



Propranolol reduces emotional distraction in working memory: A partial mediating role of propranolol-induced cortisol increases?

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ABSTRACT

Noradrenalin modulates prefrontal function, such as working memory (WM), and is associated with enhanced distractibility, and enhanced memory for emotional events and stimuli. The beta-blocker propranolol has been shown to reduce memory for emotional stimuli. Herein we describe investigations aimed at assessing whether the administration of propranolol would reduce the interference by emotional distractors during WM performance. In a between-subjects design, 48 young, healthy men received 80 mg propranolol ($n = 25$) or placebo ($n = 23$), before performing an “emotional Sternberg task” with neutral and negatively arousing distractors. Compared to placebo, propranolol impaired WM at low load, however, it also reduced the interference by emotional distractors at high load. Furthermore, an explorative moderated-mediation analysis indicated that the observed propranolol effects on emotional distraction were partially mediated by cortisol. In future non-clinical and clinical memory studies using propranolol administration, cortisol elevations should be monitored to further investigate the potential mediating role of cortisol.

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1. Introduction

When stressed, one of the neurohormonal systems that is activated is the locus coeruleus-noradrenergic system (Berridge & Waterhouse, 2003). This system plays a key modulatory role in prefrontal function (Minzenberg, Watrous, Yoon, Ursu, & Carter, 2008; Ramos & Arnsten, 2007; Berridge & Waterhouse, 2003), and is critically involved in emotional memory (McGaugh & Roozendaal, 2002; Roozendaal, Barsegyan, & Lee, 2008). Optimal levels of noradrenalin (NA) can improve functioning of the prefrontal cortex (PFC), whereas excessive NA or a depletion of NA impairs PFC function (Ramos & Arnsten, 2007; Arnsten, 2009). Stress-induced elevated NA is thought to take the reflective PFC “of-line” in favor of other more posterior brain areas, such as amygdala, hippocampus, and sensory- and motor areas, to allow for rapid emotional, or more habitual and reflexive behaviors (Ramos & Arnsten, 2007; Arnsten, 1997). Given the importance of the PFC in working memory (WM) performance (Kane & Engle, 2002; Ranganath, Johnson, & D’Esposito, 2003), it is of no surprise that high levels of NA have also been found to be associated with impaired WM performance

(Arnsten, Mathew, Ubriani, Taylor, & Li, 1999; Birnbaum, Gobeske, Auerbach, Taylor, & Arnsten, 1999; Mao, Arnsten, & Li, 1999).

WM can be defined as the capacity to maintain relevant information and to suppress irrelevant information. Patients with stress-related psychiatric disorders such as PTSD and depression, show poor WM performance and stronger interference from irrelevant negative emotional material (Joormann & Gotlib, 2008; Morey et al., 2009). Typically, in PTSD patients, pharmacological challenge tests or exposure to traumatic reminders are associated with increased noradrenergic responsiveness (Bremner, Krystal, Southwick, & Charney, 1996), and hypoactive responding in medial PFC, along with a hyperactive amygdala (Elzinga & Bremner, 2002; Etkin & Wager, 2007; Liberzon & Sripada, 2008; Shin, Rauch, & Pitman, 2006). When instructed to ignore emotional images shown during a WM task, PTSD patients displayed a similar pattern of decreased activity in dorsal areas, associated with WM and attention, and an enhanced neural activity in ventral areas (including the amygdala) associated with emotion processing relative to the trauma-exposed non-PTSD control group (Morey et al., 2009). These observations may be described as an exaggerated form of a “normal” response to emotional distractions during WM. That is, healthy individuals also pay more attention to emotional stimuli than neutral ones, because of their salience and significance for survival even when these are deemed irrelevant, for example, in a context of an ‘emotional WM task’, where emotional stimuli are used as distractors (Kensinger & Corkin, 2003). As a result,

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WM performance slows down during the emotional distraction trials (Dolcos & McCarthy, 2006; Kensinger & Corkin, 2003).

The response to emotional stimuli by the amygdala is mediated by NA (Berridge & Waterhouse, 2003; van Stegeren, 2008; van Stegeren et al., 2005). Elevated NA enhances amygdala response (Onur et al., 2009) and enhances the attention for emotional stimuli (DeMartino, Strange, & Dolan, 2008). Imaging studies have shown that administration of propranolol, a highly lipophilic non-selective beta-adrenergic receptor blocker, that blocks the action of adrenalin on both beta1 and beta2 adrenergic receptors, reduces the activity in the amygdala during emotional processing (Strange & Dolan, 2004; van Stegeren et al., 2005). A number of studies aimed at elucidating the role of NA in emotional memory, have further shown that propranolol generally reduces memory for emotional events and stimuli (see for a review Chamberlain, Muller, Blackwell, Robbins, & Sahakian, 2006), when encoding takes place after propranolol administration (Cahill, Prins, Weber, & McGaugh, 1994; Cahill & van Stegeren, 2003; van Stegeren et al., 2005). Taken together, these findings suggest that propranolol might improve emotional WM performance, owing to the diminished interference of emotional distractions.

The main aim of the present study was to investigate whether propranolol would improve emotional WM performance in young healthy men, by reducing the impact of emotionally negative distracters. Furthermore, we also performed an explorative analysis to investigate whether the stress hormone cortisol might mediate the effects of propranolol on emotional WM performance. There were two indicators that point towards a possible mediating role of cortisol in this regard: First, propranolol administration had been previously shown to elevate the levels of cortisol in the present sample (Tollenaar, Elzinga, Spinhoven, & Everaerd, 2009), as well as in other memory studies in which propranolol was administered (Maheu, Jooper, Beaulieu, & Lupien, 2004; Maheu, Jooper, & Lupien, 2005). Secondly, as part of the present study, we have also found that cortisol administration leads to enhanced performance on the present emotional WM memory task (Oei, Tollenaar, Spinhoven, & Elzinga, 2009).

2. Methods

2.1. Participants

Male volunteers were recruited by means of a sign-up board and advertisements posted at the Faculty of Social and Behavioural Sciences of Leiden University. Fifty-four participants who were part of a larger study on the effects of hydrocortisone and propranolol on memory functioning (Tollenaar et al., 2009) were included and randomly assigned to a propranolol and a control group in a double blind placebo-controlled between-subjects design (see Oei et al. 2009, for the study which compared hydrocortisone versus placebo). All participants had been screened before inclusion. Eligibility criteria were: no hypotension (blood pressure lower than 100/70 mm Hg), no history of disease, no current use of prescribed medication or the use of remedies containing corticosteroids, no use of psychotropic drugs, no current and past psychiatric problems, a Body Mass Index (BMI; kg/m²) between 19 and 26, and age between 18 and 35 years. Each participant gave signed informed consent in which confidentiality, anonymity, and the opportunity to withdraw without penalty were assured. The experimental group received a fixed dose of 80 mg of propranolol (Inderal; peak 1–4 h, half-time 3–6 h), and the control group received placebo. Characteristics of the sample ($n = 54$) were as follows (mean \pm SD): Age, 20.13 \pm 1.92 years; BMI, 21.99 \pm 2.32; trait anxiety as assessed with the STAI (Spielberger, 1983), 32.65 \pm 8.06; WM estimate as measured with the subtest Digit

Span Total score of the Wechsler Adult Intelligence Scale (WAIS), 10.59 \pm 2.47; psychoneuroticism, as assessed with the Symptom Checklist-90 (SCL-90, Arrindell & Ettema, 1986), 118 \pm 22.08. The experimental group (mean age \pm SD resp., 20.74 \pm 2.21, range: 18–25 years) was older than the control group (19.52 \pm 1.37 years, range: 18–24 years) ($F[1, 53] = 5.96, p = .02$). There were no other significant group differences (all $ps > .05$). The Medical Ethical Committee of the Leiden University Medical Center approved of the study protocol, and it was carried out according to the standards of the Declaration of Helsinki (2000). Participants received course credit or a monetary compensation for taking part in the study.

2.2. Physiological recordings

2.2.1. Cardiovascular measures

Systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), and heart rate (HR, bpm) were recorded using an automatic wrist blood pressure monitor (OMRON, R5-1).

2.2.2. Saliva sampling

Cortisol and alpha-amylase were assessed via saliva samples (before pill-ingestion, and before and after task performance at about peak propranolol levels) using Salivettes (Sarstedt, Germany). Saliva sampling is a stress-free method to assess unbound cortisol and alpha-amylase (Kirschbaum & Hellhammer, 1994). Saliva samples were centrifuged and stored at -20°C until assayed at Prof. Kirschbaum's laboratory (<http://biopsychologie.tu-dresden.de>). Cortisol and alpha-amylase concentrations in saliva were measured using a commercially available chemiluminescence-immunoassay kit with high sensitivity of 0.16 ng/ml (IBL, Hamburg, Germany). Inter- and intra-assay coefficients of variation were below 10%.

2.3. Working memory task

WM was measured using an adapted version of the Sternberg item-recognition task (Sternberg, 1966) previously described by Oei and colleagues (Oei et al., 2009). The WM processing load was manipulated by varying the numbers of uppercase letters (1–4 targets) that had to be held in memory for later recognition, and by varying the number of letters (1–4 displayed) presented in the recognition display after a short delay (1500-ms), which led to a load of 2–16 comparisons. For example, if the participant had to hold four items in memory (e.g., E, R, F and S), while searching for one of the items in a recognition display containing four items (D, M, U, and Z), this led to 16 possible comparisons (E–D, E–M, E–U, E–Z, R–D, R–M, R–U, R–Z, S–D, S–M, S–U, F–D, F–M, F–U, F–Z and S–Z). There were three blocks with low comparison load (loads 2, 4, 6) and three with high comparison loads (loads 8, 12, 16). In the delay-phase between target- and recognition display that originally contained a fixation cross (Lupien, Gillin, & Hauger, 1999; Oei, Everaerd, Elzinga, van Well, & Bermond, 2006), distracters were presented that consisted of pictures selected from the International Affective Pictures System (Lang, Bradley, & Cuthbert, 2001). Half of the distracters was emotionally neutral, the other half was of negatively arousing content. A red fixation cross was shown at the center of each picture. Participants had to ignore the distracters and press a 'yes' button indicating they had recognized a target (present-target trials), or a 'no' button, when no target letter was recognized (absent-target trials). Only one target letter was present in the present-target trials. Blocks with differing loads were randomly delivered. A total of 136 trials were delivered, which lasted approximately 10 min. Stimulus software (WESP) developed at the University of Amsterdam was used which randomizes and presents stimuli, and records reaction times and errors.

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