Perspectives Series: Cytokines and the Brain

Neural-immune Interactions in Health and Disease

Esther M. Sternberg (Series Editor)
National Institute of Mental Health, Bethesda, Maryland 20892

Cytokines interact with the nervous system in numerous ways. These molecules are expressed within the central nervous system (CNS)[1] and play an important role in neuronal cell death and survival. In addition, peripheral cytokines released from immune cells during inflammation can stimulate a variety of physiological, neuroendocrine, and behavioral responses of the CNS, including fever, sleep, hypothalamic-pituitary-adrenal (HPA) axis activation, sickness, and other behaviors. The nervous system, in turn, regulates the immune system via several routes, systemic and local, including neuroendocrine pathways and the autonomic and peripheral nervous systems (Fig. 1).

To date, virtually all known cytokines or their receptors have been sought (and found) in many CNS cells, including neurons (1–7). Many experimental approaches have been used to define the extent to which cytokines and their receptors are expressed in nervous system tissues and the extent to which these tissues respond to cytokines. These include in situ hybridization and Northern blot analysis for mRNA expression; radioimmunoassay and ELISA for peptide content; autoradiographic localization of receptors by radiolabeled cytokine binding in brain slices; immunohistochemistry to define cytokine pathways in the nervous system; neuropeptide secretion by brain explants, primary cell cultures, or cell lines exposed to cytokines and cytokine production by brain explants, primary cell cultures, or cell lines exposed to neuropeptides (7). Table I shows the extent to which these molecules have been identified in neurons, astrocytes, oligodendrocytes, and microglia by these approaches.

Cytokines can be expressed under resting physiological conditions in these resident CNS cells, but are also induced during injury and development. In addition, under pathological conditions, cytokines can be expressed in infiltrating macrophages in the brain. Northern blot analysis, RT-PCR, and in situ hybridization for cytokine mRNAs have been used to identify cytokine overexpression in CNS tissue in various disease states. These studies show many different patterns of expression of cytokines throughout the brain in the context of different diseases. Such different patterns of expression may reflect different cell sources of cytokines, or different stimuli (antigenic, proinflammatory, neuropeptide).

In all these situations, cytokines appear to play an important role in neuronal cell death and survival, although the precise mechanisms are still being elucidated. In vitro studies in mixed neuronal/glial cultures show that several cytokines play dual context-dependent maturation roles in either promoting or preventing apoptotic neuronal cell death. For example, IL-lα exhibits a dose-related neurotoxic effect in mature fetal dorsal root ganglion cells in culture (8) which can be blocked with neutralizing IL-1 antibody. In contrast, in immature neurons in culture, IL-1α prevents the naturally occurring apoptotic neuronal cell death that occurs during electrical blockade with tetrodotoxin. Other cytokines that exhibit such dual context-dependent effects on neuronal cell death and survival include TNF-α, which mediates apoptosis through a TNF-α–ceramide signaling pathway and mediates survival through TNF-α–NFκB signaling pathways (9). In nondepolarizing, low K^+ culture conditions, TNF-α, IL-10, and IL-13 all promote survival (10). This dual effect of cytokines expressed within the CNS is similar to the role played by cytokines in the periphery, that of helping to select populations of mature cell types by enhancing survival of some and eliminating others through apoptosis. In immune cells, and similarly in neurons, the transcription factor NFκB may play a pivotal role in these context-dependent effects on cell survival or death, acting much like a switch that when induced can block death signals and when suppressed or blocked can allow death signal activation of apoptotic pathways. Further discussion of these mechanisms will be presented in the second article in this series (11).

Although the mechanisms for these effects remain to be fully elucidated, the role of such cytokine expression in CNS disease can be deduced by the combined evidence of in vitro and in vivo studies. Several lines of evidence strongly suggest that the neurotoxic effect of cytokines overexpressed in pathological conditions could contribute to many neurodegenerative features of CNS diseases previously not considered to be inflammatory in origin. In vivo studies, using transgenic mice in which cytokines are targeted to the brain with a specific GFAP promoter, strongly suggest that cytokine overexpression in the brain plays an important role in the pathogenesis of several CNS neurotoxic and neurodegenerative disorders. Transgenic mice have been used successfully to define the pathological and clinical effects of excessive cytokine expression in the CNS. Such studies indicate that despite targeting with the same GFAP promoter, different transgenes, such as IL-6, IL-3, TNF-α, and IFN-α, are expressed in different locations in the CNS and are associated with very different local pathology, including inflammation, neurodegeneration, and demyelination.

Address correspondence to Esther M. Sternberg, M.D., Chief, Section on Neuroendocrine Immunology and Behavior, Clinical Neuroendocrinology Branch, NIMH/NIH, Bldg. 10, Rm. 2D-46, 10 Center Dr. MSC 1284, Bethesda, MD 20892-1284. Phone: 301-402-2773; FAX: 301-402-1561.

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1. *Abbreviations used in this paper:* ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; BBB, blood brain barrier; CNS, central nervous system; CRH, corticotropin-releasing hormone; HPA, hypothalamic-pituitary-adrenal.

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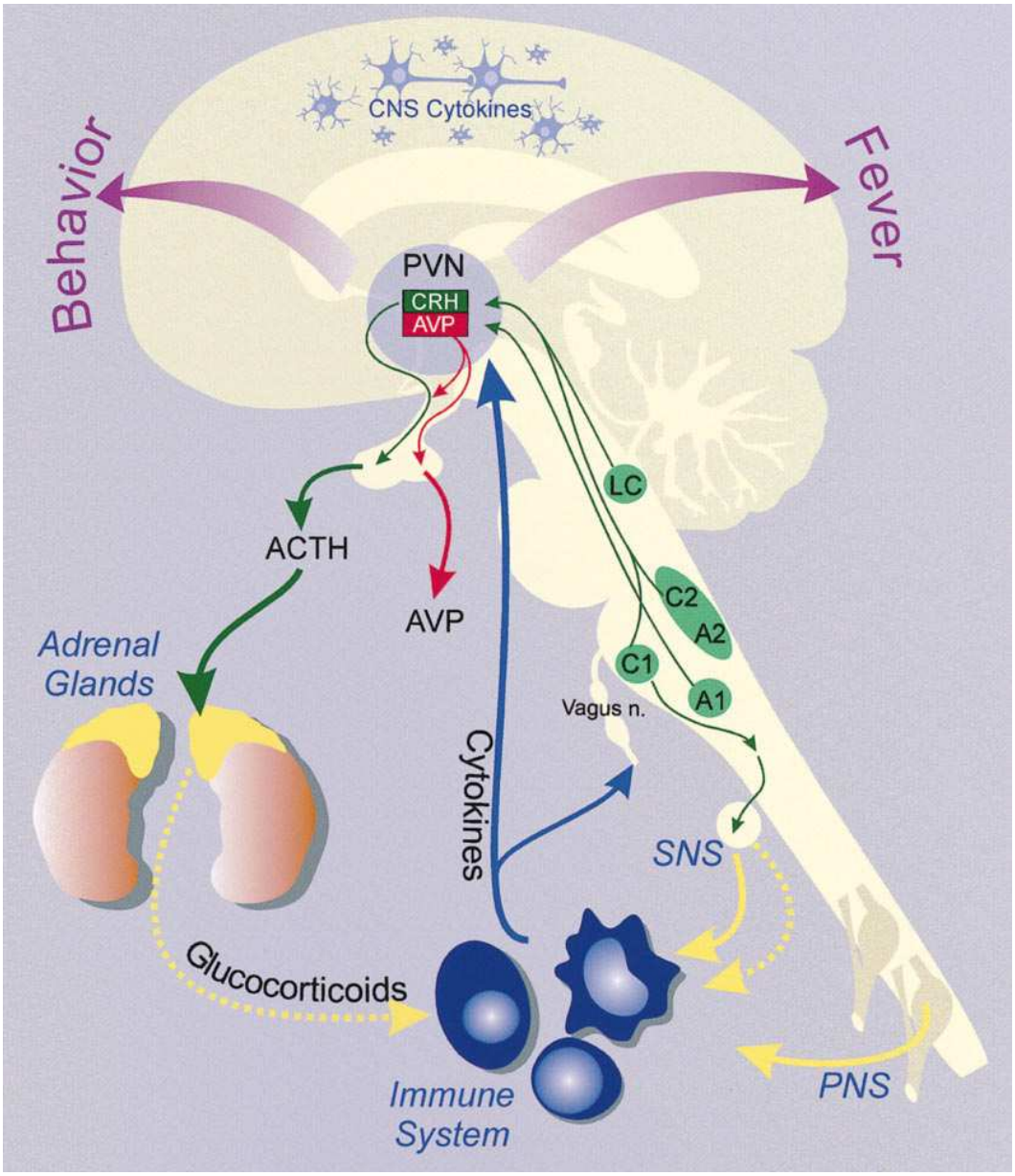

Figure 1. Neural-immune interactions. Schematic of the communication between the immune and central nervous systems. Peripheral cytokines stimulate a variety of CNS functions, including neuroendocrine responses, behavioral patterns, sleep, and fever. They do so through several routes, including by directly crossing the BBB, by stimulating second messengers, and via the vagus nerve. Peripheral cytokines stimulate the hypothalamus to release CRH and the pituitary gland to release ACTH. Once hypothalamic CRH is released, it stimulates ACTH release from the anterior pituitary. Hypothalamic AVP can act as a costimulator with CRH to ACTH release. Pituitary ACTH stimulates the adrenal glands to release glucocorticoids which suppress inflammation, completing this counterregulatory feedback loop between the immune and central nervous systems. Neural communications between the hypothalamus, the locus ceruleus, and brainstem noradrenergic nuclei (*C1* and *A1*) stimulate the sympathetic nervous system, which also modulates inflammation. The immune system is also regulated by neuropeptides released from peripheral nerves. *PNS*, Peripheral nervous system; *SNS*, sympathetic nervous system. Broken arrows indicate inhibitory effects and solid arrows indicate stimulatory effects. Cytokines expressed within the brain play a different role than peripheral cytokines, and may activate the acute phase response and play a role in neuronal cell death and survival. Illustration by Naba Bora, Medical College of Georgia.

Resultant clinical symptomatology varies in these transgenic animals, as would be predicted from the location of the pathological lesions associated with expression of each transgene (12).

That the neurotoxic effect of cytokines plays a role in human neurodegenerative diseases is also suggested by the pattern of overexpression of specific cytokines in human brain in patients dying from dementia associated with infection. For example, in the brains of victims dying from neuroAIDS, in contrast to those dying from accidents or myocardial infarction, there is an increased concentration of cytokine expression around infiltrating giant cells. This suggests, although it does not prove, a role for cytokines in the dementia associated with AIDS. Similarly, in brains of patients dying from Alzheimer's disease, there is marked expression of TGF-β_2 in glial cells and in neurofibrillary plaques and tangles (13). However, the role of TGF-β, if any, in these conditions is not yet fully understood. Other clinical CNS syndromes associated with dementia in which the neurotoxic effects of cytokines may play an important role include inflammatory/autoimmune diseases such as multiple sclerosis; vascular illnesses such as stroke; infectious illnesses, such as *Toxoplasmosis gondii*; and nerve trauma. The striking feature of this list is that although previously these illness were considered wholly unrelated, their boundaries are blurring, since an important final common pathway to neurodegeneration in all these syndromes appears to be mediated through neurotoxic effects of cytokines released from accumulated inflammatory cells. In other articles in this series, the neurotoxic effects of cytokines, their patho-

Table I. Cytokines and Their Receptors That Have Been Identified in Brain

Cytokine	Neurons	Astrocytes	Oligodendrocytes	Microglia
IL-1	C/R	C/R	C/R	C
IL-2	C/R		R	R
IL-3	C/R	C/R	R	R
IL-4		R	R	R
IL-5		C		C/R
IL-6	C/R	C/R		C/R
IL-7		R	R	R
IL-8	R	C/R		R
IL-9		R		
IL-10		C/R		C/R
IL-11		C		
IL-12				C
IL-13				
IL-14				
IL-15		C		C
TNF-α	R	C/R	R	C/R
IFN-γ		C/R		R
TGF-β		C/R	C/R	C/R
GM-CSF	R	C/R	R	R
M-CSF		C	R	C/R

C, Cytokine; *R*, receptor.

logical and clinical implications, and potential therapies derived from this information will be discussed in detail in relation to neuroAIDS, other CNS infections (Griffin article to appear in next issue of *The Journal*), and stroke (11).

It is important to distinguish between effects on neuronal cell death and survival of cytokines expressed within the brain, and the effects of peripheral cytokines in stimulating brain functions. Peripheral-derived cytokines act more like hormones, stimulating neuroendocrine and other neuronal pathways, such as the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes and sympathetic nervous system responses. Stimulation of these pathways ultimately sets into motion a series of neuronal and neuroendocrine events that regulate the immune system at many levels. CNS stimulation by peripheral cytokines can also result in characteristic behavioral patterns, including sickness and other behaviors, sleep, and fever.

A central question that concerned neurobiologists early on in this field was how or even whether molecules as large as cytokines (in the range of 15 to 20 kD) released from peripheral immune cells could cross the relatively impermeable blood brain barrier (BBB) to stimulate the brain (14). Recent studies suggest that not only does this happen, but there are several mechanisms by which this can occur. For example, cytokines can cross at leaky areas in the BBB, the circumventricular organs. Convincing evidence has also been presented recently for active transport of specific cytokines across the BBB. Another very rapid means by which peripheral cytokines can signal the brain directly is via the vagus nerve (15, 16). Cytokines also bind to their receptors expressed in cerebral blood vessels, and thus signal the brain through second messengers such as nitric oxide (NO) and prostaglandins by induction of their synthesizing enzymes (17). The routes and mechanisms by which peripheral cytokines signal the brain will be discussed in detail in a later article in this series (Licinio article to appear in next issue of *The Journal*).

After peripheral cytokine stimulation of the CNS, the central hormonal stress response is activated and a cascade of hormones is released, including corticotropin-releasing hormone (CRH) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the pituitary gland, and glucocorticoids from the adrenal glands (Fig. 1). The final effector molecules in this loop (cortisol in humans and corticosterone in rodents) play an important role in regulating immune function. Initially it was thought that glucocorticoids were largely immunosuppressive. However, more recent studies indicate that they are more accurately classed as immunomodulatory, although their overall effect is still immunosuppressive. Thus, glucocorticoids do not uniformly suppress production of all cytokines; they selectively suppress some, while stimulating the production of others. In a human whole blood cytokine stimulation and glucocorticoid suppression assay, some cytokines show differential sensitivity to glucocorticoid suppression, with IL-12, TNF-α, and IL-1 most sensitive and IL-6 relatively resistant to glucocorticoid suppression (18). In rodents, physiological concentrations of glucocorticoids stimulate IL-4 and IL-10. We have found recently similar increases in IL-10 in ex vivo studies of human whole blood, suggesting that this effect may not be simply due to lymphocyte redistribution in vivo (our unpublished data). The overall result of these selective effects of glucocorticoids on suppressing proinflammatory cytokines and stimulating antiinflammatory cytokine production is to push the immune response away from a TH1 and toward a TH2 pattern of response (Fig. 2). This relatively specific effect of glucocorticoids on immune response patterns provides further support for the thesis that glucocorticoids play a role in regulating immune responses in physiological settings.

The mechanism by which glucocorticoids exert these differential effects on cytokine production and suppression is not known. However, it is known that glucocorticoids generally exert their effects through binding to a soluble cytoplasmic receptor, displacing heat shock protein, and moving to the nucleus. Once there, the ligand receptor complex binds directly to DNA binding sites, or GREs, and induces protein synthesis. By interfering with availability of transcription factors directly, such as by competition with NFκB binding sites (19) or indirectly, by induction of the NFκB binding protein IκB, glucocorticoids can downregulate protein synthesis (Fig. 3). It is likely that a similar mechanism exists for cytokine production and suppression, although this remains to be proven.

In addition to these neurohormonal routes by which the CNS can modulate immune function, there is also a rich network of innervation of immune organs that likely plays an important role in local immune modulation, either at the sites of inflammation or in immune organs as cells traffic through them. Virtually all immune organs, including the spleen, thymus, bone marrow, and lymph nodes, are densely innervated by various components of the autonomic and peripheral nervous systems. Interruptions of the sympathetic nervous system in animals have been shown to enhance or suppress inflammation, depending on the stage of development at which the system is ablated, and whether the system is interrupted at a local or systemic level (20). In these anatomical connections, nerve endings and immune cells are in close apposition (21), in some

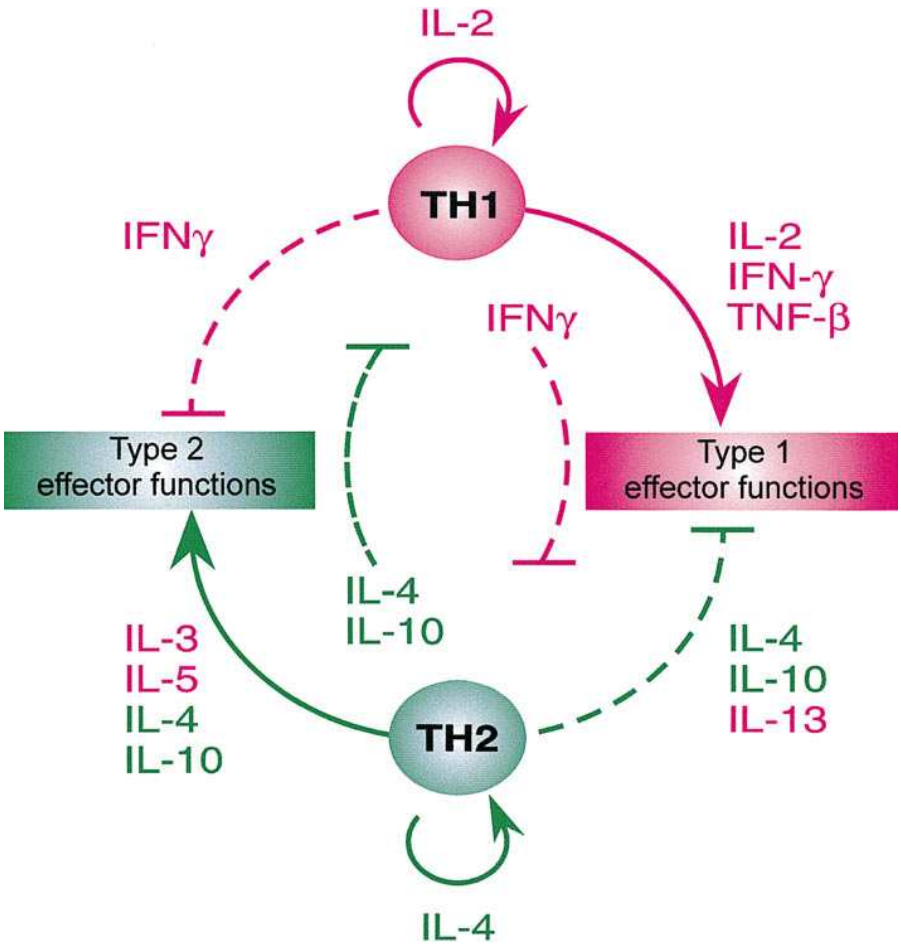

Figure 2. Effect of glucocorticoids on TH1 and TH2 patterns of immune responses. Immune responses and cytokine production can be classed as type 1 (TH1) or type 2 (TH2), representing cellular (TH1) and humoral (TH2) immune functions of mature immune cells. These patterns are characterized by different patterns of cytokine production, as shown. Cytokines that stimulate TH2 responses include IL-3, IL-5, IL-4, and IL-10; cytokines that stimulate TH1 responses include IL-2, IFN-γ, and TNF-β. Solid arrows represent stimulation and broken lines represent inhibition. By stimulating cytokines highlighted in green and suppressing cytokines shown in red, glucocorticoids tend to cause a shift from TH1 to TH2 patterns of response. Figure modified from reference 31 to show effects of glucocorticoids on TH1 and TH2 patterns of immune responses.

cases so tightly related that they appear to make synapse-like connections. In such close microenvironments, neuropeptides and neurotransmitters could exert different effects on immune cell function than in systemic hormonal settings. In general, neuropeptides, neurohormones and neurotransmitters, such as vasoactive intestinal polypeptide, substance P, or CRH released at sites of inflammation have a proinflammatory, immunostimulatory effect (22, 23).

Numerous interactions have been described between neuropeptides and cytokines at the paracrine, or local cellular level. Not only do neuropeptides affect immune cell function locally, but various cytokines are also released in large quantities from different nervous system cell types. For example, astroglial cultures stimulated with vasoactive intestinal polypeptide release a wide range of cytokines, including IL-3, GM-CSF, IL-6, TNF-α, IFN-γ, IL-1β, and IL-1α (24), and astroglia and microglia release different quantities of specific cytokines, such as IL-1β, in a dose-related manner. Given the variety of cytokines and neuropeptides that could be released locally by closely spaced but heterogeneous populations of cells, the potential for complex interactions in such microenvironments becomes enormous.

The physiological and pathophysiological effects of this signaling of the CNS by the immune system, and the countermodulation of the immune system by the CNS are profound and are just beginning to be understood. Organisms in which neuroendocrine-immune regulatory loops are impaired have an increased susceptibility to inflammatory diseases, while overstimulation of neuroendocrine responses can lead to impaired immune function and enhanced susceptibility to infectious disease. Table II lists human clinical illnesses that have been associated with a depressed HPA axis function. Table III lists animal models in which interrupting or reconstituting the HPA plays a role in susceptibility, resistance, or severity of illness. Manipulations of inbred animal strains provide more direct evidence than can be obtained in humans that both the HPA axis

Table II. Human Illnesses Associated with Blunted HPA Axis Responses

Allergic
Asthma
Atopic dermatitis
Inflammatory/autoimmune
Rheumatoid arthritis
Fatigue states
Burn-out
Post-traumatic stress disorder
Fibromyalgia
Chronic fatigue syndrome
Psychiatric
Atypical depression

Table III. Animal Models of Inflammatory Disease in which Altered HPA Axis Responses Are Associated with Inflammatory Disease Susceptibility

Chicken
Spontaneous thyroiditis
Avian scleroderma
Rat
Inflammation (carrageenan)
Arthritis (scw, adjuvant)
EAE
Septic shock
Mouse
SLE
Infections: TB, viral

and the autonomic nervous system play an important role in immune regulation and pathophysiology of susceptibility and resistance to inflammatory and infectious diseases.

One primary example is the Lewis rat. This rat is an inbred animal strain that has long been used in the study of a variety of inflammatory/autoimmune diseases, including many models of inflammatory arthritis (SCW, collagen, adjuvant), experimental allergic encephalomyelitis, uveitis, and thyroiditis. This animal's enhanced susceptibility to inflammatory disease is related, at least in part, to its blunted HPA axis responses to inflammatory and other stimuli. In contrast, HPA axis hyperresponsive Fischer rats are relatively resistant to developing disease in response to the same inflammatory stimuli (25). Reconstitution of the HPA axis in Lewis rats by intracerebroventricular transplantation of fetal hypothalamic tissue from inflammatory resistant Fischer rats substantially reduces both

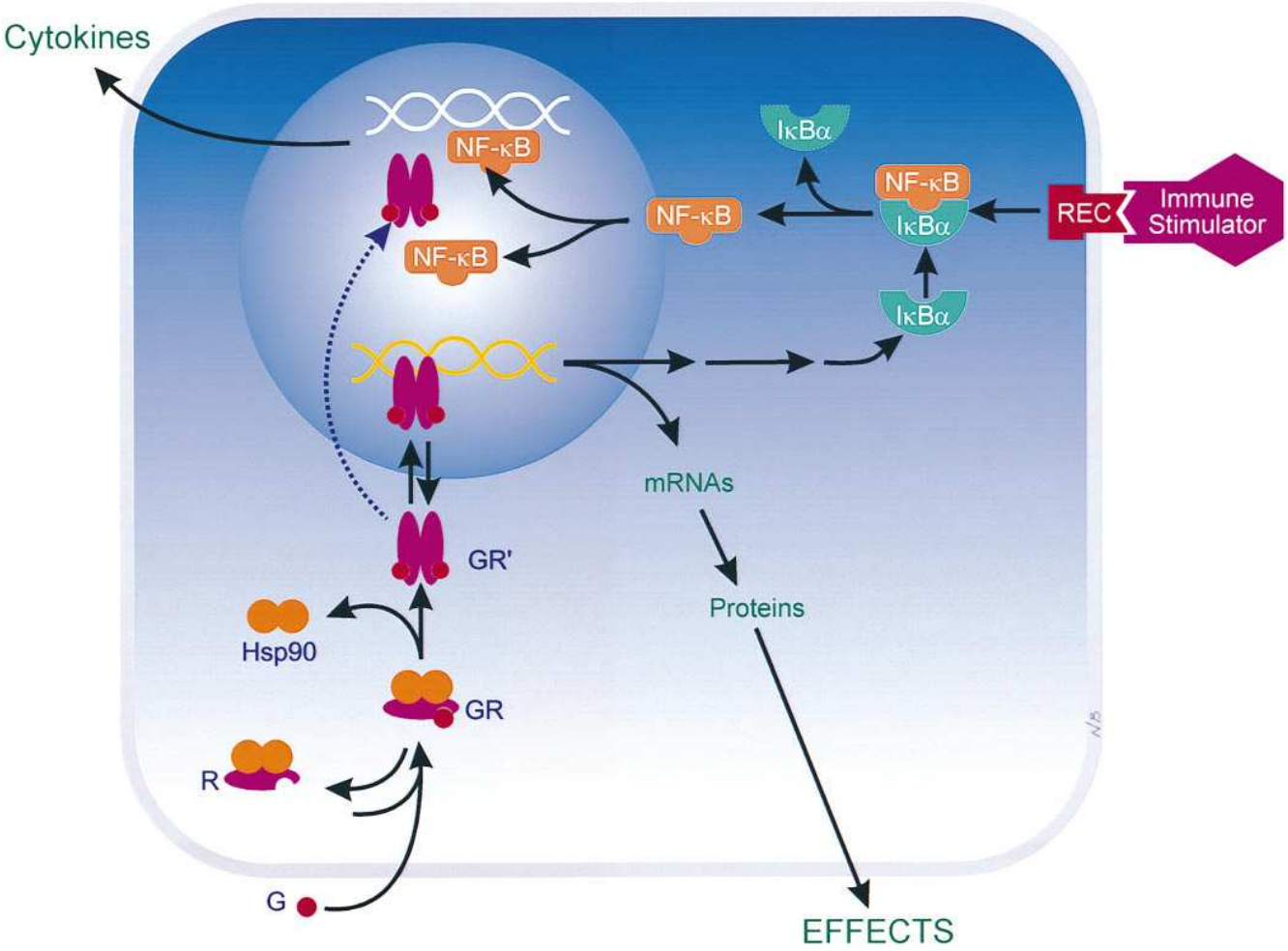

Figure 3. Molecular mechanisms of glucocorticoid effects on cytokine production. Schematic of glucocorticoid receptor binding and translocation to nucleus and interactions with nuclear transcription factors. Glucocorticoid hormone (*G*) binds to the cytosolic glucocorticoid hormone receptor (*GR*), displacing heat shock protein 90 (*Hsp90*). The activated hormone receptor complex (*GR′*) dimerizes and moves to the nucleus (GR′n), binds to DNA at glucocorticoid response elements (GREs), and induces or decreases mRNAs and proteins encoded by the gene to which it has bound. Glucocorticoids can also regulate gene transcription by interfering with transcription factor binding to DNA response elements, such as NFκB. Glucocorticoids can block NFκB stimulation of gene transcription directly by competing with NFκB at DNA binding sites, or indirectly by induction of the NFκB binding protein, IκBα. Solid arrows represent stimulatory pathways. Broken arrows represent inhibitory pathways. Illustration by Naba Bora, Medical College of Georgia.

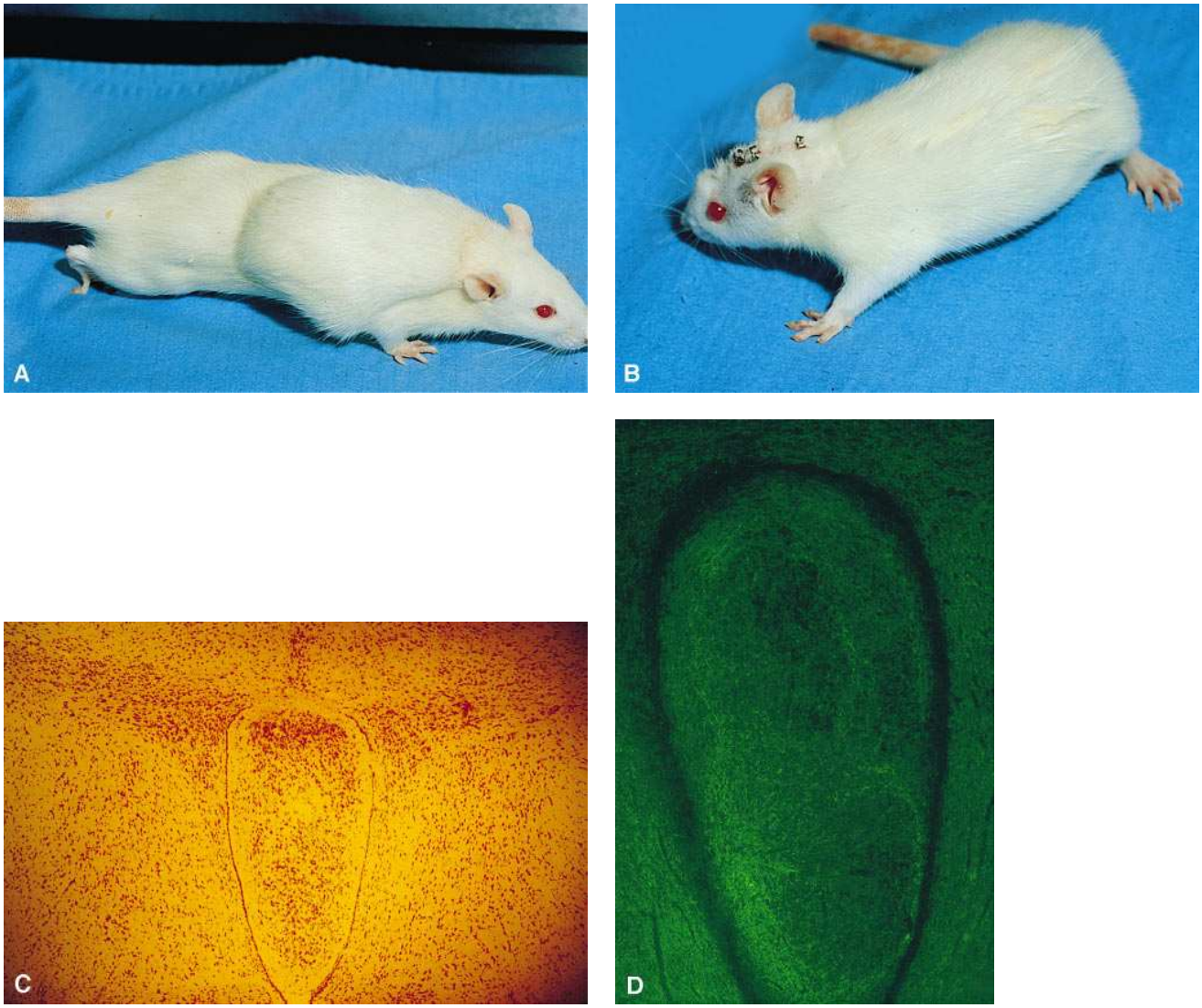

Figure 4. Effect of intracerebroventricular transplantation on the peripheral carrageenan response. (*A*) Large inflammatory pouch that develops in naive Lewis rats in response to subcutaneous carrageenan and (*B*) absence of inflammatory pouch in a Lewis rat which has received an intracerebroventricular hypothalamic transplant from an inflammatory resistant Fischer rat. (*C*) Section through the third ventricle, at the level of the paraventricular nucleus, from a transplanted rat. The graft tissue can be seen growing within the third ventricle. (*D*) Graft within the third ventricle stained for neurofilaments with the monoclonal antibody SMI-31.

peripheral carrageenan-induced inflammation (a model for innate inflammation) (Fig. 4) and clinical features of experimental allergic encephalomyelitis (a thymic-dependent autoimmune disease). This effect is mediated in part by enhanced host HPA axis responses, as evidenced by reconstitution of LPS-induced plasma corticosterone responses, and increased host hypothalamic CRH expression in transplanted rats (26). However, host hypothalamic CRH expression is also enhanced in control nonhypothalamic fetal neuronal tissue transplantation conditions that do not significantly suppress peripheral inflammation, suggesting that factors other than hypothalamic CRH may play a role in the inflammatory suppressive effects of the transplants. Intracerebroventricular transplantation of fetal neuronal tissue as well as sham surgery are associated with increased norepinephrine content in the spleen, suggesting that conditions in which both HPA axis and autonomic responses are augmented may play a role in mediating peripheral inflammatory susceptibility.

Various other abnormalities in neural pathways known to both regulate these neuroendocrine responses and to modulate inflammation are seen in Lewis rats, including blunted late-phase, sympathoneuronal noradrenergic responses to glucoprivic stress (27). Lewis rats also exhibit enhanced IL-1–induced hypothalamic secretion of arginine vasopressin (AVP) compared with Fischer rats (28), suggesting a shift in Lewis rats from CRH to AVP control of the stress response. Such shifts from a primarily CRH to AVP driven stress response have been shown to occur in situations of chronic stress, such as chronic peripheral inflammation and after a single injection of IL-1 (29). Such a shift to a back-up mechanism for control of the stress response would tend to confer an evolutionary advantage and might promote survival in this CRH hyporespon-

sive strain. Or it could simply be secondary to repeated subclinical exposures to IL-1 in this highly inflammatory susceptible strain. Lewis rats also show lower serotonin (5-hydroxytryptamine, 5-HT1A) receptor number and 5-HT content in the hippocampus as compared with Fischer rats, and higher GABA-benzodiazepine receptor number in the hypothalamus. Many of these differences in neurotransmitter pathways known to regulate CRH in CRH hyporesponsive, inflammatory susceptible Lewis rats compared with CRH hyperresponsive, inflammatory resistant Fischer rats may be secondary to their relative low and high glucocorticoid responses. However, an alternative explanation is that multiple neurotransmitter/neuropeptide systems that regulate CRH and inflammation could differ in these two inbred strains.

Whether these multiple differences in the molecular components of the stress response are related to multiple genes, or to a single gene that resets several neurotransmitters, is not resolved. Mounting evidence from genetic linkage and segregation studies in humans and animal models of autoimmune inflammatory disease suggests that multiple disease susceptibility genes, each with relatively small effects, may be operating to predispose to inflammatory and autoimmune disease susceptibility. A number of loci on several chromosomes consistently link to disease susceptibility (30). Candidate genes in these areas include a range of immune, signaling pathway and neuroendocrine markers, which may or may not play a direct role in inflammatory disease susceptibility. At present, only suggested marker regions link to disease in any of these model systems, and further work is required to determine the genes involved in conferring host susceptibility and resistance to inflammatory disease.

All these studies underline the importance of the interplay between the immune and the nervous systems in susceptibility and resistance to inflammatory diseases, and in pathogenesis of many CNS diseases not previously thought to be inflammatory. Thus, in the search for candidate genes in such illnesses, it is clear that the scope must be broadened from classical candidates, to encompass the wide range of neurohormonal factors that affect the immune response and the numerous cytokines that could play a role in the pathogenesis of CNS diseases.

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