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Green, P G

Levine, J D

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Sexual dimorphism in the effect of nonhabituating stress on neurogenic plasma extravasation

Paul G. Green¹ and Jon D. Levine^{1,2}

¹Department of Oral and Maxillofacial Surgery, NIH Pain Center, C522/Box 0440, University of California San Francisco, 521 Parnassus Avenue, San Francisco, CA 94143-0440, USA

²Department of Medicine, University of California San Francisco, San Francisco, USA

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Abstract

The sympathoadrenal axis contributes to the sexual dimorphism of the inflammatory response. As stress both activates the sympathoadrenal axis and profoundly affects inflammation and inflammatory disease, we evaluated whether stress exerts a sexually dimorphic effect on a major component of the inflammatory response, plasma extravasation. We evaluated the effect of a nonhabituating stress, repeated intermittent sound (30 min/day for 4 days), on neurogenic synovial plasma extravasation, induced by bradykinin in the rat knee joint. Sound stress profoundly inhibited bradykinin-induced plasma extravasation in male rats, but profoundly enhanced it in female rats. These effects took 24 h to fully develop after the last exposure to stress. In gonadectomized males, bradykinin-induced plasma extravasation was lower than intact males, and sound stress now enhanced it, i.e. gonadectomized males were phenotypically like intact females. In gonadectomized females, bradykinin-induced plasma extravasation was greater than in intact adult females, and sound stress still enhanced it. Adrenal enucleation significantly attenuated the effect of sound stress on bradykinin-induced plasma extravasation in both male and female rats. We tested the hypothesis that these effects of sound stress were due to sustained enhanced plasma levels of stress hormones. Corticosterone and epinephrine, only when administered in combination, over five days, produced a qualitatively similar effect as sound stress, i.e. bradykinin-induced plasma extravasation was significantly decreased in males and increased in females. These findings suggest that a combined effect of the hypothalamic-pituitary adrenal and sympathoadrenal stress axes are responsible for the marked sexual dimorphism in the effect of stress on the inflammatory response.

Introduction

The stress response is an adaptive process that exerts powerful effects on the endocrine, neural and immune systems, and the effects of stress on these systems is complex (reviewed in Black, 2002). For example, stressors activate both the hypothalamic-pituitary adrenal cortical axis to release glucocorticoids as well as the sympathoadrenal medullary axis to release catecholamines, and these stress axis mediators affect the synthesis and release of cytokines and inflammatory mediators, which influence immune cell trafficking, proliferation and function. While there is much evidence that stress affects inflammatory diseases (Black, 2002; LeResche & Dworkin, 2002; Eskandari *et al.*, 2003), the complexity of the neuroendocrine circuits involved has hindered the elucidation of the underlying mechanisms.

The effect of stress on the inflammatory response is dependent on a number of factors including type and duration of the stressor. We have investigated these variables on an early component of the inflammatory response, plasma extravasation. We have demonstrated that repeated, but not single exposure to restraint, noise or ether inhibits a key feature of inflammation, plasma extravasation produced by the potent inflammatory mediator bradykinin (Strausbaugh *et al.*, 1999; Strausbaugh *et al.*, 2003), and that while repeated restraint stress inhibits plasma extravasation immediately after exposure to the stressor, via activation of the hypothalamic-pituitary adrenal cortex

(HPA) axis, stress produced by exposure to repeated sound or to ether inhibits plasma extravasation 24–48 h after the last exposure to the stressor, via activation of the sympathoadrenal medulla axis.

It is likely that the sympathoadrenal axis modulates the inflammatory response by releasing epinephrine, which acts on adrenergic receptors present on leucocytes. For example, the β_2 -adrenergic receptor subtype mediates several of the observed effects of catecholamines (Benschop *et al.*, 1996), such as generation of reactive oxygen intermediates in granulocytes in response to activation with fMLP (Opdahl *et al.*, 1993) and interleukin-8 production in macrophages (Kavelaars *et al.*, 1997), while epinephrine acts via β_1 -adrenergic receptors to increase inflammatory response and leucocyte migration (Jain *et al.*, 2003).

As the stress response is sexually dimorphic (Rivier, 1994; Chisari *et al.*, 1995; Vamvakopoulos, 1995; Spinedi *et al.*, 2002), it is possible that this could mediate the sexual dimorphism in inflammatory responses and inflammatory disease. The question of whether stress affects the inflammatory response in a sexually dimorphic manner has not been directly addressed, however, there are several lines of evidence to support the suggestion that this may be so. For example, stress-induced increase in plasma catecholamines is sexually dimorphic (Kudielka *et al.*, 1998; Weinstock *et al.*, 1998; Hawk *et al.*, 2000; Ross *et al.*, 2001; Stein & Wade, 2001), and cell-mediated immune responses are inhibited in males after haemorrhagic shock, whereas they are unchanged or enhanced in females (Angele *et al.*, 2000). In this study, we investigated for sexual dimorphism in the effect of a nonhabituating repeated stress on plasma extravasation.

Correspondence: Dr Paul Green, as above.
E-mail: paul@itsa.ucsf.edu

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Materials and methods

Animals

The experiments were performed on male and female Sprague–Dawley rats (280–320 g). Rats were anaesthetized by intraperitoneal injection of sodium pentobarbital (65 mg/kg, Abbott Laboratory, Chicago, IL) for knee joint perfusion, terminal experiments. For recovery procedures, 2–3% isoflurane was used to anaesthetize animals. Animal care and use conformed to the NIH guidelines for the care and use of experimental animals. The University of California at San Francisco, Committee on Animal Research, approved all experimental protocols used in these experiments; all efforts were made to minimize number of animals used.

Sound stress

Sound stress was performed on days 1, 3 and 4, as previously described (Singh *et al.*, 1990; Strausbaugh *et al.*, 2003). Animals were placed in a 55 × 55 × 70 cm sound-insulated box in a cage 25 cm away from a speaker. The box was closed and animals were exposed to a 105 dB tone of mixed frequencies ranging from 11 to 19 kHz. Over 30 min, rats were exposed to 5-s or 10-s sound epochs presented every minute at random intervals during the minute. Rats were then placed back in their home cages and returned to the animal care facility until plasma extravasation measurements were performed, 24 h later. All stress exposures occurred between 08:00 h and 12:00 h.

Gonadectomy

Gonadectomies were performed prepubertally as we have previously shown that during puberty, sex steroids in males permanently influence inflammatory phenotype (Green *et al.*, 2001). Three-week-old female rats were anaesthetized with isoflurane (2–3% in oxygen) and ovariectomy was achieved via a bilateral flank incisions. Vascular bundles were ligated with 4–0 silk suture, the fascia closed with 5–0 chromic gut suture and the skin closed with metal wound clips.

Isoflurane (2–3% in oxygen) anaesthetized three-week-old male rats were castrated through a single scrotal incision. Vascular bundles were ligated with 4–0 chromic gut suture and the skin closed with metal wound clips (Waynforth & Flecknell, 1992).

Adrenal enucleation

Adrenal enucleation was performed 5 weeks prior to experiments to allow for recovery of adrenal cortical function (Wilkinson *et al.*, 1981). Rats were anaesthetized with isoflurane (2–3% in oxygen), the adrenal gland was located through an incision in the lateral abdominal wall, exposed and the encapsulated adrenal medulla enucleated. After the surgery, the rats was given 0.5% saline to drink, in place of water, for the first 7 days after surgery.

Plasma extravasation

Plasma extravasation was evaluated as described previously (Coderre *et al.*, 1989). Rats were anaesthetized with sodium pentobarbital (65 mg/kg, intraperitoneal) and were then given a tail vein injection of Evans blue dye (50 mg/kg), which binds stoichiometrically to serum albumin. Fluid was perfused through the knee joint at a constant rate (250 µL/min) and perfusate samples were collected every 5 min for a

period of 75–90 min. After establishing vehicle baseline levels of PE, bradykinin (150 nM, a concentration that stimulates plasma extravasation in a sympathetic postganglionic neuron-dependent manner) was added to this perfusing fluid (0.9% saline) and remained present in the fluid for the duration of the experiment. Samples were centrifuged to determine if red blood cells were present; only data from rats that produced blood-free samples were analysed. Using spectrophotometric measurement (absorbance at 620 nm) samples were then evaluated for Evans blue dye concentration, which is linearly related to protein albumin concentration (Carr & Wilhelm, 1964).

Chronic corticosterone and epinephrine administration

We administered corticosterone and epinephrine over 5 days to evaluate the effect of plasma stress levels of these hormones on bradykinin-induced plasma extravasation. Corticosterone was administered as a slow-release pellet of 100 mg fused corticosterone that produces plasma levels in rats of ≈ 20 µg/dL (la Fleur *et al.*, 2004), which compares to a plasma corticosterone level of 32.64 ± 2.82 µg/dL (Strausbaugh *et al.*, 2003) 1 h after the last exposure to stress; $4.5 \times 4.5 \times 5$ mm pellets were implanted subcutaneously in isoflurane-anaesthetized rats. Epinephrine was administered via osmotic minipumps, filled to deliver 10.8 µg/h epinephrine bitartrate (Racotta *et al.*, 1986) in a vehicle of 0.9% saline containing 1% ascorbic acid. This produces plasma epinephrine levels in rats of ≈ 1.4 ng/mL (Khasar *et al.*, 2003), and 24 h after the last exposure to sound stress the mean plasma level are 0.818 ± 0.031 ng/mL ($n = 6$); plasma epinephrine levels were measured using HPCL with electrochemical detection, as previously described (Khasar *et al.*, 2003). Rats were anaesthetized with isoflurane and osmotic minipumps (Alzet, Model Number 1007D, Durect, CA, USA) were implanted subcutaneously in the dorsal interscapular region.

Statistics

All data was compared simultaneously using a repeated measures analysis of variance with treatment as the between-subjects factor followed by Fisher's PLSD for comparisons between treatments. Of note, naïve and 24 h post-stress data appear in more than one figure to avoid having more than four data lines on one graph.

Results

Sexual dimorphism in sound stress-induced change in bradykinin-induced plasma extravasation

As we have previously reported (Strausbaugh *et al.*, 2003), in male rats nonhabituating sound stress markedly inhibits bradykinin-induced plasma extravasation beginning 5 h after the final stress, maximal at 24 h and returning to non-stress levels at 48 h; we now demonstrate that in female rats, the same sound stress paradigm markedly enhances bradykinin-induced plasma extravasation, beginning at 5 h and being maximal at 24 h and returns to non-stressed levels 48 h post stress (Fig. 1A–C).

Role of sex steroids in sexual dimorphism in sound stress-induced change in bradykinin-induced plasma extravasation

Gonadectomies were performed on prepubertal male and female rats to determine the contribution of sex steroids to the effects of sound stress on bradykinin-induced plasma extravasation. Gonadectomy in males significantly lowers bradykinin-induced plasma extravasation

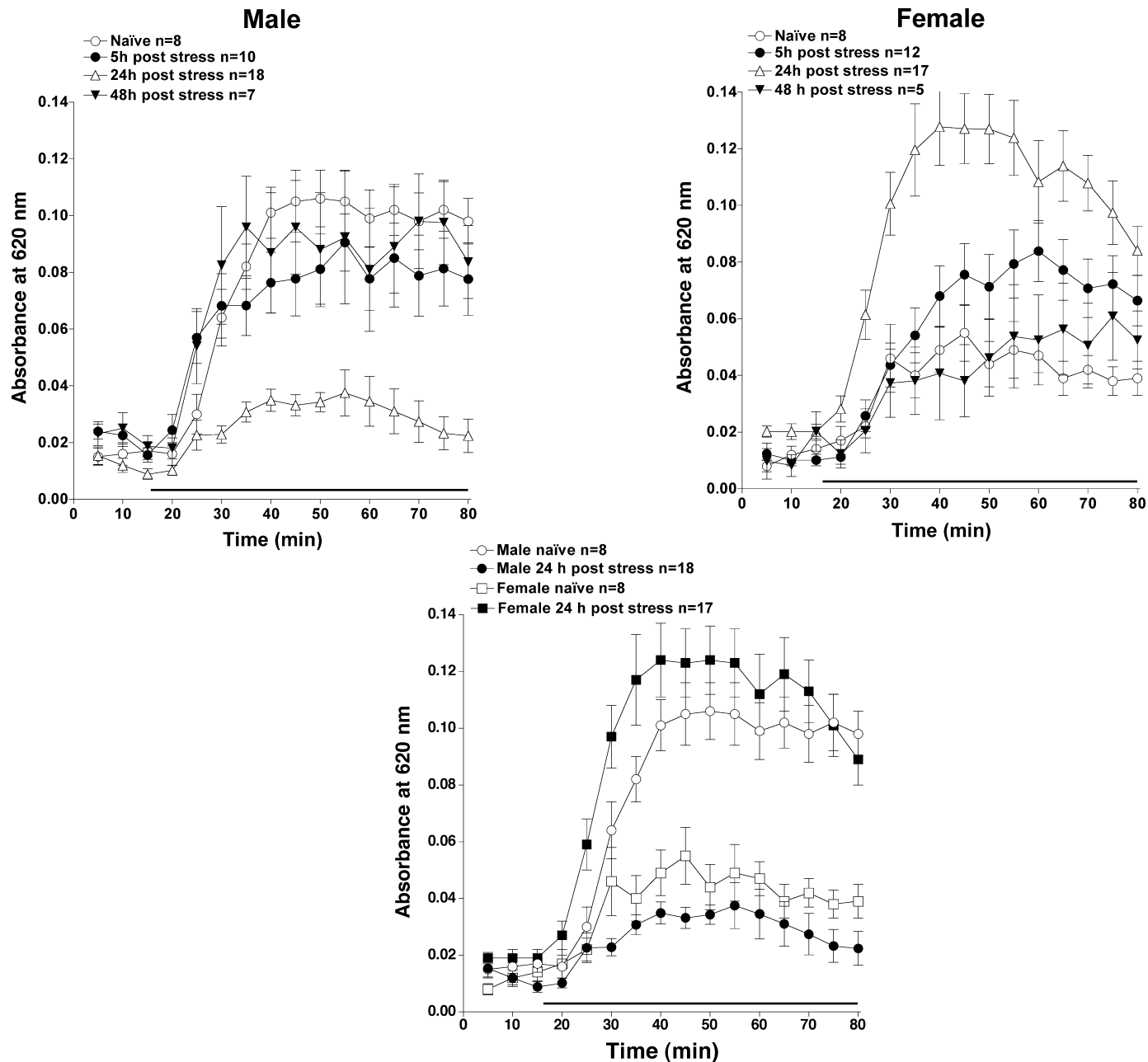


FIG. 1. Stress inhibits bradykinin-induced plasma extravasation in males and increases it females. Compared to non-stressed rats (naïve), sound stress inhibited bradykinin-induced plasma extravasation in males ($P < 0.05$), but sound stress enhanced it in females ($P < 0.05$). The effect of stress was present 5 h following the last stress exposure, reached a maximal 24 h post stress and was absent 48 h post stress. Results are expressed as mean \pm SEM (n = number of knees, horizontal line indicates when bradykinin is perfused through the knee).

compared to intact males, as we have previously noted (Green *et al.*, 1999; Green *et al.*, 2001), and sound stress significantly increases bradykinin-induced plasma extravasation in gonadectomized males, i.e. gonadectomy in males produced a female phenotype (Fig. 2A). Gonadectomy in females significantly enhances bradykinin-induced plasma extravasation compared to intact females, as we have previously noted (Green *et al.*, 1999; Green *et al.*, 2001), and while sound stress still increases bradykinin-induced plasma extravasation, the magnitude of increase in gonadectomized females is approximately half that seen in intact females.

Role of adrenal medulla in sexually dimorphic effect of sound stress on bradykinin-induced plasma extravasation

In males, adrenal medullectomy significantly attenuated the inhibition of bradykinin-induced plasma extravasation produced by sound stress (Fig. 3). In females, adrenal medullectomy, which itself significantly increased bradykinin-induced plasma extravasation in females, compared to intact females also significantly attenuated sound stress-induced increase in bradykinin-induced plasma extravasation females (Fig. 3).

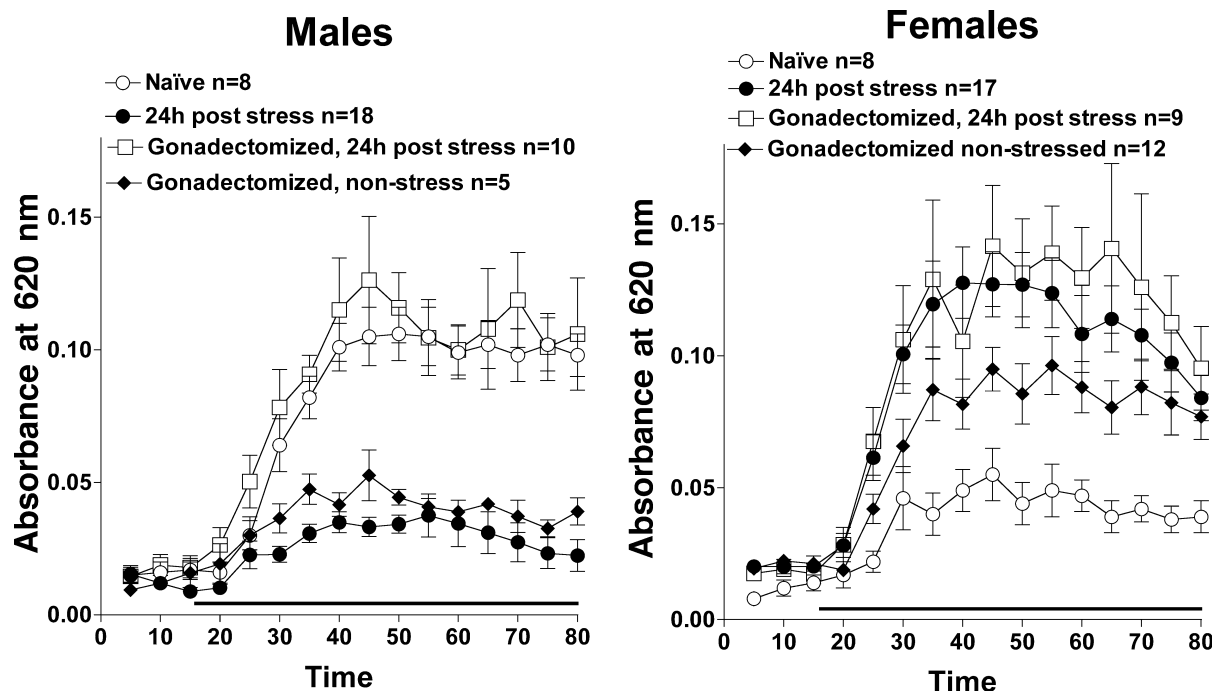


FIG. 2. Effect of gonadectomy on the effect of stress on bradykinin-induced plasma extravasation. In adult males, gonadectomized prepubertally, bradykinin-induced plasma extravasation was significantly less than intact males and stress significantly enhanced bradykinin-induced plasma extravasation (both $P < 0.05$), i.e. gonadectomized males had an intact female phenotype. In adult females, gonadectomized prepubertally, bradykinin-induced plasma extravasation was significantly greater than intact females ($P < 0.05$), and stress produced a small, but significant, increase in bradykinin-induced plasma extravasation ($P < 0.05$). Results are expressed as mean \pm SEM (n = number of knees, horizontal line indicates when bradykinin is perfused through the knee).

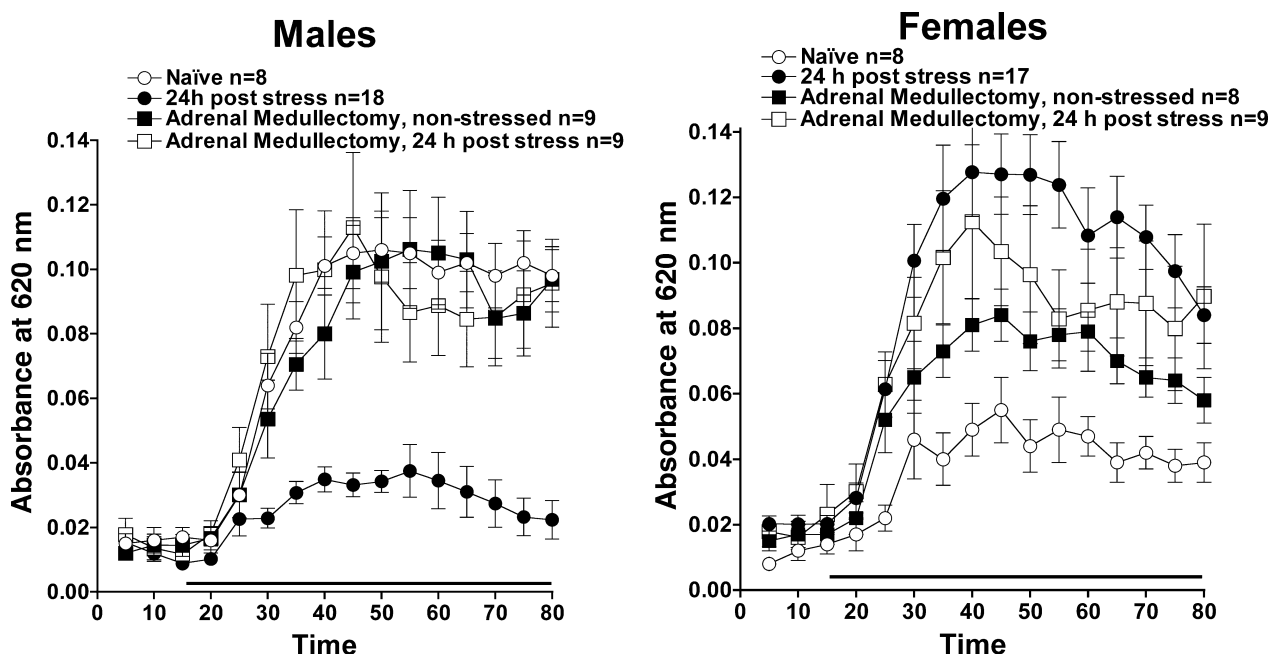


FIG. 3. Effect of adrenal medullectomy on bradykinin-induced plasma extravasation. In adrenal medullectomized males, bradykinin-induced plasma extravasation was not significantly different from intact males, however, adrenal medullectomy completely prevented the stress-mediated inhibition of bradykinin-induced plasma extravasation ($P < 0.05$). In females, adrenal medullectomy, significantly increased bradykinin-induced plasma extravasation in females, compared to intact females ($P < 0.05$) and significantly attenuated sound stress-induced increase in bradykinin-induced plasma extravasation females ($P < 0.05$) (n = number of knees, horizontal line indicates when bradykinin is perfused through the knee).

Effect of chronic epinephrine and corticosterone, alone and in combination, on bradykinin-induced plasma extravasation

Neither epinephrine (10.8 $\mu\text{g}/\text{rat}/\text{h}$) nor corticosterone (100 mg implanted pellet) when administered alone affected the magnitude of

plasma extravasation in either males or females (both $P > 0.05$, Fig. 4). However, epinephrine and corticosterone administered in combination significantly inhibited bradykinin-induced plasma extravasation in males and significantly increased it in females,

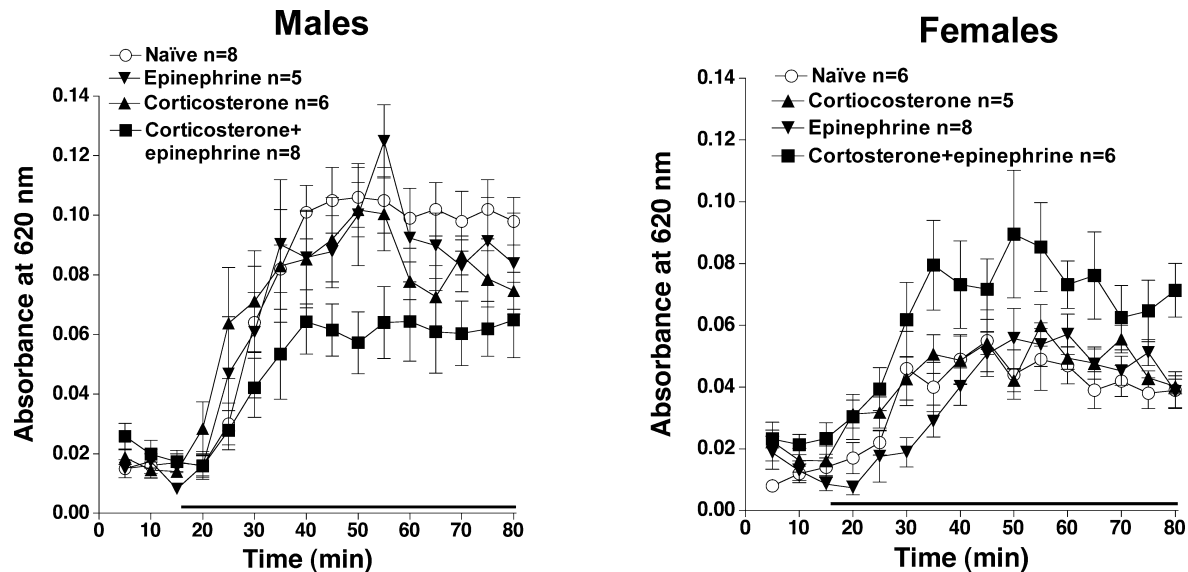


FIG. 4. Effect of chronic corticosterone + epinephrine on bradykinin-induced plasma extravasation. Administration of corticosterone (100 mg pellet) or epinephrine (10.8 $\mu\text{g}/\text{h}$) over 5 days did not significantly affect the magnitude of bradykinin-induced plasma extravasation, however, when given in combination corticosterone + epinephrine significantly inhibited bradykinin-induced plasma extravasation in males and significantly enhanced it in females (both $P < 0.05$). The magnitude of these effects was less than that seen 24 h post stress (cf. Fig. 1) (n = number of knees, horizontal line indicates when bradykinin is perfused through the knee).

compared to naïve controls (both $P < 0.05$, Fig. 4). However, the magnitude of the effect of epinephrine + corticosterone was significantly less than that produced by sound stress ($P < 0.05$).

Discussion

While the effect of stress on the inflammatory response is sexually dimorphic, to date the relationship between sex, stress and inflammation has been little studied. We have now demonstrated that nonhabituating sound stress has a highly sexually dimorphic effect on the magnitude of the inflammatory response, with stress markedly inhibiting bradykinin-induced plasma extravasation in males while markedly enhancing it in females. Prepubertal gonadectomy converted this effect of stress in males to a similar response observed in intact females, and greatly attenuated the effect of stress in females. The effect of stress on bradykinin-induced plasma extravasation is adrenal medulla-dependent in both males and females. Finally, in both sexes chronic coadministration of corticosterone or epinephrine administered alone did not affect bradykinin-induced plasma extravasation, but when combined, corticosterone with epinephrine qualitatively mimics the effect of stress on bradykinin-induced plasma extravasation in rats of the same sex, an effect not seen with either mediator administered alone.

The magnitude of rat knee joint plasma extravasation is inversely related to joint injury in experimental arthritis (Coderre *et al.*, 1990; Coderre *et al.*, 1991; Green *et al.*, 1991; Miao *et al.*, 1992), indicating that plasma extravasation exerts a protective effect by, for example, increasing the rate of removal of tissue damaging products of the inflammatory response (Basbaum & Levine, 1991; Kozik *et al.*, 1998). While it is well established that repeated stress exacerbates severity of inflammatory diseases (Li *et al.*, 2004), our observation that stress inhibited plasma extravasation in males and enhanced it in females suggests that repeated stress may aggravate inflammatory disease symptoms more in men than women. There are few reports that have addressed this question, however, it has been shown that stress worsens psoriatic skin and joint symptoms (Harvima *et al.*, 1996) and the

incidence of colitis, and asthma (Sekas & Wile, 1980) in men but not women.

The data we have presented indicate that the stress-induced effect on plasma extravasation in both male and female rats is dependent on an intact sympathoadrenal axis. Although it has previously been shown that adrenal medulla-derived epinephrine enhances inflammation in female rats (Nordling *et al.*, 1992), it is unlikely that epinephrine is the sole mediator of the effect of sound stress as, when given alone, continuously administered stress levels of epinephrine did not affect the magnitude of bradykinin-induced plasma extravasation. However, coadministration of stress levels of epinephrine and corticosterone resulted in a suppression of bradykinin-induced plasma extravasation in males and an enhancement in females, i.e. the sound stress-induced phenotypes; of note, the sound stress paradigm we used produces a sustained elevated concentration of both epinephrine (see Materials and methods) and corticosterone (Strausbaugh *et al.*, 2003). While the magnitude of change in bradykinin-induced plasma extravasation following epinephrine + corticosterone administration was less than that seen following sound stress, this could be due to differences in plasma levels or their time course obtained following stress and following exogenous administration of epinephrine and corticosterone. Also, epinephrine + corticosterone administration is likely to produce a stable plasma concentration, while exposure to sound stress and normal diurnal variation is likely to produce variable plasma concentrations. As both the HPA and sympathoadrenal axes are coactivated during stress, catecholamines and glucocorticoids are likely to act in concert to regulate the inflammatory response, and it has been shown that catecholamines sometimes synergize with and, at other times, attenuate the actions of glucocorticoids (McEwen, 2003). For example, corticosterone attenuates isoproterenol-induced desensitization of β -adrenergic receptors (receptor-adenylate cyclase coupling) (Davies & Lefkowitz, 1983) and increases β -adrenergic receptor density (Davies & Lefkowitz, 1980) on human neutrophils. Furthermore, stress-induced suppression of cytotoxic T-lymphocyte activation in mice is mediated by a coactivation of both

glucocorticoid and β -adrenergic receptors (Dobbs *et al.*, 1993), and corticosterone and epinephrine regulate leucocyte TNF α production (Pettipher *et al.*, 1997) and epinephrine and corticosterone additionally enhance skin delayed-type hypersensitivity (Dhabhar & McEwen, 1999). While stress may affect immune function in the absence of glucocorticoids, and elevated glucocorticoids may not affect immune function (reviewed in Moynihan, 2003), it is likely that the tight anatomical and functional integration between the adrenal cortex and medulla (Bornstein *et al.*, 1994; Einerjensen & Carter, 1995; Wurtman, 2002) is likely to have a counterpart in an integration between the principal effectors (i.e. epinephrine and glucocorticoids).

The results of the current study have not addressed the question of the mechanism by which epinephrine + corticosterone affects plasma extravasation. Both epinephrine (Green *et al.*, 1993) and corticosterone (Ahluwalia *et al.*, 1995) have been shown to inhibit plasma extravasation in male rats, possibly by acting directly on postcapillary venules. Plasma extravasation, produced by several inflammatory mediators including bradykinin (Coderre *et al.*, 1989; Green *et al.*, 1993), serotonin (Pierce *et al.*, 1996) and prostaglandin (Mathison & Davison, 1994), is dependent on the postganglionic sympathetic neuron and on circulating neutrophils (Bjerknes *et al.*, 1991), and repeated stress is likely to affect both these systems. For example, sound stress activates the sympathetic postganglionic neuron (Okada *et al.*, 1985) to release norepinephrine (Mormede *et al.*, 1990), which acts directly on endothelial cells to inhibit plasma (O'Duffy & Chahl, 1979) and neutrophil extravasation (Doukas *et al.*, 1987). Catecholamines also act on circulating leucocytes via α_1 -, α_2 - and β -adrenergic receptors on leucocytes to suppress (Elenkov & Chrousos, 1999; Maes *et al.*, 2000) or release (Boers *et al.*, 1992; Liao *et al.*, 1995; Giovambattista *et al.*, 2000) proinflammatory cytokines, and the sympathetic nervous system mediates the stress-induced increased susceptibility to bacterial infection (Cao *et al.*, 2002) and suppression of natural killer cell cytotoxicity (Jiang *et al.*, 2004).

While the mechanism mediating the marked sexual dimorphism in the effect of stress on plasma extravasation is currently unknown, it is likely that the adrenal medulla plays a key role as its ablation powerfully inhibits the sexual dimorphic effects of stress and moreover, stress-evoked release of epinephrine is sexually dimorphic in both animals and humans (Hinojosa-Laborde *et al.*, 1999; Dart *et al.*, 2002). An alternative mechanism could depend on the action of sex steroids on leucocytes, for example 17 β -estradiol affects pro-inflammatory cytokine production (Dienstknecht *et al.*, 2004), as well as directly affecting endothelial cell expression of adhesion molecules and leucocyte extravasation (Dietrich, 2004). Future studies evaluating for a sexual dimorphism in stress-induced changes in plasma levels of pro- and anti-inflammatory cytokines could provide additional insight into the mechanism of the effects of stress on the inflammatory process.

The relationship between stress, inflammation and sex steroids has been evaluated in a Siberian hamster model (Bilbo & Nelson, 2003); stress enhanced the delayed-type hypersensitivity inflammatory response in females, but this effect was abolished in females with low estradiol steroid levels (short-day lengths). While stress had no effect on the inflammatory response in males, inflammation was enhanced by stress in males with low testosterone induced by short-day lengths.

In summary, these findings suggest that the sympathoadrenal and hypothalamic-pituitary adrenal axes contribute to the marked sexual dimorphism in the effect of stress on the inflammatory response, and suggest a mechanism for the observed sexual dimorphism of inflammatory diseases.

Acknowledgements

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