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Effects of cytokines and infections on brain neurochemistry

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Abstract

Administration of cytokines to animals can elicit many effects on the brain, particularly neuroendocrine and behavioral effects. Cytokine administration also alters neurotransmission, which may underlie these effects. The most well studied effect is the activation of the hypothalamo–pituitary–adrenocortical (HPA) axis, especially that by interleukin-1 (IL-1). Peripheral and central administration of IL-1 also induces norepinephrine (NE) release in the brain, most markedly in the hypothalamus. Small changes in brain dopamine (DA) are occasionally observed, but these effects are not regionally selective. IL-1 also increases brain concentrations of tryptophan, and the metabolism of serotonin (5-HT) throughout the brain in a regionally nonselective manner. Increases of tryptophan and 5-HT, but not NE, are also elicited by IL-6, which also activates the HPA axis, although it is much less potent in these respects than IL-1. IL-2 has modest effects on DA, NE and 5-HT. Like IL-6, tumor necrosis factor- α (TNF α) activates the HPA axis, but affects NE and tryptophan only at high doses. The interferons (IFN's) induce fever and HPA axis activation in man, but such effects are weak or absent in rodents. The reported effects of IFN's on brain catecholamines and serotonin have been very varied. However, interferon- γ , and to a lesser extent, interferon- α , have profound effects on the catabolism of tryptophan, effectively reducing its concentration in plasma, and may thus limit brain 5-HT synthesis.

Administration of endotoxin (LPS) elicits responses similar to those of IL-1. Bacterial and viral infections induce HPA activation, and also increase brain NE and 5-HT metabolism and brain tryptophan. Typically, there is also behavioral depression. These effects are strikingly similar to those of IL-1, suggesting that IL-1 secretion, which accompanies many infections, may mediate these responses. Studies with IL-1 antagonists, support this possibility, although in most cases the antagonism is incomplete, suggesting the existence of multiple mechanisms. Because LPS is known to stimulate the secretion of IL-1, IL-6 and TNF α , it seems likely that these cytokines mediate at least some of the responses, but studies with antagonists indicate that there are multiple mechanisms. The neurochemical responses to cytokines are likely to underlie the endocrine and behavioral responses. The NE response to IL-1 appears to be instrumental in the HPA activation, but other mechanisms exist. Neither the noradrenergic nor the serotonergic systems appear to be involved in the major behavioral responses. The significance of the serotonin response is unknown.

Keywords

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

1. Introduction

Once it had been accepted that the immune system communicated with the nervous system, and that the nervous system could exert important influences on the immune system, the

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important question became how. The ‘how’ is obviously complex: how does the immune system send signals to the central nervous system (CNS), and what are the effects on the brain? How does the CNS respond to those effects and communicate with the other organs in the body to implement any necessary responses, and how does the CNS signal the immune system and affect its functions? This chapter addresses these questions: what are the responses in the brain to signals from the immune system, and what effects do those responses induce?

The first indications that the immune system might affect brain neurochemistry arose from studies that indicated that neurophysiological changes in the brain occurred to immune challenges. A study of Besedovsky et al. indicated that an immune challenge to rats with red blood cells from sheep (SRBC) altered the firing of neurons in the hypothalamus [1], and some similar observations were reported by Klimenko [2]. This finding complemented earlier studies that showed that challenges with SRBC, trinitrophenyl-hemocyanin or trinitrophenyl-horse red blood cells elevated plasma concentrations of corticosterone [3]. Subsequent studies by Besedovsky et al. indicated that injection of SRBC also affected norepinephrine (NE) metabolism in the hypothalamus, specifically the SRBC challenge decreased the turnover of NE in the hypothalamus [4]. This was one of the earliest reports linking immune system function to neurochemical changes in the brain.

There are only two major mechanisms, by which organ systems can communicate, neural and endocrine (using endocrine in the broadest sense of a systemic chemical messenger). Thus, the immune system most likely uses an endocrine-like mechanism, sending messages to the brain, using chemical messengers released by immune cells or organs. By the 1980s, the immune system was known to synthesize and secrete a number of chemical messengers, which were known generically as cytokines (originally a distinction was made between lymphokines (from lymphocytes) and monokines (from monocytes), but this has now been abandoned in favor of calling all such factors cytokines). Thus, attention was immediately focused on cytokines as the immune messengers to the brain. Besedovsky et al. challenged lymphocytes in vitro with concanavalin A (ConA), and administered the supernatants to rats and observed an increase in plasma corticosterone [5]. It was also shown that similarly prepared supernatants when injected into rats reduced the concentrations of NE in the hypothalamus and brainstem [4]. Thus, they suggested that some soluble factor secreted by the immune cells in vitro (e.g. a lymphokine or cytokine) was responsible for this response.

A second seminal discovery, also arose from Besedovsky’s laboratory, namely that purified recombinant interleukin-1 (IL-1) administered intraperitoneally (ip) to rats potently activated the hypothalamo–pituitary–adrenocortical (HPA) axis, elevating plasma concentrations of ACTH and corticosterone (the major glucocorticoid hormone in the rat) [6]. This property of IL-1 was rapidly confirmed by several other groups in several different species (see review [7]). Subsequently, Dunn, in mice [8], and Besedovsky’s group, in rats [9], showed that ip IL-1 activated NE metabolism in the brain, especially in the hypothalamus. Because, NE had long been known to be involved in activation of the HPA axis [10,11], this immediately suggested that the NE activation was instrumental in the HPA activation. Dunn and Kabiersch et al. also showed that the neurochemical effects of IL-1 were not confined to NE, but serotonin (5-hydroxytryptamine, 5-HT) metabolism was also increased, as were concentrations of tryptophan (the essential precursor for 5-HT) were also increased throughout the brain [8,9].

2. Neurochemical responses to cytokines

(A summary of these effects appears in Table 1.)

2.1. Interleukin-1 (IL-1)

2.1.1. Effects on catecholamines—As indicated above, a key observation was that ip IL-1 administration to mice or rats increased the brain concentrations of the catabolites of NE, suggesting that the release of this neurotransmitter was increased [8,9,12,13]. The initial reports were based on an increase in the brain content of 3-methoxy,4-hydroxyphenylethyle-neglycol (MHPG), a major catabolite of NE. This response occurred in every brain region studied, but the magnitude of the response was greatest in the hypothalamus, and other structures innervated by the ventral noradrenergic projection system (the ventral noradrenergic bundle, VNAB). It was smaller in those innervated by the dorsal noradrenergic bundle (DNAB), such as the cerebral cortex, hippocampus and cerebellum. Within the hypothalamus, the greatest response occurred in the medial part containing the paraventricular nucleus (PVN). The interpretation of these catabolite studies as reflecting increased neurotransmitter release were supported by subsequent studies using microdialysis which can directly assess extracellular concentrations of neurotransmitters. Microdialysate NE from the hypothalamus was increased following peripheral IL-1 administration [14-17]. Complementary data were obtained from studies with push-pull cannulation [18], and by studies of NE turnover, using α -methyl-*p*-tyrosine (metyrosine) to inhibit tyrosine hydroxylase, measuring the consequent depletion of NE [19]. IL-1 administration to rats also decreased the hypothalamic content of NE [20], suggesting that IL-1-induced NE release exceeded the synthetic capacity.

Zalcman et al. [12] reported increases in 3,4-dihydroxyphenylacetic acid (DOPAC, the major catabolite of dopamine (DA) in rodents) in the mouse prefrontal cortex and other brain regions, but the effects were not regionally selective. Mohankumar et al. [21] reported increases in DA and DOPAC in the PVN of the rat, and of DA in the arcuate nucleus following hIL-1 α (2 μ g ip). However, most reports have not indicated significant increases in DOPAC [8]. In a large number of experiments involving ip IL-1 administration to mice, we have occasionally observed statistically significant increases of DOPAC and DOPAC:DA ratios in various brain regions, but these responses were not observed consistently. When they did occur, the anatomical patterns did not resemble those typical of stress responses, in which increases in the prefrontal cortex are far greater than in other brain regions. DA was not altered by ip IL-1 β in microdialysates from the prefrontal cortex, nucleus accumbens or hippocampus [16]. IL-1 β has also been reported to increase tyrosine hydroxylase activity in the median eminence of rats [22]. Interestingly, administration of low doses of IL-1 β to rats in the first few days of life, results in permanent decreases in DA in the hypothalamus and superior cervical ganglion [23].

There are two forms of IL-1, IL-1 α and IL-1 β , which differ substantially in structure (there is only 27% sequence homology), but both forms bind to IL-1-receptors. There are also two forms of the IL-1 receptor, but the Type 1 receptor appears to be the only active one; the Type 2 receptor has no intracellular signaling sequence, and is considered to be a 'decoy' receptor, perhaps regulating extracellular concentrations of free IL-1 [24]. There are also substantial differences in the structures of IL-1 in different species; rat, mouse and human IL-1 α display only 61–65% sequence homology, and IL-1 β only 27–33%. Yet in general, IL-1's from most species are active in the rat and mouse. However, human and rodent IL-1's are not active in birds [25]. Nevertheless, the neurochemical effects of IL-1 occur with most forms of IL-1. We have observed very similar responses to IL-1 α and IL-1 β [8,26], although some have reported IL-1 α to be less potent than IL-1 β in activating the HPA axis [27,28]. Similar responses have also been observed using IL-1 from different species (mouse, rat or human), consistent with the similar binding affinities of the various forms of IL-1 for the IL-1 Type I receptor [29]. Similar HPA and neurochemical responses are observed in response to ip or subcutaneous (sc) injections. Intravenous (iv) administration induces smaller and briefer neurochemical (and

HPA) responses [30]. Intracerebroventricular (icv) administration also induces noradrenergic and serotonergic activation at considerably lower doses [26].

Cyclooxygenase (COX) enzymes appear to be involved in the IL-1-induced noradrenergic activation. COX inhibitors, such as indomethacin, prevented the increases in MHPG in mice [30], and NE turnover measured by synthesis inhibition [19,31]. In studies of the mechanism of action of ip-injected IL-1 in rats, we have measured hypothalamic NE secretion by in vivo microdialysis while simultaneously drawing blood samples for determination of plasma ACTH and corticosterone. The results showed that pretreatment with indomethacin completely prevented the increase in dialysate NE and that in body temperature, but only attenuated the HPA axis activation [17].

The opiate receptor antagonist, naloxone, did not alter the NE response to IL-1 [19]. Terao et al. [19] also reported that an antibody to corticotropin-releasing factor (CRF) decreased the noradrenergic response to IL-1 in rats, but we observed normal neurochemical responses to ip mL-1 β in CRF-knockout mice, although the increase in plasma corticosterone was absent [32]. Lesions of the area postrema attenuated the IL-1 β -induced increase in NE in hypothalamic dialysates [15].

Subdiaphragmatic vagotomy prevented the decrease in hypothalamic NE induced by ip IL-1 β [20] indicating an involvement of the vagus nerve. Abdominal vagotomy also attenuated the IL-1 β -induced increase in hypothalamic dialysate NE [15]. In experiments in which, we measured hypothalamic NE release in the rat by microdialysis in parallel with measurements of plasma ACTH and corticosterone we found that subdiaphragmatic vagotomy completely blocked the increase in apparent NE release, while it only attenuated the increases in plasma ACTH and corticosterone [33]. However, there may be species differences, because we observed that subdiaphragmatic vagotomy in mice only slightly attenuated the IL-1-induced increases in hypothalamic MHPG [34].

2.1.2. Effects on serotonin and tryptophan—IL-1 administration also increases brain concentrations of tryptophan and the major catabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA) [8,9,26]. Interestingly, neither of these responses to IL-1 displays any regional selectivity; they are of similar magnitude throughout the brain, and do not appear to be related to the concentration of 5-HT-containing cells in the region.

The noradrenergic and indoleamine responses to IL-1 differ, and appear to involve distinct mechanisms. The maximal responses in the metabolite studies of NE activation occurred around 2 h following ip administration [8,9,26] in parallel with the increases in plasma ACTH and corticosterone [8,26]. The microdialysis studies indicated a similar time course [14-17]. The peak responses in tryptophan and 5-HIAA occur significantly later, typically around 4 h after IL-1 administration [8,9,26,33]. Pretreatment with nitric oxide synthase (NOS) inhibitors prevents the tryptophan and 5-HIAA response to IL-1, but has no effect on the NE or HPA responses [35]. Studies with selective NOS inhibitors suggest that the inducible form of NOS (iNOS) may be the critical one [36]. However, the tryptophan and 5-HIAA responses to IL-1 appear in iNOS, nNOS, and eNOS knockout mice, suggesting redundancy among the forms of NOS [37]. Further evidence for the dissociation derives from studies with endotoxin-resistant (C3H/HeJ) mice which exhibit very small HPA responses to LPS and no changes in MHPG, while the increases in tryptophan and 5-HIAA were similar to those in the control (C3H/HeN) strain [38]. The HPA and neurochemical responses to IL-1 were similar in both endotoxin-resistant and normal strains. In contrast to the effects on NE, treatment with COX inhibitors did not affect the increases in brain tryptophan and 5-HIAA [30]. Moreover, subdiaphragmatic vagotomy in mice did not alter the IL-1-induced increases in brain

tryptophan and 5-HIAA [34]. Thus, the NE and indoleamine responses can be independently manipulated, and must involve distinct mechanisms.

The brain content of tryptophan increases in response to a large variety of stimuli, including several psychotropic drugs, increases in body temperature and several different stressors [39-43]. In our experience, increases in brain tryptophan are a very sensitive index of an animal's state of health. Illness associated with infection, wounds or surgery or food or water deprivation is almost invariably associated with increases in brain tryptophan. These increases are often accompanied by increases in 5-HIAA, probably driven by the increased tryptophan. Peripheral administration of relatively high doses of tryptophan, results in increases in brain tryptophan and 5-HIAA [37,44], although the increased 5-HIAA may not reflect increased synaptic release [45,46]. The increases in tryptophan 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 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 [43]. Thus, the increases in brain tryptophan appear to reflect sympathetic activation. This is consistent with the activity of β_2 -adrenergic agonists, such as clenbuterol, to increase brain concentrations of tryptophan [47]. However, β_2 -adrenergic antagonists do not prevent the IL-1-induced increases in brain tryptophan 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 brain tryptophan, and that the effects of β_3 -adrenergic agonists can double the brain concentrations of tryptophan in mice [48]. This may explain why β_2 -adrenergic antagonists alone were not effective.

2.1.3. Effects on other neurotransmitters—IL-1 β (hIL-1 β ip) decreased the secretion of acetylcholine (ACh) from the hippocampus, measured by microdialysis in freely moving rats [49]. Effects occurred at doses of 20 and 50 μ g/kg, a lower dose (7.5 μ g/kg) was ineffective. Kang et al. showed increased histamine turnover (assessed by accumulation following inhibition of degradation by pargyline) in the hypothalamus of the rat (IL-1 β 25 ng icv) [50]. In a microdialysis study, Niimi et al. found increased release of histamine from the hypothalamus following intrahypothalamic injection of IL-1 β [51]. Intraperitoneal injection of hIL-1 β (20 μ g/kg, but not 10 μ g/kg) decreased hippocampal concentrations of glutamate, glutamine and GABA 1 h later [52]. Most authors have found 3–5 μ g/kg IL-1 to induce maximal HPA activation in the rat, so the physiological significance of these effects at substantially higher doses is not clear. Mascarucci et al. [53] showed that ip hIL-1 β (4 μ g/rat ip) increased apparent glutamate release from the nucleus tractus solitarius (NTS), although heat-treated IL-1 also elicited a partial response.

2.1.4. Other neurochemical responses—Peripheral administration of IL-1 increased the expression of Fos protein in a number of brain regions [54-56]. The structure most markedly affected is the hypothalamic PVN, which contains the cell bodies of the neurons that synthesize CRF involved in the activation of the HPA axis. Increases in Fos are also commonly observed in the central amygdaloid nucleus, the medial preoptic area, the bed nucleus of the stria terminalis, and the NTS. mRNA for Fos (c-fos) is also induced in most of the same structures [57-59]. The Fos response to IL-1 appears to depend on activation of the PVN by noradrenergic neurons because it is markedly attenuated in mice depleted of NE with 6-hydroxydopamine (6-OHDA) [60].

The rate of protein synthesis in the brain was altered by sc injection of hIL-1 β in the rat [61]. Increases were observed in the subfornical organ, choroid plexus, medial habenula, dentate gyrus and the anterior and posterior lobes of the pituitary, but decreases were observed in the cingulate cortex and the pineal gland.

2.2. Interleukin-2

Zalcman et al. [12] observed that IL-2 (200 ng ip) increased MHPG concentrations and MHPG:NE ratios in the hypothalamus of BALB/c mice 2 h after injection. DOPAC:DA ratios were also increased in prefrontal cortex. Interestingly, in contrast with this, a microdialysis study indicated decreased release of DA from the nucleus accumbens following systemic administration of IL-2 [62]. Pettito et al. [63] showed that IL-2 had dose-dependent effects on DA release from striatal slices, excitation at low doses, inhibition at higher ones. In another study, icv IL-2 administration (10 U/day for 6–7 days) reversed the decreases in NE in the amygdala of olfactory bulbectomized rats, as well as the increased open-arm entries in the elevated plus-maze [64]. Icv IL-2 (500, but not 50 ng) markedly increased 5-HT and 5-HIAA in hippocampal microdialysates [65]. Systemic IL-2 administration (550–18,000 U) increased MHPG in the PVN, whereas daily IL-2 administration for 7 days, extended the NE activation to the median eminence, the arcuate nucleus, and the hippocampus [66]. Ip injection of human IL-2 (5 µg/kg) induced small increases in glutamine in the cortex and hippocampus of mice 1 h later [52]. IL-2 administration to humans decreased plasma tryptophan, and increased plasma concentrations of kynurenine and neopterin [67].

In vitro, IL-2 induced release of CRF and arginine vasopressin (AVP) from slices of the amygdala, but not the hypothalamus [68]. It also increased the spontaneous and K⁺-stimulated DA release from striatal slices [69], whereas it inhibited the K⁺-stimulated, but not the spontaneous, NE release from hypothalamic slices, but not that of DA, 5-HT, glutamate or GABA [70]. IL-2 also increased the K⁺-induced release, but not the spontaneous release of methionine–enkephalin and β-endorphin, but not of leucine–enkephalin [70]. The interpretation of slice data, like most in vitro data, is complex, so these findings need to be verified in vivo.

2.3. Interleukin-6

Many studies have indicated that IL-6 administration activates the HPA axis as indicated by elevations of plasma ACTH and corticosterone, although it is much less potent than IL-1 [71] (see [72]). However, no effects of IL-6 on NE metabolism were observed, nor were there any effects on NE turnover (using metyrosine) [19]. Zalcman [12] et al. noted an increase in DOPAC in the prefrontal cortex with human IL-6 (200 ng, ip). The same dose increased 5-HIAA in the hippocampus and prefrontal cortex. We found that injection of mIL-6 into mice iv or ip elicited modest increases in plasma ACTH and corticosterone; maximal concentrations were much lower than observed with IL-1 and did not last as long [71]. mIL-6 (iv or ip) consistently elevated tryptophan in all brain regions at around 2 h, and 5-HIAA in the brain stem at the same time, but had no significant effect on MHPG or DOPAC in any brain region [71]. Icv mIL-6 at lower doses had similar endocrine and neurochemical effects [71]. The effects of IL-6 on serotonin were confirmed in a microdialysis study, which showed increases in 5-HT and 5-HIAA from the hypothalamus of rats injected ip with rat IL-6 (2 µg per rat) [73]. In a separate study, the same dose of rIL-6 increased 5-HT and 5-HIAA in dialysates from the striatum [74]. Amperometric measurements indicated that ip IL-6 enhanced the 5-HT-like signal obtained from the striatum following electrical stimulation of the dorsal raphe nucleus [74]. Another microdialysis study found synergism in the effects of IL-1 and IL-6 administered directly into the PVN on 5-HT release [75].

Because, IL-1 and LPS administration both stimulate the synthesis and secretion of IL-6, it is possible that IL-6 mediates the indoleamine responses to IL-1 and LPS. However, Wang and Dunn found that pretreatment with a monoclonal antibody to mIL-6 that inhibited (but did not block) the ACTH and corticosterone responses to ip IL-1β at 2 h, failed to alter the tryptophan and 5-HIAA responses [76]. The IL-6 antibody also attenuated the ACTH and corticosterone responses to ip LPS at 3 h, and the increases in tryptophan and 5-HIAA [76]. These results

suggest that IL-6 contributes to the HPA and indoleamine responses to IL-1 and LPS, especially in the later phases of the response, but IL-6 cannot be the only factor. Consistent with this, we observed no significant changes in tryptophan and 5-HIAA, but normal corticosterone responses to IL-1 and LPS in IL-6-knockout mice [77].

Changes in Fos have also been reported in response to peripheral administration of IL-6, but the results have varied. The PVN was affected in some studies [78], but not others [79]. Other structures implicated, include the central amygdala, the bed nucleus of stria terminalis, the suproptotic nuclei, the nucleus of the solitary tract, and the superchiasmatic nucleus [80].

2.4. Tumor necrosis factor- α

The human forms of IL-1 and IL-6 are active on their respective cytokine receptors in the mouse and the rat, so that the responses to the human and rodent cytokines are similar. This is not necessarily the case for TNF α . Although, the amino acid sequence homology between mouse and human TNF α is 79% [81], mouse TNF α (mTNF α) is a glycosylated dimer whereas human TNF α (hTNF α) is not glycosylated [82]. hTNF α does not bind to mouse type 2 TNF receptors (mTNF-R2), whereas mTNF α binds to both mTNF-R1 and mTNF-R2 [83]. Therefore, hTNF α lacks some of the actions of mTNF α in mice [84], so that physiologically relevant effects can only be studied using the homologous cytokines.

TNF α administration activates the HPA axis. This has been reported with hTNF α in humans [85] and in rodents [86-88]. In most of these studies, TNF α was significantly less potent than IL-1 in rats [86,89] and mice [90], but in one study in rats, hTNF α was reported to be almost equipotent with hIL-1 β [91]. Mouse TNF α iv and ip elicited modest increases in plasma corticosterone; 1 μ g was needed to produce significant elevations [92]. The specificity of the HPA responses to TNF α was verified when the responses were observed to be markedly diminished in mice deficient in the p55 TNF α receptor [93].

mTNF α increased brain MHPG and tryptophan, but only at relatively high doses (1 μ g or more) [92]. Terao et al. observed no effects of TNF α on NE turnover [19]. Icv mTNF- α (50 or 100 ng) elevated body temperature and plasma corticosterone, but did not alter hippocampal dialysate concentrations of 5-HT or 5-HIAA [65].

An interesting sensitization to repeated administration of TNF α has been reported [94]. A second administration of TNF α (1 μ g ip) 28 days later induced a marked enhancement of the increase in MHPG in the hypothalamic PVN that was accompanied by profound decreases in activity and social exploration, along with increases in the corticosterone response. Such effects were not observed if the second dose of TNF α was given within 1 week. Surprisingly, a second dose of TNF α 24 h after the first, enhanced the MHPG response in the prefrontal cortex and the amygdala, but this did not occur at 28 days. A higher dose of TNF α (4 μ g ip) induced complex changes in immunoreactivity for Fos, as well as CRF and AVP in the hypothalamus and the amygdala [95,96].

In contrast to the above excitatory effects of TNF α on central noradrenergic systems, TNF α inhibited NE release from the median eminence [97]. Similarly TNF α inhibited NE release from hippocampal slices [98]. Interestingly, chronic treatment with the antidepressant, desmethyylimipramine, reversed this in vitro effect, such that TNF α stimulated NE release [98]. In the periphery, TNF α inhibited NE release from the rat myenteric plexus [99], and the mouse heart [100].

2.5. Interferons

A clear distinction should be made between the Type I interferons (IFN α and IFN β) which share a common receptor (the type I receptor, which consists of two subunits: IFNAR-1 and IFNAR-2), and Type II interferons (IFN γ), which act on the Type II receptor (IFNGR).

2.5.1. Interferon- α —Reports of the effects of interferons on brain catecholamines have been quite varied (see also the recent review by Schaefer et al. [101]. Shuto et al. reported that chronic (but not acute) administration of hIFN α (15×10^6 Units ip) to mice induced small decreases in whole brain (minus cerebellum) DA or DOPAC, but there were no changes in the DOPAC:DA ratio, nor in NE [102]. They also reported a decrease in the apparent turnover of DA, assessed by blocking its synthesis with metyrosine. Kumai et al. [103] found that seven daily treatments of rats with hIFN α (300,000 U/kg sc) increased the DA and NE contents of the cortex, hypothalamus and medulla, but not of the hippocampus or thalamus. We observed no effects of a single ip injection of mice with mouse IFN α (1000 or 10,000 U/mouse) on DA, NE or any of their metabolites 2 h later [104]. The interferon used was the same used in the studies of Crnic et al. (supplied by Dr Crnic) which had been shown to decrease locomotor activity and feeding [105,106]. In contrast, a single icv injection of IFN α (200 or 2000 U of hIFN α A/D) in rats was reported to decrease frontal cortical NE [107]. However, in another study, 1000 U hIFN α injected icv into rats increased apparent DA turnover (DOPAC:DA ratio) in the hippocampus (primarily caused by a substantial decrease in the measured hippocampal DA), but no such effect was observed in the prefrontal cortex or striatum [108]. Unfortunately, this study was based on a small number of animals (only three rats in the IFN group). Interestingly, in a subsequent study, no effects of acute hIFN α administration (10^5 U/kg ip) on DA or NE were observed, whereas 14 daily treatments with hIFN α decreased prefrontal cortex DA [109]. In preliminary studies, using hIFN α or homologous IFN α injected at various doses ip or icv into mice or rats, we have observed no consistent changes in DA, NE or its metabolites.

There are few data on the effects of IFN's on brain 5-HT. A single icv injection of 200 or 2000 U of hIFN α to rats was reported to decrease the 5-HT content of the frontal cortex, and both 5-HT and 5-HIAA were decreased in the midbrain and the striatum [107]. However, we observed no effects of ip human or mouse IFN α on 5-HT or 5-HIAA in mice at doses (400–16,000 U/mouse) that induced behavioral changes [104]. However, in another study a single icv injection of IFN α (1000 U) increased 5-HIAA:5-HT ratios in the prefrontal cortex, but not in the striatum or the hippocampus of rats [108]. This latter effect was prevented by pretreatment with the COX inhibitor, diclofenac. In a subsequent report, from the same laboratory, no effect of acute hIFN α administration (10^5 U/kg ip) on 5-HT or 5-HIAA was observed, whereas 14 daily treatments with hIFN α decreased 5-HT and 5-HIAA:5-HT ratios in the amygdala [109]. In preliminary studies, using hIFN α or homologous IFN α injected at various doses ip or icv into mice or rats, we have observed no consistent changes in tryptophan, 5-HT or 5-HIAA.

2.5.2. Interferon- γ —IFN γ has profound effects on tryptophan metabolism and hence may indirectly affect brain 5-HT. IFN γ and, to a lesser extent IFN α , induce indoleamine-2,3-dioxygenase (IDO) in circulating immune cells, primarily macrophages. IDO converts tryptophan to kynurenine, which is subsequently converted to quinolinic acid [110]. Thus, administration of IFN γ , or induction of endogenous IFN γ secretion decreases plasma concentrations of tryptophan and increases plasma kynurenine. Tryptophan is an essential amino acid, and appears to be the rate-limiting amino acid for protein synthesis [111]. Tryptophan is also the essential precursor for 5-HT, and there is good evidence that 5-HT synthesis in the brain depends on available tryptophan [112]. Thus, the peripheral catabolism of plasma tryptophan may limit the availability of tryptophan to the brain for 5-HT synthesis. This led Bonaccorso et al. [113] and Capuron et al. [114] to speculate that these peripheral

effects of IFN's may cause depression by limiting brain 5-HT synthesis. It has also been speculated that this could account for the depression-inducing properties of the interferons observed clinically [115].

Chronic treatment of mice with IFN γ increased brain concentrations of quinolinic acid and the activity of the enzyme indoleamine-2,3-dioxygenase (IDO), a key enzyme in indoleamine degradation [116]. In a voltammetric study, Clement et al. found that peripheral administration of recombinant IFN γ had no effect on the appearance of 5-HIAA in the dorsal raphe nucleus, although IL-1 β and TNF α increased 5-HIAA [117]. However, icv administration increased 5-HIAA following all three cytokines. In cultured immune cells, IFN γ stimulated the activity of GTP cyclohydrolase, a critical enzyme for the synthesis of tetrahydrobiopterin [118]. Tetrahydrobiopterin is an essential co-factor for NO synthase, and also, for the biosynthesis of catecholamines and serotonin.

2.6. Other cytokines

Granulocyte/macrophage colony-stimulating factor (GM-CSF) administration to rats (5 and 10 μ g ip) significantly reduced hypothalamic glutamate, glutamine, aspartate and GABA, as well as NE and 5-HT, but not DA [119].

3. Mechanisms of the neurochemical effects of cytokines

Section 2 described the known neurochemical effects of peripherally administered cytokines. Cytokines are typically small proteins but are too large to readily pass the blood–brain barrier. However, a number of possible mechanisms by which cytokines may affect the brain have been identified (see Table 2, and reviews [120,121]). Cytokines could act on one or other of the brain regions that lack a blood–brain barrier, the circumventricular organs (CVO's), such as the median eminence, organum vasculosum laminae terminalis (OVLT), or the area postrema. Some researchers believe that IL-1 in the general circulation (as when administered iv) may act directly on CRF-containing terminals in the median eminence to initiate HPA axis activation [122]. Local application of IL-1 in the median eminence elevates plasma ACTH and corticosterone in rats, and these responses were prevented by local administration of α - and β -adrenergic receptor antagonists [123] or indomethacin [124]. There is also evidence for action of IL-1 on the area postrema [125].

A second possibility is that cytokines may cross the blood–brain barrier using specific uptake systems. Banks et al. have demonstrated specific uptake of many cytokines from the blood to the brain [126]. Uptake has been demonstrated for IL-1 α , IL-1 β , IL-1ra, IL-2, IL-6, and TNF α , as well as the soluble receptors for IL-1 and TNF α . However, the capacity of these uptake systems is quite low, and it is not known whether the uptake enables active concentrations of the cytokines to be attained in the appropriate brain regions [127]. However, in a clever experiment, Banks et al. showed that peripherally administered hIL-1 α impaired memory in mice, and that this effect could be prevented by injecting into the septum an antibody that recognized hIL-1 α but not mIL-1 α [128].

An important mechanism for cytokine actions on the brain involves the vagus nerve, and possibly other neural afferents. Initially, it was demonstrated that a subdiaphragmatic vagotomy prevented the cerebral Fos response to ip LPS [129]. Subsequently, several groups demonstrated that vagal lesions could prevent the CNS effects of ip IL-1 or LPS on behavior [130,131]. Subdiaphragmatic vagotomy also attenuated the HPA response to IL-1 and prevented the decreases in hypothalamic NE [20]. Abdominal vagotomy attenuated the IL-1 β -induced increase in hypothalamic dialysate NE [15,33] (for a review, see [132]). It is believed that vagal activation occurs when IL-1 binds to receptors on parasympathetic cells associated with the vagal ganglia in the abdominal cavity [133]. The vagal afferents terminate

in the NTS in the brain stem, which also contains cell bodies of the A1/A2 noradrenergic projection system, thus providing a clear pathway for activation of the VNAB and thence the PVN.

Yet another possibility is that cytokines act on tissues that can secrete molecules that can pass the blood–brain barrier (e.g. lipophilic molecules such as the eicosanoids). Interestingly a major target may be cerebral blood vessels. Receptors for IL-1 and LPS are known to be present on endothelial cells, including those in the brain. These receptors appear to be coupled to COX enzymes, which enable production of prostaglandins, leukotrienes, thromboxanes and other lipid mediators that can easily pass into and through the brain. Despite the remarkable sensitivity of the brain to IL-1, the brain contains very few receptors for IL-1. Binding sites for IL-1 have not been adequately demonstrated in the brain of the rat, and in the mouse brain they appear only in the hippocampus [134,135]. mRNA for IL-1 receptors has also been difficult to demonstrate in the parenchyma of normal brain. However, IL-1-receptors are common in the capillary endothelium and choroid plexus.

Cytokines may also be synthesized by immune cells that infiltrate the brain. High doses of LPS administered peripherally are known to induce migration of IL-1-positive microglia (thought to be derived from peripheral macrophages), which penetrate the endothelia [136,137]. A similar immigration of microglia occurs in response to tissue damage (e.g. the insertion of a cannula or a microdialysis probe). It is likely that these distinct mechanisms operate in parallel, so that when cytokines are administered, more than one mechanism operates.

4. Neurochemical responses to endotoxin (LPS)

It has been known for more than half a century that administration of LPS activates the HPA axis [138]. An early study suggested that NE utilization was activated by high doses of LPS (2.5 mg/rat ip or 50 µg icv) [139]. Administration of LPS significantly decreased the brain content of NE, but did not affect that of 5-HT. LPS also accelerated the disappearance of [³H] NE administered icv [139]. In mice, low doses of LPS (1 µg/mouse ip) induced elevations of plasma ACTH and corticosterone, both of which reached peaks at around 2 h [26]. Increased concentrations of MHPG and MHPG:NE ratios also appeared throughout the brain with a similar time course [26,140-143]. This response was greatest in the hypothalamus, suggesting a relatively greater activation of the VNAB compared to the DNAB. LPS also induces small increases of DOPAC in most brain regions, including prefrontal cortex, hypothalamus and brain stem [26,140-144]. Peak responses in both DA and NE occurred around 2 h [26]. LPS also increased tryptophan and 5-HIAA in a regionally nonselective manner [26,140, 143-145]. However, these latter changes reached a maximum much later at around 6–8 h in the mouse [26]. Similar changes were observed following icv LPS and the effective doses were quite similar [26].

In vivo microdialysis studies have indicated increased extracellular concentrations of DA, DOPAC, NE, DHPG, MHPG and 5-HIAA (5-HT was not measurable in this study) in the medial prefrontal cortex and hypothalamus following ip LPS administration in rats [146]. Other studies have indicated elevations of 5-HT release from the hippocampus [147,148], as well as NE, MHPG, 5-HT and 5-HIAA in the preoptic area [149]. In the nucleus accumbens, LPS injection (100 µg ip) increased DA and 5-HIAA [150]. Mascarucci et al. showed that ip LPS (10 µg/rat ip or iv) increased apparent glutamate release from the NTS [53]. Smith et al. showed that LPS 200 µg/kg ip) increased prostaglandin *E*₂ and cyclic AMP in hypothalamic dialysates [151].

5. Neurochemical responses to infections

Bacterial infections have long been known to activate the HPA axis [152,153]. Administration of Newcastle disease virus (NDV) to mice elevated plasma concentrations of corticosterone, indicating an activation of HPA axis [154]. More recent work has extended this observation to other viruses (see review by Silverman et al. [155]). NDV administration also caused neurochemical changes; MHPG and MHPG:NE ratios, DOPAC and DOPAC:DA ratios, and 5-HIAA and 5-HIAA:5-HT ratios were all increased in a number of brain regions [156,157]. Tryptophan was also elevated in all regions of the brain. The HPA and neurochemical changes were short-lived. However, NDV does not cause a true infection in mice; although the viral RNA is copied, there is no production of infective virus.

We have also studied infection of mice with influenza virus. Infusion of the virus into the lungs (the normal site of influenza virus infection) induced a chronic elevation of plasma corticosterone [158]. This contrasted with the transient elevation seen with most commonly studied stressors. The changes in corticosterone were accompanied by neurochemical ones. MHPG and MHPG:NE ratios were elevated in all brain regions studied, but the magnitude of the responses was greater in the hypothalamus than in the other brain regions studied [158]. DOPAC and DOPAC:DA ratios, and HVA and HVA:DA ratios were not significantly altered. Concentrations of tryptophan were elevated in all regions studied, as well as 5-HIAA and 5-HIAA:5-HT ratios. These changes appeared around 24–36 h after infection with influenza virus and continued as long as the animals appeared sick. Similar HPA and neurochemical changes have been associated with infection with other viruses, e.g. Herpes virus [159], Pichinde virus [160], lymphocytic choriomeningitis virus (LCMV) [161], as well as infection with *Mycoplasma fermentans* [162]. Thus, it seems that infections are generally associated with activation of the HPA axis, as well as brain noradrenergic systems, and brain tryptophan and serotonin.

This pattern of responses clearly resembles the neurochemical and physiological responses to stressors commonly used in the laboratory, such as footshock or restraint [104]. In the CNS, the major response occurs in noradrenergic neurons, but responses also occur in dopaminergic and serotonergic neurons [163,164]. The NE response is widespread and appears to affect similarly both the locus coeruleus (A6) system innervating dorsal structures, via the DNAB, and the NTS A1/A2 system via the VNAB. The DA response is also widespread such that all the major neuronal systems show responses (nigrostriatal, mesolimbic, mesocortical), but the magnitude of the response is much greater in the mesocortical (i.e. in the prefrontal and cingulate cortices) compared to the other systems. The 5-HT response is not markedly regionally specific, although some have reported regional differences (e.g. [165]). There is also a robust elevation of concentrations of tryptophan in all regions of the brain. This latter increase is quite uniform in magnitude, and does not appear to be related in any obvious way to the extent of the serotonergic innervation of a region [41,42].

The responses associated with what has been termed ‘immune stress’ are not identical to those associated with physical and psychological stressors. A major difference is that the HPA activation associated with infection is continuous and not transient as it is to stressors such as electric shock. A significant neurochemical difference is that infections and illness are associated with larger NE responses in the hypothalamus (the VNAB system) relative to other brain regions, whereas the responses to footshock and restraint are relatively uniform on a regional basis. The second important difference is the relative lack of DA responses associated with infections, especially in the prefrontal cortex. However, small DA responses are occasionally observed throughout the brain.

6. Cytokine involvement in the responses to LPS and infections

The neurochemical effects of LPS and infections described above resemble quite closely those observed with IL-1, except for the addition small changes in DA. This is also true for the HPA and behavioral responses. Because, LPS administration is known to elicit the synthesis and secretion of IL-1, it is tempting to speculate that IL-1 is the mediator of these responses. Similarly, influenza virus infection is associated with increases in IL-1 [166]. However, although LPS is a potent stimulator of IL-1 production, little IL-1 appears in the first hour, and the peak response in the plasma occurs around 2 h. Therefore, if IL-1 were the mediator of the responses to LPS, the endocrine, neurochemical and behavioral responses should be delayed more than is observed [26,167]. More definitively, the administration of the natural IL-1-receptor antagonist, IL-1ra, at doses (100–300 µg/mouse ip) adequate to prevent neurochemical and HPA responses to exogenous mL-1β (100 ng ip) failed to attenuate the HPA, NE, 5-HIAA, and tryptophan responses 2 h after ip LPS (1 µg) [167]. However, there was a significant attenuation of the increase in corticosterone at 4 h. Thus, although IL-1 probably contributes to the neurochemical and HPA responses to LPS, other mechanisms must exist. Qualitatively similar findings were obtained in behavioral experiments. Neither the LPS-induced nor the influenza virus infection-induced reductions in milk drinking were significantly affected by IL-1ra pretreatment [168]. Consistent with these findings, LPS was found to induce normal increases in HPA responses and hypophagia in IL-1β-knockout mice [169]. However, combined pretreatment with IL-1ra, a monoclonal antibody to IL-6, and a TNF-binding protein was able to prevent the LPS-induced reductions in milk intake, although not those induced by influenza virus infection [170]. This suggests that all three cytokines (IL-1, IL-6 and TNFα) contribute to the response to LPS.

Experiments with antibodies to IL-6 have suggested a role for IL-6 in the HPA responses to both the administration of LPS [76,87] and IL-1 [76]. In our experiments, the sensitivity to IL-1 antibody was confined to the later phases of the HPA response, consistent with the delay necessary for the production and secretion of IL-6 [76]. Pretreatment with a neutralizing monoclonal antibody to mouse IL-6 also attenuated the increases in tryptophan and 5-HIAA following LPS administration to mice, but not that to IL-1. This suggests that IL-6 contributes only to the indoleamine responses to LPS, and is not critical for those to IL-1 [76]. Treatment with a neutralizing antibody to TNFα also failed to prevent the HPA and neurochemical responses to LPS, even when supplemented with IL-1ra [76].

7. The functional significance of the neurochemical responses to cytokines

The functional significance of the neurochemical responses to cytokines has largely been explored with regard to their potential role in the HPA and the behavioral responses to IL-1, as well as to LPS and infections. The critical question is whether any of the neurochemical responses observed following cytokine administration are instrumental in the HPA or the behavioral responses.

7.1. Neurochemical involvement in HPA axis activation by cytokines

Hypothalamic NE and 5-HT have both been implicated in HPA activation (i.e. of CRF-containing neurons in the PVN [11], and are thus obvious candidates for mediating the responses to IL-1, LPS and infections [171]. The hypothalamic NE response and those in plasma ACTH and corticosterone are closely linked in time, and in our experiments in mice, have been very highly correlated within individual animals over a large number of experiments involving a large number of different manipulations. This association has been confirmed in microdialysis studies in freely moving rats in which a very close temporal relationship between extracellular concentrations of NE in the hypothalamus and plasma concentrations of corticosterone was observed following both iv and ip IL-1β [14,17,33]. An association between

the activation of hypothalamic NE and that of the HPA axis is also supported by other data. When 6-OHDA was injected into the VNAB or the PVN of rats, it depleted PVN NE by 75% or more, and the plasma corticosterone response to ip IL-1 was largely prevented [172]. A similar result was obtained using icv IL-1 in 6-OHDA-treated rats [173]. A similar 6-OHDA treatment prevented the increase in plasma corticosterone following infection with Herpes simplex virus, whereas lesioning of brain serotonergic systems with 5,7-dihydroxytryptamine (5,7-DHT) did not [159].

In microdialysis studies, it was shown that the ip IL-1 β -induced increase in dialysate NE from the medial hypothalamus of rats, was completely prevented by subdiaphragmatic vagotomy [15,33], but the responses in plasma ACTH and corticosterone in the same animals were only moderately attenuated [33]. Similarly indomethacin pretreatment more or less completely blocked the IL-1-induced increase in dialysate NE, but the increases in plasma ACTH and corticosterone were only slightly reduced [17]. Also, α - and β -adrenergic receptor antagonists had little effect on the ACTH response to IL-1 in rats [122]. Thus, it seems that hypothalamic NE does play a role in the HPA axis activation, but it is not essential in rats. There are no data to suggest that 5-HT plays a significant role in this response.

The results obtained in mice differ somewhat. As in rats, the β -adrenergic receptor antagonist, propranolol, and the α_1 -adrenergic receptor antagonist, prazosin, attenuated the HPA response in mice only at high doses [174]. When whole brain NE was depleted by around 98% with 6-OHDA, there was only a small reduction in the plasma corticosterone response to ip IL-1 β [60]. However, subdiaphragmatic vagotomy in mice, only slightly attenuated the IL-1-induced increase in hypothalamic MHPG, and the increases in plasma ACTH and corticosterone [34]. Thus, although hypothalamic NE is likely to be involved in the HPA response to IL-1, it does not appear to be essential in mice.

The role of IL-6 in HPA activation is unclear [72,175]. There is some evidence that IL-6 can act directly on the pituitary to elicit ACTH release, but it may also act on the hypothalamus, and even the adrenal gland to elicit corticosterone secretion (see [72,175,176]). Little is known regarding the HPA-activating effects of other cytokines, most of which are far less potent than IL-1 [72,175].

7.2. The neurochemical involvement in behavioral responses to cytokines

Most illnesses are associated with all-too-familiar alterations in behavior, now known as sickness behavior [177,178]. Sickness behaviors are remarkably unspecific for the nature of the illness. They include decreased activity, eating, exploration and sexual activity, and increased sleep [179,180]. IL-1 and LPS both induce behaviors that closely resemble those observed in sick animals [179,180].

We have employed a simple behavioral test in which mice are presented with sweetened milk for a short period (10–30 min) every day. Mice typically drink 2–3 ml of the milk in a 10–30 min period. The model is very sensitive to low doses of IL-1 (50 ng ip) and LPS (1 μ g ip) [181]. We have used this milk drinking model to study the potential involvement of a number of different neurochemicals. Because IL-1 activates both NE and 5-HT, and both neurotransmitters have previously been implicated in hypophagia [182] they are both good candidates for mediation of this response. NE appeared more likely to be involved because the time course of its response paralleled that of the hypophagia. However, neither α_1 -, α_2 -, nor nonselective α - or β -adrenergic receptor antagonists, alone or in combination induced significant reductions in the IL-1- or LPS-induced decrease in milk drinking or food pellet intake in mice [183]. Moreover, pretreatment with 6-OHDA or DSP-4 to deplete cerebral NE did not alter the hypophagic response to IL-1 or LPS [183].

Experiments with 5-HT antagonists were no more successful. We failed to find any effects of cerebral 5-HT depletion with 5,7-DHT or pretreatment with a variety of different 5-HT-receptor antagonists [184]. However, this result is consistent with the lack of effect on milk intake of NOS inhibitors which prevent the increases in tryptophan and 5-HIAA in responses to IL-1 and LPS [35], and also with the observation that administration of IL-6 which induces increases in brain tryptophan and 5-HIAA like those to IL-1 [71] fails to alter milk drinking in mice [170]. We also failed to find effects of histamine H₁, H₂ and H₃ antagonists and the histamine synthesis inhibitor, α -fluoromethylhistidine, as well as dopamine and muscarinic receptor antagonists [183]. For a more detailed review, see Dunn [185].

However, eicosanoids appear to be involved in these responses, because the reductions in ingestive behavior induced by IL-1 are largely prevented by COX inhibitors, such as indomethacin [183,186]. However, such inhibitors are less effective against the LPS-induced behavioral changes [183,187], and have only small effects on the behavioral changes associated with influenza virus infection [183]. Interestingly, the early responses to IL-1 and LPS involve the COX1 isozyme, whereas COX2 is involved in the later phases of the response [188]. The latter parallels COX2 induction in brain endothelia (Dunn, Swiergiel and Quan, unpublished observations).

However, studies of other cytokine-induced behaviors have produced some evidence implicating noradrenergic mechanisms. For example, Ovadia et al. found that pretreatment with 6-OHDA, the β -adrenoreceptor blocker, propranolol, or the α_2 -adrenoreceptor blocker, yohimbine, prevented IL-1-induced fever [189]. Also, 6-OHDA pretreatment or prazosin prevented the antinociceptive effect of icv hIL-1 α determined in the hotplate test [190]. These findings may reflect the different neural pathways involved in these responses.

8. Implications of cytokine-induced effects on neuro-transmission for neurology and psychiatry

Cytokine effects on the brain have not been clearly linked to any major disease. The strongest association has been speculation of a role for cytokines in depression. Both schizophrenia [191] and depression [192] have often been associated with immune abnormalities, but the clinical data have been inconclusive and often conflicting [193]. The link to depression was proposed based on the apparent similarities between sickness behavior and depression [194-197].

Depression has long been associated with a hyperactivity of the HPA axis, elevated cortisol [198], resistance to dexamethasone suppression [199], enhanced responsivity to CRF [200], and hyperactivity of brain CRF [201]. Moreover, there is evidence for increased CRF in the CSF of depressed patients [201,202]. There is also substantial evidence for a hyperactivity of noradrenergic systems in depression. CSF concentrations of MHPG have often been found to be elevated [203], and more recently CSF concentrations of NE itself have also been shown to be increased [204].

Because IL-1 is a potent inducer of sickness behavior, and because it activates the HPA axis, and both noradrenergic and serotonergic systems, both of which are implicated in current treatments for depression, IL-1 became the obvious target for study. Thus, the cytokine hypothesis of depression was born (see [205]). Unfortunately, the literature on abnormalities in IL-1 in depressed patients is very inconsistent. An extensive and thorough meta-analysis concluded that there was no consistent evidence for elevated IL-1 in the plasma of depressed patients [206]. However, an elevation of CSF IL-1 has been reported in a limited study [207], but this has not yet been confirmed.

Nevertheless, it has been argued that sickness behavior in animals may be a model for depression [195-197]. It has also been argued that because COX inhibitors can attenuate IL-1-induced sickness behaviors, that they should be tested for the treatment depression. However, numerous depressed patients have taken COX inhibitors (more commonly known as non-steroidal anti-inflammatory drugs, NSAIDS, such as aspirin and ibuprofen) and psychiatrists would have noticed any significant antidepressant effects long ago.

Yirmiya [194] showed that LPS administration to rats reduced their consumption of saccharin solution and argued that this represented anhedonia, which is a hallmark of depression. He also showed that chronic treatment with the antidepressant, imipramine, reversed the reduction of saccharin ingestion by LPS, reinforcing the concept that LPS treatment could model depression. The ability of antidepressant drugs to prevent the reduction in apparently pleasurable activities in animals by LPS has been replicated by some, but not others (for a review, see [205]). A further problem is that the antidepressant treatments do not prevent the effects of IL-1.

The similarities between the responses to IL-1 and depression do not hold up very well to close scrutiny. Although, depression is frequently associated with decreased activity, anorexia, and loss of libido, it can also be associated with hyperactivity and over-eating. Proponents of the cytokine theory have pointed out that both depression and IL-1 administration can be associated with abnormalities in sleep [195-197]. However, IL-1 increases the duration of slow-wave sleep [208], whereas by far the most common sleep abnormality in depressed patients is insomnia. Also, IL-1 and LPS induce hyperalgesia in rats, although depressed patients more commonly display hypoalgesia. Thus, cytokine administration and depression may share certain aspects, perhaps because they are both stress-like states. IL-1 (and perhaps other cytokines) may contribute to depressive symptoms, but are unlikely to be the major cause of depression.

Yet another link between depression and cytokines was made, when it was learned that interferon- α and IL-2 used to treat various illnesses often induced depression in the patients. However, neither cytokine induces classical sickness behavior in animal studies.

Cytokine concentrations in the brain are likely to increase with the tissue damage associated with strokes or neurodegenerative diseases. It is certainly possible that CSF IL-1 would be increased, because of the increased phagocytic activity associated with the tissue damage. Elevation of CSF IL-1 could induce behavioral symptoms, including those of depression. There is a substantial literature on increases in CSF IL-1 associated with Alzheimer's disease [209], but the results have been very conflicting, and the issue is unresolved.

9. Conclusions

The foregoing review has indicated that certain cytokines have substantial effects on neurotransmitters in the brain, especially the catecholamines and serotonin, but also including acetylcholine and the amino acid neurotransmitters. This may reflect to some extent the neurochemicals that have been studied most often. Certain other neurochemicals may also be changed, most notably Fos protein, which is considered to be a sign of activation of neurons. The known activities appear to be confined to certain cytokines and are very specific to those cytokines. By far the most potent cytokine in this respect is IL-1, although activities of IL-2, IL-6, TNF α , IFN α and IFN γ , and GM-CSF. The neurochemical responses are likely to be involved in the endocrine and behavioral promoting properties of the cytokines. The only clear example is the effects of IL-1 on norepinephrine, which appear to be instrumental in the IL-1-induced activation of the HPA axis. However, in this case IL-1 appears to be able to stimulate the HPA axis by at least one other mechanism. This redundancy may reflect the importance of

the HPA activation when secretion of IL-1 occurs reflecting tissue damage or infection. The mechanisms of the behavioral actions of cytokines have not yet been identified, but at least for some behavioral responses to IL-1 they do not appear to involve DA, NE, 5-HT, ACh, histamine and several other common neurotransmitters. Eicosanoids (e.g. prostaglandins) do appear to be involved in the behavioral and body temperature responses, and also in the noradrenergic responses in the brain. Further research may reveal the nature of the neurochemistry underlying other responses to cytokines and immune stimulation.

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Comparison of HPA and brain neurochemical responses to viral infection, LPS and some cytokines

Stimulus	Corticosterone	NE	DA	Tryptophan	5-HT
Influenza virus	+	+	0	+	+
LPS	+	+	+	+	+
IL-1 α /IL-1 β	+	+	0	+	+
IL-2	0	+	+	n.d.	0
IL-6	+	0	0	+	+
TNF α	+	(+)	0	(+)	0
IFN α	0	0	0	0	0

+, increased; 0, no change; n.d., not determined; (+), indicates increases only at high doses.

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Table 2

The principal known mechanisms for cytokine signalling of the brain

1.	Cytokines can act on the brain at sites where the blood–brain barrier is weak or non-existent (i.e. the circumventricular organs, CVO's).
2.	Cytokines can be transported into the brain to a limited extent by selective uptake systems (transporters), thus bypassing the blood–brain barrier.
3.	Cytokines may act directly or indirectly on peripheral nerves that can send afferent signals to the brain.
4.	Cytokines can act on peripheral tissues, inducing the secretion of molecules whose ability to penetrate the brain is not limited by the barrier. A major target appears to be endothelial cells, which bear receptors for IL-1 (and endotoxin).
5.	Cytokines can be synthesized by immune cells that infiltrate the brain