainly involved in memory consolidation, whereas MRs are involved in the initial appraisal of a situation and the coordination of different cognitive processes (Barsegyan et al., 2010; Oitzl and de Kloet, 1992; Schwabe et al., 2010a). In other words, it is well-documented that MRs can have fast effects on cognitive processes. Based on these findings, one may hypothesize that if glucocorticoids are involved in potential stress effects on response inhibition, these effects should be mediated by MRs rather than by GRs. Accordingly, stress effects on response inhibition should disappear after MR blockade.

In the present experiment, we examined whether stress influences response inhibition and, if so, whether this effect is mediated by the MR. Healthy participants received first the MR antagonist spironolactone or a placebo and were later exposed to a stressor or a control manipulation. Shortly after the stressor, inhibitory control was tested with the well-known stop-signal task, which requires participants to rapidly suppress an ongoing, well-established response whenever an auditory signal is present (Logan et al., 1997).

2. Materials and methods

2.1. Participants and design

Seventy-two healthy, right-handed university students with normal or corrected-to-normal vision and without medication intake, any current medical condition, any substance abuse or lifetime history of any neurological or psychiatric disorder participated in this experiment (32 men, 40 women; mean age = 24.4 years, range 20—32 years). Smokers and women using (any type of) hormonal contraceptives were excluded from participation because smoking and hormonal contraceptives are known to change the endocrine stress response (Kirschbaum et al., 1999; Rohleder and Kirschbaum, 2006). Moreover, women were not tested during their menses. The study protocol was approved by the Review Board of the Medical Faculty of the Ruhr-University Bochum. All participants provided written informed consent.

We used a fully crossed, double-blind, placebo-controlled between-subjects design with the factors treatment (control vs. stress condition) and drug (placebo vs. spironolactone), thus resulting in four experimental groups (n = 18 per group): control condition/placebo (CON/PLAC), control condition/spironolactone (CON/aMR), stress condition/placebo (STRESS/PLAC), and stress condition/spironolactone (STRESS/aMR).

2.2. Experimental procedure

In order to control for the diurnal rhythm of the stress hormone cortisol, all testing took place between 1.30 and 6.30 pm. Upon their arrival at the lab, participants gave a first saliva sample (see below) and completed a German mood questionnaire (MDBF; Steyer et al., 1994) that assesses subjective mood on three scales: restlessness vs. calmness, depressed vs. elevated mood, and sleepiness vs. wakefulness. Moreover, we measured participants' blood pressure with a Dinamap system (Critikon, FL) on the left upper arm. Afterwards, participants were randomly assigned to one of the four experimental groups.

2.2.1. Drug administration

Depending on the experimental group, participants were administered orally either 300 mg of the MR antagonist spironolactone (Ratiopharm) or a placebo. This dosage of spironolactone seemed likely to result in effective MR blockade on the one hand (Cornelisse et al., 2011) and to minimize potential discomfort on the side of the participants on the other hand. Behavioral testing started 90 min after drug intake; until then, participants remained reading in a quiet room adjacent to the testing room.

2.2.2. Stress induction

Ninety minutes after drug intake, participants underwent a stressor or a control manipulation. In the stress condition, participants were exposed to the socially evaluated cold pressor test (SECPT) as described in detail elsewhere (Schwabe et al., 2008). In brief, participants immersed their right hand up to and including the wrist for 3 min (or until they could not stand it any longer) into ice water (0—2 °C). During hand immersion, they were videotaped and monitored by a non-reinforcing, rather cold and unsociable experimenter. In the control condition, participants submerged their right hand up to and including the wrist for 3 min into warm water (35—37 °C). They were neither videotaped nor monitored by an unsociable experimenter.

In order to assess the efficacy of the SECPT, we measured subjective and physiological stress responses at several time points across the experiment. Participants completed a subjective mood questionnaire (MDBF) after their arrival at the lab, immediately before and immediately after the stress/control manipulation. In addition, participants rated immediately after the stress/control manipulation on a scale from 0 ("not at all") to 100 ("very") how stressful, painful, and unpleasant they had experienced the previous treatment. We measured participants' blood pressure after their arrival as well as before, during and immediately after the stress/control manipulation. Moreover, participants collected saliva samples with the help of salivette collection devices