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Short Communication

The stress hormone cortisol blocks perceptual learning in humans

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ABSTRACT

Cortisol, the primary glucocorticoid (GC) in humans, influences neuronal excitability and plasticity by acting on mineralocorticoid and glucocorticoid receptors. Cellular studies demonstrated that elevated GC levels affect neuronal plasticity, for example through a reduction of hippocampal long-term potentiation (LTP). At the behavioural level, after treatment with GCs, numerous studies have reported impaired hippocampal function, such as impaired memory retrieval. In contrast, relatively little is known about the impact of GCs on cortical plasticity and perceptual learning in adult humans. Therefore, in this study, we explored the impact of elevated GC levels on human perceptual learning. To this aim, we used a training-independent learning approach, where lasting changes in human perception can be induced by applying passive repetitive sensory stimulation (rss), the timing of which was determined from cellular LTP studies. In our placebo-controlled double-blind study, we used tactile LTP-like stimulation to induce improvements in tactile acuity (spatial two-point discrimination). Our results show that a single administration of hydrocortisone (30 mg) completely blocked rss-induced changes in two-point discrimination. In contrast, the placebo group showed the expected rss-induced increase in two-point discrimination of over 14%. Our data demonstrate that high GC levels inhibit rss-induced perceptual learning. We suggest that the suppression of LTP, as previously reported in cellular studies, may explain the perceptual learning impairments observed here.

1. Introduction

Cortisol, the primary glucocorticoid (GC) in humans, influences neuronal excitability and plasticity by acting on mineralocorticoid and glucocorticoid receptors (De Kloet et al., 2005). Cellular studies have shown that increased GC levels, due to activation of the glucocorticoid receptor (GR), can inhibit neuronal plasticity by reducing hippocampal long-term potentiation (LTP) (Diamond et al., 2007; Pavlides et al., 1993). This in turn is thought to affect learning processes.

Indeed, at a behavioural level, numerous studies have reported impaired hippocampal function after treatment with GCs (Wolf, 2009). With respect to episodic memory, a detrimental effect of GCs on memory retrieval has been shown repeatedly (e.g. de Quervain et al., 2000). In contrast, memory consolidation is enhanced by GC administration post-training (Wolf, 2009). The formation of implicit memories, such as priming, are thought to be relatively insensitive to the effects of pharmacological cortisol (e.g. Kirschbaum et al., 1996). In addition to its effects on the limbic system, cortisol has also been shown to influence the prefrontal cortex (PFC) and elicit negative effects on working memory (for a recent meta-analysis see (Shields et al., 2015)).

However, little is known about the impact of GCs on adult cortical plasticity and on human perceptual learning. Several years ago, Daw et al. reported reduced plasticity in the developing visual cortex in kittens, following long-term treatment with cortisol, implicating a role for cortisol in ocular dominance plasticity (Daw et al., 1991). Oral administration of hydrocortisone has also been shown to modify plasticity in the human motor cortex (Sale et al., 2008).

Thus, the aim of this study was to determine how elevated GC levels might affect human perceptual learning. To this aim, we used a training-independent learning approach, which can induce lasting changes in perception by applying passive repetitive sensory stimulation (rss). Regarding the timing of the stimulations, the parameters were adapted from cellular LTP studies (Dinse

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et al., 2003; Beste and Dinse 2013). Numerous studies have shown that LTP-like tactile rss induces improvements in tactile perception, which parallels major reorganization in the cortex (Dinse et al., 2003; Pleger et al., 2003; Ragert et al., 2008). Therefore, training-independent learning offers the unique possibility of linking cellular plasticity to human perceptual learning. Owing to suppression of LTP caused by elevated GC levels previous cellular studies (Diamond et al., 2007; Pavlides et al., 1993), we predicted that the administration of hydrocortisone in humans would also affect stimulation-induced learning.

2. Material and methods

2.1. Participants and procedure

This study was approved by the Ethics Committee of the Ruhr-University of Bochum, and all participants provided written informed consent. We conducted a placebo-controlled double-blind study. In total, 30 right-handed male participants were randomised into two groups: 1) cortisol group and 2) control group. The cortisol group received a single 30-mg dose of hydrocortisone, while the control group were treated with a placebo drug. The dose of hydrocortisone administered was based on previous studies showing that a dose of 30 mg can impair hippocampus-dependent memory retrieval (e.g. Kuhlmann et al., 2005). Tests were carried out late in the morning throughout the entire experiment. Participants and experimenter were blinded against drug treatment. Tactile acuity was assessed on the tip of the index-finger by measuring spatial two-point discrimination thresholds, as a marker of tactile perceptual ability. To induce tactile plasticity, we applied tactile LTP-like rss. Discrimination thresholds were measured before and after rss. Saliva samples were obtained at baseline, 80 min, and 120 min after the administration of hydrocortisone or placebo to assess salivary cortisol concentrations (see Fig. 1 for the timeline of the experiment). Participants had no history of neurological or psychiatric illness, drug abuse, or use of medication affecting the nervous system. Upon completion of all experiments, subjects were asked to report their subjective experiences and feelings following the administration of the drug and rss.

2.2. Tactile acuity assessment

Tactile acuity of the right index-finger was assessed by measuring two-point discrimination thresholds using the method of constant stimuli as described previously (Dinse et al., 2003; Pleger et al., 2003; Ragert et al., 2008). The stimuli consisted of seven pairs of needles with different distances, ranging from 0.7 to 2.5 mm, and a single needle of zero distance which served as a control. Tactile stimuli were applied for ~1 s, with an application force of 150–200 mN. Participants had to determine if they had the sensation of one or two needles immediately after the application of the stimulus, and report their perception of a single needle or a doubtful stimulus as 'one', while the perception of two distinct stimuli was reported as 'two'. The stimuli were presented 10 times in a random order resulting in 80 trials per session. The percentage of presentations identified as 'two' for each distance was plotted against the needle distances. This resulted in the generation of a psychometric function which was fitted by a binary logistic regression. The threshold was determined as 50% of correct responses. All participants were required to complete one training session prior to testing to become familiar with the procedure.

2.3. Statistical analysis

Statistical comparisons of effects of cortisol administration and of rss effects were performed in IBM SPSS Statistics for Windows using multivariate ANOVAs with Group as a between-subjects factor and Time as a within-subjects factor. Group data are presented as mean ± standard error of the mean (SEM) unless otherwise specified.

2.4. Repetitive sensory stimulation

Rss was applied for 30 min to the right index-finger. The stimulation sequence was the same as that described previously (Ragert et al., 2008) and consisted of 20-Hz bursts for 1.4 s with 5 s inter-train intervals, a ramp fall-time of 0.3 s and a 0.2-ms pulse width. The pulses were transmitted via adhesive surface electrodes (1 × 4 cm) fixed on the first and third finger segments (cathode proximal). The stimulation intensity was adjusted individually with an average stimulation intensity of 5.57 ± 0.41 mA in the cortisol group, and 5.33 ± 0.30 mA in the placebo group.

3. Results

3.1. Cortisol concentrations

The mean age of the cortisol group was 26.6 years ± 0.91and that of the control group was 27.1 years ± 0.99. In the cortisol group, cortisol levels were increased from a baseline (pre-rss) level of 18.3 ± 2.7 nmol/l to a post-rss level of 199.8 ± 20.2 nmol/l $p < 0.001$ for GROUP and TIME). In the placebo group, the cortisol levels remained unchanged (pre-rss: 15.5 ± 1.8 nmol/l; post-rss: 10.1 ± 1.6 nmol/l; $p > 0.1$).

3.2. Tactile learning

As expected, the placebo group showed a stimulation-induced improvement in two-point discrimination as indicated by a 14.6% reduction in the threshold level, which corresponds to an effect size of 0.70 (Cohen's d). In this group, the threshold decreased from 1.69 mm ± 0.07 at baseline to 1.46 mm ± 0.10 post-stimulation. In contrast, in the cortisol group, a single dose of hydrocortisone (30 mg) completely blocked the stimulation-induced improvement in tactile acuity. Instead, we observed a slight, non-significant increase in the threshold of 1.9% (Fig. 1; 0.04 Cohen's d; $p = 0.006$ for GROUP and TIME). We also observed a significant GROUP x TIME interaction ($p = 0.014$). The discrimination thresholds in the cortisol group were 1.92 mm ± 0.11 pre-rss and 1.94 mm ± 0.10 post-rss. There was no significant difference in the baseline performance between the two groups ($p = 0.09$).

4. Discussion

Our data show that high GC levels affect implicit/cortical learning by blocking the increase in tactile perceptual abilities typically observed following rss. Numerous lines of evidence indicate that intensive training may not be necessary for the induction of implicit/procedural learning. It has been suggested that the effectiveness of rss stems from the fact that the stimulation protocols used are optimized to alter synaptic transmission and efficacy, thus providing novel ways to investigate the relationship between learning processes and their underlying cellular and molecular mechanisms in humans. In the tactile domain, rss leads to improved tactile perceptual abilities, which is associated with increased cortical activation and representational map changes (Pleger et al., 2003), and enhanced cortical excitability and is NMDA-receptor