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For whom the bell (curve) tolls: Cortisol rapidly affects memory retrieval by an inverted U-shaped dose—response relationship

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Summary Stress and cortisol are generally considered to impair declarative memory retrieval, although opposite results have also been reported. Dose-dependent effects and differences between genomic and non-genomic cortisol effects are possible reasons for these discrepancies. The aim of the current experiment was to assess the non-genomic effects of escalating doses of intravenous cortisol on cued recall of socially relevant information in humans. 40 participants (age range 20—30 years; 20 females) learned associations between male faces with a neutral facial expression and descriptions of either positive or negative social behaviors and were tested one week later in a cued recall paradigm. Escalating doses of cortisol (0, 3, 6, 12, 24 mg) were administered 8 min before testing according to a between-subjects design. An inverted U-shaped dose—response relationship between salivary cortisol levels and recall performance was observed, with moderate elevation of salivary cortisol resulting in the best recall performance. This is the first study in humans demonstrating that cortisol rapidly modulates declarative memory retrieval via a dose-dependent, non-genomic mechanism that follows an inverted U-shaped curve. Our result further emphasizes the importance of fast cortisol effects for human cognition.

1. Introduction

Evolution fostered the emergence of neural mechanisms able to voluntarily retrieve behavior-guiding information from our memory. This is of crucial importance during stress, challenging situations, and attack, when different survival strategies and behavioral options need to be rapidly evaluated on the basis of their previous failure and success. Given that human stress often evolves in social context

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(Dickerson and Kemeny, 2004), information on the past social behavior of others will become useful for predicting their future behavior in upcoming distress and conflict. Indeed, stress was found to support the discrimination of potential allies and helpers from antagonists and non-helpers (Lass-Hennemann et al., 2010), based on its effects on memory consolidation. However, our current knowledge of the exact influence of stress and stress-hormones on memory retrieval processes is limited.

Acute stress activates the hypothalamus–pituitary–adrenal cortex (HPA) axis, and leads to the release of glucocorticoids (cortisol in humans, corticosterone in rodents) into the blood stream. Cortisol crosses the blood–brain-barrier to act on the central nervous system in order to regulate magnitude and duration of the stress response by negative feedback mechanisms (de Kloet et al., 2005), as well as affecting memory and behavior processes (Schwabe et al., 2010).

Cortisol has been shown to impair episodic memory retrieval (de Quervain et al., 1998, 2000, 2007; Wolf, 2009). However, opposite effects (Domes et al., 2002; Nater et al., 2007) have also been found, which may in part be due to different dosing and timing (Het et al., 2005). In particular, time and dose effects of cortisol on memory retrieval may not follow a linear relationship. An inverted U-shaped relationship between salivary cortisol levels and verbal memory performance was observed after oral cortisol administration (Domes et al., 2005), and would also explain why autobiographic memory retrieval was reduced after a high dose but not after a low dose of IV-cortisol (Young et al., 2011). However, more studies are needed to understand the exact dose–response relationship between cortisol and memory retrieval. Such studies should employ dose-escalating designs with more than two different dose steps, to evaluate the possibility of a quadratic relationship between cortisol and retrieval.

Recent findings in rodents show that the influence of cortisol on memory retrieval may be mediated via a fast, non-genomic mechanism in the dorsal hippocampus which does not involve changes in protein expression (Dorey et al., 2011; Schutsky et al., 2011). However, the effects of cortisol on memory retrieval in humans have so far only been studied at longer time intervals, making it impossible to distinguish whether the effects have been mediated by a genomic or a non-genomic mechanism. This is very important, because genomic and non-genomic mechanisms may lead to different effects. For example, dissociations between "slow" genomic and "fast" non-genomic cortisol effects have been described in trace eyeblink conditioning (tEBC). High cortisol is associated with reduced tEBC (Grillon et al., 2004; Vythilingam et al., 2006), and low cortisol is associated with enhanced tEBC (Nees et al., 2008, 2010). This dose–response relationship is found hours after cortisol manipulation or in states of chronic hypo- or hypercortisolism, allowing these effects to be mediated by genomic mechanisms. However, enhanced speed of tEBC acquisition was found on a non-genomic timescale (Kuehl et al., 2010), shortly after cortisol administration, suggesting opposite effects of cortisol on tEBC via a genomic vs. a non-genomic mechanism. tEBC requires awareness of the CS-US relationship and, like episodic memory formation, it depends on an intact hippocampus (Clark and Squire, 1998; Squire, 2004). It is therefore possible that such discrepancy between fast and slow cortisol effects might also be present in episodic memory retrieval. It has already been shown that excess cortisol may impair episodic memory retrieval when following a genomic timescale (de Quervain et al., 2000, 2007). Assuming analogy to the cortisol effects on tEBC, supportive effects of cortisol on episodic memory retrieval might be expected when following a non-genomic timescale, but this has never been tested before.

The current study was designed to explore fast effects of exogenous cortisol administration on memory retrieval. Associations between neutral male faces and descriptions of either positive or negative social behaviors were learned one week before cued recall testing. Cortisol was administered intravenously 8 min before the retrieval test, to exclude effect mediation by genomic mechanisms. In order to study the shape of the dose–response curve, cortisol was given in escalating doses of 3 mg, 6 mg, 12 mg, and 24 mg, with a 0 mg control condition.

2. Methods

2.1. Sample

40 human participants (20 males, 20 females) took part in the experiment and received a monetary reward for participation. Exclusion criteria were determined by a physician during a standard medical examination and interview. Exclusion criteria were any acute or chronic somatic or psychiatric illness, any history of psychiatric, cardiovascular, or stress-related disorders, glaucoma, pregnancy, smoking, increased caffeine consumption or any illicit drug intake within the last six months, or any family history of epilepsy or aneurysms. There was no control of menstrual cycle phase, and women were allowed to take oral contraceptives other than those containing drospirenon, because this substance may interact with mineralocorticoid receptors. The German version of the Beck Depression Inventory (BDI) (Hautzinger et al., 1994) was used to screen for heightened depression ratings (BDI cutoff < 11). Additionally, participants had to be free of uneasiness toward medical settings or procedures. Participants gave their informed written consent and were told that they had the right to stop the experiment at any time. The study was approved by the Ethical Committee of the State's Medical Association (Landesärztekammer Rheinland-Pfalz) and was in accordance with the latest revision of the Declaration of Helsinki.

2.2. Procedure

Participants came to the laboratory twice, with one week time between visits. The first appointment lasted 1 h and took place in the morning. The second lasted 4 h and started after 1200 h. On the first appointment participants were seated in a comfortable chair in front of a computer screen. Next, pictures of male faces with a neutral facial expression and a description of the person were presented on a computer screen one at a time. The participant's task was to learn the association between the face and the description of the person. The description could either be a positive social behavior (example: 'he can easily cheer up other people'), a negative social behavior (example: 'he likes to get drunk at parties and then becomes aggressive') or a

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