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The effect of beta-adrenergic blockade on inflammatory and cardiovascular responses to acute mental stress

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ABSTRACT

Acute mental stress elicits increases in plasma cytokine concentrations in humans, but the underlying mechanisms remain poorly understood. We assessed the impact of beta-adrenergic blockade on plasma interleukin 6 (IL-6) and IL-1 receptor antagonist (IL-1Ra) responses in a parallel group, double-blind randomised placebo-controlled trial involving 64 healthy young adult volunteers. Participants were administered 80 mg slow-release propranolol or placebo daily for 7 days before the stress testing session in which responses to 3 behavioural challenges (public speaking, mirror tracing, mental arithmetic) were evaluated. Propranolol administration was associated with reduced baseline levels of heart rate and IL-1Ra, and systolic blood pressure (BP) in men. Tasks stimulated increased plasma IL-6 concentrations sampled 45 min and 75 min after challenge, but these responses were blocked by propranolol in men ($p < 0.001$). Propranolol did not influence IL-6 responses in women, or IL-1Ra in either sex. Blood pressure and heart rate increased markedly during the tasks, but there was no differential stress reactivity in propranolol and placebo conditions. The results of the study support a role of sympathetic nervous system activation in stimulating acute IL-6 responses to stress, but only in men. The reasons for the differences between men and women remain to be resolved.

1. Introduction

Inflammation is involved in a range of serious health problems including coronary heart disease (CHD), some cancers, chronic pain, and depression (Elinav et al., 2013; Hansson and Hermansson, 2011; Louati and Berenbaum, 2015; Miller and Raison, 2016). Psychosocial factors such as early life trauma, low socioeconomic status (SES), caregiver strain and other adult stressors have also been associated with low-grade systemic inflammation (Danese and Lewis, 2017; Kiecolt-Glaser et al., 2015; Rohleder, 2014; Stringhini et al., 2013). This has led to the conjecture that inflammation mediates in part the association between psychosocial adversity and health outcomes. This link is supported by experimental studies demonstrating that acute psychological stress stimulates increased concentration of circulating inflammatory markers, notably interleukin 6 (IL-6) but also IL-1β and tumor necrosis factor alpha (TNFα) (Marsland et al., 2017; Steptoe et al., 2007). Additionally, individual differences in psychosocial factors such as loneliness and hostility appear to modulate the magnitude of inflammatory responses to acute psychological stress (Hackett et al., 2012; Hackett et al., 2015).

The biological mechanisms underlying inflammatory responses to acute stress are only partly understood. Psychological stress elicits rapid increases in expression of nuclear factor κB (NF- κB), a transcription factor promoting the production of IL-6 and IL-1β (Bierhaus et al., 2003; Kuebler et al., 2015). Increases in IL-1β and IL-6 mRNA expression from leukocytes have also been described (Brydon et al., 2005; Kuebler et al., 2015; McInnis et al., 2015). Other factors that may be relevant include redistribution of circulating white blood cell subpopulations that expression proinflammatory cytokines, and release of lymphocytes from marginal pools (Steptoe et al., 2007). Research in animal models strongly implicates sympathetic nervous system activation in these responses (Bierhaus et al., 2003; Sanders and Kavelaars, 2007). In humans, positive correlations between plasma IL-6 responses to acute stress and cardiovascular activity have also been observed, again suggestive of sympathetic nervous system involvement (Brydon et al., 2005; Kop et al., 2008).

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Another approach to investigating the pathways underlying acute inflammatory responses involves pharmacological blockade (Van Hedger et al., 2017). Rodent studies indicate that beta-adrenergic blockade inhibits stress-induced increases in inflammation (Hanke et al., 2012; Powell et al., 2013), but evidence from humans is inconclusive. The most detailed study was a double-blind analysis of 64 healthy middle-aged men and women randomised to daily 80 mg propranolol, 100 mg aspirin or placebo for 5 days (von Kanel et al., 2008). There was no effect of propranolol on plasma IL-6 responses up to 105 min after the Trier Social Stress Test (TSST), while aspirin attenuated stress-induced increases. The explanation for the lack of effect of propranolol is not clear. Rohleder (2008) suggested that the timing of stress testing might have been relevant, but it is difficult to know what would have been more appropriate. In an attempt to understand these processes better, we therefore carried out a parallel group double-blind trial evaluating the effect of propranolol vs placebo on IL-6 and cardiovascular responses to acute psychological stress in healthy young adults. We did not use the TSST but a similar battery of behavioural challenges, and measured IL-1Ra as an additional inflammatory biomarker. We hypothesised that 7 days of 80 mg propranolol would block stress-induced increases in inflammation and reduce systolic blood pressure (BP) and heart rate stress reactivity.

2. Method

2.1. Participants

Participants were 69 healthy volunteers recruited from the UCL campus for a study assessing the effects of pharmacological probes on stress responsivity. All data were collected with the written informed consent of the participants and ethical approval was obtained from the UCL Research Ethics Committee. Participants were aged 18 years and over, reportedly in good health, and not taking medications regularly (excluding the contraceptive pill). Exclusion criteria included haematological, pulmonary, liver, renal, gastrointestinal, heart, cerebrovascular, and psychiatric disease, history of thromboembolism, and participants were free of current infection. Individuals suffering from asthma, who had known allergies to the study medications, previous gastrointestinal bleedings, or who were currently pregnant or breastfeeding were excluded. Only those with BP in the normal range were included (90/60 m mHg–140/90 mmHg). Three people failed to complete the study, one dropped out because of side effects, and one was excluded after taking cold medication, leaving 64 in the final sample (20 men, 44 women). Volunteers were paid a small honorarium at the end of the study. The study was approved by the UCL Research Ethics Committee, and all participants gave signed informed consent.

2.2. Treatment conditions

Participants were randomised to propranolol or placebo conditions stratified by sex to ensure equal numbers of men and women in each group. None of the researchers involved in the study were aware of the treatment condition to which individuals were assigned. Propranolol is a non-selective beta-blocker, inhibiting the effects of catecholamines on both β1- and β2-adrenoceptors. Participants were administered 80 mg of sustained-release propranolol or identical placebo once a day after breakfast for 7 days. The dose was selected as the minimum recommended clinical dose for the treatment of hypertension, and was therefore deemed appropriate for healthy volunteers in order to minimise the likelihood of side effects.

2.3. Measures and procedure

Participants attended a brief session in the laboratory at which body composition was measured and a questionnaire containing demographic and psychosocial measures was completed. They received a bottle containing 12 pills of the study medication and were instructed to take one capsule every morning after breakfast for the following 7 days. Participants were advised not to take any other medications or herbal remedies while taking part in the study and to avoid alcohol and vigorous physical activity.

Study participants returned 7 days later for the laboratory stress session either in the morning (9:00 h) or afternoon (13:30 h), bringing back the pill bottle so that the remaining capsules could be counted. They were instructed not to exercise before the session, not to drink alcohol the evening before, and not to consume any caffeine on the morning of the testing day. They were asked to eat a light breakfast and/or lunch. Anxiety and positive affect over the past week were assessed. Then a Portapres-2 (Finapres Medical Systems, Amsterdam, NL) was fitted for the continuous monitoring of BP and heart rate, and an intravenous cannula was inserted for blood sample collection. The participant subsequently rested quietly for 30 min, followed by the baseline blood draw. Participants also rated subjective stress.

A behavioural task battery consisting of three tasks was then administered. First was a socially evaluative public speaking task as previously used by our group (Ghiadoni et al., 2000). The participant was asked to imagine a situation in which they had been falsely accused of shoplifting. They were required to prepare a statement in their defence for 2 min and to present it for 3 min. They were seated facing a video camera, and were told that images would be analysed and rated for fluency and competence. Second was a mirror tracing task used extensively in psychophysiological research (Matthews et al., 2003; Steptoe et al., 2002). The participant traced around a star seen in mirror image with a metal stylus for 5 min. Errors were indicated by a loud sound. The participant was instructed to trace around the star as many times as possible in 5 min while making minimal errors. Third was a serial subtraction task, in which the participant serially subtracted the number 13 from 1,022 as fast and as accurately as possible for 5 min (Kirschbaum et al., 1993). After every failure, the participant had to restart at 1,022. Blood pressure and heart rate monitoring continued throughout, and a second blood sample was drawn immediately after tasks. Subjective stress was rated after each task, and participants indicated how difficult they found the task. They then sat quietly for a further 75 min, with additional blood samples at 45 and 75 min after tasks.

2.4. Measures

Body composition was assessed with a Tanita Body Composition Monitor (BC-418MA) from which body mass index (BMI) was derived. Anxiety over the past week was measured with the 7-item anxiety subscale of the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), and positive affect with the positive affect subscale of the Positive and Negative Affect Scale (PANAS) (Watson et al., 1988). Scores on the anxiety scale could range from 0 to 21 and positive affect from 10 to 50, with higher ratings indicating greater anxiety or positive affect. Subjective stress and task difficulty were assessed on 7-point scales, with higher ratings indicating greater stress and perceived task difficulty.

Blood samples were drawn into EDTA tubes and immediately centrifuged at 2500 rpm for 10 min at room temperature. Plasma was removed and aliquoted into 0.5 ml portions and stored at -80° C until analysis. Plasma IL-6 was analysed with Quantikine high sensitivity two-site enzyme-linked immunosorbent assay

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