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Effects of acute stress, relaxation, and a neurogenic inflammatory stimulus on interleukin-6 in humans

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Abstract

Effects of three experimental manipulations: mental stress, relaxation, and a nociceptive inflammatory stimulus, capsaicin, on levels of interleukin-6 (IL-6) were examined. Fifty subjects were pre-trained in relaxation and then randomized to a stress (Stroop test), relaxation (tape), or control (video) manipulation. Subjects participated in an evening reactivity session including 20 min of stress, relaxation, or control followed by a capsaicin injection in the forearm. Cardiovascular variables and levels of IL-6 were measured before and after the manipulation, and at regular intervals up to 60 min post-capsaicin. Group assignment did not differentially affect change in IL-6 over time, either before or after capsaicin. Small but significant increases in IL-6 were seen at 60 min post-capsaicin. These findings suggest that an acute stress manipulation does not modulate IL-6 within this time frame. Although IL-6 did increase following a neurogenic inflammatory stimulus, it did so subsequent to the maximum flare, suggesting that flare mechanisms are independent of IL-6.

Keywords: Interleukin-6; Stress; Relaxation; Pro-inflammatory cytokines; Capsaicin

1. Introduction

Interleukin-6 (IL-6) is a pleiotropic cytokine that has a critical role in the inflammatory response (Van Snick, 1990). IL-6 has also been implicated in the pathogenesis of a number of inflammatory conditions including rheumatoid arthritis (Ishihara and Hirano, 2002), psoriasis (Kwon et al., 2000), cardiovascular disease (Ridker et al., 2000a; Ridker et al., 2000b), and inflammatory bowel disease (Hosokawa et al., 1999). IL-6 is also involved in regulatory and inflammatory processes within the nervous system (Marz et al., 1998). IL-6 has been shown to be stress responsive and the IL-6 response to stress in laboratory animals has been fairly well characterized. Stressors such as immobilization, footshock, and conditioned aversive stimuli all reliably increase IL-6 in laboratory animals, usually in a dose–response fashion (Arimura et al., 1994; Zhou et al., 1993). In humans, effects of acute stress on IL-6 have been less well characterized. IL-6 has been shown to rise following acute stressors such as a speech task, mirror tracing (Goebel et al., 2000; Steptoe et al., 2001), and exercise (Pedersen et al., 2001a; Pedersen et al., 2001b). Chronic stress such as Alzheimer's caregiving has been associated with elevated IL-6 levels among older women (Lutgendorf et al., 1999). Effects of relaxation on IL-6 have been minimally studied. One report found no changes in IL-6 among patients with tinnitus following a 10-week relaxation intervention (Weber et al., 2002). Physiological mechanisms underlying stress-related alterations in IL-6 levels involve the interdependent relationship of IL-6 and the hypothalamic–pituitary–adrenal (HPA) axis (Judd and MacLeod, 1992; Spangelo et al., 1990; Van Snick, 1990; Zhou et al., 1993). Central and peripheral catecholaminergic systems may also be involved in the regulation of IL-6 (Arimura et al., 1994).

Although the role of IL-6 in the inflammatory response has been well characterized, less is known about the role of IL-6 in neurogenic inflammation, an

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inflammatory tissue reaction induced by the activation of nerve fibers (Holzer, 1988). Neurogenic inflammation is thought to be involved in the etiology of a number of inflammatory disorders such as asthma (Barnes, 2001), psoriasis (Singh et al., 1999), interstitial cystitis (Elbadawi, 1997), arthritis (Cerinic et al., 1998), inflammatory bowel diseases (Yiangou et al., 2001), and cardiovascular disease (Black, 2002).

Neurogenic inflammation is thought to be largely mediated by sensory afferent neurons (Holzer, 1988) which, when activated, release neuropeptides such as Substance P (SP) and calcitonin gene related peptide (CGRP) that directly or indirectly modulate vasodilation, microvascular permeability, and plasma extravasation (Brain and Williams, 1985; Coderre et al., 1989; Holzer, 1988). The presence of inflammatory cytokines, such as IL-6, has been documented in both sensory and autonomic nerves and the release of IL-6 with activation of nerves may act to promote inflammation (Nordlind et al., 1995). IL-6 has been implicated in neurogenic inflammatory processes related to asthma (Veronesi et al., 1999) and to pain resulting from nerve injury (Anderson and Rao, 2001). SP also directly induces the release of IL-6 and degranulation of mast cells (Zhu et al., 1996). Mast cells release histamine and pro-inflammatory cytokines, thereby activating an antigenic inflammatory process that acts synergistically with the neurally mediated inflammatory process (Coderre et al., 1989).

Neurogenic inflammation is frequently modeled using capsaicin, the active ingredient in red chili peppers (Capsicum) (Holzer, 1991). Following intradermal injection, capsaicin evokes a temporary burning sensation lasting 3–5 min and a characteristic localized flare consisting of a red flush with slight edema (Holzer, 1988). To date, attempts to isolate IL-6 in local exudates following capsaicin administration have generally not been successful (Reilly and Green, 1999). Thus the role of IL-6 in neurogenic inflammation is unclear and very few studies have been conducted in humans. Moreover, it is not known how stress may modulate effects of IL-6 with respect to neurogenic inflammation.

We previously investigated the effects of stress and relaxation on the neurogenic flare response to capsaicin and found that relaxation modulated the size of the flare (Lutgendorf et al., 2000). In this study, participants were pre-trained in relaxation and subsequently took part in a reactivity session including 20 min of a randomized stress, relaxation, or control manipulation, followed by a capsaicin injection in the forearm. Those in the relaxation condition showed smaller capsaicin-induced flares than participants in the stress or control conditions. Because of the potential role of IL-6 in both stress and in neurogenic inflammation, we were interested in changes in IL-6 during an acute stress task in humans, and whether IL-6 might be implicated in the previously observed modulation of the neurogenic flare response to capsaicin. The present study utilized plasma samples collected in the previously described investigation to determine levels of IL-6 in response to modulation of stress and to capsaicin.

The present study had three objectives. The first was to examine whether a randomized behavioral manipulation including standardized stress, relaxation, and control conditions would modulate acute changes in levels of IL-6. We hypothesized that increased IL-6 would be seen in the stress condition, decreased IL-6 would be seen in the relaxation condition, and no change would be observed in the control condition. The second objective was to examine changes in IL-6 following administration of capsaicin. We predicted that IL-6 levels would increase following capsaicin administration, and that post-capsaicin changes in IL-6 levels would be greater for those who were in the stress condition. The third objective was to investigate whether IL-6 contributed to the neurogenic inflammatory response and whether IL-6 mediated the relaxation-induced modulation of flare size. We predicted that IL-6 would be positively related to greater flare size and that IL-6 would mediate the relationship between the experimental condition and flare size.

2. Materials and methods

2.1. Subjects

Healthy, non-smoking men and women between 19 and 48 were recruited from local newspaper advertising and screened by telephone to determine eligibility as part of a larger study examining effects of modulation of stress on the size of the capsaicin flare. Individuals with inflammatory or immunomodulatory conditions, diabetes, cancer, organ transplant history, eczema, allergy to bee stings, pregnancy, or cardiac or respiratory conditions that would put the patient at potential risk following a capsaicin injection were excluded. Those taking medications that could potentially affect the physiological outcome parameters including birth control pills or other hormonal medication, corticosteroids, beta adrenergic receptor antagonists, psychotropic medication, or chronic antihistamine use were also excluded. Current or past history of major psychiatric illness or anxiety disorder, hospitalization within the last six months, or an acute infectious illness within the last month were grounds for exclusion. All females were pre-menopausal.

To ensure homogeneous groups, all potential subjects were trained in relaxation. Sixty-six individuals met initial screening criteria and were included in the relaxation training part of the study. One subject dropped out before relaxation training and five dropped out during the relaxation training due to inconvenience or