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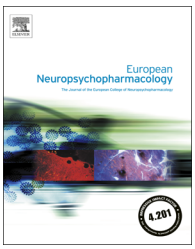

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Rapid cortisol enhancement of psychomotor and startle reactions to side-congruent stimuli in a focused cross-modal choice reaction time paradigm

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Abstract
The stress hormone cortisol has been shown to affect hemodynamic activity of human brain structures, presumably via a nongenomic mechanism. However, behavioral implications of this finding remain unknown. In a placebo-controlled, blinded, cross-over design the rapid effects of IV hydrocortisone (5 mg) on cross-modal integration of simultaneous, unilateral visual and acoustic signals in a challenging startle and reaction time (RT) paradigm were studied. On two separate days 1 week apart, 24 male volunteers responded by button push to either up- or down pointing triangles presented in random sequence in the periphery of one of the visual hemi-fields. Visual targets were accompanied by unilateral acoustic startle noise bursts, presented at the same or opposite side. Saccadic latency, manual RT, and startle eye blink responses were recorded. Faster manual reactions and increased startle eye blink responses were observed 11–20 min after hydrocortisone administration when visual targets and unilateral acoustic startle noises were presented in the same sensory hemi-field, but not when presented in opposite sensory hemi-fields. Our results suggest that a nongenomic, cortisol-sensitive mechanism enhances psychomotor and startle reactions when stimuli occur in the same sensory hemi-field. Such basic cognitive effects of cortisol may serve rapid adaptation and protection against danger stimuli in stressful contexts.

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1. Introduction

One of the most important functions of sensory-integrating systems is to instantaneously indicate whether multiple input from different senses belongs to the same environmental source or not. This task is usually solved by taking into account the spatial and temporal configuration of cross-modal input (Stein and Stanford, 2008), for example, by preferentially processing stimuli that appear simultaneously and at the same spatial position (Komura et al., 2005; Wallace et al., 1996). Given that a normal environment is noisy, full of meaningless signals, a co-appearance of spatially congruent multisensory input may 'validate' the existence of a real event and object. This is of special importance in hazardous environments, where danger cues indicate the presence of a predator or invader and urge for immediate escape or defensive reactions. Thus, improving cross-modal cue integration, especially during stress and imminent danger, may foster survival.

Stress, threat, and danger activate physiologic stress systems, such as the hypothalamic–pituitary–adrenocortical (HPA) axis (McEwen, 2008). Subsequently, glucocorticoids (cortisol in humans) are released into the bloodstream. Cortisol crosses the blood–brain barrier and acts on brain neurons both via slow, genomic pathways (de Kloet et al., 2005) as well as by rapid, nongenomic mechanisms (Groeneweg et al., 2011; Joels and Baram, 2009). The study of nongenomic cortisol effects on human cognition is still young (e.g. Richter et al., 2011; Schilling et al., 2013; van Ast et al., 2013) and the question whether cortisol influences multisensory integration by a nongenomic mechanism has never been addressed.

Recently, we showed that IV hydrocortisone administration was associated with a rapid decrease in thalamus perfusion, accompanied by reduced EEG power across different frequency bands (Strelzyk et al., 2012). The thalamus plays a prominent role in multisensory processing (Cappe et al., 2009b; Tyll et al., 2011), as evidenced by its anatomical connections (Cappe et al., 2009a) and its functional involvement in cross-modal task performance (Komura et al., 2005; Noesselt et al., 2010; van den Brink et al., 2013). Furthermore, and in line with the effect on thalamic blood flow, glucocorticoids are known to increase sensory thresholds (Born et al., 1987; Henkin and Daly, 1968; Kuehl et al., 2010). Collectively, these findings suggest that cortisol may affect the integration of cross-modal cues.

In the present study we tested the rapid, putatively nongenomic impact of a physiological dose of 5 mg of IV hydrocortisone on cross-modal cue integration in a focused cross-modal choice reaction (see Arndt and Colonius, 2003) and startle paradigm. Non-startling visual targets were presented alone and together with either bilateral acoustic startle noise or with unilateral acoustic startle noise in the same or in the opposite sensory hemi-field. Saccadic latencies and manual reactions to visual targets as well as eye blink responses to startle noises served as indices of cross-modal cue integration. Testing was carried out twice on separate days, once after hydrocortisone and once after placebo administration, according to a single blinded, placebo-controlled, and counterbalanced cross-over design. We expected hydrocortisone to rapidly influence cross-modal cue integration depending on the spatial congruency between visual targets and acoustic startle noises.

2. Experimental procedures

2.1. Procedure and experimental task

The study was approved by the Ethical Committee of the State's Medical Association (Landesärztekammer Rheinland-Pfalz) and was in accordance with the Declaration of Helsinki. 24 male volunteers (age: 19–32 years) gave informed consent and were tested on two sessions separated by 1 week, receiving hydrocortisone on the one and placebo on the other day. In order to control for variations in diurnal cortisol levels testing was carried out between 1 p.m. and 6 p.m., i.e. at a time when endogenous cortisol levels are comparatively low. Further, each participant was tested at exactly the same time on both testing days.

Upon arrival a flexible intravenous catheter was inserted followed by a one hour resting period in which the participant was prepared for the experiment (electrodes attached, headphones mounted, adjustment of chin and front support). After habituation to startle stimuli and a short practice session the experimental task started and lasted for about 30 min. Participants were instructed to react to one of two visual target categories (up vs. down pointing triangles) and to withhold a response when the other target category was presented. Targets were presented at the periphery of the screen, requiring a saccadic eye movement towards the target's location in order to correctly identify its shape. Participants

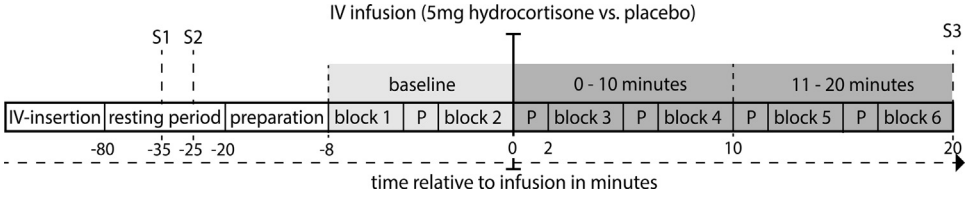

Figure 1 Procedure of the experiment. Times are given relative to the onset of the infusion of hydrocortisone or placebo. At the beginning of each session an IV catheter was inserted into the left or right arm of the participant. During a one hour resting period the participant was prepared for the experiment before starting the experimental presentation. The experiment consisted of six blocks which were separated by short pauses (P). The first two blocks of the experiment were grouped together for further statistical analysis and served as a 'baseline' (block 1 and block 2) for the subsequent post-infusion blocks. In the second pause 5 mg of IV hydrocortisone or a corresponding amount of placebo solution was infused. Changes in multisensory integration following the pharmacological manipulation were assessed in block 3 to block 6. Post-infusion blocks were grouped into the measurement times '1–10 min' (block 3 and block 4) and '11–20 min' (block 5 and block 6) after infusion for further statistical analyses. During the waiting period (S1 and S2, 'baseline') as well as after the last experimental block (S3, 'post-intervention') saliva samples were taken to assess acute cortisol levels before and after the pharmacological manipulation.