Neurochemical and Endocrine Responses to Immune Activation: the Role of Cytokines

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Abstract This chapter reviews the experimental evidence that activation of the immune system, e.g., following infection or challenge (for example, with viruses), alters the metabolism of certain neurotransmitters in the brain, most notably serotonin, and the catecholamine, norepinephrine, and the amino acid tryptophan, as well as activating the hypothalamo-pituitary-adrenal (HPA) axis. There may be causal relationships between the noradrenergic activation and the HPA axis, and the neurochemical changes are implicated in the behavioral responses, in particular the sickness behaviors associated with injuries and infections. Nevertheless, there are many gaps in our knowledge, and we do not yet have a detailed understanding of the relationships between the immune activation and the brain responses.

Keywords Cytokine · Interleukin · Interferon · Dopamine · Norepinephrine · Serotonin · Acetylcholine · Tryptophan · Fos · Neurochemistry · Behavior · HPA axis · Cyclooxygenase

1 Introduction

The immune system is able to detect environmental threats to the organism that may not be recognized by the classic six senses. For optimal survival, animals need to detect such threats, and to mount appropriate responses. There is thus a need for communication between the nervous system and the immune system, two rather different bodily systems. This chapter reviews our present understanding of the mechanisms involved in immune system signaling to the brain, indicating which brain systems are known to respond to immune system signals and how. At our present level of understanding, this is heavily focused on cytokines, the hormones of the immune system, that have the ability to signal the brain. We will also discuss the ways in which the

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brain responds to those threats, by altering behavior, and the other bodily systems necessary to maintain homeostasis, and thus support the survival of the organism.

2 Brain Responses to Immune System Activation

It has been known for some considerable time that stressful situations in animals and man cause a co-activation of the sympatho-adrenal system (the sympathetic nervous system plus the adrenal medulla), and of the hypothalamo-pituitary-adrenocortical (HPA) axis. This is the classical physiological stress response. Activation of the sympatho-adrenal system elevates circulating concentrations of the catecholamine, norepinephrine (NE) from terminals of sympathetic nerves, and of NE and epinephrine (Epi) from the adrenal medulla. The HPA axis activation is initiated by the secretion of corticotropin-releasing factor (CRF) from cells in the paraventricular nucleus (PVN) of the hypothalamus that project to the median eminence (Fig. 1). The CRF is carried in the portal blood to the anterior pituitary gland where it stimulates the secretion of adrenocorticotrophic hormone (ACTH) and β-endorphin. ACTH enters the general circulation reaching the adrenal cortex where it stimulates the secretion of glucocorticoid hormones (cortisol in most animals; corticosterone in rats and mice; Fig. 1). The catecholamines (NE and Epi) circulating in the blood increase heart rate and blood pressure enabling the blood to supply more nutrients to tissues such as muscles which are likely to be needed for the "fighting or fleeing" associated with stress. The glucocorticoids, as their name implies, shift metabolism to mobilize glucose, elevating plasma glucose concentrations. The latter is complemented by a catecholamine-enhanced degradation of glycogen to glucose.

Many laboratories have studied the effect of various stressors, such as electric footshock and short-term restraint on various chemical constituents of the brain. The results using a variety of different techniques have shown clearly that footshock and restraint both activate catecholamine-containing neurons in the brain, primarily NE, but probably also dopamine (3,4 dihydroxyphenylethylamine, DA) and Epi. Specifically, the release and metabolism of NE is enhanced throughout the brain, induced by activation of several brain stem nuclei, such as the locus coeruleus (LC) which innervates much of the cerebral cortex, parts of the diencephalon, and the cerebellum, and the nucleus of the solitary tract (NTS; see Chapter 3 by Goehler). Epi-containing neurons are believed to be activated also, although there have been relatively few studies of the epi-containing systems. The secretion of DA is also activated to differing extents in various regions of the brain. The metabolism of the indoleamine, serotonin (5-hydroxytryptamine, 5-HT) is also increased throughout the brain, as are the concentrations of tryptophan (Trp), an essential amino acid for protein synthesis that is also an essential precursor for the synthesis of serotonin. Subsequent experiments using more sophisticated techniques, such as in vivo microdialysis and in vivo voltammetry have indicated that the increased metabolism of NE, DA, and 5-HT reflects increased secretion of these neurotransmitters in the brain. The release of NE is ubiquitous in the brain, reflecting the widespread distribution of axons and terminals of NE from brain stem nuclei, such as the LC and the

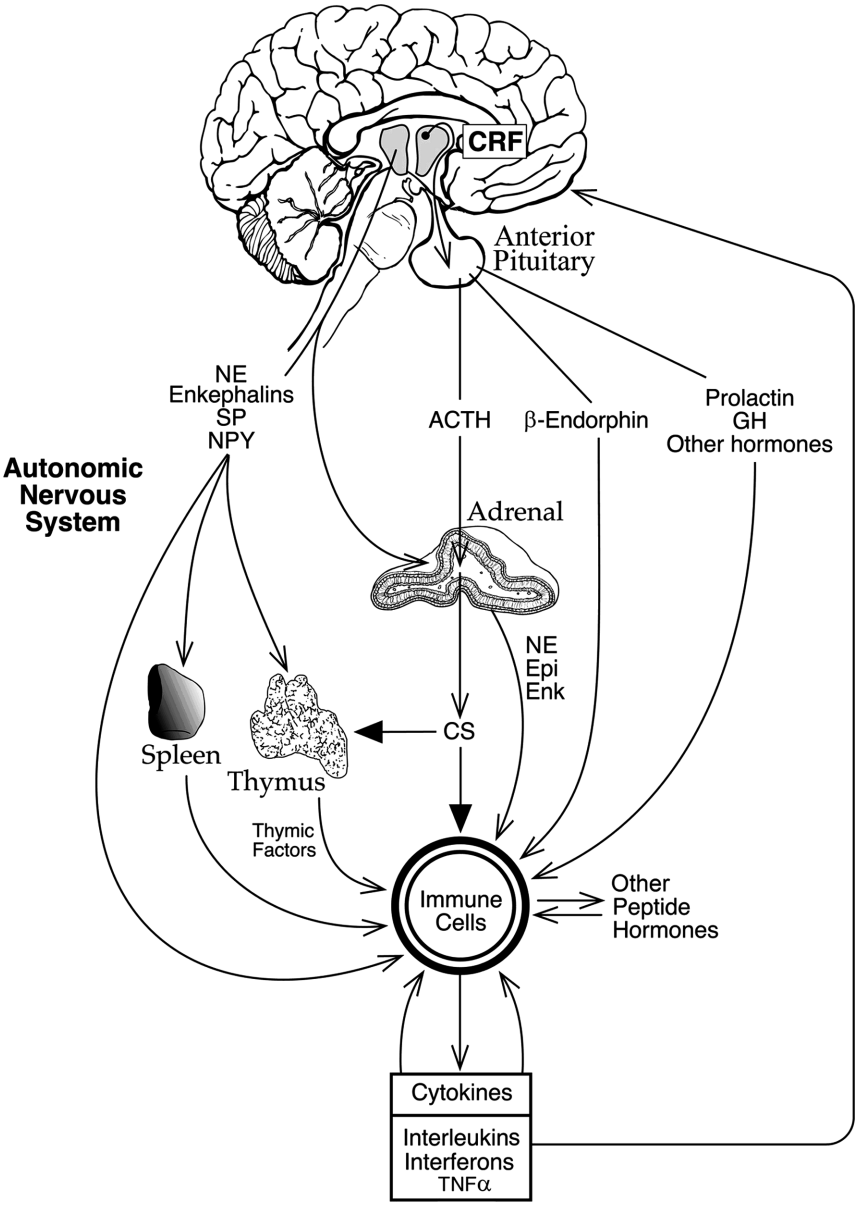

Fig. 1 Schematic of the interactions between the brain and components of the endocrine and immune systems. The ability of the brain to alter immune system function via a variety of endocrine pathways and the autonomic nervous system, and conversely the routes by which peptides and cytokines produced by cells of the immune system act on the brain are indicated. Abbreviations: E, epinephrine; ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor; CS, corticosteroids; Enk, enkephalins; GH, growth hormone; NE, norepinephrine; NPY, neuropeptide Y; SP, substance P; TNF, tumor necrosis factor (Modified from Dunn and Wang 1999)

NTS (Chapter 3). Similarly, the effects of stress on 5-HT are widespread reflecting the global distribution of terminals of projections from the raphe nuclei in the brain stem. However, dopaminergic systems are selectively activated in the mesolimbic and mesocortical projection systems (to the prefrontal cortex), and little, if at all, in the nigrostriatal system.

The response of the immune system during stress has long been considered anomalous, because immune system functions appeared to be inhibited during stress. This is primarily because glucocorticoids have long been known to have potent anti-inflammatory effects suppressing immune function (Munck and Guyre, 1986), even though it would be expected that the immune system would be important during stress, for example to coagulate blood, and to expel or destroy potential pathogens. A major factor contributing to this was a misinterpretation of the observation that during stress the thymus and the spleen were depleted of immune cells, and there were fewer immune cells in the circulation. These responses are now considered to reflect the mobilization (and hence apparent depletion) of immune cells to attack invading pathogens and/or repair wounds. The analogy is sending the soldiers from the barracks to the battle front (Dhabhar, 2002). The prevailing dogma that the immune system is inhibited when the organism is under stress has also been challenged, because many of the anti-inflammatory effects reflect the use of high doses of exogenous steroids, and/or potent synthetic glucocorticoids that far exceed concentrations achieved physiologically. Moreover, recently it has been shown that glucocorticoids are not exclusively anti-inflammatory, and can be immunoenhancing in some circumstances in the brain (e.g., Sorrells and Sapolsky, 2007).

There were a few reports in the literature that sickness might be associated with an activation of the HPA axis as indicated by increased concentration of glucocorticoids (Yelvington et al. 1987). We ourselves had noted increased plasma concentrations of corticosterone in mice that appeared to be sick or were wounded. Thus we decided to study the effect of infection of mice with influenza virus which was being studied in a nearby laboratory. The mice were infused intranasally with the virus, which caused an infection in the lungs, the normal site of infection for influenza. The dose chosen was such that the mice would become sick after about 2 days, and would normally die starting around 7 days. Mice were sacrificed at various times following infection with the virus, and HPA axis function was assessed by measuring plasma concentrations of ACTH and corticosterone. It was clear that as the mice became sick, plasma concentrations of ACTH and corticosterone increased progressively (Fig. 2; Dunn et al., 1989). Because there was no acute stimulus, the HPA axis was apparently chronically activated in contrast with the HPA responses to footshock or brief restraint after which plasma concentrations of ACTH and corticosterone normally return to baseline within an hour. This HPA axis activation extended the validity of its use to define stress, because influenza virus infection would clearly be regarded as stressful in man.

We also examined the neurochemical responses of the catecholamines and serotonin in the brains of the influenza virus-infected mice. Most interestingly, the influenza virus infection activated the brain noradrenergic and serotonergic systems as determined by measurement of their catabolites in a pattern resembling that

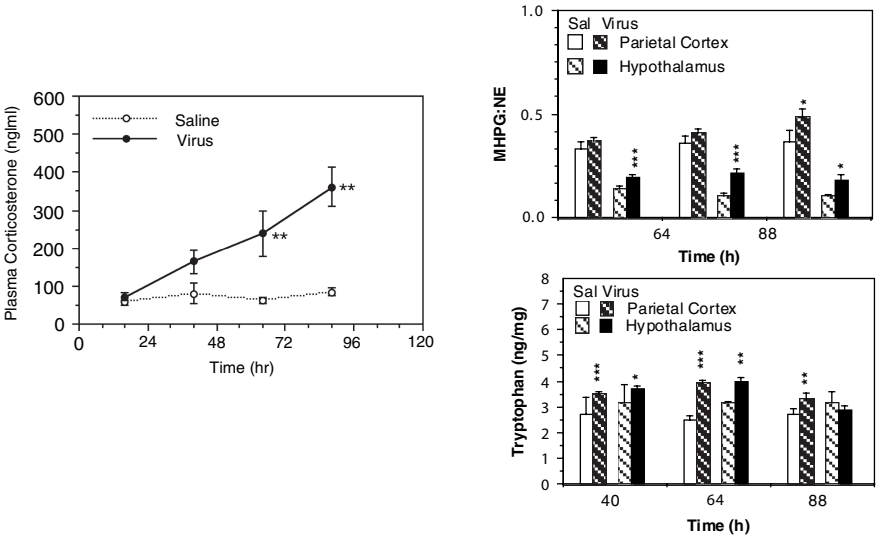

Fig. 2 The hypothalamo-pituitary–adrenocortical (HPA) and neurochemical responses at various times following influenza virus infection in mice. (Modified from Dunn et al., 1989)

observed following footshock and restraint, although there was little or no response in dopamine (Fig. 2; Dunn et al., 1989). Moreover, Trp concentrations were also elevated in a regionally nonselective manner. We had previously shown that treatment of mice with Newcastle disease virus (NDV) activated the HPA axis and brain noradrenergic and indoleaminergic systems (Dunn et al., 1987), so that it is likely that the responses we observed were a rather general response to viral infections (see review by Silverman et al., 2005). Similar findings have subsequently been made for a variety of different infectious agents (viruses, bacteria, protozoa, etc.) confirming the generality of these responses (see review by Besedovsky and del Rey, 1996). Thus two very different stressful treatments induced very similar physiological and neurochemical responses. These results support Selye's much maligned "nonspecificity" of the stress response. There was indeed similarity in the patterns of the physiological responses to different stressors.

The significance of the various physiological responses is partially understood. As mentioned above, the peripheral noradrenergic response serves to increase bloodflow to muscles and other organs that need more energy. The role of the glucocorticoid response is still controversial, but clearly it complements the sympathetic activation in generating more glucose as fuel for fighting and/or fleeing. The significance of the central noradrenergic response is thought to be to alert the brain and focus attention on novel stimuli in the environment that are likely to be the source of the stress, and hence target the response appropriately (Mason, 1980). The role of Trp and the indoleamines is unclear. Increasing brain concentrations of Trp may well be a precautionary measure, to prevent the brain running short of Trp, essential for the synthesis of proteins and serotonin.

3 The Mechanism(s) of Infection-Related Activation of the Stress Axis – The Involvement of Interleukin-1 (IL-1)

So what is the mechanism by which the body detects infections and initiates the stress responses? It seemed likely, a priori, that it would involve the immune system, because the immune system is the one responsible for surveillance of foreign antigens. We already had a clue, because in earlier work with NDV, we sought immune factors that might be responsible for its HPA and neurochemical effects. An important key was the seminal finding of Besedovsky et al. (1986) that peripheral administration of the cytokine, interleukin-1 (IL-1) potently stimulated the HPA axis in rats. Thus we injected mouse IL-1 which we prepared ourselves from stimulated mouse spleen cells, and recombinant human IL-1α intraperitoneally (ip) into mice, and observed not only a substantial HPA axis activation (increases in plasma ACTH and corticosterone), but also increases in brain 3-methoxy,4-hydroxyphenylethylene glycol (MHPG, the major brain catabolite of NE) and 5-hydroxyindoleacetic acid (5-HIAA, the major catabolite of 5-HT; Dunn 1988, see Fig. 3). Thus the mechanism appeared to be that immune cells recognized the administered pathogens, and initiated the synthesis and secretion of IL-1. The IL-1 then somehow signaled the brain to initiate the secretion of CRF necessary to initiate the activation of the HPA axis (Fig. 1). IL-1 also activated brain noradrenergic systems, and increased brain Trp and serotonin secretion.

IL-1 also elevates body temperature and is believed to be the major mediator of the fever associated with bacterial and viral infections (see review by Dinarello 1992). This fever is believed to be another aspect of the defensive mechanisms associated with sickness behavior, because viral replication is typically reduced at higher body temperatures (Hart, 1988; Dinarello, 1992).

4 Brain Responses to Other Cytokines

There is now a substantial literature on the neurochemical responses to immune activation in general, and in response to administration of cytokines and other immune factors. This literature has been reviewed relatively recently (Dunn, 2006), and the interested reader is referred to that source which will not be repeated here in detail.

Various results have been reported with IL-2, which is normally considered a growth-promoting cytokine for the immune system. There are reports of increases in NE and DA metabolism in mice (Zalcman et al., 1994), but decreased DA metabolism has also been reported (Dunn, 2006).

IL-6 is a cytokine that responds rapidly to almost any kind of infection or tissue damage. Like IL-1, it can activate the HPA axis, although it is far less potent than IL-1 (Wang and Dunn 1998). Peripherally administered mouse IL-6 is not pyrogenic (Wang et al., 1997), but IL-6 within the brain can induce fever. The

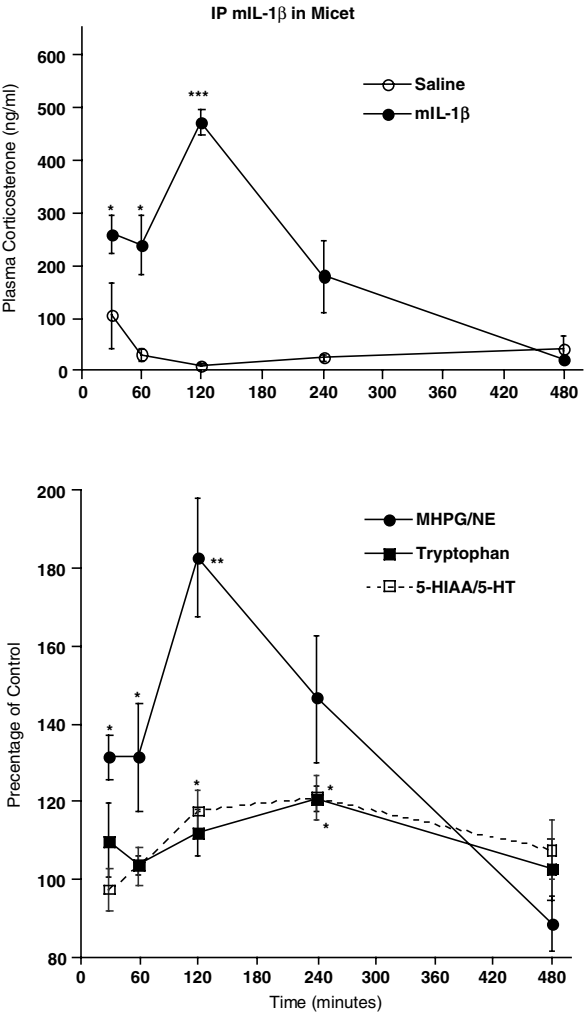

Fig. 3 The responses in plasma corticosterone (i.e., the HPA response) and certain neurochemical measures at various times following intraperitoneal (ip) administration of saline or 100 ng mouse interleukin-1β (IL-1β? to mice. Upper figure: Open circles – plasma concentrations of corticosterone (ng/ml) after injection of saline; filled circles – plasma corticosterone after ip injection of 100 ng IL-1β. Lower figure: Neurochemical measures made in the hypothalamus of the same animals as the upper figure: Filled circles: (3-methoxy,4-hydroxyphenylethylene glycol : norepinephrine) MHPG:NE ratios (an index of NE release); Open squares: (5-hydroxyindoleacetic acid : 5-hydroxytryptamine) 5-HIAA:5-HT ratios (an index of 5-HT release); Filled squares: Tryptophan concentrations, all expressed as the percentage of control (saline-injected) mice. Note the parallelism between the plasma corticosterone concentrations and the noradrenergic responses, while the tryptophan and 5-HIAA:5-HT responses parallel each other, but with a very different time course (Modified from Dunn 1988)

neurochemical responses to IL-6 reported have been somewhat variable. Zalcman et al. (1994) reported increases in prefrontal cortex DA and 5-HT metabolism, but Wang and Dunn (1998) observed effects on only Trp and 5-HT. Microdialysis and amperometric studies have also revealed activation by IL-6 of serotonergic systems (Barkhudaryan and Dunn, 1999; Zhang et al., 2001).

Tumor necrosis factor-α (TNF-α) has also been studied, but the interpretation of the literature is complicated by the failure of some studies to use homologous TNF, important because not all forms of TNF bind to receptors across species. At high doses, mouse TNF-α increased MHPG and Trp in mice (Ando and Dunn, 1999), along with a modest HPA activation which has been observed in several other reports (Dunn, 2006). TNF-α has little effect on body temperature in mice, although there was a small transient decrease at high doses (Wang et al., 1997).

The literature on the responses to the administration of interferons (IFNs) is markedly contradictory. IFN-α is used clinically to treat various forms of cancer, and it is well known to induce fever and HPA axis activation in man. However, studies in rodents have generated diverse results (Dunn, 2006). We have failed to observe any changes in body temperature in rats and mice using central or peripheral administration of homologous IFN-α or IFN-β. Likewise, we have not observed HPA activation in rats or mice, nor consistent effects on catecholamines or serotonin. We have, however, observed behavioral responses in tests for depression using recombinant rat IFN-α in rats, and natural mouse IFN-α in mice.

IFN-γ can profoundly affect indoleamine metabolism, although largely in the periphery. Its administration induces indoleamine-2,3-dioxygenase which converts Trp to kynurenine, and quinolinic acid. This can deplete circulating concentrations of Trp thus limiting the availability of this amino acid for protein and serotonin synthesis.

5 The Role of Catecholamines in the HPA Activation

The time courses of the brain noradrenergic response and the HPA response to IL-1 were very similar, suggesting that they might be related. This was also true for lipopolysaccharide (LPS) and viral infection. Because it was already known that noradrenergic neurons could activate the CRF-containing neurons in the PVN to initiate the HPA axis cascade (Saphier and Feldman, 1989; Al-Damluji, 1993), it seemed very likely that IL-1 stimulation of noradrenergic neurons was responsible for the CRF secretion. This was tested using the catecholamine-selective neurotoxin, 6-hydroxydopamine, by injecting it into the ascending noradrenergic bundle of rats to lesion the noradrenergic projection from the brain stem to the hypothalamic PVN, the nucleus in which the CRF-containing neurons considered critical for activating the secretion of ACTH are located (Saphier and Feldman, 1989; Al-Damluji, 1993). The results showed that such lesions in rats substantially reduced the IL-1-induced increases in plasma corticosterone, although there was a small residual response (Chuluyan et al., 1992). However in mice, whole brain depletion of NE resulted in

only a very modest reduction in IL-1-induced plasma corticosterone, not evident in all experiments (Swiergiel et al., 1996). This suggested that NE may be involved in the IL-1-induced HPA axis activation, but that it was not the only mechanism.

A study by Nance's group (Wan et al., 1993), followed by studies from Bluthé et al. (1994) and Watkins et al. (1994), indicated that the vagus nerve was involved in the brain's response to LPS and suggested a potential route by which peripheral agents could signal the brain. Subsequent experiments verified that the HPA axis activation induced by ip IL-1 was indeed mediated at least in part by the vagus nerve (Fleshner et al., 1995). Our experiments in mice showed that subdiaphragmatic vagotomy attenuated, but did not prevent the neurochemical changes (NE and 5-HT) nor the HPA activation induced by ip administration of IL-1 or LPS (Wieczorek et al., 2005).

More recent experiments in rats have indicated that subdiaphragmatic vagotomy (Wieczorek and Dunn 2006a) and indomethacin pretreatment (Wieczorek and Dunn 2006b) largely prevented the increases in NE secretion in the hypothalamus induced by ip administered IL-1, but failed to block the increases in plasma ACTH and corticosterone. However, the combination of subdiaphragmatic vagotomy and indomethacin completely blocked both the noradrenergic activation, and the HPA axis activation to ip IL-1 in both rats and mice (Wieczorek and Dunn unpublished data). These results are consistent with the previously observed failures to block completely the neurochemical and endocrine responses with either treatment alone, and suggest strongly that there are indeed redundant pathways for the IL-1- and LPS-induced activation of the central noradrenergic system and the HPA axis in both species. Redundancy in what appears to be a critical defensive response is to be expected in biological systems.

6 The Significance of the Indoleamine Responses

The time courses of the brain indoleamine responses to IL-1 and LPS are distinct from those of the noradrenergic responses. As indicated above, the noradrenergic response in mice and rats peaks around 2 h, and has dissipated by 4 h, whereas the increases in Trp and 5-HIAA concentrations do not peak until 4–8 h, and dissipate slowly after that. This suggests that the two neurochemical responses involve different mechanisms and probably serve distinct functions. This conclusion is reinforced by the fact that whereas the noradrenergic responses are sensitive to cyclooxygenase (COX) inhibitors, the indoleamine responses are not (Dunn and Chuluyan, 1992). Moreover, the mechanism does not appear to involve the vagus, because the increases in Trp and 5-HIAA were not prevented in vagotomized mice (Wieczorek et al., 2005).

The brain content of Trp increases in response to a large variety of stimuli, including several psychotropic drugs, increases in body temperature and several different stressors (Dunn, 2006). The increases in Trp and 5-HIAA in response to footshock, restraint, IL-1, and LPS appear to depend upon peripheral sympathetic activity, because they can be blocked by pretreatment with the autonomic ganglionic

blocker, chlorisondamine, and largely prevented by the β-adrenergic receptor antagonist, propranolol, but not by the α-adrenergic receptor antagonist, phentolamine, or the muscarinic receptor antagonist, scopolamine (Dunn and Welch, 1991). So the increases in brain Trp appear to reflect sympathetic activation. This is consistent with the ability of β_2-adrenergic agonists, such as clenbuterol, to increase brain concentrations of Trp (Edwards et al., 1989). However, β_2-adrenergic antagonists do not prevent the IL-1-induced increases in brain Trp, although some attenuations have been observed (unpublished observations). Recent studies in our laboratory have shown that both β_2- and β_3-adrenergic agonists increase net concentrations of brain Trp, and that β_3-adrenergic agonist administration can double the brain concentrations of Trp in mice (Lenard et al., 2003). Moreover, a β_2-adrenergic agonist increases brain Trp in β_3-knockout mice.

Nitric oxide synthase (NOS) also appears to be involved in the immune-induced activation of serotonergic neurons. Nonselective inhibitors of NOS attenuate or prevent the responses to IL-1 and LPS (Dunn, 1993), as well as to footshock (Dunn, 1998). Studies with selective NOS inhibitors indicate that iNOS is the principal form of NOS involved in the responses to IL-1 and LPS. However, the indoleamine responses in knockout mice lacking each of the various forms of NOS were not impaired, suggesting that there may be redundancy among the various forms of NOS (Dunn unpublished observations). The precise mechanism and significance of the NOS involvement is unclear. In particular the location of the NOS involved has not been identified.

7 The Relationship of the Neurochemical Responses to the Behavioral Responses

Infections and immune activation can profoundly influence behavior. It is a commonplace that this is also the role of brain neurotransmitters. The focus of behavioral studies has long been on sickness behavior. Sickness behavior was coined by Hart as a loose collection of behavioral responses that benefit a sick animal allowing it to avoid threatening situations (e.g., predators), while it is impaired by the illness. Hart (1988) wrote "The behavior of a sick individual is not a maladaptive and undesirable effect of illness but rather a highly organized strategy that is at times critical to the survival of the individual if it were living in the wild state." The concept of sickness behavior truly derived from Selye who called it "the syndrome of just being sick." ("Sick people are all indisposed, they look tired, have no appetite, gradually lose weight, do not feel like going to work, lie down rather than stand up. They all present a syndrome simply indicative of being ill" (Selye, 1979). Sickness behaviors include hypomotility (lethargy), hyperthermia, hypophagia (anorexia), decreased interest in exploring the environment, decreased libido, and increased sleep time.

To a first approximation, there are parallels between sickness behavior induced by immune activation and those induced by IL-1. One would anticipate that there would be clear relationships between the neurochemical changes associated with immune

activation, but there are very few data to support this, even though the temporal aspects of the noradrenergic response and sickness behavior are very similar. Destruction of noradrenergic neurons in the brain, or the use of adrenergic receptor antagonists do little to alter behavioral responses to IL-1 administered either peripherally or centrally (Swiergiel et al., 1999). The only treatments identified that do impair IL-1-induced behavioral responses are COX inhibitors, such as indomethacin (Dunn and Swiergiel, 2000). When we studied the consumption of sweetened milk by mice (it may be thought of as the murine equivalent of ice cream!), we found that both COX1 and COX2 appear to be involved in the anorexic effects of IL-1, but at different times following its administration. In the first 30 min to 1 h, COX1 is involved, and the anhedonic effects of IL-1 can be inhibited by nonselective COX inhibitors, such as indomethacin, or SC-560, a COX1-selective inhibitor (Swiergiel and Dunn, 2002). In the second hour, indomethacin still inhibits the response, but SC-560 is not effective, whereas the COX2-selective inhibitors celecoxib and piroxicam are. Consistent with this, COX1-knockout mice do not show anorexia in the first hour, whereas COX2-knockout mice are not affected in the second (Swiergiel and Dunn 2002). Thus we conclude that the anorexic effects are mediated via prostaglandins or other eicosanoids.

Surprisingly, a host of other selective inhibitors for potential mediators had no significant amelioration of the depression of milk drinking by IL-1: including antagonists of dopaminergic receptors (haloperidol), α-adrenergic receptors (prazosin and phentolamine), β-adrenergic receptors (propranolol), 5-HT_1-, 5-HT_2-5-HT_3-receptors; muscarinic cholinergic receptors (scopolamine), H_1-, H_2- and H_3-receptors, the opiate-receptor antagonist (naloxone), neurokinin-receptors (L659,877 and L703,606), CRF-receptors (alpha-helical $CRF_{9–41}$), melanocortin-4-receptors (SHU9119), NPY1 (BIBP3226), Substance P receptor antagonist (L703,606) 5-HT_{1A}- and 5-HT_{1B}-receptor agonists, selective neurotoxins for depleting DA and NE (6-hydroxydopamine) and NE (DSP-4), 5-HT (5,7-dihydroxytryptamine), the histamine synthesis inhibitor (α-fluoromethylhistidine), and NOS inhibitors (L-NAME, L-NMMA).

8 Does IL-1 Mediate the Neurochemical, Endocrine and Behavioral Responses to Immune Activation?

The foregoing has indicated that many of the responses to viral stimulation and immune activation are shared by IL-1, specifically the activation of the HPA axis, the activation of the central noradrenergic and serotonergic systems, the increase in brain Trp, and the behavioral effects. Because the synthesis of IL-1 is a ubiquitous response to immune stimulation, whether associated with pathogens or stimulants, such as LPS, is it the mediator of these responses? The answer is not simple. We have conducted a number of experiments to determine the involvement of IL-1 and certain other cytokines, such as IL-6, TNF-α, and the interferons. We have also studied responses to LPS, which is a relatively straightforward activator of the immune system, as well as number of challenges with pathogens.

8.1 Endotoxin (Lipopolysaccharide, LPS)

Peripheral administration of low doses of LPS is a very useful model for immune activation. It acts by binding to TLR-4 receptors in various organs, including endothelia. This ultimately results in the synthesis and secretion of IL-1. Not surprisingly, LPS elicits very similar neurochemical, endocrine, and behavioral responses to those of influenza virus and IL-1. It elevates plasma concentrations of ACTH and corticosterone, indicating HPA axis activation. It also increases brain MHPG, indicating activation of the brain noradrenergic systems, preferentially in the ventral (diencephalic) system, and increases brain 5-HIAA, indicating activation of brain serotonergic systems, and increasing brain concentrations of Trp (Dunn, 1992a, b). Each of these responses resembles those to IL-1. The differences are that the increases in plasma ACTH and corticosterone and the neurochemical responses were significantly slower, perhaps reflecting the delay involved in the induction of IL-1 by LPS. The distinction between the MHPG responses in the dorsal and ventral projection systems is less marked with LPS than with IL-1, and LPS also exhibits a significant activation of dopaminergic systems (i.e., increases in 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) not normally observed with IL-1. Whereas, the responses to icv IL-1 were quite similar to those of ip IL-1, icv LPS was less effective than ip. Thus it appears that induction of IL-1 cannot explain all the neurochemical effects of LPS.

LPS not only induces IL-1, but also IL-6 and TNF-α (IL-1 itself also induces IL-6; Zuckerman et al., 1989). Ip administration of IL-6 causes HPA axis activation in mice, but the effect is short lived, and IL-6 is far less potent than IL-1 (Wang and Dunn, 1998). IL-6 administration does not increase brain MHPG, but it does elevate brain concentrations of 5-HIAA and Trp, although it is significantly less potent in this respect than IL-1. Pretreatment with an antibody to mouse IL-6 did not alter the responses to IL-1, indicating that IL-6 does not the mediate the HPA or indoleaminergic effects of IL-1 (Wang and Dunn, 1999). However, the anti-IL-6 treatment did diminish the HPA response to LPS at later times, and attenuated the serotonin/Trp responses, suggesting that IL-6 contributes to the later responses to LPS. Administration of mouse TNF-α to mice also elevates MHPG and 5-HIAA, but only at relatively high doses (Ando and Dunn, 1999).

We have not observed significant anorexic effects of mouse IL-6 in mice, and mouse TNF-α induced anorexia only at very high doses (Swiergiel et al., 1997). Administration of the natural IL-1-receptor antagonist (IL-1ra) to mice at doses that substantially attenuated the anorexic response to mouse IL-1β significantly attenuated, but did not block, the anorexic response to low doses of LPS (Swiergiel et al., 1997; Swiergiel and Dunn 1999). Whereas the combination of IL-1ra with TNF-binding protein (TNFbp) significantly attenuated LPS-induced anorexia, the combination of IL-1ra, with the TNFbp, and a monoclonal antibody to IL-6 did prevent the anorexic response to low doses of LPS (Swiergiel and Dunn, 1999).

IL-1ra failed to alter the anorexic response to influenza virus infection when it was injected every 4 h for 5 days, however, when introduced continuously into

mice using osmotic minipumps primed to deliver 50 μg/h, a statistically significant amelioration of the anorexia was observed, indicating that IL-1 participated in this response, although the anorexic effects were not prevented, perhaps because of the inability to block completely the actions of IL-1 (Swiergiel et al., 1997). In a subsequent series of experiments we tested the effects of continuous infusion of IL-1ra, repeated injection of TNFbp, and an IL-6 antibody. Statistically significant effects were observed on food pellet and sweetened milk intake, the anorexic effects, but the progression of the disease was not prevented (Swiergiel and Dunn, 1999).

9 Conclusions

Immune activation in the periphery causes profound changes in the brain. There is a sustained activation of noradrenergic and serotonergic neurons throughout the brain, resulting in an outpouring of NE and serotonin, however, the serotonergic response occurs much later than the noradrenergic response. There are also increases in brain concentrations of the essential amino acid, Trp. CRF-containing neurons are also activated resulting in an activation of the HPA axis, increasing the secretion of ACTH from the anterior pituitary gland, and consequent elevation of glucocorticoids from the adrenal cortex. This activation is mediated by the activation of brain stem noradrenergic neurons, and also by eicosanoids synthesized by COX in the hypothalamus. IL-1 secreted by macrophages and other immune cells is a major factor in the activation of the brain noradrenergic and serotonergic systems, but other immune factors (e.g., other cytokines) may also be involved. The glucocorticoid hormones alter metabolism and mobilize glucose to fuel the functions of the immune system. They also provide negative feedback limiting the activation of the immune system. IL-1 also initiates mechanisms, most notably behavioral ones, to limit activity of the animal (e.g., sickness behavior), and conserve energy for defensive fighting and/or escape. IL-1 (via eicosanoids) also increases body temperature inducing fever that limits viral replication, and enhances immune activity to neutralize pathogens.

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