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Activation of the HPA Axis by Immune Insults: Roles and Interactions of Cytokines, Eicosanoids, and Glucocorticoids

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BUCKINGHAM, J. C., H. D. LOXLEY, H. C. CHRISTIAN AND J. G. PHILIP. *Activation of the HPA axis by immune insults: Roles and interactions of cytokines, eicosanoids, and glucocorticoids.* PHARMACOL BIOCHEM BEHAV **54**(1) 285–298, 1996. – It is now well established that challenges to the immune system (e.g., infection, inflammation) initiate diverse changes in neuroendocrine function, the most overt of which is activation of the hypothalamo-pituitary-adrenocortical (HPA) axis. The glucocorticoids that are released as a consequence fulfill a vital role in the maintenance of homeostasis that is effected in part through their ability to quench the immune/inflammatory response and thereby prevent them accelerating to a point where they become hazardous to the host. This article discusses the putative mechanisms by which immune insults stimulate the HPA axis, with particular reference to the roles and interactions of the interleukins, eicosanoids and glucocorticoids.

HPA axis Cytokines Eicosanoids Glucocorticoids Stress Neuroimmunology

RECIPROCAL communication between the immune and brain-neuroendocrine systems is critical to host defence in conditions of both health and disease, as it provides a means whereby the central nervous system can detect alterations in immune status and initiate a coordinated series of responses (behavioral, physiological and immunoregulatory) designed to protect the host and, thus, to restore homeostasis. Particular emphasis in this regard has been placed on the fundamental role of the hypothalamo-pituitary-adrenocortical (HPA) axis, which provides an essential interface between the internal and external environment and enables the organism to adapt to diverse noxious stimuli, whether they be noncognitive (e.g., immune insults) or cognitive (e.g., emotional or physical trauma). This axis is promptly activated in conditions of stress and is duly responsible for the secretion of substantial quantities of glucocorticoids, which serve to restore homeostasis through multiple mechanisms that include modulation of immune/inflammatory processes and manifestation of a wide array of metabolic and behavioral changes (77,78). Failure to mount an appropriate adrenocortical response in conditions of stress is potentially hazardous and, indeed, disturbances in HPA function are now considered to represent a significant contributory factor in the etiology of a variety of disease processes. For example, excessive glucocorticoid secretion (which may arise from a primary disorder of the HPA axis or from causes as diverse as, e.g., ectopic ACTH-producing tumors, depression, alcoholism, anorexia) causes diverse metabolic and behavioral disturbances together with immunosuppression, which may, in turn, predispose the individual to other disease processes, e.g., infections, cancer. Conversely, adrenocortical insufficiency (which may reflect either adrenal failure or steroid resistance in the target tissues) not only precipitates a vulnerability to stress (a phenomenon amply illustrated by the potentially lethal effects of stresses such as endotoxin, cold, and surgery in adrenalectomized rats) but is also increasingly implicated in the pathogenesis of autoimmune, inflammatory, and allergic disorders (34).

Among the most severe stresses an individual encounters are diseases that challenge and potentially threaten the body's defence mechanisms (e.g., infections, inflammation). This article will discuss the putative mechanisms by which the HPA axis responds to such insults, placing particular emphasis on the actions and interactions of the interleukins, eicosanoids, and glucocorticoids.

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HPA RESPONSES TO IMMUNE CHALLENGE

Mechanisms of HPA Activation

The concept that challenges to the immune system such as those provoked by infection, tissue injury, or inflammation effect a pronounced increase in HPA activity is supported by a substantial body of data [reviewed in (12)]. Early evidence to this effect emerged from the studies of Besedovsky and colleagues, who showed that innocuous antigens (noninfective, nonself-replicating or nonneoplastic) produce significant increases in the serum corticosterone concentration in rodents (11). Similar responses occur in animals subjected to viral or bacterial infections (14,36,137) and in those bearing transplanted tumors (13). The magnitude of the adrenocortical response normally varies according to the intensity of the immune insult (99), although some antigens (e.g., phosphocholine-keyhole limpet hemocyanin) are reported to trigger a robust immunological response at doses below those required to activate the HPA axis (107). Not surprisingly, the data in humans are less exhaustive but, nonetheless, there is substantial evidence for increased cortisol secretion in conditions of infection (e.g., septicaemia) and inflammation (41,51,134).

The mechanisms by which immune insults activate the HPA axis are the focus of much current research. Several workers have drawn attention to evidence that in many such instances the neuroendocrine and immune systems produce and use common chemical mediators (16). For example, following challenge with endotoxin, leukocytes and lymphocytes synthesize peptides and receptors that are classically associated with the neuroendocrine system (e.g., ACTH, β-endorphin, corticotrophin releasing hormone- (CRH-like) peptides), while neural/glial and endocrine tissues generate cytokines (e.g., IL-1). These factors undoubtedly fulfill important local regulatory functions and may thereby contribute to the manifestation of the reciprocal communication between the neuroendocrine and immune systems (see section Production of neuroendocrine peptides within the immune system). However, the bulk of evidence accumulated over the past decade argues unequivocally that the sustained hypersecretion of glucocorticoids precipitated by an immune challenge is initiated primarily by the army of mediators (immunokines) released from the activated immune/inflammatory cells (12,104). The list of substances known to be active in this regard is lengthy and includes for example, interleukins (notably IL-1α and β, IL-2, IL-6, IL-8, tumor necrosis factor-α, TNF-α), interferons, lipid metabolites (e.g., eicosanoids, PAF), amines (e.g., histamine, 5-HT), and peptides (e.g., substance P, bradykinin, angiotensin II, thymic peptides) together with enzymes such as PLA_2, which are released into the systemic circulation in substantial quantities in conditions such as septicaemia (42,118).

The mechanisms by which the mediators increase glucocorticoid secretion are complex and varied. Some (e.g., ILs, PLA_2, eicosanoids) may target the HPA axis directly, acting at the levels of the hypothalamus and possibly elsewhere in the CNS, the anterior pituitary gland and the adrenal cortex. Others, however, may act locally at the site of the immune/inflammatory lesion to stimulate primary nociceptive afferents and thereby initiate a neuroendocrine reflex that triggers CRH-41/AVP release. In addition, the majority of mediators themselves cause severe pathological effects in the body (e.g., hypotension, hypoglycaemia, elevated lactic acid), which themselves are perceived as stressful and thereby activate the HPA axis by other routes. Particular emphasis has been placed on the roles/actions of the interleukins, eicosanoids and, more recently, primary sensory afferents; these are reviewed briefly in the sections below.

Interleukins

Of the many cytokines known to influence HPA function, IL-1, IL-6, and TNF-α have been studied the most. Evidence of a role for IL-1 first emerged from the demonstration in mice that systemic injection of IL-1-rich conditioned medium (harvested from human polymorphs stimulated with Newcastle Disease Virus) produces marked increases in the serum corticosterone concentration, which are quenched specifically by anti-IL-1 antisera. Subsequent studies revealed that passive immunisation of rodents against IL-1 attenuates the HPA response to endotoxin while systemic injection of IL-1 itself (purified or recombinant) causes a profound increase in corticosterone secretion (10). Complementary experiments showed that IL-6 and TNF-α are also potent activators of the HPA axis (51,80,98) and that antisera to these cytokines effectively impair the HPA responses to a variety of immunological stimuli, including endotoxin (85).

Evidence from a variety of in vivo, in vitro, and histological studies suggests that the marked rises in ACTH and corticosterone secretion initiated by the cytokines are triggered mainly by an increase in the hypothalamic drive to the corticotrophs. Thus, in the rat the increases in ACTH secretion provoked by systemic injections of IL-1β are effectively abrogated by pretreatment with antisera to CRH-41 (95). Furthermore, peripheral administration of IL-1β increases the turnover of CRH-41 in the hypothalamic parvocellular neurones that project from the paraventricular nucleus (PVN) to the median eminence and regulate ACTH secretion; this has been demonstrated by induction of c-*fos* (38) and CRH-41 mRNA (48) in the parvocellular cells of the PVN, decreased CRH-41 immunostaining in the median eminence (5), and increased secretion of CRH-41 into the hypophyseal portal blood (95). IL-6 and TNF-α also increase the release, although not the synthesis (48,128), of CRH-41 when given peripherally and, thus, produce increases in ACTH and corticosterone secretion which, like those provoked by IL-1β, are blocked by passive immunisation against CRH-41 (9). Further evidence of an action at the hypothalamic level has emerged from reports that intracerebroventricular injections of IL-1β and IL-6, but not TNF-α, stimulate the release of ACTH and corticosterone in the rat (67) and from demonstrations that a number of cytokines (including IL-1α, IL-1β, IL-2, IL-6, IL-8, and TNF-α) initiate the release of CRH-41 from the rat hypothalamus in vitro (67,83,105). Some controversy has arisen as to whether the increases in CRH-41 release provoked by these cytokines are accompanied by concomitant release of the second corticotrophin releasing factor, AVP, from the parvocellular neurones in the PVN (5,66,67,95,105,127). Histological studies argue against this and suggest that the cytokines act selectively on a population of CRH-41 neurons that do not normally express AVP (5). Similar conclusions were drawn from a study in which AVP was determined in the hypophyseal portal blood of rats after intravenous injection of IL-1β (95). On the other hand, in vivo experiments involving measurements of AVP within the rat median eminence by microdialysis have demonstrated significant increases in AVP release, apparently of parvocellular origin, following local administration of IL-1β (127). Furthermore, central but not peripheral injections of IL-1β augment the expression of AVP mRNA in the parvocellular neurones of the PVN and produce increases in ACTH secretion that are attenuated by AVP antisera (63). Additional

evidence has emerged from in vitro studies and, while there are reports to the contrary (105), we (66,67,110) and others (136) have observed marked concentration dependent effects of IL-1α, IL-1β, IL-6, IL-8, and TNF-α on the release of AVP from the rat hypothalamus in vitro. However, we believe that at least some of the peptide released is of magnocellular origin and destined for secretion from the neurohypophysis and, thus, to serve as an antidiuretic agent and vasoconstrictor.

Within the immune system cytokines almost invariably act synergistically, potentiating each other's actions in a complex cascade of events. Surprisingly, few investigators appear to have addressed the potential for cytokine synergy within the neuroendocrine system. Interestingly, in a study performed some years ago on isolated rat hypothalami we observed that the concentration-dependent increases in the release of CRH-41 and AVP provoked in vitro by conditioned media from endotoxin stimulated peritoneal macrophages are considerably greater than the maximal secretory responses elicited by IL-1α, IL-1β, IL-6, IL-8, and TNF-α (67), suggesting that synergism does, indeed, occur at the hypothalamic level (Fig. 1). Furthermore, a subthreshold concentration of TNF-α markedly potentiates the increases in AVP release induced in vitro by IL-1β (Fig. 2). In accord with these data, a recent in vivo study provided convincing evidence that the HPA responses to bacterial lipopolysaccharide (LPS) are dependent on the synergistic actions of IL-1, IL-6, and TNF-α within the hypothalamus and may involve stimulation of intrahypothalamic IL-6 production by IL-1β and TNF-α (85). A further study has revealed that, when given peripherally, IL-1β and TNF-α act synergistically to promote the release of ACTH and corticosterone in the rat (121).

The molecular and cellular mechanisms by which the cytokines elicit the synthesis/release of CRH-41/AVP are unclear. Numerous studies based on diverse methodologies (including direct intrahypothalamic administration of interleukins and/or agents that block their receptors or neutralize their biological activity, sophisticated histological methods, and in vitro systems) favor a direct action on the parvocellular neurones of the PVN (5), which is dependent on increased generation of eicosanoids [(83,89,103); see Modulation by Glucocorticoids section]. Others, however, argue that the effects are largely indirect and dependent upon the activation of the noradrenergic (37,129), serotonergic (64), and/or histaminergic (60) inputs to the PVN. Receptor studies have provided little insight in this regard. Within the CNS, IL-1, IL-6, and TNF receptors are found in particular abundance in the hippocampus and the brain stem, a view consistent with reports that these areas may contribute to the cytokine activation of the HPA axis through serotonergic and adrenergic mechanisms respectively (38,60, 62). IL-6 and TNF receptors are also readily detectable in the hypothalamus. Studies showing that the increases in ACTH secretion provoked by peripheral or intramedian eminence injection of IL-1β are readily blocked by IL-1 receptor antagonist [IL-1ra; (73)] and central administration of the antagonist also blocks the HPA responses to endotoxin (54) favor a hypothalamic site of action. However, reports that in the rodent the receptor is detected only by reverse transcriptase polymerase chain reaction (RT-PCR) and not by conventional methods of ligand binding, autoradiography, immunostaining, or in situ hybridization suggest that only very low levels of the receptor are constitutively expressed in this tissue (91). Alternatively, the responses may be mediated by a novel IL-1 receptor subtype that defies detection by the probes presently available.

A pertinent question remains unanswered, viz. how do cytokines produced in the periphery by activated immune/inflammatory cells gain access to targets in the CNS? Cytokines

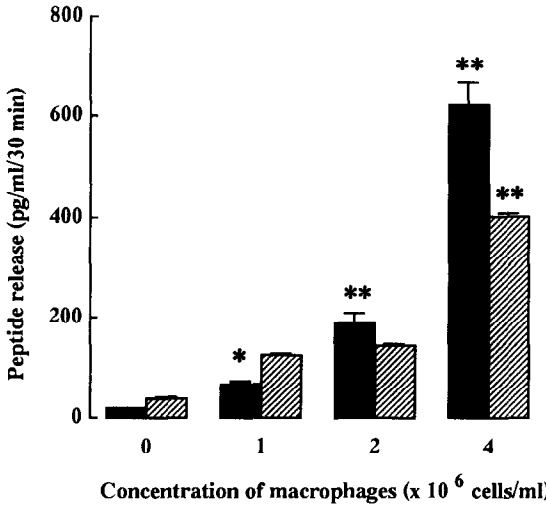

FIG. 1. The effects of conditioned medium from rat peritoneal macrophages stimulated in vitro with bacterial lipopolysaccharide (K235, 25 μg/ml, 2 h) on the release in vitro of ir-CRH-41 (solid column) and ir-AVP (slanted line column) from isolated rat hypothalami in vitro. Each value represents the mean ± SEM (n = 4-5). *p < 0.05; **p < 0.01 vs. macrophage-free control (ANOVA plus Fishers' test). Exposure of hypothalamic tissue to K235 (25 μg/mL, 30 min) did not affect the release of ir-CRH-41 or ir-AVP (p > 0.05, n = 5). In this preparation IL-1α, IL-1β, IL-6, IL-8, and TNF-α typically produce at maximum fivefold increases in CRH-41/AVP release (67).

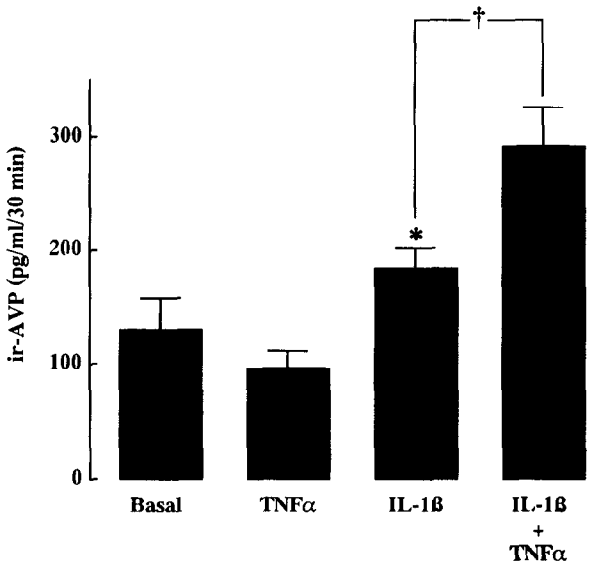

FIG. 2. Effects of a subthreshold concentration of human recombinant TNF-α (60 pg/ml/30 min) on the release of ir-AVP from hypothalamic tissue induced in vitro by human recombinant 1L-1β (50 pg/ml/30 min). Each value represents the mean ± SEM (n = 4-5). *p < 0.05 vs. basal; †p < 0.05 vs. IL-1β (Mann-Whitney U-test).

such as IL-1β and IL-6 (molecular mass ~17–26 kDa) are unlikely to cross the blood–brain barrier readily, and there is little evidence to support the existence of specific transport mechanisms. It is possible that these cytokines enter the brain via a fenestrated region of the barrier (e.g., organum vasculosum lamina terminalis, OVLT) or through an area in which permeability is increased by, for example, local inflammation. Alternatively, cytokines produced within the periphery may act at the level of the endothelium to increase the local expression of cytokines in the CNS by mechanisms dependent on prostanoid generation. This concept is supported by several recent studies showing increased IL-1 expression in the hypothalamus and other brain areas of rodents subjected to endotoxin challenge (32,47). Muramami and colleagues (79) also observed pronounced increases in IL-6 mRNA transcripts in the hypothalamus within 2 h of a central or peripheral (intraperitoneal) injection of LPS. Others, by contrast, have failed to detect any changes in IL-6 mRNA in the brains (hypothalamus, hippocampus, and cerebellum) of rats injected intraperitoneally with LPS (97). Contrary to earlier studies (5), a further argument voiced recently is that IL-1 produced in the periphery acts at the level of the median eminence to elicit CRH-41 release and does not, therefore, need to penetrate the blood–brain barrier (74).

While there can be little doubt of the importance of the hypothalamus in effecting the HPA responses to cytokine challenge, increasing evidence suggests that at least some of these proteins may exert supplementary actions at the levels of the anterior pituitary gland and possibly the adrenal cortex that serve to augment and possibly sustain the adrenocortical response. For example, although lesions in the PVN effectively ablate the HPA responses to systemic injections of IL-6 and TNF-α, they only partially attenuate the rise in ACTH secretion provoked by IL-1β (62). Furthermore, while data from a number of acute in vitro studies on freshly removed pituitary tissue have argued against an action of cytokines at the pituitary level (67,104,115), others, based on more prolonged contact times, have demonstrated significant increases in both ACTH release (with IL-1β and IL-6) and in POMC gene expression (with IL-1β) in primary pituitary cell cultures and in the AtT20 corticotroph cell line (56,104,115). In addition, the cytokine-rich conditioned media harvested from endotoxin stimulated macrophages readily elicits the release of ACTH from rat anterior pituitary tissue in vitro (Fig. 3). Evidence that IL-1β and IL-6 are synthesized in the adenohypophysis (61,97) and that the expression of the latter is greatly enhanced by central or peripheral administration of endotoxin (79,97) also supports a role for the pituitary gland in maintaining the HPA responses to immune insults as, too, does the recent report that the sensitivity the corticotrophs to the ACTH releasing activity of IL-1β is enhanced by CRH-41 (84). With respect to the adrenal cortex, several cytokines have been shown to exert weak stimulatory actions on the synthesis and the release of the glucocorticoids (4,94). The significance of these effects to the overall HPA response to an immune insult is unclear, although it is perhaps interesting to note that one group reported recently that the increases in circulating corticosterone elicited by a local inflammatory lesion are sustained for some hours while those in ACTH decline rapidly (117). Furthermore, IL-6 gene expression in the adrenal cortex is increased by LPS administration (79).

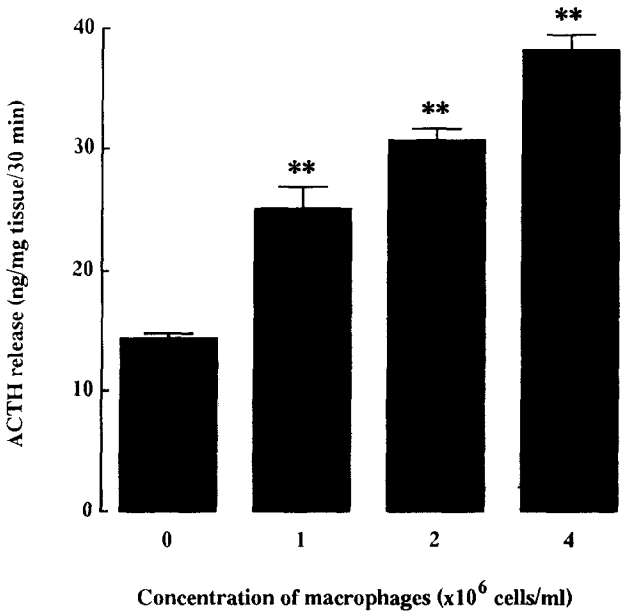

FIG. 3. The effects of conditioned medium from rat peritoneal macrophages stimulated in vitro with bacterial lipopolysaccharide (K235, 25 μg/ml, 2 h) on the release of ACTH from segments of rat anterior pituitary tissue in vitro. Each value is the mean ± SEM (n = 8). **p < 0.01 vs. macrophage-free control (ANOVA plus Fisher's test). Exposure of anterior pituitary tissue to K235 (25 μg/ml; 30 min) did not affect the release of ir-ACTH.

Phospholipase A_2 and Eicosanoids

Following the pioneering studies of Hedge and colleagues (49,50,113), interest in the role of eicosanoids in the regulation of the secretion of ACTH and its hypothalamic releasing factors has gained considerable momentum, and it is now apparent that these inflammatory mediators are important players in the cascade of events that triggers the HPA responses to immune insults. At the pituitary level, arachidonic acid metabolites generated via the lipoxygenase and cytochrome P450-dependent (epoxygenase) pathways contribute to the intracellular signal transduction mechanisms effecting the corticotrophic responses to CRH-41 (29,30,70,108). Platelet-activating factor (PAF) also stimulates ACTH release (6), but prostanoids (prostaglandins, thromboxane A_2, and prostacyclin), which are released locally by AVP (the second corticotrophin releasing factor), are inhibitory in this regard and may fulfill a significant local feedback role (30,49,59,113,122). At the hypothalamic level by contrast, prostanoids exert a powerful stimulatory influence on the release of CRH-41 in vivo and in vitro (8,113). Some controversy has arisen over the relative importance of PGE_2 and $PGF_2\alpha$ in this regard. The majority of data suggest that $PGF_2\alpha$ has a higher efficacy but, nonetheless, both prostaglandins trigger CRH-41 release producing effects that are additive and, therefore, probably effected by different receptors/signal transduction mechanisms (7,8,74, 126). Weak stimulatory effects have also been ascribed to PAF (6) and to products of lipoxygenase (7) and epoxygenase (71), although other data do not accord with these findings (83).

The cellular origin and the processes that trigger the release of the eicosanoids that activate the HPA axis remain a subject of some considerable debate. Particular attention has focused on the interrelationships of cytokines and eicosanoids in the hypothalamus and a substantial body of evidence now supports the view that the release of CRH-41 and AVP initiated by IL-1β, IL-6, and TNF-α is dependent on the local genera-

tion of prostanoids (7,55,83,103), possibly via activation of cytosolic PLA_2. Certainly, the increases in CRH-41 and AVP release provoked in vitro by these cytokines, unlike those elicited by IL-2 (24), are readily blocked by cyclo-oxygenase inhibitors such as indomethacin and ibuprofen (7,83). Similarly, in vivo, indomethacin attenuates the corticotrophic responses to intramedian eminence injections of IL-1β (74). Furthermore, IL-1β and IL-6 produce increases in the release of PGE_2 from hypothalamic tissue in vitro and in vivo which, on a temporal basis, parallel the release of CRH-41 and AVP (82,126). From the data available, it is unclear whether the prostaglandins are synthesized in the CRH-41/AVP producing neurons and thus form an integral part of the signal transduction cascade leading to peptide release and/or whether they are released from adjoining cells (e.g., glia) and act as paracrine agents. Interpretation of the data is further complicated by the existence of a complex positive feedback system through which the prostanoids released within the hypothalamus by cytokines trigger the further generation of cytokines (31,82). Indeed, several workers have postulated that the increases in cytokine expression observed in the CNS following systemic administration of LPS are dependent on cytokine-driven prostanoid generation by endothelial cells or adjacent leukocytes (27,31,55,82).

Consideration must also be given to the possibility that the eicosanoids that modulate HPA function are generated by mechanisms independent of cytokines. In conditions of infection or chronic inflammation (92) eicosanoids are released into the systemic circulation by peripheral immune/inflammatory cells and may, therefore, target the hypothalamus and pituitary gland directly to which they would have ready access (15,125). Similarly, in conditions such as septic shock, PLA_2 is released by, for example, leukocytes into the blood stream (42,118) and may thereby serve to enhance eicosanoid production not only in the periphery but also in the brain-neuroendocrine system. In support of this argument, we have shown that human recombinant PLA_2 and PLA_2 derived from snake venom (*Naja naja*) stimulate the release in vitro of CRH-41 and AVP from the hypothalamus (66) and ACTH from the anterior pituitary gland (30). The responses, which are mimicked by the PLA_2 activator mellitin, appear to be specific and in both tissues they are blocked by the PLA_2 inhibitors, quinacrine and dexamethasone (30,66). Furthermore, they are coupled with a rise in eicosanoid production (30,66). At the hypothalamic level, the increases in CRH-41 release provoked by the enzyme, like those elicited by IL-1β and IL-6, appear to be dependent on prostanoids; they are, thus, abrogated by the cyclo-oxygenase inhibitors indomethacin and ibuprofen but unaffected by inhibitors of 5-lipoxygenase (BW A4C) and epoxygenase (SKF 525A) pathways [(68), Fig. 4]. However, the increases in AVP release provoked by PLA_2 contrast with those elicited by IL-1β and IL-6 (136) in that they are unaf-

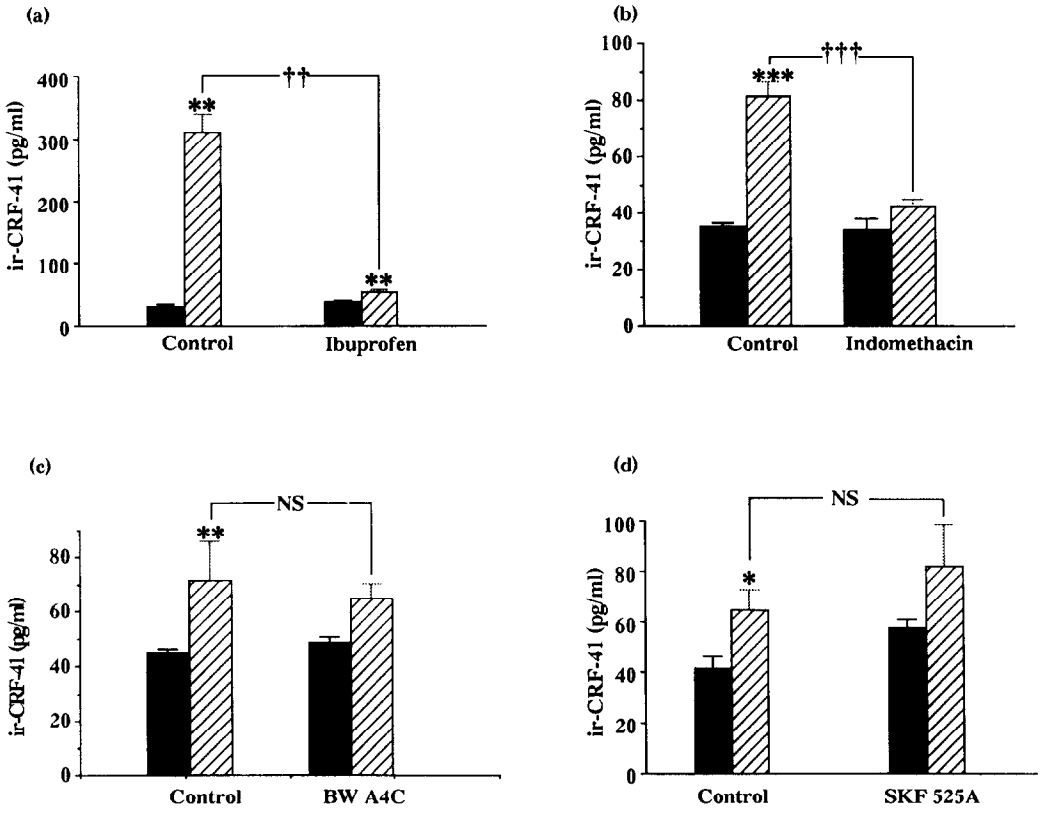

FIG. 4. The effects of inhibitors cyclo-oxygenase [ibuprofen, 0.1 mM (a) and indomethacin, 0.1 mM (b)], 5-lipoxygenase [BWA4C 30 mM (c)], and cytochrome P450-dependent epoxygenase [SKF 525A 0.1 mM (d)] on the release of ir-CRH-41 from rat hypothalamic tissue evoked in vitro by PLA_2 (*Naja naja* venom). Solid columns = vehicle (0.2% ethanol); slanted rule columns = PLA_2 (25 U/ml). Each value represents the mean ± SEM (n = 5). *$p < 0.05$; **$p < 0.01$ vs. vehicle alone; ††$p < 0.01$; †††$p < 0.001$ vs. PLA_2 alone. NS = Not significant (Mann-Whitney U-test). Basal and PLA_2-evoked peptide release were unaffected by the vehicle.

fected by ibuprofen but inhibited by BW A4C; indomethacin is also weakly inhibitory, but SKF 525A is not [(68), Fig. 5]. Because much of the AVP released in vitro is inevitably of magnocellular rather than parvocellular origin, these data may be interpreted to suggest a role for products of lipoxygenase in the regulation of neurohypophyseal AVP release. The weak inhibitory effect of indomethacin we observed may also be targeted at the neurohypophyseal system; alternatively, it may reflect an action on the parvocellular system leading to concomitant inhibition of prostanoid-dependent AVP and CRH-41 release. Further studies are now necessary to address these issues.

Primary Sensory Afferents

Increasing evidence favors a role for primary sensory afferents in initiating the HPA responses to tissue injury. For example, in the rat electrical stimulation of C-fibers causes a pronounced increase in ACTH secretion while treatment of neonatal rats with capsaicin (which causes degeneration of the primary sensory afferents) impairs the HPA responses to local inflammatory lesions induced by surgery. Capsaicin treatment also inhibits the immediate rise in ACTH release induced by injection of turpentine, a potent inflammogen (117). Similarly, studies in humans strongly suggest that the sensory connections of a wound represent an important route for activation of the HPA axis (81). The mediators responsible have not been identified, but potential candidates include histamine, 5-HT, bradykinin, substance P, and eicosanoids, all of which are known to stimulate sensory neurones.

Modulation by Glucocorticoids

The activity of the HPA axis is tightly regulated by glucocorticoids that act on specific receptors in the anterior pituitary gland, the hypothalamus, and elsewhere in the CNS (notably the hippocampus) to depress the secretion of ACTH and its hypothalamic releasing factors [reviewed in (23,57)]. Thus, increases in steroid levels brought about by for example adrenocortical tumors, stress, or administration of glucocorticoids effectively suppress ACTH release, while reductions in circulating corticosteroids evident in, for example, Addison's disease or following adrenalectomy, lead to a sustained hypersecretion of ACTH that is reversed by replacement therapy with glucocorticoids. In addition to suppressing the activity of the HPA axis, glucocorticoids also block the release and pathophysiological actions of cytokines and other inflammatory mediators (78). It is not surprising that the HPA responses to immune insults are sensitive to the steroid milieu. This has been amply illustrated by the demonstration that dexametha-

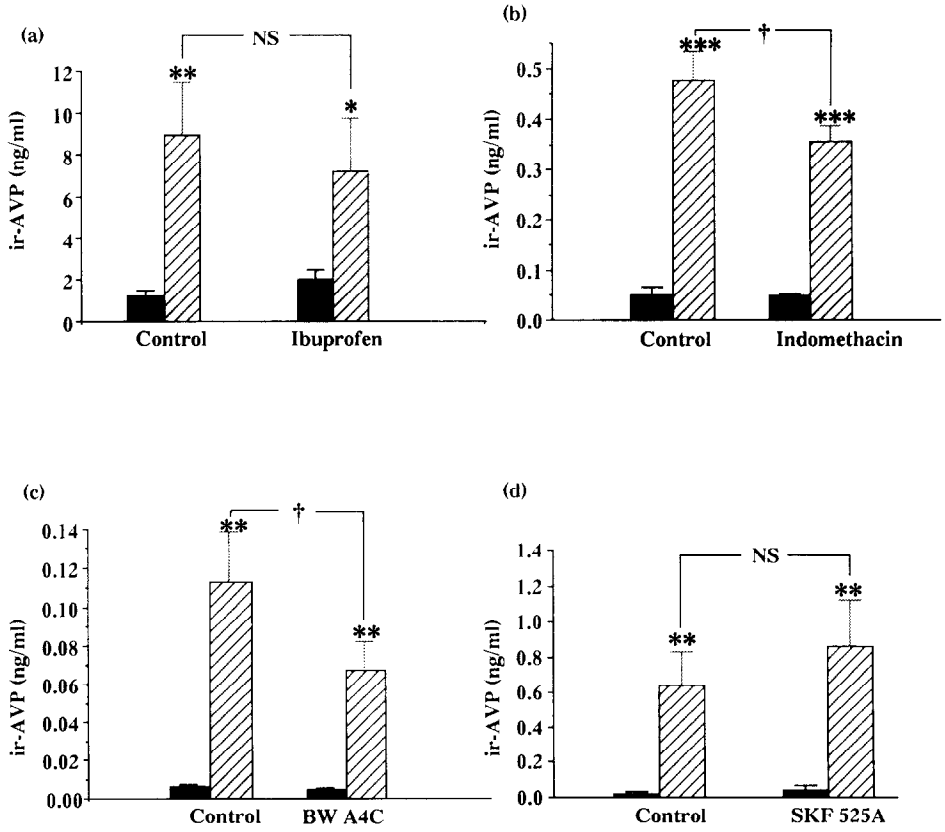

FIG. 5. The effects of inhibitors of cyclo-oxygenase [ibuprofen, 0.1 mM (a); indomethacin, 0.1 mM (b)] 5-lipoxygenase [BWA4C, 30 mM (c)], and cytochrome P450-dependent epoxygenase [SKF 525A, 0.1 mM (d)] on the release of ir-AVP from rat hypothalamic tissue evoked in vitro by PLA_2 (*Naja naja* venom). Solid columns = vehicle (0.2% ethanol) = PLA_2 (25 U/ml). Each value represents the mean ± SEM ($n = 5$). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ vs. Mann-Whitney U-test). Basal and PLA_2-evoked peptide release were unaffected by vehicle.

sone effectively suppresses the rises in ACTH and corticosterone induced by central or peripheral injections of IL-1β. Similarly, the increases in CRH-41 and AVP release provoked in vitro by IL-1α, IL-1β, IL-6, and IL-8 are greatly exaggerated in tissues taken from adrenalectomized rats but suppressed by inclusion of dexamethasone in the incubation medium (22,67).

The molecular mechanisms underlying the complex inhibitory actions of the glucocorticoids on ACTH secretion are not fully understood. However, it is apparent that, in addition to acting at multiple sites in the brain and pituitary gland, the steroids also utilize at least three distinct molecular mechanisms that are effective over different time domains; these are called the rapid, early-delayed, and late-delayed phases of feedback inhibition, respectively [reviewed in (23)]. Rapid feedback operates within minutes of a rise in circulating glucocorticoids; it is of only short duration (< 15 min) and, unlike the more sustained delayed phases of feedback inhibition, may occur by mechanisms other than the occupation of intracellular steroid receptors and subsequent modulation of protein synthesis. Late-delayed feedback has a latency of 12–24 h and is associated with suppression of the genes encoding POMC in the adenohypophysis and CRH-41 and AVP in the parvocellular neurons of the hypothalamic paraventricular nucleus; indeed, it is, in effect, an exaggeration of the tonic inhibitory effect the endogenous glucocorticoids exert on the expression of these genes. By contrast, early delayed feedback, which develops within 1–2 h of a steroid challenge and persists for up to 24 h, is dependent on the de novo generation of protein second messengers, which inhibit the release rather than the synthesis of ACTH and its hypothalamic releasing factors. The nature of the second-messenger protein(s) is/are obscure but recent studies in our laboratory suggest that lipocortin 1 (LC1), a 37 kDa Ca^{++} and phospholipid binding protein strongly implicated in the anti-inflammatory and antiproliferative actions of the steroids [reviewed in (1)], may be important in this regard, particularly with respect to modulation of the HPA responses to cytokines.

LC1 is readily detectable in the brain and pituitary gland by Western blotting, ELISA, and immunostaining (17,87, 100,101,109,135). Particularly high concentrations occur in the anterior pituitary gland and the median eminence area of the hypothalamus (100), the zone from which CRH-41 and AVP are released into the portal blood. Moderate but lesser amounts are also expressed in several other hypothalamic nuclei, but only small amounts are found elsewhere in the brain (100). As in a number of peripheral tissues [e.g., macrophages reviewed in (1)], the synthesis of LC1 in the anterior pituitary gland is upregulated by endogenous and exogenous glucocorticoids (53,100,102). The situation in the brain is less clear and, while some workers have observed significant changes in LC1 immunoreactivity in discrete brain areas after adrenalectomy or glucocorticoid treatment (43,109), others have not (17,40, 100,102). The reason for this controversy is unclear, but may relate to the binding characteristics of the different antisera employed. Using a panel of antibodies directed against different epitopes of the LC1 molecule, we have recently obtained data that suggest that at least two molecular species of the protein may exist in the CNS, which differ in their distribution and in the factors that govern their expression (86). For example, using a polyclonal antibody (coded anti-LC1 pAbα) raised in sheep against full length human recombinant LC1 (hu-r-$LC1_{1-347}$), we have observed overt increases in LC1 expression in the hypothalamus and hippocampus of rats following treatment with dexamethasone; no such changes were apparent when the same samples were analyzed using an antibody raised against an *N*-terminal LC1 peptide ($LC1_{2-26}$), despite the fact that this antibody (coded anti-LC1 pAb S2) detects LC1-like immunoreactivity in rat brain although, unlike anti-LC1 pAbα, not in macrophages, which are rich in bioactive LC1.

A number of recent studies suggest that, in addition to influencing the synthesis of LC1, glucocorticoids also alter the subcellular distribution of the protein causing its translocation from intracellular pools contained within the cytoplasm and the plasma membrane to a pericellular site where it attaches to the outer surface of the cell membrane by a Ca^{++}-dependent mechanism. Thus, using anti-LC1 pAbα as a probe, we have observed a pronounced increase in pericellular LC1 and concomitant fall in intracellular LC1 in a variety of tissues (anterior pituitary gland, hypothalamus, hippocampus, cortex) following treatment with glucocorticoids [e.g., dexamethasone, corticosterone; (67,111,112)]. This process of externalisation, which has also been described in immune/inflammatory cells [e.g., peritoneal macrophages; (19)], may provide an important means whereby LC1 gains access to targets on the outer surface of cells and thereby exerts local (autocrine or paracrine) regulatory effects (67,112). Our functional studies, performed both in vitro and in vivo, accord with this view and suggest that this mechanism is critical to the early delayed feedback inhibition of HPA activity at the levels of the hypothalamus and the anterior pituitary gland.

In vitro, dexamethasone (1 nM–1 μM) provokes a concentration-dependent inhibition of the release of ACTH from pituitary tissue initiated by submaximal concentrations of a variety of secretagogues including CRH-41, the adenyl cyclase activator, forskolin, and the L-Ca^{++} channel opener BAY K8644. On a temporal basis, the onset of the inhibitory response parallels closely the appearance of LC1 on the outer surface of the cells, both being evident within 30 min and maximal within 90 min of steroid contact. Furthermore, both are effectively blocked by inhibitors of protein (cycloheximide) but not RNA (actinomycin D) synthesis. Like dexamethasone, hu-r-LC1 and a stable *N*-terminal LC1 fragment ($LC1_{1-188}$) also inhibit, in a concentration-dependent manner, the release of ACTH provoked by CRH-41, forskolin, or BAY K8644. Conversely, a monoclonal anti-LC1 antibody (anti-LC1 mAb) substantially reverses the inhibitory effects of dexamethasone on the release of ACTH evoked by these secretagogues while a corresponding dilution of an isotype-matched control antibody (antispectrin α and β) is without effect. Parallel experiments at the hypothalamic level have yielded a complementary profile of data. Thus, dexamethasone readily inhibits the release of CRH-41 from isolated hypothalamic tissue evoked in vitro by a number of cytokines (IL-1α, IL-β, IL-6, and IL-8); its actions are mimicked by hu-r-LC1 and by $LC1_{1-188}$ and specifically reversed by anti-LC1 mAb (67,110). Moreover, the concentration and time-dependent responses to the steroid coincide with the appearance of LC1 on the outer surface of the hypothalamic cells (67). Similarly, in vivo intracerebroventricular administration of LC1 attenuates the HPA responses to central injections of IL-1β (67) while passive immunisation of rats against LC1 reverses the ability of dexamethasone to suppress the pituitary-adrenocortical responses to cytokine stimulation (110).

The mechanisms whereby LC1 produces its inhibitory effects on peptide release are unknown but several lines of evidence suggest that the protein acts via a cell surface receptor rather than within the cell. First, as discussed earlier, glucocorticoids promote the transfer of LC1 from intracellular to pericellular sites and, thus, provide opportunity for an interaction with membrane-bound receptors; in the hypothalamus

and the anterior pituitary gland the processes of externalization and the inhibition of peptide release, both of which are glucocorticoid specific (111), develop in parallel and are sensitive to the same pharmacological manipulations (112). Secondly, although not impossible, the anti-LC1 antisera used in our immunoneutralisation studies are unlikely to reach LC1 within cells but could readily sequester the protein at an extracellular site and thereby interfere with its biological activity, processing, or phosphorylation. Similarly, neither hu-r-$LC1_{1-347}$ nor $LC1_{1-188}$ would be expected to penetrate cell membranes easily. For technical reasons it is not possible to use conventional ligand binding or autoradiographic methods to identify the putatative LC1 receptors. However, using computerized flow cytometric analysis, we have recently demonstrated the presence of high affinity (estimate $K_d \sim 13$ nM), saturable LC1 binding sites on the surface of anterior pituitary cells (26), which closely resemble those essential for LC1 action in certain peripheral cell types [e.g., monocytes, polymorphonuclear leukocytes, (44,45)]. Binding is Ca^{++} and temperature dependent and is destroyed by preincubation of the cells with trypsin (0.025%), suggesting that the site is protein in nature (26). The signal transduction system used by these receptors remains to be characterized. However, reports that the actions of IL-1β and IL-6 on the hypothalamus and of CRH-41 and forskolin on the pituitary gland are dependent on the generation of eicosanoids (29,30,82,83,113) together with evidence that in other systems LC1 inhibits the activity of PLA_2 [reviewed in (1)] raise the possibility that inhibition of cytosolic PLA_2 contributes to events downstream of the receptor.

Production of Neuroendocrine Peptides Within the Immune System

It is now well established that activated immune/inflammatory cells synthesize a spectrum of peptides classically associated with the neuroendocrine system, which includes the various components of the CRH-ACTH/POMC pathway (including opioids) and their respective receptors (16). Although their precise function is poorly defined, these factors are well positioned to influence the progression of inflammatory or immune responses either directly by modulating immune/inflammatory cell function or indirectly by elevating glucocorticoid secretion. ACTH, β-endorphin and other pro-opiomelanocortin (POMC)-derived peptides have all been shown to posses significant immunoregulatory properties as also have the two major corticotrophin releasing hormones, CRH-41 and arginine vasopressin (AVP). Teleological arguments favor a local role (intracrine, autocrine, or paracrine) for these peptides within the immune system but increasing evidence that binding proteins facilitate the transportation and delivery of peptides such as CRH to distant immune cells (65) suggests that they may also fulfill a rather wider brief. In addition, because migratory cells of immunological lineage (notably macrophages) are found in abundance in both the pituitary gland and the adrenal cortex, it is possible that the peptides they release target the endocrine system directly and thereby provoke the release of ACTH and the glucocorticoids.

Age and Gender Dependent Factors

The functional development of the HPA axis begins in utero and by the late stages of gestation the fetus secretes substantial quantities of cortisol/corticosterone. It also responds to stress with increases in adrenocortical activity, which are driven by the hypothalamo-pituitary axis and which are sensitive to the negative feedback actions of the glucocorticoids. Paradoxically, in the rat and several other species HPA function regresses postnatally, and a period ensues during which the neonate fails to release adequate amounts of glucocorticoids in response to a variety of traumatic stimuli (90). This phase of adrenal insufficiency (termed the stress hyporesponsive period, SHRP) develops at about postnatal day 5 and persists for up to 4 to 5 weeks; it thus coincides with an important phase of immunological development and, indeed, the ensuing reduction in glucocorticoid tone may be significant in this respect as well as for other aspects of development (76). The etiology of the SHRP is ill defined. Several lines of evidence suggest that the primary cause is immaturity of the central mechanisms that drive the secretion of CRH-41 and AVP, although significant functional defects at the levels of the pituitary gland and adrenal cortex have also been described [reviewed in (90)].

The data available suggest that the temporal pattern of development of the HPA response to stress varies according to the nature of the stimulus. For example, weak (vs. adult) responses to electric shock emerge at the time of weaning [day 18, (124)], whereas small responses to hypoglycaemia are apparent as early as day 12 (131). Surprisingly, few workers have examined the ontogeny of the HPA responses to immune challenge despite the fact that neonatal rats are highly sensitive to the potentially lethal effects of bacterial endotoxin. In one study the adrenocortical response to LPS was shown to be attenuated in rats aged 5–14 days but to attain adult proportions by day 21 (133); parallel measurements of ACTH suggested that the failure of the neonate to release corticosterone in this instance was due to decreased sensitivity of the adrenal cortex to ACTH rather than impaired ACTH secretion. By contrast, Rivier (88) noted that the ability of exogenous IL-1β to raise the plasma ACTH concentration is markedly reduced in rats aged 21 to 22 days compared to the adult. Similarly, in a recent in vitro study we found that, unlike adult tissue, hypothalami removed from rats aged 5 or 15 days are only weakly responsive to IL-1α, IL-1β, IL-6, and IL-8 with regard to CRH-41 and AVP release (69). However, a clear age-dependent maturation of the responses occurs in the later stages of the SHRP [(69), Fig. 6], which parallels closely the ontogenesis of adult responses in vivo to stimuli such as histamine. A number of previous workers have suggested that the apparent immaturity of the neuroendocrine responses to stress may be due in part to a supersensitivity to the powerful negative feedback actions of the glucocorticoids (90,123). Our preliminary accord with this view and suggest that LC1 may be a significant factor in this regard. Certainly, in the neonatal hypothalamus (15 days) dexamethasone readily suppresses the small increases in CRH-41/AVP release provoked by cytokines and, as in the adult, its effects are specifically reversed by anti-LC1 antisera (69). Moreover, pronounced tissue specific changes in LC1 expression occur in the glucocorticoid responsive areas of the HPA axis (hippocampus, hypothalamus, and anterior pituitary gland) during the SHRP (58). Furthermore, in the absence of glucocorticoids, exposure of hypothalami from rats aged 15 days to anti-LC1 antisera (but not control antisera) potentiates to adult proportions the small but significant increases in AVP release provoked by IL-1α, IL-1β, and IL-6, suggesting that LC1 may tonically suppress AVP release from the hypothalamus at this stage of development (69).

In the adult, distinct sexually dimorphic patterns of glucocorticoid secretion emerge. Serum glucocorticoid concentra-

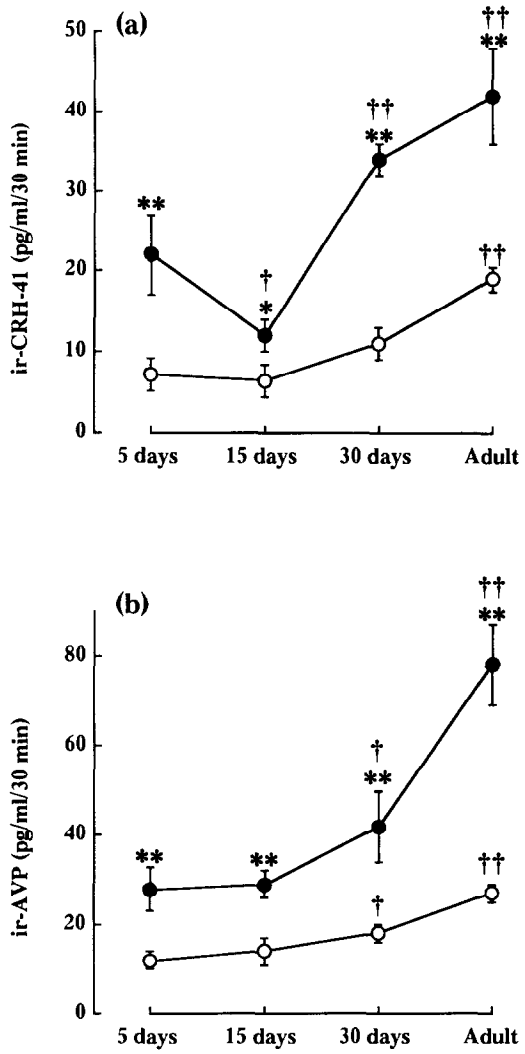

FIG. 6. Secretion in vitro of (a) ir-CRH-41 and (b) ir-AVP from hypothalami from neonatal and adult rats in the presence (●) and absence (○) of human recombinant IL-1β. Each value is the mean ± SEM (n = 5). *$p < 0.05$; **$p < 0.01$ vs. corresponding age-matched basal control. †$p < 0.05$; ††$p < 0.01$; vs. rats aged 5 days (ANOVA plus Fisher's test).

tions are consistently higher in the female than the male with further increases occurring towards the middle of the menstrual/estrous cycle (21) just prior to ovulation and in the later stages of pregnancy. These changes have been ascribed partly to the positive effects of estrogen on the expression of the corticosteroid binding globulin (transcortin). In addition, estrogen exerts significant effects at the hypothalamic level increasing the synthesis and the release of CRH-41 (20,119), a phenomenon that may be implicated in the etiology of the relatively high incidence of emotional disorders (e.g., depression, anxiety) in the female, which are characterized by enhanced CRH-41 secretion (120). Further modulation may be brought about by progesterone which, when present in large amounts (e.g., in the premenstrual phase or pregnancy), binds readily to but is only weakly active at mineralocorticoid receptors in the hippocampus (33,39). Although numerous workers have shown that the stress-induced excursions in serum glucocorticoids are more robust in the female than the male (120), to our knowledge few have studied the responses to immunological stimuli. However, overt sexual dimorphism in the adrenocortical responses to endotoxin has been reported in adult mice (106). Similarly, the adult rat the ACTH responses to IL-1β in are more vigorous in the female, a sex difference that is abolished by gonadectomy (88). Because the incidence of immune/inflammatory reactions and autoimmune disorders is higher in the female (46,52,132), these data are perhaps surprising. However, several lines of evidence suggest that estrogens also exert significant regulatory actions at the locus of immune/inflammatory lesions that serve to augment the pathophysiological responses (2,132); of particular interest in this regard is the possibility that they upregulate the expression of immune CRH (120), now recognized as an inflammogen (3,65).

Significant elevations in the resting and stress-induced secretion of glucocorticoids occur in elderly subjects of either sex who are depressed or physically diseased. The cause of this phenomenon, which together with the concomitant decline in the production of the immune-enhancing hormone dehydroepiandrosterone sulphate may be important contributory factor to the age-related decline in immunocompetence, is poorly defined but may be related to a loss in hippocampal corticosteroid receptors (75).

CONCLUSION

Although it is not the purpose of this article to discuss the mechanisms by which glucocorticoids released in response to an immune challenge may confer protection from stress, it is pertinent to comment briefly on the reciprocal modulatory actions of the steroids on immune function and, hence, on the body's defence mechanisms. In normal circumstances, endogenous glucocorticoids exert a tonic inhibitory influence on immune/inflammatory cells (see below) but they are not present in sufficient quantities to prevent the host mounting an effective immune response. The hypersecretion of glucocorticoids triggered by an immune insult is largely dependent on and, thus, occurs after the activation of immune/inflammatory response. This time course of events precludes any possibility that the steroids released modulate important events that occur during the early stages of an immune/inflammatory response (e.g., clonal proliferation of lymphocytes); however, it provides ample opportunity for the steroids to contain events at a later stage and, thus, prevent the response proceeding to a point where it threatens the host (12,77,78). This facet of steroid action, first recognized by Munck and colleagues (78), is now considered to be critical to the well documented stress-protective properties of the glucocorticoids. However, there are some circumstances in which such a hypersecretion of glucocorticoids is not advantageous to the host; for example, the immunosuppression consequent upon steroid release in response to a viral infection is well known to render the host susceptible to opportunist bacterial infections (12). In the same vein, sustained elevations in circulating glucocorticoids resulting either from primary or secondary (e.g., depression, alcoholism) disorders of the axis or from the administration of exogenous steroids are frequently linked to a decline in immunocompetance and increased incidence of disease as also is the elevation in serum cortisol/corticosterone evident in aging individuals. Similarly, numerous studies suggest that the persistent elevation of glucocorticoids caused by chronic stress

(cognitive or noncognitive) may increase susceptibility to viral and bacterial infections (18,35). For example, repeated restraint stress reduces the ability of mice to combat infections such as influenza virus or mycobacterium; the hazardous effects of the stress are effectively attenuated by concomitant administration of the glucocorticoid receptor blocker, RU486. Inevitably, the data from studies in humans are more difficult to interpret but, nonetheless, the positive correlation between psychological stress (e.g., bereavement, unemployment) and the prevalence of diseases such as infections and cancer cannot be denied (34).

While excessive glucocorticoid secretion leads to immunosuppression, further evidence suggests that adrenocortical insufficiency may be an important contributory factor to the etiology of autoimmune/inflammatory disorders. The data have emerged largely from scientific studies in laboratory animals, in particular, on the Lewis rat, which is used widely as a model of rheumatoid arthritis and multiple sclerosis. This strain, unlike the histocompatible Fischer (F344/N) strain, is highly susceptible to inflammatory disease and develops, for example, erosive polyarthritis when challenged with streptococcal cell wall extracts or experimental allergic encephalomyelitis (EAE) when immunized with myelin basic protein (MBP) (active EAE) or treated with splenocytes cultured in vitro with MPB (passive EAE). The significance of the HPA axis in the manifestation of these inflammatory responses was first recognized by Sternberg and colleagues, who noted firstly that in comparison to disease-resistant Fischer rats, the adrenocortical responses of Lewis rats to streptococcal cell wall extracts are severely compromised, and secondly, that arthritic responses provoked by the extract are abrogated effectively by administration of glucocorticoids (34). An impaired HPA response also accompanies the manifestation of EAE in the Lewis rat. Furthermore, while exogenous glucocorticoids quell the progression of EAE, spontaneous recovery is associated with sustained elevations in the circulating corticosterone concentration (72). Other experiments have shown that surgical adrenalectomy produces an increase in the vulnerability of disease-resistant Piebald Viral-Glaxo (PVG) rats to EAE, which is readily corrected by exogenous corticosteroids while pharmacological adrenalectomy (administration of RU 486) renders F344/N rats susceptible to the potentially lethal proinflammatory effects of bacterial cell wall products. Furthermore, transplantation of hypothalami from F344/N rats to Lewis rats (i.e., replacement of the source of CRH-41) has been shown to reduce specifically carageenin-induced peripheral inflammatory responses (34). Deficiencies in glucocorticoid secretion have also been identified in a variety of other animal models of autoimmune disease including the MRL/Mp-lprlpr mouse, which develops a generalized autoimmune syndrome resembling human systemic lupus erythematosus (28), the nonobese diabetic mouse (a model for type I diabetes) in which invading lymphocytes destroy the insulin-producing β-islets cells (96), and the obese strain of chicken, which develops spontaneous autoimmune thyroiditis (130).

Although hard clinical data are difficult to obtain, evidence is beginning to emerge that disturbances in HPA function occur in at least some patients with autoimmune disorders and that peripheral glucocorticoid resistance may be a further factor in the etiology of inflammatory disease. For example the HPA responses to surgical trauma are attenuated in patients with rheumatoid as opposed to osteoarthritis as also is the resting secretion of cortisol (25). Small reductions in adrenal function have also been reported in cohorts of patients with multiple sclerosis and fibromyalgia (34), while interestingly patients with systemic lupus erythematosus are frequently glucocorticoid resistant, suggesting that the glucocorticoid receptor and/or associated signal transduction mechanisms may be defective.

Glucocorticoids are released in response to all types of stress, be they cognitive or noncognitive. The mechanisms that initiate their release are highly complex, and it appears that the complement of neural pathways and humoral mediators that serve at the hypothalamic level to trigger the secretion of the corticotrophin-releasing factors depends on the precise nature of the stimulus. For example, the HPA responses to hypotension (caused by hemorrhage or injection of sodium nitroprusside, i.e., visceral stress) depends on the integrity of the noradrenergic pathways that project from the brain stem to the hypothalamus. By contrast, those evoked by emotional trauma are effected at least in part by inputs from the limbic system, while those provoked by cold require connections between the peripheral C fibers and the PVN. Until comparatively recently cytokines have been associated with the body's responses to only one type of stress, viz. immune/inflammatory insults. However, recent studies indicate that IL-6 release is also a feature of certain physical and psychological stresses (electric foot shock, physical restraint, conditioned aversive stimuli), despite the fact that there is no evidence of infection or, in the case of restraint or aversive stimuli, of tissue damage or inflammation (138). The physiological significance of this response is as yet unclear. Nevertheless, these exciting findings raise the possibility that the role of IL-6 in the maintenance of homeostasis in stress extends well beyond our original concepts of immune-endocrine communication (138); whether other cytokines are similarly involved remains to be determined.

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