



Hydrocortisone infusion exerts dose- and sex-dependent effects on attention to emotional stimuli

Alaina Breitberg^a, Wayne C. Drevets^b, Suzanne E. Wood^c, Linda Mah^d, Jay Schulkin^e, Barbara J. Sahakian^f, Kristine Erickson^{g,*}

^a Department of Psychology, Hospital for Special Care, New Britain, CT, United States

^b Laureate Institute for Brain Research, The University of Oklahoma Health Sciences Center, Tulsa, OK, United States

^c Temple University, Philadelphia, PA, United States

^d Department of Psychiatry, Division of Geriatric Psychiatry, University of Toronto, Ontario, Canada

^e Department of Neuroscience, Georgetown University, Washington, DC, United States

^f Department of Psychiatry and MRC/Wellcome Trust Behavioural and Clinical Neurosciences Institute, University of Cambridge, Cambridge, UK

^g Department of Psychology, American University, Washington, DC, United States

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ABSTRACT

Glucocorticoid administration has been shown to exert complex effects on cognitive and emotional processing. In the current study we investigated the effects of glucocorticoid administration on attention towards emotional words, using an Affective Go/No-go task on which healthy humans have shown an attentional bias towards positive as compared to negative words. Healthy volunteers received placebo and either low-dose (0.15 mg/kg) or high-dose (0.45 mg/kg) hydrocortisone intravenously during two separate visits in a double-blind, randomized design. Seventy-five minutes post-infusion, the subjects performed tests of attention (Rapid Visual Information Processing [RVIP]), spatial working memory (Spatial Span) and emotional processing (Affective Go/No-go task [AGNG]). On the attention task, performance was impaired under both hydrocortisone doses relative to placebo, though the effect on error rate was not significant after controlling for age; Spatial Span performance was unaffected by hydrocortisone administration. On the AGNG task, relative to the placebo condition the low-dose hydrocortisone infusion decreased response time to emotional words while high-dose hydrocortisone increased response time. In the females specifically, both high and low dose hydrocortisone administration attenuated the normal attentional bias toward positively valenced words. These data suggest that, in healthy women, the modulation of attention by the emotional salience of stimuli is influenced by glucocorticoid hormone concentrations.

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1. Introduction

During exposure to acute or chronic stress, secretion of the glucocorticoid hormone cortisol increases (Nejtek, 2002), an effect which exerts wide-ranging effects on memory and emotional processing (Abercrombie, Kalin, & Davidson, 2005; Abercrombie, Speck, & Monticelli, 2006; Buchanan, Brechtel, Sollers, & Lovallo, 2001; Buchanan & Lovallo, 2001; Heffelfinger & Newcomer, 2001; Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Kuhlmann, Kirschbaum, & Wolf, 2005; Lerner, Gonzalez, Dahl, Hariri, & Taylor, 2005; Lupien et al., 1994, 1997; Nakayama,

Takahashi, & Radford, 2005; Newcomer et al., 1999; van Honk et al., 2000, 2003; Wagner, Degirmenci, Drosopoulos, Perras, & Born, 2005; Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001b; Wolf et al., 2001a; Wolkowitz et al., 1990). The relationship between acute glucocorticoid administration and cognitive performance is complex, being dependent on variables such as the administered dose (Het, Ramlow, & Wolf, 2005; Lupien et al., 2002), the timing of glucocorticoid administration in relation to the testing procedure (e.g. pre-initial learning vs. pre-recall), the timing of administration during the diurnal pattern of cortisol secretion (Maheu, Collicutt, Kornik, Moszkowski, & Lupien, 2005), and the nature of the task stimuli.

Increased glucocorticoid hormone concentrations may have an adaptive or protective role under certain contexts or conditions (Erickson & Gabry et al., 2005b), and memory for both neutral (Erickson, Drevets, & Schulkin, 2003; Korte, 2001) and emotional material (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson,

Abbreviations: CANTAB, Cambridge Neuropsychological Test Automated Battery; AGNG, Affective Go/No-go; RVIP, Rapid Visual Information Processing.

* Corresponding author. Address: Department of Psychology, American University, 4400 Massachusetts Ave., NW, Washington, DC 20016, USA.

E-mail address: erickson@american.edu (K. Erickson).

2003; Beckwith, Petros, Scaglione, & Nelson, 1986; Wolf et al., 2001b) can be enhanced by glucocorticoid administration. Enhanced memory, whether for neutral or emotional information, is usually associated with pre-learning administration of hydrocortisone. However, most studies report that manipulation of glucocorticoid levels have maladaptive effects on mood, cognition (Forget, Lacroix, Somma, & Cohen, 2000; Korte, 2001; Naber, Sand, & Heigl, 1996) and neurophysiology (McKittrick et al., 2000), particularly when levels are chronically elevated. Acute hydrocortisone administration can have detrimental effects on working memory and declarative memory when administered prior to recall (de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; de Quervain et al., 2003; Kuhlmann et al., 2005; Lupien, Gillin, & Hauger, 1999). Nevertheless, cortisol depletion also exerts detrimental effects on declarative memory performance, and restoration of cortisol levels attenuates this effect (Lupien et al., 2002).

Glucocorticoid administration appears to prominently influence memory for emotionally valenced information (Buchanan & Lovullo, 2001; Buchanan et al., 2001; Kuhlmann et al., 2005; Rimmele, Domes, Mathiak, & Hautzinger, 2003). In women, 30 mg hydrocortisone administered orally prior to recall led to impaired retrieval for negative but not neutral words (Kuhlmann et al., 2005). Relatively small doses of hydrocortisone (10 mg orally) have been shown to impair retrieval for autobiographical memory (Buss, Wolf, Witt, & Hellhammer, 2004), a mnemonic process for which the consolidation is modulated by emotional arousal during memory acquisition (Cahill & McGaugh, 1995; Talarico, LaBar, & Rubin, 2004). In contrast, moderate doses can enhance incidental long-term memory for emotional pictures, as a single 20 mg dose of hydrocortisone, given one hour before exposure to emotionally arousing pictures, enhanced memory for those pictures in a cued recall test 1 week later (Buchanan & Lovullo, 2001). Notably, this enhancement of memory for arousing stimuli may be partly attributable to an effect of glucocorticoid hormones on the magnitude or perception of arousal itself; as arousal judgments of neutral stimuli are affected by hydrocortisone administration in a dose-dependent manner, with higher (40 mg) doses resulting in higher arousal judgments than smaller (20 mg) doses (Abercrombie et al., 2005).

These previous studies of glucocorticoid effects on cognitive and/or emotional tasks in humans generally employed memory paradigms. In contrast, the effects of glucocorticoid hormones on attention have been relatively under-explored (Buss et al., 2004; Newcomer et al., 1999; Schmidt, Fox, Goldberg, Smith, & Schulkin, 1999; Wolf et al., 2001b). A moderate dose (10 mg) but not a high dose (40 mg) of orally administered hydrocortisone increased attentional inhibition to angry faces but found no significant effect for sad or happy faces 60–145 min later (Taylor, Ellenbogen, Washburn, & Jooper, 2011). The current study investigated the effects of glucocorticoid administration on attention towards emotionally-valenced words using an Affective Go/No-go (AGNG) task. In a previous study using this task, we reported that healthy humans manifest an attentional bias towards positive words, compared to negative words, reflected by faster reaction times to the positive words (Erickson & Drevets et al., 2005a). Whether glucocorticoids modulate performance on such tasks has not previously been investigated. We hypothesized in the current study that manipulation of cortisol levels would alter behavioral performance of healthy individuals on this task, and provide an indication of change in attentional bias toward positive or negative words. More specifically, based on the findings of Buchanan et al. (2001), we hypothesized that administration of a hydrocortisone dose sufficient to elevate cortisol concentrations to levels associated with moderate stress (0.15 mg/kg) would facilitate attention for emotional stimuli presented more than 1 h following hydrocortisone administration, as evidenced by faster reaction times and/or fewer errors on the AGNG task compared to placebo performance. We

further hypothesized that administration of a hydrocortisone dose sufficient to raise cortisol concentrations to levels associated with severe stress (0.45 mg/kg) would impair emotional processing because of prior report of opposing effects of low and high-dose hydrocortisone infusion (Buchanan et al., 2001), reflected by slower reaction times and/or more errors following infusion. Faster reaction times and/or decreased omission (target) errors toward a stimulus type generally are interpreted as evidence of an attentional bias towards that stimulus type, while slower reaction times or increased omission errors would reflect the opposite bias (i.e., away from the emotional stimulus type). Neuropsychological testing began 75 min post-infusion to capture the timecourse of previous reports of effects on performance (e.g., 50–80 min post-administration (Buchanan & Lovullo, 2001), 30–120 min post-administration (Buchanan et al., 2001), 60 min (Buss et al., 2004), 60–145 min post-administration (Taylor et al., 2011), and to overlap the 1–2 h time period during which glucocorticoids were found to enhance the excitability of basolateral amygdala neurons (Duvarci & Pare, 2007).

2. Method

2.1. Participants

The participants were right-handed subjects ($n = 44$; 18 female) between 18 and 50 years of age who were psychiatrically and medically healthy. Volunteers were recruited from the community through the National Institutes of Health. Subject screening included physical examination by a physician, laboratory assessments of blood and urine chemistry, electrocardiogram, structural MRI scan, unstructured interview with a psychiatrist, structured psychiatric interview using the Structured Clinical Interview for DSM-IV Disorders (SCID), and the Family Interview for Genetic Studies (FIGS). The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) was administered following screening to estimate full-scale Intelligence Quotient (IQ).

Volunteers were excluded if they had major medical, neurological or psychiatric disorders, first degree relatives with mood or anxiety disorders, abnormalities of brain structure in morphological MRI scans, exposure to medications likely to influence cerebral or endocrine function within 3 weeks of testing, a lifetime history of substance dependence or substance abuse within 1 year, regularly use of tobacco products within the preceding 6 months, full scale $IQ \leq 85$, weight ≥ 220 lbs, or indices of thyroid function or plasma cortisol levels outside the normal range. In addition, pregnancy, menopausal status, and hormone-based contraceptive use were exclusionary criteria for females. Because cortisol response to stress varies in women during the menstrual cycle, females were tested during the luteal phase defined as beginning after the 16th day of the start of menstruation, until the beginning of the following menstruation. Written informed consent was obtained as approved by the National Institutes of Mental Health Internal Review Board.

2.2. Procedures

The experiment was constructed with a double-blind randomized design. Prior to each experimental session, vital signs were assessed for all subjects and urine pregnancy testing was performed in women of childbearing age. Participants received hydrocortisone (0.15 mg/kg or 0.45 mg/kg) or saline administration during two separate visits as an intravenous bolus in a double-blind crossover design. Subjects were randomly assigned to the low- or high-dose hydrocortisone administration groups, and placebo and hydrocortisone administration visits were counterbalanced

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