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Stress effects on declarative memory retrieval are blocked by a β -adrenoceptor antagonist in humans

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Summary Previous evidence indicates that stress hormone effects on memory consolidation depend on concurrent emotional arousal-induced noradrenergic activity. Here, we asked whether this is also true for stress effects on memory retrieval and hypothesized that administration of the β -adrenoceptor antagonist propranolol would block the effects of stress on declarative and procedural retrieval performance. In a double-blind, placebo-controlled, crossover study, 44 healthy young men learned a list of emotional and neutral words (declarative memory task) and completed a serial reaction time task (procedural memory task). On the following day, participants received either a placebo or 40 mg propranolol orally. One hour later, they were exposed to stress (socially evaluated cold pressor test (SECPT)) or a control condition 30 min prior to retention testing. Stress selectively enhanced the retrieval of emotionally arousing words. Pretreatment with propranolol had no effect on memory alone but blocked the stress-induced memory enhancement for emotional words, confirming the importance of noradrenergic activity in stress effects on memory retrieval. Memory for neutral words and the procedural task was neither affected by stress nor by propranolol. The present findings suggest that stress (hormone) effects on emotional memory retrieval require concurrent noradrenergic activation. Procedural memory retrieval and the retrieval of neutral verbal material appear to be less susceptible to stress.

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1. Introduction

Stress elicits numerous physiological reactions including the release of catecholamines (epinephrine and norepinephrine)

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and glucocorticoids (GCs; cortisol in humans), which are known to influence memory function. Importantly, stress effects on memory depend critically on the timing of the stress (hormone) exposure. Converging evidence from animal and human studies shows that stress or GC administration immediately after learning facilitates memory *consolidation* (Cahill et al., 2003; Diamond et al., 2006; Roozendaal et al., 2006). By contrast, stress and GCs administered before retention testing impaired memory *retrieval* in rodents (de Quervain et al., 1998; Diamond et al., 2006). In humans,

findings on the effect of stress and GCs on retrieval performance are mixed. While some authors reported stress- or GC-induced retrieval impairments (de Quervain et al., 2000; Kuhlmann et al., 2005a), others showed that stress and GCs can also enhance memory retrieval (Domes et al., 2005; Nater et al., 2007; Buchanan and Tranel, 2008).

A recent model that aims to explain the influence of stress and GCs on memory postulates that concurrent glucocorticoid and noradrenergic activity within the basolateral amygdala (BLA) is critical for stress effects on memory functions (McGaugh and Roozendaal, 2002). In line with this model, Roozendaal et al. (2006) reported that the consolidation enhancing effect of corticosterone is blocked by administration of a β -adrenoceptor antagonist. Furthermore, the authors showed that corticosterone (the main GC in rodents) injections after training in an object recognition memory task enhanced memory in naïve rats but not in rats that were previously habituated to the training context, i.e. in which novelty-induced arousal was reduced. Similarly, Cahill et al. (2003) found an enhancing effect of post-learning stress on memory for emotionally arousing but not for neutral material in humans.

Findings from animal studies suggest that noradrenergic activity may also be essential for stress hormone effects on memory retrieval. For instance, Roozendaal et al. (2004) showed that retrieval impairing effects of corticosterone were blocked by a β -adrenoceptor antagonist administered before retention testing. Comparable data from humans are largely missing. Very recently, de Quervain et al. (2007) presented the first evidence that noradrenergic activity is required for the effects of pharmacologically (i.e. exogenously) raised GCs on memory retrieval in humans. Whether the effects of stress-induced (i.e. endogenous) GC elevations on memory retrieval in humans can be prevented by β -adrenoceptor blockade is not known. Moreover, most memory studies, including the study by de Quervain et al. (2007), focused exclusively on hippocampus-dependent declarative memory, while the effects of stress and β -adrenoceptor blockade on the retrieval of non-declarative, procedural memory have not been tested yet (for a recent review see van Stegeren, 2008).

The present study examined whether the influence of stress and stress-induced GCs on the retrieval of declarative and procedural memory can be blocked by administration of a β -adrenoceptor antagonist. We used a double-blind, placebo-controlled, within-subjects design. Healthy young men learned a list of 24 emotional and neutral words and performed a serial reaction time task. Twenty-four hours later, participants were exposed to a stress (socially evaluated cold pressor test) or control condition 1 h after they received propranolol or a placebo and 30 min before a free recall test for the words and a retention test for the serial reaction time task.

2. Materials and methods

2.1. Participants and design

Forty-four healthy, non-smoking men (age: $M = 23.7$ years, $S.D. = 3.3$ years, range: 19–33 years; BMI (kg/m^2): $M = 23.5$, $S.D. = 2.2$, range: 19–27) recruited at the University of Trier

participated in this study. Exclusion criteria were checked by a physician and comprised current or chronic psychiatric disorders, any medical condition and current treatment with psychotropic medications, narcotics, beta-blockers or steroids. Participants had to refrain from excessive exercise (e.g. long run or weightlifting), caffeine, alcohol and meals within the 3 h prior to testing. The study was approved by the local ethics committee and all subjects provided written informed consent.

We used a double-blind, placebo-controlled, within-subject design. On the first day of each experimental session participants learned a list of words (declarative memory task; for details see below) and were trained in a serial reaction time task (procedural memory task; for details see below). Twenty-four hours later, subjects were administered orally either a placebo ($n = 22$) or a propranolol (40 mg, Dociton[®], Mibe, Germany; $n = 22$) pill 1 h before they took part in a stress test (socially evaluated cold pressor test) or a control condition. Thirty minutes after the treatment (stress vs. control) subjects completed a free recall test for the word list and a retention test for the serial reaction time task. Dosage and timing of propranolol administration were chosen according to the study by Quervain et al. (2007). Propranolol reaches peak levels 60–90 min after tablet administration and has a half-life of about 3 h whereas the duration of pharmacological effect may be even longer (Wojcicki et al., 1999). Salivary cortisol concentrations in response to the socially evaluated cold pressor test reach peak levels after 20–30 min and return to baseline levels after about 90 min (Schwabe et al., 2008a,b). Thus, the beta-blocker was effective during both the stress/control condition as well as during retrieval testing and saliva cortisol peaked at retrieval testing.

After a 2-week washout period, participants returned to the laboratory and the procedure was repeated with another list of words and another version of the serial reaction time task. Subjects received the same pharmacological intervention (placebo vs. propranolol) as 2 weeks before but the treatment (stress vs. control) they had not received in the first session. We decided to vary the treatment and not the pharmacological intervention within-subjects because previous research showed that repeated exposure to a stressor might lead to habituation effects (Schommer et al., 2003). Order of treatment, word lists and versions of the serial reaction time task was counterbalanced across subjects. All tests took place between 1330 h and 1700 h to control for diurnal variation of cortisol.

2.2. Declarative memory task

Participants were presented a word list containing 24 German two-syllable nouns with variable emotionality, ranging from neutral (valence ($M \pm S.E.M.$): 0.01 ± 0.01 ; word length ($M \pm S.E.M.$): 5.9 ± 0.3 words) to positive (valence: 1.20 ± 0.05 ; word length: 5.6 ± 0.4) and negative words (valence: -1.35 ± 0.07 ; word length: 6.3 ± 0.6 ; eight words per category; two parallel word lists available). The words were drawn from a German word database (Hager and Hasselhorn, 1994). They were comparable with respect to word frequency and semantic cohesion (norms taken from a German internet database). Positive and negative words were associated with comparable

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