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Immune Modulation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis during Viral Infection

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Abstract

Compelling data has been amassed indicating that soluble factors, or cytokines, emanating from the immune system can have profound effects on the neuroendocrine system, in particular the hypothalamic-pituitary-adrenal (HPA) axis. HPA activation by cytokines (via the release of glucocorticoids), in turn, has been found to play a critical role in restraining and shaping immune responses. Thus, cytokine–HPA interactions represent a fundamental consideration regarding the maintenance of homeostasis and the development of disease during viral infection. Although reviews exist that focus on the bi-directional communication between the immune system and the HPA axis during viral infection (188,235), others have focused on the immunomodulatory effects of glucocorticoids during viral infection (14,225). This review, however, concentrates on the other side of the bi-directional loop of neuroendocrine-immune interactions, namely, the characterization of HPA axis activity during viral infection and the mechanisms employed by cytokines to stimulate glucocorticoid release.

INTRODUCTION

Maintenance of homeostasis during immune challenge involves activation of the immune system, resolution of the challenge, and protection of the host against potentially toxic inflammatory processes. Examples of immune challenges include infection with viruses, bacteria, fungi, or parasites; tissue damage and destruction; and inappropriate responses to auto-antigens that may result in the development of autoimmune disease. Upon immune challenge, the immune system is activated to release numerous protein hormones called “cytokines.” One functional group of cytokines is that which mediates the innate immune response, including the proinflammatory cytokines tumor necrosis factor–alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), and the type I interferons (IFN-α/β). These cytokines are released in the early stages of an immune response from a variety of cell types, including activated immune cells, such as macrophages (and their CNS counterparts microglia), vascular endothelial cells, fibroblasts, and neurons. Another group of cytokines is that which mediates later, adaptive immunity, such as the T cell cytokines IL-2 and IFN-γ (type II interferons), which are especially important in mediating anti-viral defenses. In addition to contributing to the progression of the immune response against viral infection, cytokines released as part of the innate or adaptive immune response can activate the HPA axis, resulting in the release of adrenal glucocorticoids (37, 57,120,178,258,290) (Fig. 1). In turn, glucocorticoids negatively feedback onto immune cells

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to suppress the further synthesis and release of cytokines, thereby protecting the host from the detrimental consequences of an overactive immune response (e.g., tissue damage, autoimmunity, septic shock). In addition, glucocorticoids play an important role in shaping immunity by influencing immune cell trafficking to sites of inflammation and altering downstream, adaptive immune responses by causing a shift from cellular (Th1/inflammatory) to humoral (Th2/anti-inflammatory) type immune responses (72). Therefore, in contrast to the traditional view of glucocorticoids as immunosuppressant hormones, they are more accurately conceptualized as immunomodulatory hormones, that can stimulate as well as suppress immune function, depending on the type of immune response, the immune compartment, and the cell type involved.

Although hypothalamic corticotropin-releasing hormone (CRH) is considered a primary mechanism by which cytokines stimulate glucocorticoid release, increasing evidence supports a direct action of cytokines at the level of the pituitary and adrenal glands, as well. Cytokine receptors have been detected at all HPA axis levels, and therefore, each level can serve as an integration point for immune and neuroendocrine signals. In addition, cytokines are synthesized in the brain, the anterior pituitary, and the adrenal gland. The production of local cytokines in these tissues may function in a paracrine manner to amplify and maintain elevated HPA activity during chronic inflammation. Once glucocorticoids are released, maintenance of appropriate glucocorticoid activity is accomplished by local tissue regulation of glucocorticoid availability and action by factors such as corticosterone binding globulin (CBG), 11β-hydroxysteroid dehydrogenase (11β-HSD), the multidrug resistance transporter (MDR), and ultimately, the glucocorticoid receptor (GR) (274).

The kinetics and magnitude of HPA axis stimulation, and hence glucocorticoid release, induced by viral infection may be specific to the virus, the kinetics of the immune response to the virus, and the extent of virus/immune-induced pathology. Viruses that induce early, innate NK cell-mediated anti-viral defenses, characterized by early proinflammatory cytokine production, cellular infiltration, and inflammation, tend to produce early glucocorticoid responses, thereby protecting the host from proinflammatory cytokine-mediated pathology. On the other hand, viruses that induce later, adaptive T cell–mediated anti-viral defenses, characterized by late Th1/CTL cytokine production, cellular infiltration, and inflammation, tend to produce late glucocorticoid responses, thereby protecting the host from T cell–mediated pathology. Viruses that elicit both strong early proinflammatory and later T cell responses may exhibit a biphasic glucocorticoid response, whereas those that induce little or no inflammation, may not stimulate significant glucocorticoid release. Examples of these different responses are presented in this review, as we describe what is currently known about HPA axis activation during infections with Newcastle disease virus (NDV), murine cytomegalovirus (MCMV), lymphocytic choriomeningitis virus (LCMV), influenza, herpes simples virus type-1, (HSV-1), and human immunodeficiency virus (HIV).

Given the critical role of the HPA axis and glucocorticoid responses in maintaining a balance between the beneficial and detrimental effects of proinflammatory cytokines, as well as shaping downstream immune responses, it has become increasingly apparent that cytokine–HPA axis interactions are fundamental to immune regulation during viral infection. Moreover, redundant pathways of glucocorticoid induction, incorporating all three levels of the HPA axis, exist to ensure the survival of the host during immune challenge. Indeed, the essential role of glucocorticoids in protecting the host against a lethal overactivation of inflammatory responses has been demonstrated in a number of animal model systems, including viral infection (148, 243,254,268).

THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS

In considering HPA axis activity during viral infection, it is important to review the functional anatomy and physiology of the HPA axis. Activation of the HPA axis is well known to subserve the body's response to a stressor, which can be defined as any physical or psychological stimulus that disrupts an organism's homeostatic balance. Viral infections, in general, are physiologically stressful, as indicated by the concomitant activation of the HPA axis (89). Along with catecholamines (the end-product of sympathetic nervous system activation), glucocorticoids orchestrate the "fight or flight" response, which consists of the rapid mobilization of energy (glucose, amino acids, and fatty acids) from storage sites to critical muscles and the brain, concomitant with increased heart rate, blood pressure, and breathing rate to facilitate the rapid transport of nutrients and oxygen to relevant tissues. During such emergency situations, activation of the HPA axis also assists the body in shunting metabolic resources from growth, digestion, reproduction, and certain aspects of immunity to the more immediate challenge at hand. Particularly pertinent to infection as a stressor, according to Munck (196), "the physiological function of stress–induced increases in glucocorticoid levels is to protect not against the source of stress itself, but against the normal defense reactions (e.g., immune response/inflammation) that are activated by stress; glucocorticoids accomplish this function by turning off those defense reactions, thus preventing them from overshooting and themselves threatening homeostasis." Therefore, some glucocorticoid actions may help mediate the recovery from the stress response, rather than mediate the stress response itself.

Activation of the HPA axis begins with the release of corticotropin-releasing hormone (CRH). CRH neurons originate in the parvocellular division of the paraventricular nucleus (PVN) of the hypothalamus and terminate in the external layer of the median eminence (ME), releasing CRH into the hypophysial-portal circulation (Fig. 2). CRH, in turn, acts on CRH-R1 receptors on anterior pituitary corticotrophs to stimulate the rapid release of adrenocorticotropic hormone (ACTH) from cellular stores, and, after a delay, the synthesis of the ACTH precursor peptide proopiomelanocortin (POMC) to replenish ACTH stores. ACTH then is released into the peripheral circulation and stimulates the release of glucocorticoids (cortisol in humans and non-human primates; corticosterone in rodents) from the adrenal cortex by acting on the MC2-R (type 2 melanocortin receptor) (for review, see (127)). Whereas both CRH-R1 and MC2-R are membrane bound, G-protein coupled receptors (linked to the adenylate cyclase–cAMP–PKA pathway), glucocorticoid receptors (GR's) are cytosolic steroid receptors, that when activated by binding of its ligand (glucocorticoids), translocate into the nucleus to interact with other relevant transcription factors (e.g., NFκB or AP-1) or to directly alter the transcription of glucocorticoid-sensitive genes (by binding to a glucocorticoid response element [GRE] in their promoter region). Every nucleated cell in the body expresses glucocorticoid receptors; hence the widespread effects of glucocorticoids on practically every system of the body (e.g., metabolic, endocrine, nervous, cardiovascular, immune).

CRH neurons of the PVN serve as a final common stress pathway by receiving converging inputs from multiple areas of the brain, allowing CRH to coordinate the behavioral, neuroendocrine, and autonomic responses to stress (264). These afferent pathways include projections from (a) ascending brainstem noradrenergic pathways (from the ventrolateral medulla [VLM] and the nucleus of the solitary tract [NTS]) that relay visceral sensory information, (b) descending cortical and limbic pathways (from the septum, amygdala, and hippocampus) via the bed nucleus of the stria terminalis [BNST] that relay cognitive and emotional information, (c) intrahypothalmic connections receiving innervation from brainstem and limbic structures, and (d) circumventricular organs [CVO's] (e.g., organum vascularis of the lamina terminalis [OVLT], subfornical organ [SFO]) that relay blood-borne chemosensory signals. Therefore, hypothalamic CRH neurons are strategically situated to intercept and disperse signals from and to the body about the internal and external environment.

In response to prolonged stress, the expression of hypothalamic CRH mRNA and pituitary POMC mRNA increase, along with hypersecretion of CRH and ACTH. However, upon continued exposure to CRH, pituitary CRH-R1 receptors downregulate, desensitizing the pituitary corticotroph to CRH signals and hence reducing ACTH release to the primary stressor (127). Although parvocellular PVN expression of arginine vasopressin (AVP) (co-expressed in CRH neurons) is low at baseline, it increases substantially in response to chronic stress. In the presence of CRH (although not alone), AVP acts synergistically to potentiate ACTH release via the vasopressin V1b receptor (linked to the PLC–Ca^{2+}/DAG–PKC pathway) (without affecting POMC transcription) (127,163). Therefore, AVP action on pituitary corticotrophs is able to maintain corticotroph responsiveness, and hence ACTH release, to novel stressors following repeated activation of the HPA axis, despite concomitant CRH-R1 desensitization.

HPA axis activity itself also needs to be kept in check, therefore, glucocorticoids exert negative feedback at the hypothalamus and pituitary to inhibit the synthesis and secretion of CRH and POMC/ACTH, respectively (154). Moreover, glucocorticoid negative feedback causes a reduction in corticotroph CRH-R1 mRNA expression and an increase in CRH-R1 downregulation, leading to a decrease in CRH-R1 number, and hence, the desensitization of the corticotroph to the stimulatory effects of CRH on ACTH release. In addition, the hippocampus, which displays a high density of GR, exerts a negative influence on the PVN, and hence HPA axis activity, as well (129). According to Paul Plotsky (240), “One may speculate that attenuation of the ACTH secretory-response by glucocorticoid feedback conserves the response capacity of the HPA axis to subsequent stressors, and acts to limit the duration of total tissue glucocorticoid exposure, thus minimizing catabolic, anti-reproductive, and immunosuppressive effects, and counter-balancing the tendency of central circuitry to over-respond to a repeated stressor.”

BIDIRECTIONAL COMMUNICATION BETWEEN NEUROENDOCRINE AND IMMUNE SYSTEMS: HISTORICAL PERSPECTIVE

That substances released from the adrenal gland could affect immune function was one of the initial indications that there are meaningful interactions between the neuroendocrine and immune systems. Indeed, as early as the 1850s, Thomas Addison described a patient with adrenal insufficiency who exhibited an excess of circulating lymphocytes, thus providing some of the first evidence of a reciprocal relationship between adrenal hormones and immunologic parameters. In the 1920s, H. Jaffe demonstrated that adrenalectomized rats exhibited hypertrophy of the thymus, and conversely, in the 1930s, Hans Selye reported that animals exposed to a variety of stressors exhibited enlarged adrenal glands coupled with thymic involution. In the 1940s, Philip Hench discovered that patients with autoimmune disorders, such as rheumatoid arthritis, produced an endogenous substance under “stressful” conditions that had anti-inflammatory/immunosuppressive properties and hence, ameliorated the symptoms of the autoimmune disease. Isolation and characterization of this endogenous compound by Kendall led to the discovery of the adrenal steroid, cortisone, which along with other glucocorticoids, have become a mainstay in the treatment of autoimmune and inflammatory diseases. Of note, Hench and Kendall shared the Nobel prize in Medicine for their discovery in 1950.

Although the immunomodulatory effects of glucocorticoids initially were believed to be mediated by pharmacological rather than physiological concentrations of steroid, seminal work by Besedovsky and colleagues in the 1970s and 1980s substantiated a physiological role for glucocorticoids in regulating immune responses. For example, physiologic concentrations of glucocorticoids were found to facilitate antigenic specificity (40) and reduce splenic weight and cellularity (83). Besedovsky was also one of the first to demonstrate that immune system activity could influence the release of glucocorticoids. Indeed, his work demonstrated that

circulating glucocorticoids increase in the rat during the immune response to foreign antigens (i.e., sheep red blood cells [SRBCs]) (37). Furthermore, rats injected with culture supernatants from peripheral blood or spleen cells stimulated with mitogens *in vitro* produce increases in plasma glucocorticoid levels similar in magnitude to those reached at the peak of the immune response after antigen exposure (41). Besedovsky and colleagues concluded that lymphoid cells produce a glucocorticoid increasing factors (GIF) (41,43), that completes an immunoregulatory feedback circuit, in which immune cells secrete "hormones" that stimulate the release of adrenal glucocorticoids, that in turn negatively feedback on immune cells to prevent overactivity and preserve specificity of immune responses.

The concept of bi-directional communication between immune and neuroendocrine systems became firmly established with the work of Blalock and colleagues in the 1980s. These investigators demonstrated the synthesis/expression of common ligands and receptors in immune and neuroendocrine systems, for example, neuropeptides in immune cells and cytokines in endocrine glands (48,327). In addition, they proposed the concept of a "lymphoid-adrenal axis," in which ACTH produced by virus (Newcastle disease virus [NDV])–stimulated lymphocytes was able to directly stimulate corticosterone release in the absence of pituitary-derived ACTH (in hypophysectomized mice) (275,277). Of note, subsequent studies failed to replicate Blalock's findings and reported that extra-pituitary sources of ACTH were not sufficient to stimulate NDV-induced adrenal steroidogenesis (38,88,91,220). Complementary to these latter studies, Besedovsky et al. (43) showed that rats injected with culture supernatants from mitogen-stimulated peripheral blood or spleen cells produced an increase in plasma ACTH concentrations (along with increased glucocorticoid levels—like NDV-infected animals); however, when the rats were hypophysectomized, the glucocorticoid response was abolished. These studies suggested that immune-induced glucocorticoid release is dependent on a functioning pituitary gland, and that "GIFs" do not directly stimulate the adrenals in the absence of pituitary-derived ACTH. Furthermore, Besedovsky et al. observed changes in hypothalamic electrical activity (36) and norepinephrine turnover (42) in SRBC-injected rats, concomitant with peak immune and corticosterone responses, suggesting that the brain is involved in immune-neuroendocrine regulation.

In the mid-1980s, a series of papers in the journal *Science* demonstrated that the monocyte-derived, proinflammatory cytokine IL-1 fulfilled the requirement of a GIF. These studies showed that administration of IL-1 to rats and mice increased plasma ACTH and corticosterone levels (32,35,262) and did so by acting at multiple levels of the HPA axis. Although none of these early studies provided evidence for a direct action of IL-1 on glucocorticoid release from the adrenal gland (262,333), some demonstrated a direct IL-1 effect on ACTH release from pituitary cells (34,333) and some did not (32,262). These latter studies confirmed a role for hypothalamic CRH in the IL-1–induced ACTH and glucococorticoid responses (32,262). In addition, IL-1 was shown to be a critical mediator of the HPA response during viral (NDV) infection (35). Subsequent to this early landmark work, a plethora of studies have examined the direct impact of various cytokines (e.g., IL-1, IL-6, TNFα, IFN's, IL-2) alone or in combination, on HPA axis function. Interestingly, more recent data from both *in vivo* and *in vitro* studies indicate that cytokines may have the capacity to stimulate the adrenal gland directly, and therefore may activate glucocorticoid release independent of central nervous system (CNS) neuroendocrine pathways (see section on cytokine effects on the adrenal gland).

THE IMMUNE RESPONSE TO VIRUSES

Prior to considering the pathways by which cytokines activate the HPA axis, it is important to review some general features of the immune response to viral infection, including the role of relevant cytokines.

Immune responses to viral infections share certain characteristics that are distinct from bacterial and parasitic infections (1,136) (Fig. 3). The presence of a virus in infected cells is recognized by the detection of double-stranded RNA, generated during viral replication. This signal leads to the transcription and secretion of type I interferons (IFN-α and IFN-β), which protect neighboring cells not yet infected by making them resistant to viral replication, and hence, inducing an anti-viral state. In addition to inhibiting viral replication, type I IFN's activate natural killer (NK) cell cytotoxicity and increase MHC class I expression, allowing for more effective antigen presentation to $CD8^+$ cytolytic T cells (CTLs). NK cells are one of the principal mechanisms of innate immunity against viruses early in the course of infection, before late, specific immune responses have developed. In addition to their lytic functions, NK cells can be stimulated by IL-12 (released by macrophages and dendritic cells; acts in synergy with TNFα) to release IFN-γ (type II interferon), which is crucial in controlling infections before T cells have been activated to produce more IFN-γ. In the presence of IL-12 and IFN-γ, $CD4^+$ T cells are encouraged to develop into inflammatory T cells (Th1), which promote cellular immunity through the activation of macrophages (via IFN-γ release) and $CD8^+$ T cells (via IL-2 release). IL-2 is a crucial cytokine for T cell proliferation and differentiation. The principle mechanism of specific immunity against established viral infections, especially with non-cytopathic viruses, is the $CD8^+$ CTL. During the early, innate immune response to viral infections (as well as other types of infections), the proinlfammatory cytokines, TNFα, IL-1, and IL-6, also are induced to aid in the progression of anti-viral immunity.

When considering the HPA axis effects of cytokines, it is important to keep in mind that (a) cytokines are pleiotropic (one cytokine can exert many actions), (b) they are redundant (different cytokines can exert the same action), (c) they often influence the synthesis of other cytokines (e.g., TNF → IL-1 → IL-6, while IL-6 inhibits TNF and IL-1 synthesis), and (d) they often influence the action of other cytokines (e.g., TNF, IL-1, and IL-6 can act synergistically). The importance of synergistic actions of cytokines in HPA axis stimulation has been demonstrated by several studies. For example, in an *in vitro* preparation of isolated rat hypothalami, Buckingham et al. (59) showed that the release of CRH by conditioned media from lipopolysaccharide (LPS)–stimulated peritoneal macrophages (containing multiple cytokines) was much greater than that observed in response to TNFα, IL-1, or IL-6 alone. In addition, there is *in vivo* evidence that supports the role of synergistic actions of these proinflammatory cytokines in stimulating a complete, LPS-induced ACTH response (236) and in stimulating greater HPA axis activity together compared to their individual effect (310).

CYTOKINE–HPA AXIS INTERACTIONS: POTENTIAL MECHANISMS

Given the importance of the glucocorticoid response in restraining potentially detrimental immune responses, redundant or complementary pathways of glucocorticoid induction are activated by cytokines at all three levels of the HPA axis, including the hypothalamus, pituitary, and adrenal gland. Although hypothalamic CRH is considered a primary mechanism by which cytokines stimulate glucocorticoid release, increasing evidence supports a direct action of cytokines at the level of the pituitary and adrenal glands as well. Cytokine receptors have been detected at all HPA axis levels and therefore, each level can serve as an integration point for immune and neuroendocrine signals. In addition to circulating cytokines being able to act upon all three levels of the HPA axis, cytokines are synthesized in the brain, the anterior pituitary, and the adrenal gland. The production of local cytokines may function in a paracrine manner to amplify and maintain elevated HPA activity during chronic inflammation. Therefore, each level of the HPA axis contains a local cytokine network, which can be stimulated by a variety of circulating cytokines. In examining the effects of cytokines on HPA axis function, the innate proinflammatory cytokines—IL-1, IL-6, and TNFα—have been the most studied. However, other cytokines (e.g., IFN's and IL-2) also have been shown to influence HPA axis activity.

Brain/hypothalamus (PVN)

The majority of evidence indicates that activation of hypothalamic CRH is the primary means by which cytokines stimulate the release of ACTH and glucocorticoids. Since cytokines are large, soluble peptides, significant consideration has been given as to how cytokines cross the blood–brain barrier (BBB) and activate CRH-producing neurons in the PVN. Several mechanisms, which are not mutually exclusive, have been identified. Cytokines may (a) stimulate visceral (vagal) afferents that project to the nucleus tractus solitarius (NTS) in the brainstem, activating the release of norepinephrine (NE) from catecholaminergic terminals (of the ventral noradrenergic bundle [VNAB]) in the PVN, (b) passively cross the BBB at "leaky" regions where the BBB is not intact, such as the circumventricular organs (CVO's) [e.g., organum vascularis of lateral terminalis (OVLT), subfornical organ (SFO), and area postrema (AP)], and directly activate neurons that project to the hypothalamus, (c) exert a direct effect on CRH nerve terminals in the median eminence (ME), (d) act on endothelial cells of brain vasculature or glial cells in the CVO's, inducing the synthesis/release of secondary messengers such as central cytokines, prostaglandins (PG's), or nitric oxide (NO), which in turn activate hypothalamic neurons, and (e) cross the BBB themselves via active transport. Evidence exists to support all of these pathways, depending on the cytokine dose, time interval, and route of administration (247,300,302,322) (Fig. 4).

Cytokine network in the brain

Cytokine receptors: Once the peripheral immune signal reaches the brain, cytokines can interact with their receptors in multiple brain regions involved in HPA axis regulation, including the hypothalamus (PVN) and the hippocampus, which provides negative feedback regulation on PVN activity (129). In addition, many of the aforementioned brain regions involved in relaying the circulating cytokine message to the PVN have been shown to express cytokine receptors.

Of the two types of IL-1 receptors, both IL-1RI (activating) and IL-IRII (decoy) mRNA and protein have been detected in the mouse brain (102,230). In the mouse, high levels of IL-1RI mRNA expression are found in the hippocampus (dentate gyrus), the midline raphe system, the choroid plexus, meninges, and endothelial cells of post-capillary venules throughout the brain (78,173). However, only a scattered signal for IL-1RI mRNA has been detected in the ME, and no signal in the hypothalamus has been found. In contrast, IL-1RI mRNA in the rat brain is predominantly expressed over blood–brain barrier–related cells and not strongly expressed in certain neuronal populations as seen in the mouse brain (173). More specifically, constitutive expression of IL-1RI mRNA has been detected at the interface of the vascular wall and perivascular glia (335) and on endothelial cells (308) of the rat brain. In addition, IL-1 binding sites are detected in vagus nerve paraganglia (115). Peripheral administration of LPS has been shown to either downregulate (178,291) or upregulate (106,200) IL-1 receptors in the mouse brain.

Binding of IL-6 to IL-6R is followed by the rapid association of the gp130 molecule, the signal transducing component of the IL-6R complex, which increases the affinity of the IL-6R for IL-6. In the untreated rat, IL-6R mRNA has been detected in numerous brain regions that have been implicated in playing a role in HPA axis regulation, including the hippocampus, hypothalamus, and circumventricular organs such as the median eminence (ME) (266,305). However, the PVN displays no specific hybridization signal for IL-6R mRNA under basal conditions (266,305). Valliere et al. (305) have demonstrated that intraperitoneal (ip) injection of LPS in rats is able to upregulate the expression of IL-6R mRNA in selective regions of the brain that constitutively express IL-6R mRNA. Interestingly, LPS also induces IL-6R mRNA expression in some areas in which no IL-6R mRNA is detected under basal conditions, such as the PVN and endothelial cells of cerebral blood vessels (305). IL-6R mRNA has been

localized to glial cells, ependymal cells, and neurons (263,266). Gp130 immunoreactivity also has been observed in both glial and neural cells, and its distribution in the rat brain overlaps with that of IL-6R (320). Gp130 mRNA expression is detected throughout the rat brain (including the PVN) and is upregulated in the OVLT and in endothelial cells of cerebral microvasculature in response to peripheral administration of LPS (305).

TNF exerts its functions through two structurally related, but functionally distinct receptors, TNF-R1 (p55) and TNF-R2 (p75). Whereas TNF-R1 mRNA is constitutively expressed in the CVO's (including the ME), choroid plexus, meninges, and microvasculature, and to a lesser extent in the PVN, TNF-RII mRNA is barely detectable in the rat brain under basal conditions (198). Systemic treatment with LPS induces an increase TNF-RI mRNA expression in cells of blood–brain barrier–associated structures (198). Specific binding sites for TNF in mouse brain homogenates have been shown to be widespread, but maximal in the brainstem (159). Both types of TNF receptors have been localized to cerebrovascular endothelial cells (22), glial cells (86), and neurons (49).

Even though IFN-α and IFN-β show little structural similarity to each other, they both bind to the same receptor, the type I IFN receptor (type I IFN-R). In humans, type I IFN-R protein is constitutively expressed in microglia and its expression is increased in central inflammatory conditions (339). In addition, binding sites for IFN-α have been identified in the rat brain, the hypothalamus in particular (142). The receptor for IFN-γ is distinct from that of IFN-α/β. IFN-γR mRNA is constitutively expressed in the mouse brain, and its expression is increased by LPS (303). mRNA for IFN-α/β and -γ receptors also have been detected in astrocytes of the human brain (290).

IL-2 can bind to two distinct receptors: the IL-2Rα and the IL-2 R$\beta\gamma_c$. Binding of IL-2 to IL-2Rα alone does not lead to any detectable biological response, but requires binding to the IL-2 R$\beta\gamma_c$ as well. IL-2 first binds rapidly to IL-2Rα, which facilitates its association with IL-2 R$\beta\gamma_c$, thereby increasing the affinity of the signaling receptor for IL-2. IL-2 binding sites and/or IL-2 receptors are observed in the rat hypothalamus and hippocampus (9,168). IL-2R mRNA expression in the brain has been shown to increase upon exposure to LPS in mice (303).

Cytokine synthesis: During systemic inflammation or infection, the central production of cytokines may function in a paracrine manner to amplify the signal of circulating cytokines and maintain elevated HPA axis activity. Evidence for a role in centrally synthesized cytokines comes from the observation that centrally administered IL-1, IL-6, and TNFα stimulate ACTH release at doses much lower than the effective doses administered peripherally (300). In addition, central administration of cytokine antibodies or antagonists attenuate HPA axis activity induced by the peripheral administration of LPS and particular cytokines (194). In healthy brains, cytokines are expressed at low levels or not at all (265). Constitutive expression of cytokines tends to be localized to neurons, whereas induced central cytokines are mainly produced by glial cells, especially microglia (170).

Constitutive expression of IL-1 protein has been detected in the rat hypothalamus and hippocampus (171), although some studies have failed to detect basal IL-1 expression in the rat brain (15,98,307). The discrepancy in results may be due to a difference in sensitivity of the assays used. In response to systemic LPS administration, an increase in IL-1β immunoreactivity or mRNA expression has been detected in perivascular microglia and macrophages in the meninges, choroid plexus, CVO's, and hypothalamus in the rat brain (98,307) and in the mouse hypothalamus and hippocampus (170,239). Ip injection of LPS has been shown to induce a biphasic response in IL-1β mRNA expression in the rat brain, where an early phase of induced transcription (2 h post-injection) can be detected in areas without an effective blood–brain barrier, such as the choroid plexus, meninges, and cerebrovasculature,

followed by a later phase of expression (6 h post-injection) in the parenchyma, including areas such as the hypothalamus (336).

Whereas Schobitz et al. (266) have shown that IL-6 mRNA in the rat brain is constitutively expressed in regions such as the hippocampus and hypothalamus (colocalized with IL-6R mRNA), Vallieres et al. (305) have reported that IL-6 mRNA expression is undetectable under basal conditions. Upon ip LPS administration, however, IL-6 mRNA is increased in the CVO's (including the ME) and the choroid plexus of the rat (305) and in the brainstem, hippocampus, and hypothalamus of the mouse (170,239). Whereas LPS induces a strong and transient increase in IL-1 and TNFα mRNAs in the hypothalamus and hippocampus, the induction of IL-6 mRNA tends to be progressive over time (170). *In vitro*, IL-6 mRNA and release is detected in rat medial basal hypothalamic fragments under basal conditions and is further stimulated by LPS, presumably from glial cells (284).

While no expression of TNFα mRNA has been detected in the rat brain under basal conditions (199), the mouse brain has been shown to exhibit constitutive levels of TNFα mRNA (239) and TNFα immunoreactivity in neurons of the hypothalamus, caudal raphe system, and the ventral surface of the brainstem (56). Increased TNFα mRNA expression is observed in the rat (109) and the mouse (170) hypothalamus in response to systemic LPS administration. Similar to the pattern of central induction of IL-1 mRNA, ip injection of LPS tends to stimulate a biphasic response in TNFα mRNA expression in both the rat (199) and the mouse (55) brain, where an early phase of induced transcription can be detected in blood–brain barrier–related structures such as the choroid plexus, CVOs, and meninges, followed by a later phase of expression in the parenchyma, including areas such as the hypothalamus and the NTS. Naduau et al. (199) have shown that the induced TNFα is mainly a product of microglia and brain macrophages.

IFN-α protein has been localized to microglia and neurons of the human brain and its microglial expression is increased (along with the expression of IFN-R) in central inflammatory conditions (338). IFN-α mRNA also is constitutively expressed in the human brain (54). Although IFN-γ mRNA is not constitutively expressed in the mouse brain, its expression is induced by LPS (239). A neuronal IFN-γ, which has a molecular weight distinct from that of lymphocyte-derived IFN-γ but crossreacts immunologically and shares certain bioactivities with it, has been detected in the hypothalamus and hippocampus of the rat brain (31,172, 221). IFN-γ–like immunoreactivity is abundantly present in the rat peripheral nervous system, while weaker staining has been detected in the brain, specifically in the hypothalamus and midbrain (155).

IL-2 immunoreactivity has been detected in the rat brain, in regions such as the hypothalamus, ME, and hippocampus (9,168). In addition, Araujo et al. (8) have shown that IL-2 is released from rat astroglial and microglial cells in culture and its release is enhanced by IL-1. IL-2 mRNA is detected in the hypothalamus, including the PVN, following iv injection of tetanus toxin in rats (162).

Cytokine induction of CRH—The proinflammatory cytokines—IL-1, IL-6, and TNFα—have all been shown to stimulate HPA axis activity *in vivo* in various species (39,300). Release of CRH from PVN neurons into the ME is established as a primary pathway by which cytokines stimulate the HPA axis. Early groundbreaking studies by Sapolsky et al. (262) and Berkenbosch et al. (32) concluded that ip administration of IL-1 (in rats) induces a CRH-dependent ACTH response, based on effective neutralization of the response by prior administration of CRH-antisera and detection of increased CRH release, as assessed by an increase of CRH in the hyposhysial portal blood (Sapolsky et al.) and a decrease in CRH content in the median eminence (Berkenbosch et al.). Furthermore, participation of CRH-producing neurons of the

PVN is implicated by the findings of IL-1–induced expression of c-fos mRNA (a cellular marker of neuronal activation) and an increase in CRH mRNA in the PVN (97). Similarly, it has been demonstrated that PVN lesions completely prevent the increase in ACTH induced by intravenous (iv) administration of IL-6 and TNF*α* (164), and that immunoneutralization of CRH blocks the stimulatory effects of IL-6 and TNF*α* on ACTH and/or corticosterone release (33,146,205,311). IL-1, IL-6, and TNF*α* also have been shown to stimulate the release of CRH from rat hypothalamic explants (33,206,287). Moreover, both IL-1 and IL-6 are capable of acting directly on CRH nerve terminals in the ME (181,183,270,287), thereby increasing CRH release without necessarily increasing CRH synthesis in the PVN. However, a direct action of TNF at the level of the ME has not been demonstrated. Although iv administration of TNF*α* results in an increase in CRH release from the ME (321), Sharp et al. (270) failed to show an effect of TNF*α* on ACTH secretion when injected directly above the ME.

Some studies have reported differential effects of proinflammatory cytokines on PVN activity. While IL-1 and IL-6 were able to stimulate ACTH secretion after intra-ME delivery, only IL-1 was able to stimulate ACTH secretion after injection into the PVN (181). Callahan et al. (62) also reported an increase in Fos expression in CRH-producing neurons of the PVN in response to ip administration of IL-1*β*, but not to IL-6. Moreover, an ip injection of IL-1*β*, in addition to eliciting ACTH and corticosterone responses, produced an increase in CRH mRNA expression in the PVN, while IL-6 did not induce an increase in CRH mRNA expression, despite an increase in ACTH and corticosterone (126). Initially, Vallieres et al. (304) reported that a single systemic injection of IL-6 was insufficient by itself to induce c-fos and CRH mRNA in the PVN. However, if IL-6 receptors were first induced in the PVN by prior LPS (iv) exposure (IL-6R was barely expressed in the PVN under basal conditions), then IL-6 (iv) was able to induce an increase in c-fos mRNA and CRH hnRNA in the PVN, concordant with a significant corticosterone response (306). In addition, continuous infusion of IL-6 has been shown to induce Fos expression in the PVN (207). Vallieres et al. (306) also demonstrated that although IL-6 did not appear to be essential during the early phases of endotoxemia, IL-6 was required during the later phases to prolong the activation of neurons throughout the brain and to maintain CRH expression in the PVN. In addition, iv administration of TNF*α* induces c-fos mRNA and CRH hnRNA expression in the PVN of rats, concordant with elevated plasma corticosterone levels (198). Taken together, these data suggest that IL-1 and TNF*α* may be responsible for activating CRH-producing neurons of the PVN in response to an acute immunological challenge, while IL-6 may be responsible for the PVN response to chronic inflammation or in instances where the PVN has been previously sensitized to IL-6 by prior exposure to other cytokines (i.e., TNF*α*, IL-1).

IFN-*α* is a mainstay therapy used to treat certain chronic viral infections (e.g., hepatitis C) and malignant disorders (e.g., cancer) and has been shown to cause HPA axis stimulation in humans when administered to either of these populations of patients (65,113,195,252). However, when administered to rats, either peripherally or centrally, recombinant human IFN-*α* inhibits HPA axis activity as indicated by a reduction in the electrical activity of CRH neurons in the PVN and plasma corticosterone levels (260,261). Interestingly, low doses of rat IFN-*α* (by both ip and icv administration) also decreases corticosterone levels in the rat, while increases in corticosterone concentrations were found following icv administration of high doses of rat IFN-*α* (260). Saphier et al. (260) suggest that the physiological significance of the IFN-*α*-induced inhibition of HPA activity, and hence glucocorticoid release, may be to enhance the immunopotentiating effects of IFN-*α*. Dafny et al. (80) also have shown that both peripheral and central administration of IFN-*α* in rats suppresses hypothalamic neural activity, while stimulating neural activity in other brain regions, such as the hippocampus. *In vitro*, IFN-*α* has been shown to stimulate (113,244) or to have no effect (191,206) on CRH release from rat hypothalamic cultures. IFN-*β* is a common therapy in patients suffering from multiple sclerosis. The HPA axis–stimulating effects of IFN-*β* has been less studied than IFN-*α*. In studying the

neuroendocrine effects of this cytokine, Geobel et al. (114) have demonstrated that the administration of IFN-β to healthy subjects elevates plasma cortisol levels, concomitant with increases in plasma TNFα and IL-6 concentrations. Peripheral administration of IFN-γ enhances cortisol secretion when given to healthy men (136), but fails to induce ACTH/corticosterone responses when given to mice or rats (35). Central administration of IFN-γ has been shown to potentiate the LPS-induced increases of TNFα and IL-6 protein in CSF and serum and mRNA in the rat brain (82). *In vitro*, IFN-γ has failed to exhibit an effect on CRH release from rat hypothalamic explants (206) or superinfused hypothalamic-neurohypophysial complexes (218). Disparities between results within *in vivo* and *in vitro* paradigms may be due to species-specificity effects and dose effects of the cytokines tested. In addition, some of the effects of IFN's on HPA axis activity may be attributed to the induction and action of downstream proinflammatory cytokines (e.g., TNFα and IL-6).

IL-2 also is used in immunotherapy for cancer patients and has been shown to stimulate ACTH and cortisol responses in this population (84,176). When administered to HIV-infected patients, IL-2 induces ACTH and cortisol responses and increases the ACTH/cortisol responses to CRH stimulation as well (332). On the contrary, acute (35) and chronic (201) systemic IL-2 administration to rats fail to induce an increase in ACTH and corticosterone. However, recombinant human IL-2 was used in these studies, and Naito et al. (203) have shown that iv injection of rat IL-2, but not human IL-2, is able to stimulate ACTH release in rats. Although systemic administration of IL-2 in mice induces a corticosterone response (60,69), Zalcman et al. (342) failed to show significant glucocorticoid induction following an ip injection of IL-2 in mice. Icv infusion of IL-2 in rats also is capable of activating an ACTH/corticosterone response (122). Both peripheral and central administration of IL-2 alters hypothalamic electrical activity in mice and rats, however, there is region-specificity, where decreases in activity have been observed in the lateral anterior (LAH) and ventromedial (VMH) areas and increases in the supraoptic (SON) and paraventricular (PVN) nuclei (20,46). Whereas an ip injection of IL-2 into rats does not produce an increase in CRH mRNA expression in the PVN (concordant with an increase in POMC mRNA expression in the anterior pituitary) (125), IL-2 has been shown to increase AVP mRNA in the hypothalamus of mice (227). Moreover, IL-2 stimulates the release of AVP (but not CRH) from the intact rat hypothalamus *in vitro* and hypothalamic cell cultures (132). IL-2 also failed to have an effect on CRH release from rat hypothalamic explants (132,206). Therefore, IL-2–induced ACTH responses may be driven by AVP rather than CRH. On the other hand, there are studies in which IL-2 has been shown to stimulate CRH release from rat perifused hypothalami (63), hypothalamic explants (150), and hypothalamic slices (244). Again, disparities between results may be due to species-specificity effects of the cytokine used.

Arginine vasopressin (AVP)—Aside from CRH, other hypothalamic secretagogues may contribute to cytokine–HPA axis interactions. Arginine vasopressin (AVP) is one such peptide. Although AVP on its own does not result in increased POMC mRNA expression, in the presence of permissive levels of CRH, it acts synergistically with CRH to stimulate ACTH release from the anterior pituitary. Proinflammatory cytokines have been shown in one study or another to influence AVP synthesis or release (59,300). However, a portion of this AVP response may originate from the magnocellular, rather than the parvocellular, cells of the PVN and be destined for release from the posterior pituitary and ultimately the general circulation (Fig. 2). There is strong evidence that under conditions of chronic inflammation, such as rheumatoid arthritis, cytokine effects on HPA axis activity may be driven primarily by AVP (parvocellular-derived). In arthritic rats, Harbuz et al. (124) have demonstrated an increase in POMC mRNA expression in the anterior pituitary concordant with a paradoxical decrease in CRH mRNA in the PVN and CRH release into the hypophysial portal blood (HPB), while an increase in AVP release into the HPB was detected. In addition, Lewis rats, which are susceptible to developing chronic inflammatory disease due to impaired CRH and

corticosterone secretion, have high plasma levels (magnocellular-derived AVP), hypothalamic content, and *in vitro* release of AVP in comparison with the inflammatory-disease resistant Fisher rats (232). Similar findings have been reported in animal models of other chronic inflammatory disorders, such as lupus (256,269). Taken together, these results suggest that an increase in AVP may attempt to compensate for low CRH drive in HPA axis regulation.

Pituitary Gland

Although strong evidence has been provided in support of cytokine action at the level of the CNS to activate the HPA axis, numerous *in vitro* studies indicate that cytokines can exert a direct effect on ACTH release from the anterior pituitary. In addition, *in vivo* work by our lab and others have demonstrated that animals whose CRH or CRH-R1 gene has been eliminated can produce ACTH and corticosterone responses to immune challenges (44,273,301). These data indicate that pathways are in place for direct cytokine–pituitary interactions.

Cytokine network in the pituitary gland

Cytokine receptors: Receptors for cytokines have been identified in various cell types that reside in the pituitary. mRNA for both types of IL-1 receptors, IL-1RI and IL-IRII, have been detected in the mouse anterior pituitary and in the mouse corticotropic tumor cell line AtT-20 (78,231). In addition, IL-1R1 mRNA is constitutively expressed in the rat pituitary gland (328) and is upregulated by LPS in the mouse pituitary gland (241). Furthermore, IL-1RI and IL-1RII immunoreactivity have been localized in somatotrophs in the normal mouse anterior pituitary (103). IL-6 binding sites are detected in the rat anterior pituitary and in human gonadotrophs (219). Moreover, IL-6R protein has been localized to mouse corticotrophs and mRNA's of IL-6R and gp130 are expressed in rat corticotrophs, which are upregulated in response to LPS (110). TNF binding sites are found at high concentrations in the anterior lobe of both mouse and rat pituitary glands (334). In addition, the ACTH-producing AtT-20 cells express both Type I and II TNF receptor mRNA and the folliculostellate TtT/GF cells (pituitary source of IL-6, see below) have been found to express TNF-R1 mRNA (160). IFN-γR mRNA is constitutively expressed in the mouse pituitary and is upregulated by LPS (303). IL-2R immunoreactivity has been detected in rat pituitary and its expression is upregulated by the pre-exposure to IL-2 (295). IL-2R mRNA expression in the pituitary has been shown to increase upon exposure to LPS in mice (303). More specifically, Arzt et al (10) have detected IL-2R mRNA and protein in AtT-20 cells and corticotrophs of normal rat anterior pituitary cells. Moreover, CRH increases IL-2R mRNA expression in AtT-20 cells (10,237).

Although cytokine receptors have been found on AtT-20 cells, it is unclear to what extent corticotroph tumors accurately represent normal anterior pituitary corticotrophs. The lack of evidence on some cytokine receptor localization to normal corticotrophs may suggest that paracrine interactions are involved between the endocrine cells that express those receptors and the ACTH-producing corticotrophs themselves. Moreover, the presence of cytokine receptors on non-endocrine cell types, suggests that in addition to exerting a direct effect on ACTH release, cytokines (i.e., TNFα) may indirectly modulate ACTH release by first stimulating the release of local cytokines, such as IL-6 from folliculostellate cells.

Cytokine synthesis: Like the brain, the pituitary can synthesize its own set of local cytokines and serve as an integration point for immune and neuroendocrine signals. IL-1β protein and mRNA have been detected in the rat anterior pituitary, and both are increased following ip LPS injections (161,291,328). LPS administration also upregulates IL-1α/β expression in the pituitary gland of mice (105,241). In addition, Koenig et al. (161) showed that IL-1β was localized to cytoplasmic granules in anterior pituitary endocrine cells and colocalized with TSH in thyrotrophs. IL-1α/β mRNA also have been demonstrated in monocytes in both the anterior and posterior lobes of the rat pituitary gland (98). Cultured rat anterior pituitary cells

spontaneously secrete large quantities of IL-6, which is enhanced by exposure to LPS (285) and to IL-1α/β (282,283). The source of pituitary IL-6 has been shown to be the folliculostellate cell (313), which is not a hormone-secreting cell, but a cell of monocytic lineage that is thought to be involved in paracrine regulation of hormone secretion from the pituitary (13,138). Moreover, LPS and TNFα have been shown to directly stimulate IL-6 release from mouse pituitary FS TtT/GF tumor cells (160,174), while LPS produces a similar effect on FS cells of mouse pituitary cell cultures (174). IL-6 immunoreactivity also is expressed in ACTH and FSH/LH-secreting cells in normal human pituitary glands (167) and IL-6 mRNA is induced in the rat pituitary by ip administration of LPS (197). TNFα mRNA is constitutively expressed in the mouse pituitary (239) and is upregulated in response to systemic injection of LPS in the mouse and rat (109,170,199,239). IFN-γ mRNA is constitutively expressed in the mouse pituitary and is upregulated by LPS (239). Arzt et al. (10) have detected IL-2 mRNA in human corticotrophic adenoma cells and mouse AtT-20 cells. The role of local, pituitary-derived cytokines may be to amplify and maintain elevated pituitary-adrenal activity during chronic inflammation.

Cytokine induction of ACTH—Numerous *in vitro* studies support the contention that cytokines can directly stimulate ACTH release from the pituitary gland. IL-1 has been shown to induce POMC transcription and ACTH release from cultured rat anterior pituitary cells (34,57,153), while IL-6 has been demonstrated to stimulate ACTH secretion from cultured hemipituitaries (177). In addition, both IL-1 and IL-6 have been shown to increase POMC mRNA expression or promoter activity and ACTH release from AtT-20 cells (57,104,152, 333). Moreover, Fukata et al. (104) have shown that IL-1β can sensitize AtT-20 cells to release ACTH in response to CRH. TNFα also has the ability to induce ACTH release from cultured rat anterior pituitary cells (33) and to stimulate POMC transcription from AtT-20 cells (152, 160). Although the acute effects (<4 h) of IL-1, IL-6, and TNFα alone, on POMC promoter activity in AtT-20 cells were minimal (peak responses occurred >12 h), these cytokines significantly potentiated the stimulatory effect of CRH at that time (152). However, according to Gaillard et al. (108), TNFα exerts an inhibitory effect on CRH-stimulated ACTH release from rat anterior pituitary cells, while having no effect on basal ACTH secretion.

It should be noted, however, there are studies that have failed to demonstrate a direct action of IL-1 (32,206,262), IL-6 (206), and TNFα (153,206,270) on cultured anterior pituitary cells to stimulate ACTH release. The discrepancy between these reports may be explained by differences in the incubation times used, in which short incubation periods (<4 h) may not be long enough to observe a direct effect of the cytokine on the pituitary. Therefore, CRH-dependent ACTH release may mediate the rapid onset of an acutely induced glucocorticoid response, whereas a direct action of cytokines on the anterior pituitary may mediate more latent glucocorticoid responses due to chronic inflammation. Another possible reason for the lack of an effect of individual cytokine action on ACTH release at early time points may be the need for synergistic actions between multiple cytokines. For example, Buckingham et al. (59) have demonstrated that rat anterior pituitary cells incubated with conditioned media from macrophages stimulated with LPS (which contains multiple cytokines) increase their ACTH secretion, while no effect was observed when incubated with various cytokines alone.

Although IFN-γ increases ACTH release from AtT-20 cells (152), neither IFN-α nor IFN-γ has been reported to exert a direct effect on ACTH release from rat pituitary cells (113,136,206). Interestingly, Katahira et al. (152) have shown that both IFN-α and IFN-γ exhibit acute stimulatory effects (~4 h), followed by marked inhibitory effects (~12 h) on POMC promoter activity in AtT-20 cells. IFN-γ inhibits CRH-induced ACTH release from rat anterior pituitary cell cultures, although fails to do so when AtT-20 cells are used (312). Vankelecom et al. demonstrate the dependence of this effect on the presence of folliculostellate cells in the normal pituitary cultures (312) and that this immune–endocrine interaction may be mediated by the

induction of iNOS in a subpopulation of these FS cells and other types of yet to be identified non-hormone-secreting cells (314). IL-2 has been shown to stimulate ACTH release from rat hemipituitaries (151) and pituitary cells (279). However, Navarra et al. (206) failed to show an effect of IL-2 on ACTH release from rat pituitary cells, which may be attributed to the use of recombinant human IL-2 rather than rat IL-2. Although Brown et al. (57) demonstrated that IL-2 enhances POMC mRNA in both rat primary pituitary and AtT-20 cells, other studies have failed to show an effect of IL-2 on ACTH release (104) and POMC promoter activity (152) in AtT-20 cells. The observation that one can detect an effect of cytokines on POMC transcription or ACTH release in normal pituitary cells and not in AtT-20 cells (mouse corticotrophic cell line) may be due to the presence of other cells types/accessory cells that may be important in mediating the immune-endocrine interaction.

In vivo, ip administration of either IL-1 or IL-6 has been shown to induce Fos expression in the anterior pituitary (62). However, IL-1, but not IL-6, produces an increase in POMC mRNA in the anterior pituitary with a concomitant increase in plasma ACTH (126). Perhaps IL-6 could be exerting a direct effect on the pituitary to increase ACTH release, without increasing its synthesis. Ip administration of TNFα decreases POMC mRNA in the rat anterior pituitary (255). Ip administration of IL-2 in mice induces an increase in POMC mRNA expression in the anterior pituitary along with increases in plasma corticosterone levels (69), and this increase in POMC mRNA expression in rats is seen without a concomitant induction of CRH mRNA in the PVN (125). As mentioned before, IL-2 induction of POMC mRNA may be driven by AVP rather than CRH.

Besides IL-1 being able to increase pituitary sensitivity to CRH, CRH has been shown to play a role in increasing pituitary sensitivity to circulating cytokines. Payne et al. (234) demonstrated that low levels of exogenously administered (or endogenously produced CRH) may be necessary for IL-1 to induce ACTH release via direct action on the anterior pituitary. Once sensitized, IL-1–induced ACTH release was no longer inhibited by a CRH antagonist. CRH also has been shown to increase IL-1R expression in AtT-20 cells (324) and increase IL-1α binding in the anterior pituitary (292). Moreover, PVN-lesioned rats injected (ip) with LPS exhibit a delayed ACTH response compared to CRH-intact animals (95). These data support the idea that while the initial ACTH response to cytokines may be dependent on CRH release from the hypothalamus, a more sustained ACTH response may result from a direct action of cytokines on the pituitary gland that previously has been sensitized by CRH. However, without the prior sensitization by CRH (possibly by the upregulation of cytokine receptor expression), direct cytokine action on the pituitary may occur only after prolonged exposure to circulating cytokines.

Adrenal Gland

There has been a growing body of evidence to support the idea of extrahypothalamic and extrapituitary regulation of adrenal steroidogenesis, whereby circulating cytokines act directly on the adrenal gland. The adrenal cortex is comprised of three histologically distinct layers. From the outermost to innermost (adjacent to the medulla), these layers are the zona granulosa (synthesize mineralocorticoids) and the zonas fasciculata and reticularis (synthesize glucocorticoids and androgens). Although blood flow within the adrenal gland is directed centripetally from the cortex to the medulla, secretory products released by medullary chromaffin cells (catecholamines and various neuropeptides) are able to influence steroidogenesis in the adrenal cortex in a paracrine manner (93). Rays of medullary tissue have been found to extend through the entire cortex of the human adrenal gland, and steroid producing cells occur diffusely within the entire adrenal medulla, with the two cell types located in direct apposition (52,53,330). Systemic cytokine actions at the adrenal gland and their effect on glucocorticoid synthesis/release may be dependent upon intricate intra-adrenal interactions

between cortical and medullary cells, the vascular supply, neural input, and locally synthesized cytokines and neuropeptides (e.g., an intra-adrenal CRH-ACTH system) (50,94).

Cytokine network in the adrenal gland

Cytokine receptors: Although some studies have failed to detect the presence of IL-1 receptors (mRNA or binding) in the adrenal gland (78,331), Nussdorfer et al. (215) have demonstrated the presence of IL-1β binding sites in the zona glomerulosa and medulla of the human adrenal gland, and Nazarloo et al. (241) have shown that IL-1RI mRNA is expressed in mouse adrenal glands. Furthermore, the expression of IL-1RI mRNA in the mouse adrenal gland is upregulated by LPS (241). Receptors for both IL-6 and TNFα also have been identified in the adrenal gland of numerous species. IL-6R mRNA has been detected primarily in the zona reticularis and the zona fasciculata (to a lesser extent in the zona glomerulosa and the medulla) of the mouse (44) and the human adrenal gland (233), the zona fasciculata of the bovine adrenal gland (18), and more intensely in the medulla than in the cortical regions of the rat adrenal gland (107). Based on immunohistochemical studies, TNF receptors (types I and II) have been localized to the zona fasciculata of the bovine adrenal gland (18). In addition, TNF binding has been demonstrated throughout the rat and bovine adrenal cortex and in the human adrenocortical tumor cell line H295R (143). IFN-α binding sites have been demonstrated in bovine adrenals (67). IL-2R immunoreactivity has been detected in rat adrenal cells and its expression is upregulated by the pre-exposure to IL-2 (295). In addition, the presence of IL-2 binding sites have been demonstrated in the human (215) and rat (111) adrenal gland.

Cytokine synthesis: Just as the brain and anterior pituitary can produce their own cytokines, cytokine synthesis by multiple cell types of the adrenal gland has been demonstrated. IL-1α is produced by rat chromaffin cells (19). IL-1β, IL-6 and TNFα mRNA's have been detected in steroid-producing cells and macrophages of the zona reticularis in the human adrenal gland (117–119). Macrophages have been localized in all zones of the human and bovine adrenal gland and lie in direct contact with cortical and chromaffin cells (79,116). LPS administration has been shown to induce an increase in IL-1β mRNA expression (209) and protein concentrations (58) in the rat adrenal gland, and an increase in IL-1α/β mRNA expression in the adrenal glands of mice (241). IL-6 is primarily produced by rat and bovine adrenal zona glomerulosa cells (and to a lesser extent by zona reticularis and fasciculata cells) (61,144). In addition, its release is stimulated by IL-1α/β, LPS, angiotensin II, and ACTH, with IL-1β also potentiating the stimulatory effect of ACTH on IL-6 secretion (144). IL-6 mRNA in the rat adrenal gland also is induced by ip administration of LPS (197). TNFα immunoreactivity is found throughout the bovine adrenal cortex (most prominent in the zona glomerulosa), and while its release is stimulated by IL-1α/β, LPS, and angiotensin II, it is inhibited by ACTH (61). The same has been shown for TNFα release from rat zona glomerulosa cells (145). Rats treated with LPS also exhibit an increase in adrenal IFN-γ concentrations (58). As with the pituitary, the role of local, adrenal-derived cytokines may be to amplify and maintain elevated adrenal activity in response to chronic inflammation.

Cytokine induction of glucocorticoids—Data from numerous *in vitro* studies have demonstrated that cytokines can directly affect glucocorticoid release from the adrenal gland. IL-1 has been shown to directly stimulate glucocorticoid release. Andreis et al. (6) have demonstrated that IL-1β is capable of stimulating the release of corticosterone from rat adrenal slices including both cortex and medulla (but not in adrenal cortical cells alone), showing its dependence on medullary chromaffin cells. In addition, IL-1 has been shown to stimulate corticosterone release on its own from rat (217,294) and bovine (331) adrenal cells in primary culture and to act synergistically with ACTH (294). Possible mechanisms by which IL-1 stimulates corticosterone release include the involvement of an intra-adrenal CRH/ACTH

system (6,182), catecholamines released from medullary chromaffin cells (via α-adrenergic mechanisms) (121,217), and prostaglandins (250,294,331).

IL-6 also has been shown to stimulate the release of corticosterone from primary cultures of rat, human, and bovine adrenal cells alone (18,107,233,257,323) and in synergy with ACTH (18,257). In addition, Barney et al. (18) have shown that ACTH and IL-6 act synergistically to induce corticosterone release from adrenal cell cultures at time points when IL-6 alone is ineffective. Due to the long incubation time required in the majority of the studies for IL-1 and IL-6 to stimulate glucocorticoid release (>12 h), it has been suggested that (CRH-dependent) ACTH may mediate early glucocorticoid responses to an immune challenge, while a direct action of these cytokines on the adrenal gland may mediate long-term glucocorticoid induction. Furthermore, the observation that glucocorticoid levels can remain elevated over several days despite declining plasma ACTH levels, such as it occurs during or after sepsis (24,25,317), major surgery (202,204), burn trauma (208), and chronic treatment with IL-6 (172,173,286) in humans, in response to turpentine-induced inflammation in rats (299), and in a murine model of colitis (101), lends support to the idea that proinflammatory cytokines may contribute to a sustained glucocorticoid response by directly stimulating glucocorticoid release. Nevertheless, there also have been reports in which IL-1 and IL-6 failed to stimulate corticosterone production by cultured normal rat adrenal cells (262) and by mouse adrenal tumor cells (333), which may be due to the lack of long enough incubation periods.

While IL-1 and IL-6 exert a positive influence on glucocorticoid release from the adrenal gland, TNFα has been shown to have an inhibitory effect on glucocorticoid synthesis and release. Barney et al. (18) demonstrate that TNFα inhibits basal cortisol release from bovine adrenal zona fasciculata cells after a 16 h incubation period, while inhibiting ACTH-stimulated cortisol release at 4 h. In a preparation of rat adrenal cells, TNFα also inhibited ACTH-induced corticosterone release at 6 h, but did not have an effect on basal corticosterone release at that time point (311). In addition to attenuating ACTH-stimulated glucocorticoid release, TNFα has been shown to inhibit the ACTH-induced increase in cytochrome P450 oxidase mRNA expression (a group of enzymes involved in glucocorticoid synthesis) in cultured human fetal adrenal cells (140). Interestingly, the direct effect of TNFα on the adrenal gland contradicts the stimulatory effect of circulating TNFα on HPA axis activity seen in an intact animal. Therefore, the role of intra-adrenal TNFα may be different than that of plasma TNFα.

IFN-α induces glucocorticoid secretion from human adrenal slices (66) and rat adrenal cells (113). IL-2 has been shown to stimulate corticosterone release from rat adrenal cells (at 12 h) (294). In addition to stimulating corticosterone release from adrenal cells alone, IL-2 also acts in synergy with submaximal doses of ACTH (294). However, after only a 2-h incubation period, IL-2 failed to stimulate corticosterone release by rat adrenal cells or fragments (309).

Although *in vitro* studies have demonstrated the ability of cytokines to stimulate glucocorticoid release directly from adrenal cells, numerous *in vivo* studies have shown that immune stimuli (i.e., IL-1, NDV, and MCMV) given to hypophysectomized animals can not induce a glucocorticoid response independent of pituitary-derived ACTH (88,120,220,273). In contrast, two studies have reported that NDV (277) and IL-1β (6) can induce a corticosterone response in hypophysectomized mice. However, in the NDV study (277), the results were attributed to the possibility of incomplete hypophysectomies, and the animals in the IL-1 study (6) were pre-treated with a low dose of ACTH.

Studies from our lab (273) have shown that MCMV-infected mice administered CRH-antisera are able to produce a robust corticosterone response despite their inability to produce an ACTH response. However, baseline levels of ACTH are still present (unlike hypophysectomized mice) and may serve as a permissive factor to allow for direct cytokine-adrenal interactions. In

addition, mice deficient in the CRH or CRH-R1 gene are able to mount a significant corticosterone response to a variety of immunological stressors, such as carageenan (149), turpentine (301,315), LPS (44,149,301), and MCMV (273), even though they exhibit markedly attenuated corticosterone responses to physical stressors such as restraint, ether, fasting and forced swim (193,278,293). Of note, the genetically manipulated animals (and those treated with CRH-antisera) that receive the immune stimulus, exhibit dramatically greater increases in IL-6 compared to immune challenged control animals. This marked increase in IL-6 may compensate for the lack of CRH function in driving the HPA axis, and become a predominant driving force for glucocorticoid induction by acting directly on the adrenal glands.

The mechanism by which ACTH supports the direct action of cytokines, such as IL-1 and IL-6, on the adrenal gland has not been elucidated. One possibility includes an ACTH-induced upregulation of adrenal gland cytokine receptor expression. Such upregulation of cytokine receptors by upstream neuroendocrine factors has been found in the pituitary gland following administration of CRH. On the other hand, the high levels of IL-6 may increase adrenal sensitivity to submaximal doses of ACTH. Adrenal sensitivity to ACTH is regulated by adrenal innervation (e.g., splanchnic nerve stimulation) with the subsequent release of catecholamines and vasoactive neuropeptides that affect adrenal blood flow and hence, increase the presentation of ACTH to the steroidogenic cells of the adrenal cortex and result in an increase of glucocorticoid release (21,51,68,92,96,133,134,184,297,298,329). However, the role of IL-6 and/or other cytokines, whether circulating or intra-adrenal, in this interplay requires further investigation.

OTHER CYTOKINES IN IMMUNE–HPA INTERACTIONS

Although this review has focused on the stimulatory effects of the macrophage-produced proinflammatory cytokines, TNFα, IL-1, and IL-6, the type I IFN's α and β, released during the early innate immune response by virus-infected cells, and the proinflammatory Th1–produced cytokines, IL-2 and IFN-γ (type II), numerous other cytokines and their receptors have been identified in HPA axis tissue and have been shown to modulate immune-HPA axis interactions. Some of these cytokines are briefly described below.

Leukemia inhibitory factor (LIF)

Another proinflammatory cytokine that has recently gained attention for its role in neuroendocrine function is leukemia inhibitory factor (LIF). LIF is member of the IL-6 cytokine superfamily, in which the LIF receptor (LIF-R) shares the gp130 receptor subunit for signal transduction. Serum LIF is increased in a variety of inflammatory conditions, concordant with HPA activation, and systemic injection of LIF has been shown to stimulate pituitary POMC transcription and ACTH release alone and in synergy with CRH. In addition, the local expression of mouse LIF and LIF-R in the hypothalamus and the pituitary (corticotrophs) is upregulated by various inflammatory stressors. Moreover, LIF KO mice fail to mount an ACTH response and demonstrate blunted POMC and corticosterone responses to inflammatory stressors (11,70).

Macrophage migration inhibitory factor (MIF)

Like LIF, macrophage migration inhibitory factor (MIF) is another proinflammatory cytokine that is detected in the corticotrophs (and thyrotrophs) of the anterior pituitary and is also expressed (although in lesser amounts) in brain regions such as the hypothalamus, hippocampus, and perivascular epithelial cells. The release of MIF from the pituitary is stimulated by CRH and inflammatory stimuli, such as LPS. Once released into the general circulation, MIF plays a role in opposing the anti-inflammatory actions of glucocorticoids. Interestingly, physiological concentrations of glucocorticoids stimulate macrophage release of

MIF, which is in contrast to the typical inhibitory action of glucocorticoids on proinflammatory cytokines (194,238,251).

Interleukin-10

IL-10 is an anti-inflammatory macrophage- and Th2–produced cytokine. Similar to glucocorticoids, it inhibits the production of proinflammatory cytokines from macrophages and Th1 cells. IL-10 is produced in pituitary, hypothalamic, and neural tissue. In addition, IL-10 has been shown to stimulate ME fragments to release CRH and AtT-20 pituitary cells to release ACTH and MIF. However, IL-10 seems to negatively regulate glucocorticoid release from the adrenal gland, since cold-swim and poly I:C-induced glucocorticoid responses are enhanced in IL-10 deficient mice and Y-1 adrenal cells treated with an anti-IL-10 Ab (276).

Interleukin-12

IL-12 is mainly released by activated macrophages and dendritic cells. IL-12 causes NK cells and T cells to secrete IFN-γ; acts as a differentiation factor on $CD4^+$ T cells, promoting their specialization into IFN-γ–producing, Th1 cells; and enhances the cytolytic functions of activated NK cells and $CD8^+$ T cells. Therefore, IL-12 provides an important link between innate and adaptive immunity, favoring the development of cellular immune responses that can better protect the host against viruses. Administration (ip) of IL-12 to mice induces an increase in serum corticosterone levels alone and produces a synergistic increase in the corticosterone response to LCMV infection (223). The corticosterone response in IL-12-treated, LCMV-infected mice was shown to be largely dependent on TNF (223). In addition, IL-12 mRNA has been detected in the brains (microglia) of LPS-treated mice (229), in the pituitary glands of LPS-treated rats (340), and in the adrenal glands of mice undergoing graft-versus-host disease (GVHD) (341).

Interleukin-18

Finally, IL-18 (also known as interferon-γ–inducing factor [IGIF] or IL-1γ) is a recently identified cytokine that has been detected in the brain, pituitary, and adrenal cortex, specifically in the zona reticularis and fasciculata. Microglial IL-18 mRNA expression is induced by LPS and adrenal IL-18 mRNA is upregulated by ACTH treatment (76,77,288). Interestingly, the IL-18 mRNA found in the pituitary and adrenal glands is of a different size than that found in immune tissues, indicating that IL-18 in endocrine tissue may be distinct from that in immune tissues (278). Although HPA axis stimulating activity has not yet been demonstrated for this cytokine, the localization of IL-18 in the three levels of the HPA axis suggests that it may play a modulatory role in immune-neuroendocrine interactions.

THE GLUCOCORTICOID RECEPTOR

There is no question that circulating levels of glucocorticoid hormones are relevant to steroid action, however, at the cellular level, activity of glucocorticoids is determined by local factors that regulate the access of free hormone to its receptor. Such factors include corticosterone binding globulin (CBG), 11β-hydroxysteroid dehydrogenase (11β-HSD), and the multidrug resistance transporter (MDR) (Fig. 5). All of the above have been shown to be altered under conditions of immune activation, whereby proinflammatory cytokines tend to decrease CBG levels, increase 11β-HSD-1 expression and reductase activity, and decrease MDR expression and/or function, thereby favoring an increase in glucocorticoid bioavailability (274).

The ultimate effect of glucocorticoids on immune system regulation is established at the level of the glucocorticoid receptor (GR). Upon glucocorticoid binding to cytosolic GR's, a conformational change in GR causes heat-shock protein 90 (hsp90) and other ancillary proteins to dissociate from the receptor, and the ligand-bound receptor then translocates into the nucleus.

Here, it dimerizes with another ligand-bound GR, thereby allowing it to alter the transcription rates of glucocorticoid–sensitive genes, either through protein-DNA interactions (transcriptional activation; involving GR binding to a glucocorticoid response element [GRE]) or through protein-protein interactions (transcriptional repression; involving GR binding to other transcription factors, e.g., NFκB and AP-1). A tissue's sensitivity to glucocorticoid activity can be influenced by a change in (a) GR number or affinity, or (b) GR function, including its ability for nuclear translocation, its interaction with other signal transduction pathways, and the expression of particular GR isoforms (Fig. 5). Proinflammatory cytokines have been shown to impact a number of these factors.

GR number and affinity

There is a large body of data on the impact of cytokines on GR number (188). Interestingly, however, the results are split into those studies that find an increase in GR number following cytokine administration and those that find a decrease. The discrepancy in results appears to depend on how the receptors were measured. Studies using whole-cell assay binding techniques tend to find an increase in cytokine-induced GR expression, while those using cytosolic receptor binding techniques tend to find GR number to be decreased. Results are further complicated by the fact that the studies utilizing whole-cell binding techniques tend to use longer incubation times (i.e., 24 h), whereas the studies employing cytosolic receptor binding tend to examine shorter incubation periods (i.e., 4–6 h). Few studies have documented changes in receptor affinity. However, Kam et al. (147) report that lymphocytes simultaneously exposed to Th1 and Th2 cytokines exhibit a reduced affinity of GR for glucocorticoids.

GR function

Several autoimmune/inflammatory disorders have been associated with impaired GR function, possibly contributing to the excessive inflammation characteristic of these illnesses. Proinflammatory cytokines (TNFα, IL-1, and IL-6) and cytokines that mediate lymphocyte growth and differentiation (IL-2, IL-4) have been found to inhibit GR function (188).

Although the mechanism by which cytokines inhibit GR is unknown, several possibilities have been considered. First, cytokines may influence GR function through their effects on GR translocation from the cytoplasm into the nucleus. For example, TNFα and IL-1 have been shown to block dexamethasone-induced nuclear GR translocation (2,228). Another possible mechanism by which cytokines may influence GR is through cross-talk among signal transduction pathways. For example, downstream in the IL-1 and TNFα signal transduction pathways are the transcription factors NFκB and AP-1 (which consists of jun and fos proteins). GR and NFκB/AP-1 have been shown to mutually antagonize each other's transcriptional activity through multiple mechanisms (3,81,165,280,326). In addition, IL-1 activates mitogen-activated protein kinase (MAPK) signaling pathways (i.e., p38 MAPK and jun N-terminal kinase [JNK]), which have been shown to be inhibitory to GR function (139,249,318,319). Finally, cytokines may affect GR function by altering the ratio of GRα:GRβ isoform expression. Alternative splicing of the human GR primary transcript produces two isoforms (135), GRα and GRβ, the latter of which may negatively regulate GR activity. Oakely et al. (216) have demonstrated that the GRα isoform binds hormone and activates glucocorticoid-responsive genes, while the GRβ isoform fails to bind hormone and activate glucocorticoid-responsive genes, and attenuates the trans-activation of the hormone-bound GRα isoform. These findings suggest that, when GRβ is present in excess in various tissues, it might repress glucocorticoid-mediated GRα function. In fact, Webster et al. (325) have shown that IL-1 and TNFα lead to the selective accumulation of GRβ protein in cells of lymphoid origin and the development of a glucocorticoid resistant state. Moreover, increases in GRβ levels have been found in immune cells of patients with glucocorticoid-resistant asthma (281) and colitis (137).

Although proinflammatory cytokines have been shown to exert inhibitory effects on GR function via downstream signaling molecules, we will see in the next section that GR function has been found to be stimulated during various viral infections. The differential *in vitro* effects of cytokines on GR versus *in vivo* viral effects on GR may be due to the presence of more complex interactions in an *in vivo* system and/or to the presence of a virus. Such *in vivo* changes in GR expression/function may be attributed to local factors released in immune tissues during infection or to viral components, themselves, that may act directly on brain sites involved in HPA axis regulation or on GR, itself.

HPA AXIS ACTIVATION DURING VIRAL INFECTION

Although considerable data exist describing the pathways by which purified cytokines or LPS (endotoxin) induce glucocorticoid release (274,300), HPA axis activity in response to viral infections, and the pertinent cytokines involved in such interactions, has received much less attention. By studying glucocorticoid release that is induced by a complex inflammatory stimulus, such as a virus, rather than a bolus of purified cytokine, one can study a more natural situation of immune–neuroendocrine interaction. This gives the advantage of eliciting immune and neuroendocrine responses that evolve over time and occur in the physiological milieu of an in vivo immune response (release and action of multiple cytokines at physiologically relevant concentrations). To examine the impact of viral infection on HPA axis function, investigators have employed polyinosinic polcytidilic acid (poly I:C), a synthetic double-stranded RNA used to mimic viral exposure, and Newcastle disease virus (NDV), which does not actively infect the host. As with LPS, both poly I:C and NDV produce a marked HPA response about 1–2 h post-injection. However, it cannot be concluded a priori that the delayed cytokine response usually elicited by a replicating virus (days as opposed to hours) interacts with the HPA axis in a similar manner as an acute challenge such as LPS, poly I:C, or NDV. In addition to poly I:C and NDV, we describe below what is currently known about HPA axis activation during infection with replicating viruses, including murine cytomegalovirus (MCMV), lymphocytic choriomeningitis virus (LCMV), influenza, herpes simplex virus type–1 (HSV-1), and human immunodeficiency virus (HIV). As will be demonstrated, immune–HPA interactions appear to be both virus specific and phase (of the immune response) specific.

Polyinosinic–polycytidylic acid (poly I:C)

Just as LPS has been used to model the cytokine cascade during a bacterial infection, poly I:C has been used to mimic viral infection. When administered systemically to mice or rabbits, poly I:C induces a rapid activation (1–2 h) of the HPA axis (91,190,253) (Fig. 6). This induced glucocorticoid response has been shown to be dependent on IL-6 in mice (253) and on CRH in rabbits (190). The IL-6 requirement for glucocorticoid release appears to be specific for virus-type stimuli, since IL-6 knockout mice treated with poly I:C (as well as MCMV) exhibit profoundly reduced corticosterone responses, as opposed to modest (but significant) decreases in LPS-treated mice and no significant reductions in restraint-stressed mice (253) (Fig. 7).

Newcastle disease virus (NDV)

NDV is a non-replicating virus, which like LPS and poly I:C, produces marked elevations in ACTH and corticosterone about 2h post ip injection when administered to mice or rats (although some studies report peak ACTH/corticosterone responses at 8 h post-infection) (35,38,88,91,220,248,277). Concomitant with these neuroendocrine changes, are increased brain concentrations of the norepinephrine catabolite, 3-methoxy, 4-hydroxyphenylethyleneglycol (MHPG; at 2 h p.i.) and tryptophan and the serotonin catabolite, 5-hydroxyindoleacetic acid (5-HIAA) (at 8 h p.i.) (90,91). The NDV-induced ACTH/corticosterone response also was observed when animals were injected with virus-free supernatants derived from co-cultures of human peripheral blood leukocytes or mouse spleen

cells with NDV, indicating that stimulation of the HPA axis was due to a product released from the NDV-stimulated leukocytes, and not NDV itself (35,38). It was concluded that IL-1 was the most likely mediator of the NDV-induced ACTH/corticosterone response, since pretreatment of the supernatant with IL-1–antisera blocked its stimulatory effect on the HPA axis in the NDV-injected animals (35,38). Moreover, pretreatment of NDV-infected mice with IL-1 receptor antagonist (IL-1ra) prevented the neuroendocrine and neurochemical responses to NDV (91). The NDV-induced corticosterone response also is abolished in hypophysectomized mice (38,88,91,220) and CRH-Ab–treated rats (248), demonstrating its dependence on an intact pituitary and CRH.

Murine cytomegalovirus (MCMV)

MCMV is a cytopathic virus that induces an early natural killer (NK) cell-mediated, anti-viral defense. The anti-viral immune response is characterized by high levels of IL-12 and NK cell–produced IFN-γ (224), and NK cell–mediated liver inflammation (258). In addition to the induction of the aforementioned cytokines, the proinflammatory cytokines, TNFα, IL-1, and IL-6, are induced during the innate immune response to MCMV infection. Peak serum cytokine levels occur around 36–44 h after infection and are paralleled by peak neuroendocrine (ACTH and corticosterone) responses, which occur at 36 h after MCMV infection (253) (Fig. 6). Ruzek et al. (253) have shown that the MCMV-induced corticosterone response is dependent on IL-6, with IL-1α contributing to IL-6 production (Fig. 7). TNFα is required for the development of hepatic necrotic foci and increased levels of liver enzymes in serum, both signs of liver pathology (222). As glucocorticoids have been shown to negatively regulate proinflammatory cytokine production during MCMV infection, if glucocorticoids are removed by adrenalectomy (ADX), IL-12, IFN-γ, TNFα, and IL-6 production, as well as splenic mRNA for a wider range of cytokines (including IL-1α and β), increase and the mice die due to septic shock (254). Corticosterone replacement or the administration of TNF-antisera to MCMV-infected, ADX mice restores survival (254) (Fig. 8). Therefore, the glucocorticoid response during MCMV infection is essential for protection against TNFα-mediated lethality.

To determine whether the MCMV-induced ACTH and corticosterone responses are dependent upon CRH, work in our labs has employed both CRH immunoneutralization and CRH-knockout techniques (273). Acute administration of a CRH-antibody (Ab) completely eliminated ACTH responses to both low- and high-dose MCMV. However, corticosterone responses in CRH-Ab-treated animals remained apparent in mice infected with low-dose MCMV and were robust in mice infected with high-dose MCMV (Fig. 9). CRH-knockout (KO) mice exhibited robust corticosterone responses to both MCMV doses, despite reduced baseline and MCMV-induced ACTH. Interestingly, robust corticosterone responses in CRH-Ab-treated and CRH-KO mice were associated with exaggerated IL-6 levels, and IL-6 and corticosterone concentrations in infected CRH-Ab-treated animals were significantly correlated. Neutralization of IL-6 responses in infected CRH-KO mice reduced corticosterone responses by ~70% (273) (Fig. 10). Finally, MCMV-infected mice deprived of ACTH by hypophysectomy failed to elicit glucocorticoid responses, despite elevated plasma IL-6 concentrations (273) (Fig. 11). Taken together, these results suggest that a greater than normal induction of IL-6 compensates for the absence of a normal CRH-dependent ACTH surge during MCMV infection. This enhanced IL-6 response, in turn, may mediate a direct immune-adrenal pathway that can become a predominant driving force for glucocorticoid induction in the absence of CRH. However, the presence of ACTH appears to serve as a necessary permissive factor, enabling direct cytokine actions on the adrenal gland. This requirement of an intact pituitary for corticosterone responses to an immune challenge also has been shown by Besedovsky et al. in rats injected with culture supernatants from mitogen-stimulated peripheral blood or spleen cells (43) and animals injected with NDV (36). However, the MCMV studies were the first to use an actual replicating virus and the first to demonstrate that the presence of

low, permissive levels of ACTH were sufficient (along with deficient CRH responses and exaggerated IL-6 responses) to stimulate corticosterone release.

Lymphocytic choriomeningitis virus (LCMV)

LCMV replicates in many organs, including the spleen, thymus, lymph nodes, kidney, and brain (if administered intracranially) (87). Depending on the strain, LCMV can be either cytopathic (clone 13 or WE) or non-cytopathic (clone E350). LCMV induces high levels of early circulating IFN-α/β and of NK cell-mediated cytotoxic activity. However, NK cell IFN-γ production is not induced, and NK cells do not significantly contribute to anti-viral defenses (47). Viral titers in the spleen and blood peak on days 3–5 following infection and decline rapidly thereafter (337). During LCMV infection, late $CD8^+$ T cell responses are prominent, in which CTL activity and IFN-γ production is protective (47). Our labs have worked with three strains of LCMV (systemically injected): LCMV clone 13, which induces peak corticosterone responses around day 7 post-infection, corresponding with a loss of T cell responses and viral persistence; LCMV variant WE, which induces glucocorticoid responses similar to LCMV clone 13, but is not associated with reduced T cell responses or viral persistence; and LCMV clone E350, which fails to induce a glucocorticoid response, along with the lack of significant inflammation or pathology (188) (Fig. 6).

These results suggest that immune activation alone is not sufficient for stimulation of the HPA axis. We hypothesize that (in the absence of pain or other conditions that directly limit physiological function, for example, respiratory distress in influenza virus infection) the presence of significant inflammation or immunopathology with associated release of high serum levels of proinflammatory cytokines (innate or adaptive) may be required for glucocorticoid induction (189). Despite the fact that animals infected with LCMV clone E350 exhibit no significant increase in glucocorticoid release, reduced cytosolic GR binding in immune tissues of infected animals, such as the spleen and thymus, was detected (189). Decreased cytosolic GR binding may be indicative of increased GR activation (may imply an increase in nuclear translocation of the receptor). Indeed, GR activation was enhanced in the spleen of infected animals given an acute injection of corticosterone (189). Such changes in GR expression/function may be attributed to local factors released in immune tissues during infection. Since $CD8^+$ T cells are an actively proliferating cell type in the spleen during LCMV infection, increased GR activation in the spleen might decrease the number and/or activity of this cell type, therefore restraining $CD8^+$ T cell activation at a local level (189). LCMV clone E350–infected mice do, however, exhibit significant corticosterone responses when treated with IL-12 (223). Although, IL-12 alone induces a corticosterone response in mice, the synergistic induction of corticosterone between LCMV and IL-12 has been shown to be dependent on IL-2 and TNF (223).

As mentioned before, LCMV-WE induces a late $CD8^+$ T-cell response that mediates anti-viral defenses and peak corticosterone responses around 7 days post-infection, corresponding to the time of T-cell activation. LCMV-WE–infected ADX mice exhibit increased mortality, along with greater levels of plasma and splenic IFN-γ and TNFα, and a greater number of IFN-γ^+ and TNFα^+ $CD8^+$ T cells (primed for cytokine expression) relative to sham-operated mice. $CD8^+$ KO mice (sham or ADX) no longer show an LCMV-WE induced increase in plasma and splenic IFNγ and TNFα levels and, therefore, exhibit reduced mortality (ADX). Hence, the $CD8^+$ T cell–mediated corticosterone response is essential for protection against $CD8^+$ T-cell–mediated lethality during LCMV-WE infection (although the cytokines that mediate corticosterone responses and lethality have yet to be determined) (259).

Intra-cranial (ic) inoculation of LCMV (strain Arm-53b–replicates to higher levels in the brain than in the periphery) induces a fatal $CD8^+$ T cell-mediated encephalitis (64). Central LCMV infection produces an early increase in TNFα, IL-1α/β, and IL-6 mRNA expression by resident

brain cells and infiltrating monocytes; and a later immune response, characterized by an increase in IFN-γ mRNA expression by infiltrating T cells, concomitant with further increased expression of monokine transcripts (64). In addition to a direct cytolytic action of LCMV-specific CTLs, lymphocytic choriomeningitis may be mediated by the cytotoxic effects of these cytokine, IFN-γ in particular (64). HPA axis activity has not been studied during ic LCMV infection, but one may speculate a biphasic response concomitant with the early peak in proinflammatory cytokines, followed by the later peak in T cell cytokines and may be crucial in controlling the LCMV-induced CNS inflammation and T cell–mediated encephalitis.

Influenza

Influenza virus is cytolytic for epithelial cells of the lung. As the infection progresses, the inflammatory response is dominated by monocyte and T cell infiltration to the site of virus replication (23). Elimination of the virus is dependent on T cell-mediated anti-viral mechanisms. Mice infected with the influenza virus exhibit prolonged corticosterone responses, apparent from about day 2 until about 1 week post-infection (89,130,131). Similar to NDV-injected mice, influenza-infected mice exhibit increases in brain noradrenergic activity (particularly in the hypothalamus) and tryptophan levels that parallel HPA axis activation (89). Interestingly, Hermann et al. (131) demonstrated that mice infected with influenza, actually exhibit two peaks in their corticosterone responses: the first, apparent at 2–3 days post-infection, and the second peak, apparent at 7–8 days post-infection. In the murine model of influenza viral infection, virus titers peak at 48–72 h post-infection, concomitant with the activation of macrophages and the release of proinflammatory cytokines, such as TNFα, IL-1, and IL-6 (128). Therefore, the early corticosterone peak may be due to HPA axis stimulation by these proinflammatory cytokines. The second peak in plasma cortiscoterone levels may be due to HPA axis stimulation by T cell cytokines, such as IL-2 and IFN-γ, since it is around this time that influenza-specific T cell responses occur (4,85). On the other hand, since extensive lung pathology exists at these later times, along with labored respiration, it is possible that the later corticosterone peak may be driven by physical distress (131). Increased GR activation also has been detected in the liver and lung during influenza infection (112).

Herpes simplex virus type–1 (HSV-1)

Herpes simplex virus type-1 (HSV-1) is a neurotropic virus, which when inoculated into various peripheral tissues in animals, invades the peripheral nervous system, travels to the brain, and results in encephalitis, primarily affecting temporal and limbic brain regions (100, 296). Upon corneal inoculation of HSV-1 in rats, marked increases in ACTH and corticosterone levels are apparent by day 3 post-infection, peak around day 7, and are still elevated on day 14 post-infection (28). However, no concomitant changes in hypothalamic or ME CRH content are detected (28). On day 7 post-infection, replicating virus is found only in the brainstem (asymptomatic infection) (28). In fact, corneal HSV-1 inoculation leads to the infection of brainstem regions such as the locus coeruleus and the raphe nuclei, resulting in changes in norepinephrine (NE) and serotonin (5-HT), respectively (17,186,226). In addition, corneal inoculation with a neurovirulent, but not with an avirulent strain of HSV-1, increases IL-1β mRNA expression in the brainstem and hypothalamus, coinciding with elevated serum corticosterone levels (26). Since there was no evidence of invasive cellular inflammation in these brain regions, the authors concluded that the IL-1β mRNA was expressed by resident brain cells (26). Moreover, Ben-Hur et al. (26) demonstrated that the HSV-1–induced corticosterone response is dependent upon intact NE innervation of the PVN via the VNAB. Hence, HSV-1 may indirectly affect the hypothalamus and other brain regions involved in HPA axis regulation through stimulation of brainstem monoamine release and/or through the activation of centrally induced cytokines.

The inoculation of virulent HSV-1 strains into the PVN of rats also induces elevated serum ACTH and corticosterone levels around day 3 post-infection (along with overt clinical signs of encephalitis and cellular inflammation of the PVN). However, unlike corneal inoculation, PVN inoculation of virulent HSV-1 strains is accompanied by CRH depletion from the ME (reflecting an increase in release), a more widespread induction of IL-1β mRNA in the brain, and the induction of prostaglandins (PGE_2) in various brain regions (including the hypothalamus and brainstem) (30). Because inoculation with a non-virulent HSV-1 strain failed to elicit such responses, it was concluded that activation of the HPA axis was not due to viral replication, but was dependent on neurovirulence (30). Also supporting the contention that HPA activation is not due to viral replication, is the finding that icv inoculation of HSV-1 induces early ACTH and corticosterone responses (at 3.5 h post-infection), before any virus replication could occur, which is dependent on the central induction of IL-1β (27). In addition, brain-derived cytokines and prostaglandins appear to contribute to the clinical syndrome of HSV-1 encephalitis, particularly during early stages of the disease, when virus load is low and cellular inflammation has not yet evolved (30). Nevertheless, the containment of HSV-1 replication, and hence the development of encephalitis, is dependent on a timely (relative to viral spread) and efficient, HSV-1–specific $CD8^+$ T cell response in the brain (7). Of note, immunization with a nonvirulent HSV-1 strain protects animals, not only from the lethal coutcome of infection with a neurovirulent strain, but also from all the clinical and behavioral signs of the disease, including fever, aggressive behavior and motor hyperactivity, brain prostaglandin production, and HPA axis activity (29).

As for HSV-1 effects on GR function, HSV-1 infection of primary human gingival fibroblast (HGF) cells was found to increase nuclear NFκB expression and DNA binding and increase expression and nuclear translocation of GR, while an increase in glucocorticoid-driven reporter gene activity was observed in human embryo kidney cells (99). Erlandsson et al. (99) also showed that dexemethasone (Dex) treatment of HGF cells prior to, but not simultaneously with, HSV-1 infection increased viral yield. Since NFκB activity is necessary for efficient HSV-1 replicaton (5), Erlandsson hypothesized that this phenomenon may be due to reduced cytosolic availability of GR at the time of HSV-1 infection (since GR would already be bound by Dex and translocated to the nucleus), and therefore HSV-1–induced GR activity could no longer counteract NFκB activity (99).

Human immunodeficiency virus (HIV)

Two hallmarks of immunopathogenesis in the progression of HIV-infection to AIDS are the loss of $CD4^+$ T cell function in response to antigens and the reduction in $CD4^+$ T cell numbers (271). In addition, a strong cell-mediated (Th1) immune response to HIV is more critical in preventing the progression of HIV infection to AIDS (73,74). Since glucocorticoids modulate the Th1/Th2 cytokine balance, the level of HPA axis activation in HIV-positive individuals may play a crucial role in the hosts ability to control viral spread. HIV infection is associated with neuroendocrine disturbances, including impaired regulation of the HPA axis. Many studies report that HIV-positive patients, symptomatic as well as asymptomatic, have increased basal ACTH/cortisol levels (12,45,71,75,169,175,187,316), but blunted ACTH and cortisol responses to stress (166) or a CRH challenge (12,45,175). In addition to cytokine-induced stimulation of the HPA axis, these abnormalities may be enhanced further by the release of toxic viral products, such as the envelope protein, gp120, and the structural protein, Vpr. Icv injection of gp120 into rats increases serum levels of ACTH and corticosterone (16,289), which have been shown to be dependent on the central induction of IL-1 (289) and prostaglandins (PGs) (16). In addition, Raber at al. (245) have demonstrated that gp120–overexpressing transgenic mice exhibit elevated plasma ACTH and corticosterone levels, as well as pituitary ACTH content. Gp120-treatment of rat or mouse hypothalamic explants increases CRH mRNA, intrahypothalamic CRH protein, and CRH release (242), as well as AVP release

(245). These actions of gp120 on CRH and AVP production are mediated by nitric oxide synthase (NOS). Other activities of viral products include the capacity of Vpr to act as a co-activator of the GR, thereby enhancing GR signaling and the effects of glucocorticoids on HIV replication (156,157,246,272). More specifically, recombinant Vpr can potentiate GR-meditated increases in virion production, downregulation of NFκB and proinflammatory cytokine induction, and programmed cell death (192,272). Therefore, gp120- and Vpr-induced GR activation may be deleterious to the HIV-infected host, by inducing glucocorticoid hypersensitivity and hence, further lowering $CD4^+$ T cell number and function and other required anti-viral immune responses. On the other hand, Kino et al. (158) have shown that glucocorticoids exert a direct suppressive effect on the HIV-1 promoter, thus acting protectively for the host. Interestingly, a subset of HIV-infected patients develop glucocorticoid resistance in the face of hypercortisolism, and exhibit an increased production of proinflammatory/Th1 cytokines, including IFN-α and IL-2, therefore favoring anti-viral defenses and limiting the progression of HIV infection (210–213). Moreover, macrophages from these patients show glucocorticoid receptor (GR) changes, consisting of decreased GR affinity for glucocorticoids and increased GR number (214). According to Norbiato et al. (212), reduced glucocorticoid sensitivity (due to decreased binding affinity of the GR) in HIV disease may be caused by HIV itself, the HIV-1 vpr gene, and/or the simultaneous presence of Th1 (IL-2) and Th2 (IL-4) cytokines.

Summary

Taken together, these observations suggest that the kinetics and magnitude of glucocorticoid production, as well as the changes in GR expression/function induced by systemic viral infection, may be specific to the virus, the kinetics of the immune response to the virus, and the extent of virus-induced pathology. In other words, glucocorticoids will be induced at crucial times to protect against either/both early proinflammatory cytokine-mediated pathology/lethality (e.g., MCMV, influenza, HSV-1) or later T cell–mediated pathology/lethality (e.g., LCMV clones 13 and WE, influenza, HSV-1, HIV). In cases where no significant inflammation/pathology occurs (e.g., LCMV clone E350), glucocorticoid responses may be minimal. As both HSV-1 and influenza virus infections can cause considerable additional physical distress, which may itself stimulate the HPA axis, it is likely that other (non-cytokine) pathways as well are contributing to induction of glucocorticoid responses at later times during infection.

CONCLUSION

During viral infection, the immune system, via early proinflammatory cytokines (TNFα, IL-1, and IL-6) and later T cell cytokines (IL-2 and IFN-γ), stimulates glucocorticoid release by acting at all three levels of the HPA axis. Cytokine receptors have been detected at all HPA axis levels and therefore, each level can serve as an integration point for immune and neuroendocrine signals. It appears that the initial activation of the HPA axis is mediated via CRH dependent pathways, for example, through the traditional CRH to ACTH to glucocorticoid pathway. However, when a sustained glucocorticoid response to an immunological stressor is necessary, complementary, CRH-independent mechanisms of glucocorticoid induction may occur to maintain the initial rise in glucocorticoid levels. These alternative pathways include the direct action of cytokines on the pituitary and adrenal glands. The direct action of cytokines on the pituitary and adrenal glands, however, may not be completely independent of upstream neuroendocrine factors (CRH and ACTH, respectively), where CRH/ACTH may be required as permissive factors to sensitize sub-hypothalamic levels of the HPA axis to circulating cytokines. The local production of cytokines at each level of the HPA axis also may contribute to the amplification and maintenance of elevated HPA activity

during chronic inflammation/viral infection. Therefore, each level of the HPA axis contains its own local cytokine network.

Once cytokines have stimulated glucocorticoid release to keep inflammatory responses in check, it is also important to regulate the resultant activity of glucocorticoids themselves. Either too much or too little activity of steroid hormone may result in pathological consequences, due to the inappropriate shaping of the immune response to viral infection. Therefore, several local factors are in place to maintain appropriate glucocorticoid activity at the level of the immune cell (e.g., CBG, 11β-HSD, MDR pump). Moreover, GR number/function can be altered by cytokines and viral products. In conclusion, a closed loop, regulatory feedback circuit exists, with redundant pathways for cytokines to stimulate glucocorticoid release and regulate glucocorticoid activity, which in turn, is crucial to prevent the overshoot of inflammatory responses that may be detrimental to the host organism.

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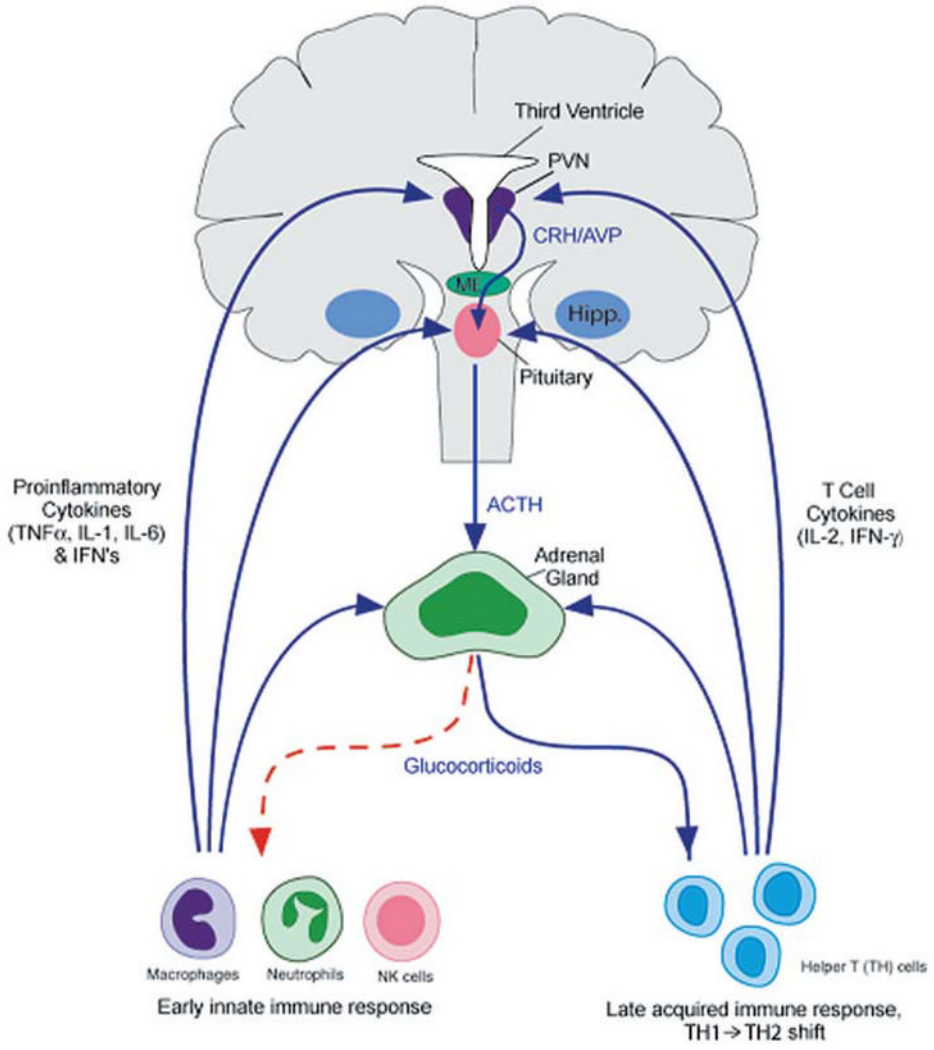

FIG. 1.

Bidirectional communication between the immune system and the hypothalamic-pituitary-adrenal (HPA) axis (human brain). The immune system, via early innate proinflammatory cytokines (TNFα, IL-1, and IL-6) and interferons, and late acquired T cell cytokines (IL-2 and INF-γ), stimulates glucocorticoid release by acting at all three levels of the HPA axis. In turn, glucocorticoids negatively feedback on the immune system to suppress the further synthesis and release of proinflammatory cytokines (red dotted line). In addition, glucocorticoids play an important role in shaping downtream acquired immune responses, by causing a shift from cellular (Th1/inflammatory) to humoral (Th2/anti-inflammatory) type immune responses. By doing so, glucocorticoids protect an organism from the detrimental consequences of overactive inflammatory immune responses. ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; CRH, corticotropin-releasing factor; hipp, hippocampus; IFN, interferon: IL, interleukin; ME, median eminence; PVN, paraventricular nucleus of the hypothalamus; TNF, tumor necrosis factor. Reprinted with modifications by permission from Silverman et al. (274).

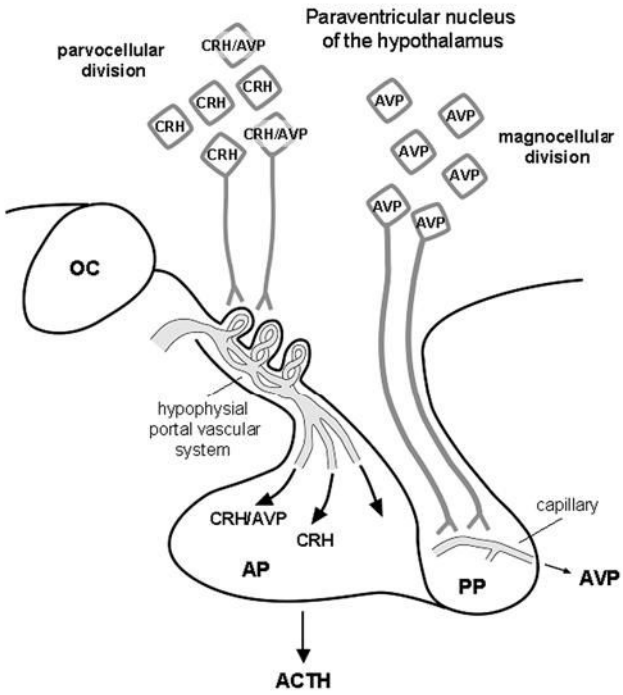

FIG. 2.

The hypothalamo-pituitary unit. CRH and CRH/AVP neurons originating from the parvocellular division of the PVN of the hypothalamus terminate in the external layer of the median eminence (ME), releasing CRH and or CRH/AVP into the hypophysial-portal circulation, which then act on corticotrophs in the AP to release ACTH into the general circulation. In addition, AVP neurons originating from the magnocellular division of the PVN pass through the internal layer of the ME and terminate on capillaries in the PP to release AVP into the general circulation. ACTH, adrenocorticotropic hormone; AP, anterior pituitary; AVP, arginine vasopressin; CRH, corticotropin-releasing factor; OC, optic chiasm; PP, posterior pituitary; PVN, paraventricular nucleus of the hypothalamus;

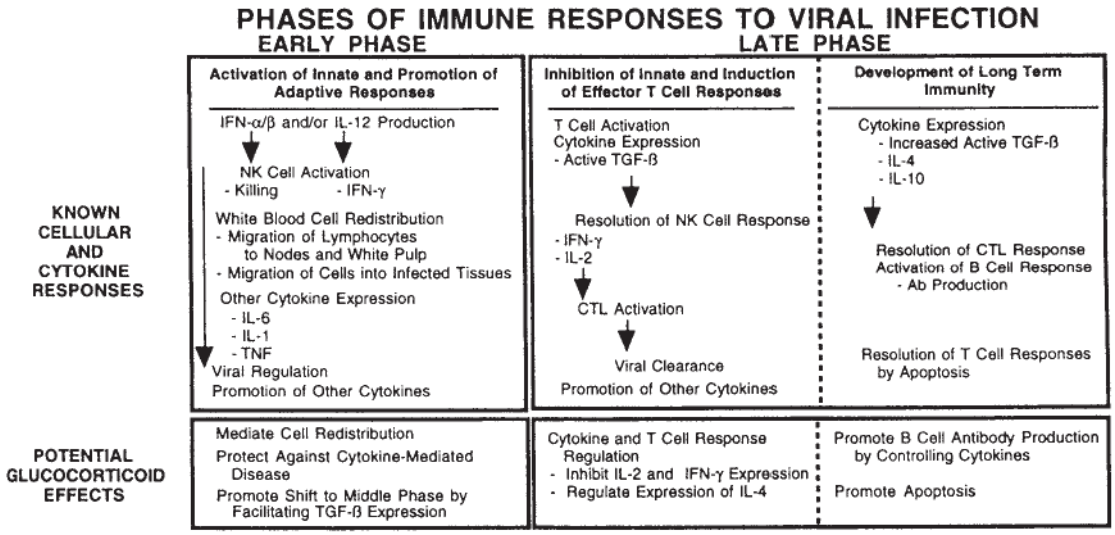

FIG. 3.

Cellular and cytokine responses to viral infection and potential immunomodulatory effects of glucocorticoids. Ab, antibody; CTL, cytotoxic T lymphocyte; IFN, interferon; IL, interleukin; NK, natural killer; TNF, tumor necrosis factor; TGF, transforming growth factor. Reprinted by permission from Miller et al. (188).

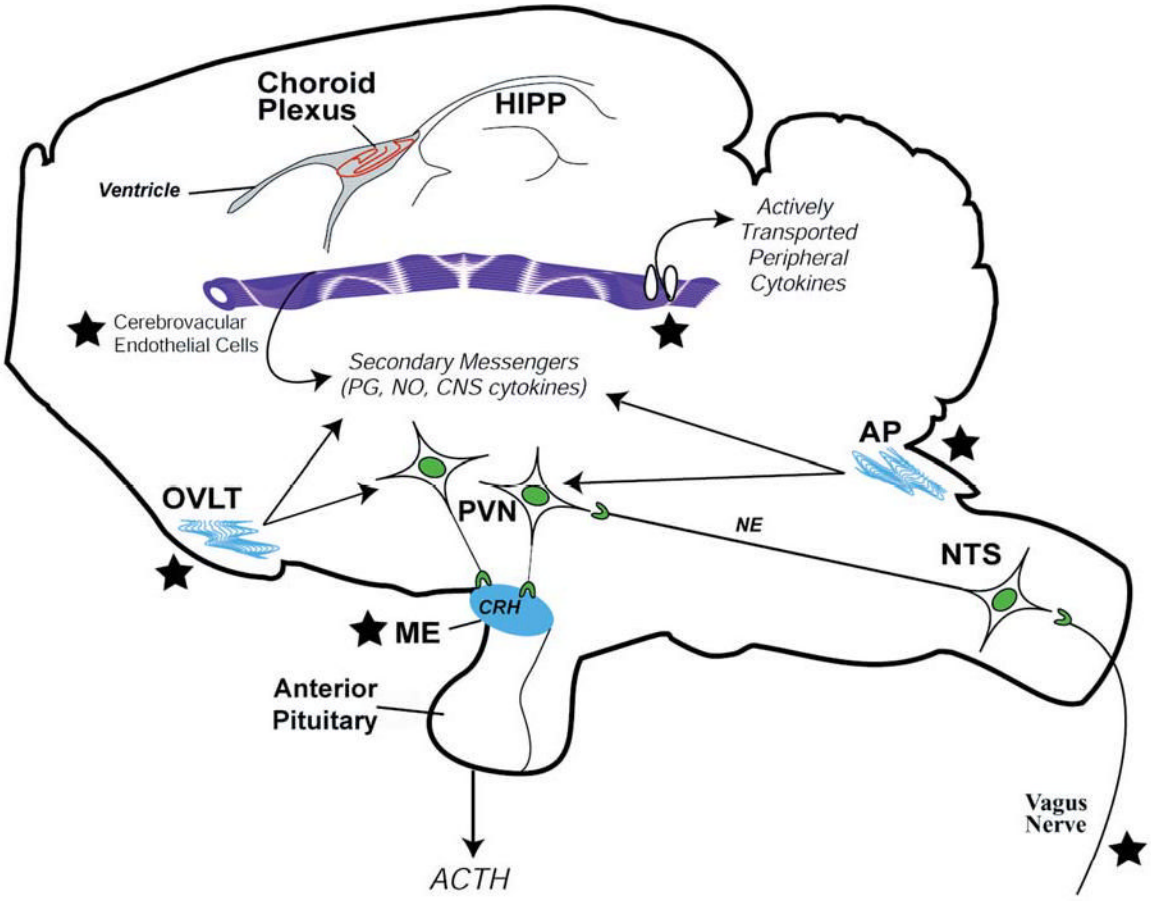

FIG. 4.

Proposed mechanisms by which peripheral cytokines activate CRH-producing neurons of the PVN in the hypothalamus (rat brain). ACTH, adrenocorticotropic hormone; AP, area postrema; CRH, corticotropin-releasing hormone; HIPP, hippocampus; ME, median eminence; NE, norepenephrine; NO, nitric oxide; NTS, nucleus tractus solitarius; OVLT, organum vascularis of lateral terminalis; PG, prostaglandins; PVN, paraventricular nucleus of the hypothalamus. ★ = site of entry of peripheral cytokine signals. Reprinted by permission from Silverman et al. (274).

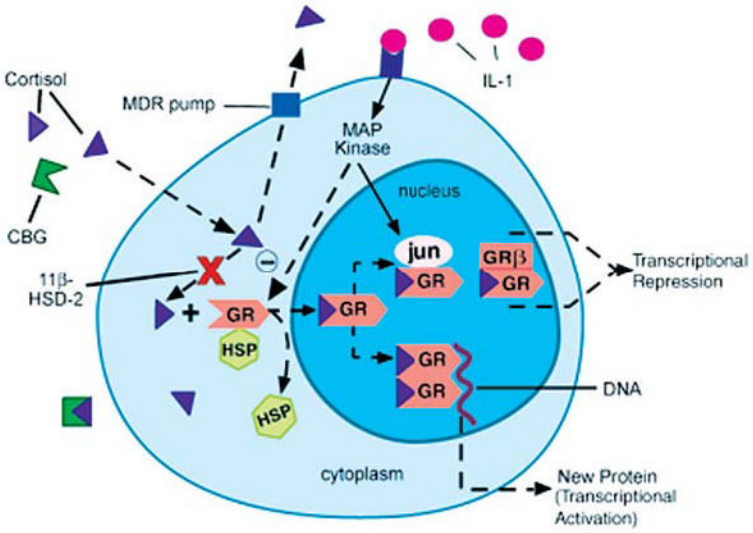

FIG. 5.

Local factors regulating glucocorticoid bioavailability and action. (**1**) corticosterone binding globulin (CBG), (**2**) 11*β*-hydroxysteroid dehydrogenase (11*β*-HSD), (**3**) multidrug resistance transporter (MDR pump), (**4**) glucocorticoid receptor (GR = GR*α*) nuclear translocation, (**5**) GR interaction with other transcription factors (AP-1 [jun/fos], NF*κ*B), and (**6**) ratio of GR*α*:GR*β* isoform expression. HSP, heat shock protein; MAP kinase, mitogen-activated protein kinase. Reprinted with modifications by permission from Silverman et al. (274).

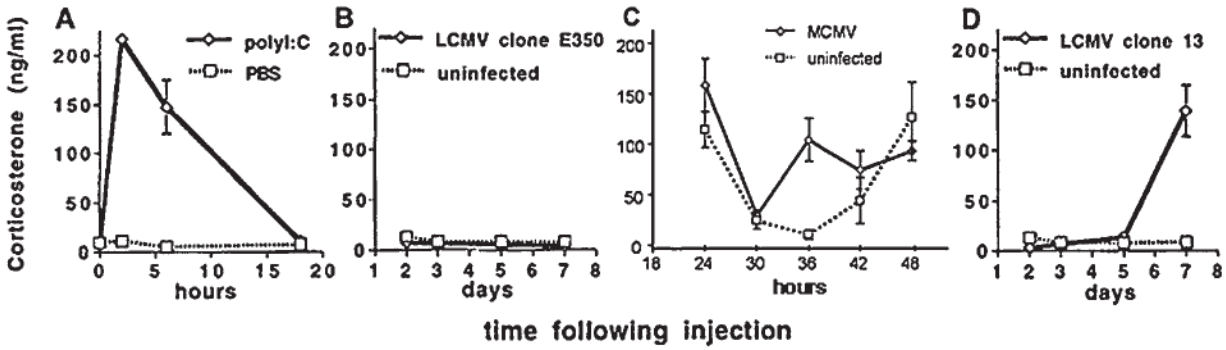

FIG. 6.

Kinetics and magnitudes of endogenous glucocorticoid responses vary depending on viral challenge. Serum corticosterone responses to polyinosinic-polycytidylic acid (poly I:C) administration and during viral infections are shown. Mice were injected with 100 μg poly I:C (**A**) or infected with 2×10^4 PFU of lymphocytic choriomeningitis virus (LCMV) clone E350 (**B**), 5×10^4 PFU murine cytomegalovirus (MCMV) (**C**), or 1×10^6 PFU LCMV clone 13 (**D**). Serum samples were collected under low-stress conditions during the morning (36 h post MCMV-infection) and examined for levels of serum corticosterone. Harvests were at indicated times following treatment or infection. Data are presented as means ± SEM. Reprinted with modifications by permission from Miller et al. (188,189).

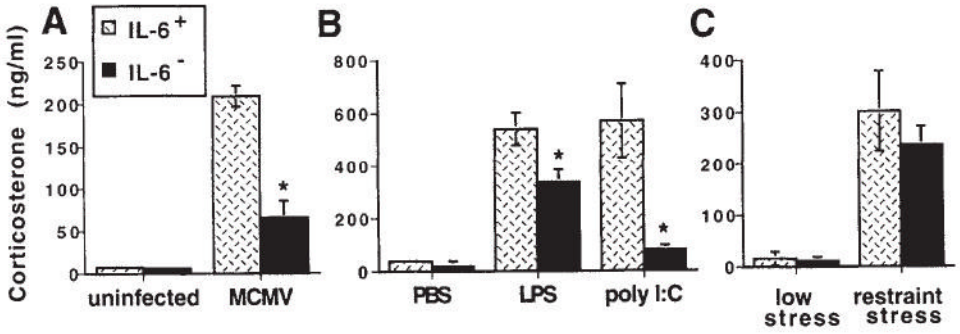

FIG. 7.

Interleukin-6 (IL-6) plays a pivotal role in the induction of endogenous glucocorticoids in response to viral challenges. Serum corticosterone levels following murine cytomegalovirus (MCMV), lipopolysaccharide (LPS), polyinosinic-polycytidylic acid (poly I:C), or restraint stress administration in IL-6–deficient and wild-type mice. Corticosterone levels were measured in serum collected from mice under low-stress conditions at 36 h following infection with 5×10^4 PFU MCMV (**A**); 2 h following injections with PBS, 50 μg LPS, or 100 μg poly I:C (**B**); or after 30 min of restraint (**C**). Data are presented as means ± SEM. Results are significant at $*p < 0.05$. Reprinted by permission from Miller et al. (188,253).

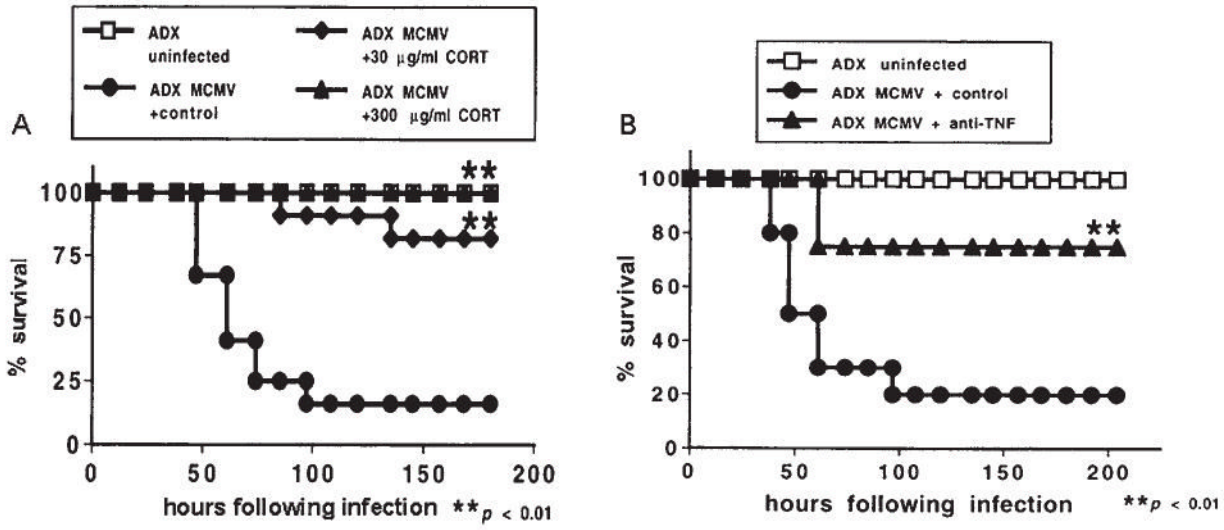

FIG. 8.

Role of glucocorticoids in protection against cytokine (TNF)–mediated lethality. (**A**) Adrenalectomized (ADX) mice were vehicle injected (squares) or infected with MCMV (1×10^5 PFU/mouse) 5 days following surgery and either not given (circles) or given corticosterone in 0.9% saline as drinking water at either 30 µg/mL (diamonds) or 300 µg/mL (triangles). Control mice received vehicle-treated water. Denoted p value represents significant differences between corticosterone and vehicle-treated MCMV-infected ADX mice. (**B**) Control (circles) or anti-TNF (triangles) antibodies (Abs) were administered 8–10 h before infection of ADX mice. Denoted p value represents significant differences between TNF and control Ab-treated MCMV-infected ADX mice. Data are presented as means ± SEM. Results are significant at $^{**}p < 0.01$. Reprinted by permission from Silverman et al. (274,254).

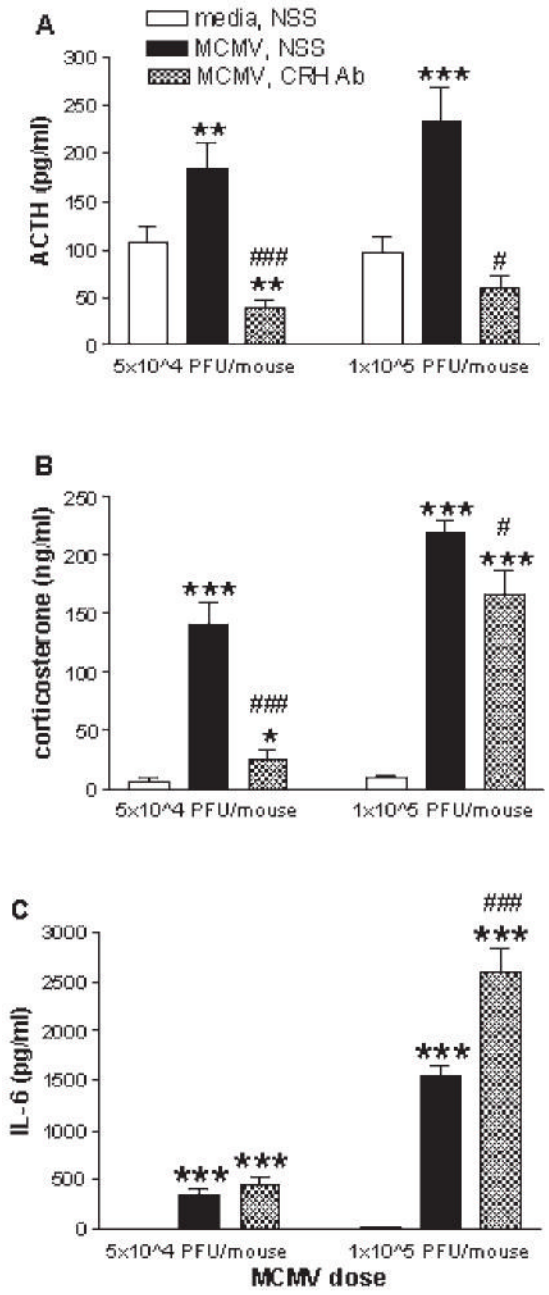

FIG. 9.

Effect of the administration (ip) of a CRH-Ab on low (5×10^4 PFU/mouse) and high (1×10^5 PFU/mouse) dose MCMV-induced plasma ACTH (**A**), corticosterone (**B**), and IL-6 (**C**) responses. Two hundred microliters of either normal sheep serum (NSS) or CRH-antisera was administered 8 h prior to the peak MCMV-induced corticosterone response (28 h post-infection). Trunk blood was collected from C57BL/6 mice at 36 h post-infection (n = 5–11 animals per group). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; compared with media/NSS group within dose. $^{\#}p < 0.05$; $^{\#\#}p < 0.01$; $^{\#\#\#}p < 0.001$; compared with MCMV/NSS group within dose. One-way ANOVA was used within dose. Because of limited amounts of Ab, a media/

CRH-Ab group was not included in this experiment. Reprinted by permission from Silverman et al. (273).

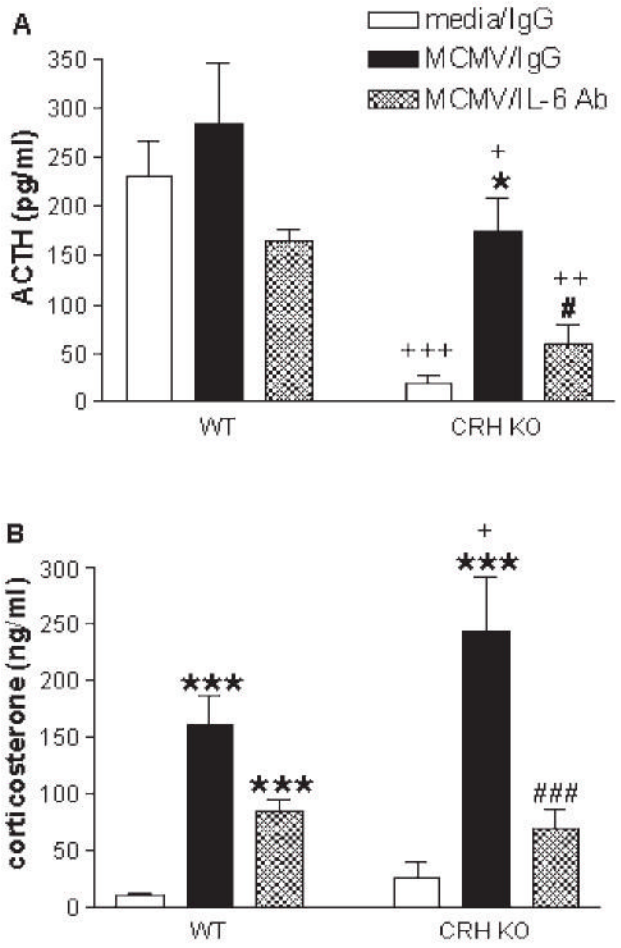

FIG. 10.

Effect of the administration (ip) of an IL-6–Ab on plasma ACTH (**A**) and corticosterone (**B**) levels in WT and CRH-KO mice after injection with MCMV (5×10^4 PFU/mouse) or vehicle. The IL-6-Ab (1 mg/mouse) was administered 16 h prior to the peak MCMV-induced corticosterone response (20 h post-infection). Trunk blood was collected from mice at 36 h post-infection ($n = 4$–8 animals per group). $^{*}p < 0.05$; $^{***}p < 0.001$ (*t* test for WT/MCMV/IL-6–Ab vs. WT/media/IgG); compared with media/IgG group within genotype. $^{\#}p < 0.05$; $^{\#\#\#}p < 0.001$; compared with MCMV/IgG group within genotype. $^{+}p < 0.05$; $^{++}p < 0.01$ (*t* test); $^{+++}p < 0.001$; compared with respective WT group. Two-way ANOVA was used (unless otherwise indicated). Because of limited amounts of Ab, a media/IL-6–Ab group was not included in this experiment. Reprinted by permission from Silverman et al. (273).

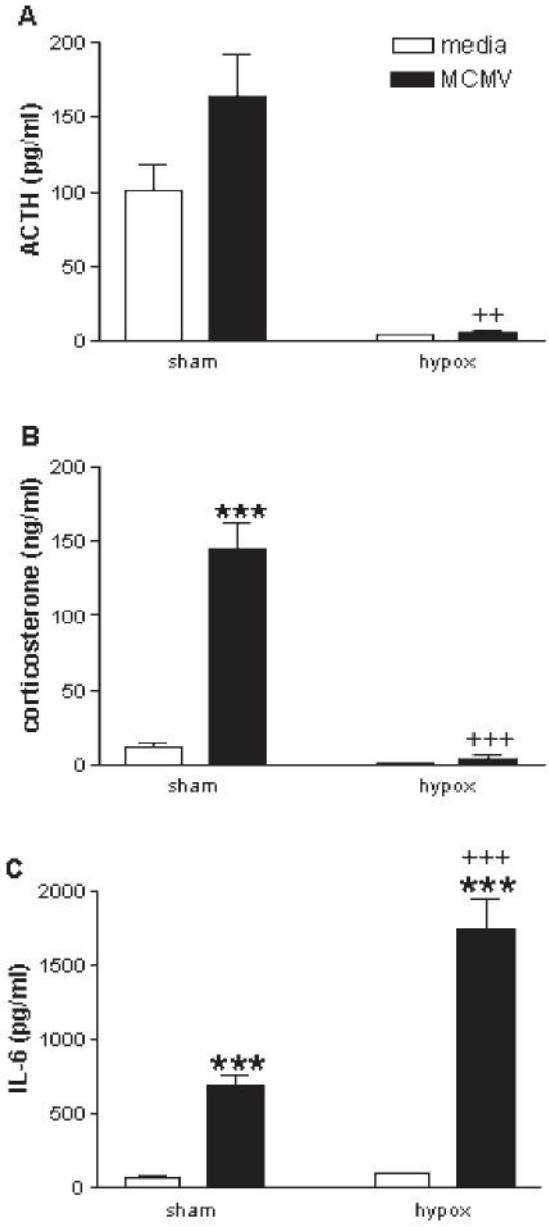

FIG. 11.

Plasma ACTH (**A**), corticosterone (**B**), and IL-6 (**C**) levels after injection with MCMV (1×10^5 PFU/mouse) or vehicle in sham-operated or hypophysectomized (hypox) C57BL/6 mice. Trunk blood was collected from mice at 36 h post-infection ($n = 3–11$ animals per group). ***$p < 0.001$; compared with media group within surgical-manipulation. $^{++}p < 0.01$; $^{+++}p < 0.001$; compared with respective sham group. Two-way ANOVA indicated a significant interaction of surgery and infection on corticosterone and IL-6 responses for MCMV. Reprinted by permission from Silverman et al. (273).