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Stress and Cytokine-elicited Neuroendocrine and Neurotransmitter Sensitization: Implications for Depressive Illness

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Stressful events, by their effects on neurotransmitter and neuroendocrine processes, are thought to favor the development or exacerbation of depressive illness. In as much as immunological challenge, may provoke stressor-like neuroendocrine and central neurochemical changes, the view was offered that immune activation essentially acts like a stressor and may contribute to the evolution of affective illness. In this respect, viral and bacterial infections appear to influence behavioral/metabolic (e.g. fever, anorexia, somnolence) and neurotransmitter functioning through the release of cytokines, which act as messengers between the immune system and brain. The present report provides a brief overview of the neurochemical consequences of proinflammatory cytokine treatments, particularly the actions of interleukin (IL)-1β and tumor necrosis factor-α. As well, synergy with psychogenic and neurogenic stressors are described, as are data showing that cytokines, like stressors, may have time-dependent proactive (sensitization) effects, so that reexposure to the treatments greatly augments hypothalamic-pituitary-adrenal activity, as well as central neurochemical changes. Indeed, the neurotransmitter alterations are not restricted to hypothalamic nuclei, but occur in several extrahypothalamic sites, including various limbic regions. It is suggested that by virtue of these neurochemical changes, cytokines may have both immediate and proactive effects on mood states.

Keywords: Cytokine; Interleukin; Tumor necrosis factor; Monoamine; Neuroendocrine; Depression

INTRODUCTION

Generally, stressors are thought of as events or stimuli that are appraised through higher order processes (Lazarus and Folkman, 1984). These stressors typically promote a cascade of central and peripheral neurochemical changes that may be of adaptive significance, ensuring that the organism is prepared to contend with the insult. Although these neurochemical changes are fairly transient (Sapolsky *et al.*, 2000), upon subsequent reexposure to a stressor some of the neurochemical processes may be more readily instigated (sensitization) and may thus impact on mood states (Anisman *et al.*, 1993).

Stressors may be of a psychological nature (psychogenic stressors; exposure to a novel environment, predators or conditioned fear cues) or they may involve physical or painful stimuli (neurogenic stressors). In addition to these "processive" stressors, it has been suggested that systemic insults, such as bacterial or viral infection, ought to be considered stressors (Herman and Cullinan, 1997), as they may induce similar neurochemical alterations. For instance, challenges with viral and bacterial products may influence central monoamine activity (Dunn, 1995; 2001; Anisman and Merali, 1999) and profoundly increase the release of stress-reactive hormones, including adrenocorticotropic hormone (ACTH) and corticosterone (Rivier, 2001; Dunn, 1995; 2001; Anisman *et al.*, 1993). The central effects of such immunological challenges are believed to be primarily mediated by the proinflammatory cytokines released by circulating leukocytes or resident brain glia (Rivier, 2001). In this regard, cytokines have been proposed to act as signaling molecules both within and between the immune and central nervous systems (CNS) (Blalock, 1994), and given the similarity between the effects of traditional stressors and immune activation

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(and particularly cytokine activation), the brain may be interpreting these challenges as if they were stressors (Dunn, 1995; Anisman and Merali, 1999).

Although processive and systemic stressors both impact on hypothalamic-pituitary-adrenal (HPA) functioning, they may do so through different neural circuits (Herman and Cullinan, 1997), and hence may have different psychological repercussions. In this respect, processive stressors have profound effects on central amygdala and prefrontal cortical neuronal functioning and may be aligned with the affective and cognitive processes related to mood and anxiety disorders. Cytokine challenges may similarly induce limbic neurochemical changes (Anisman and Merali, 1999; Konsman *et al.*, 2002), although this might not entail appraisal processes like those associated with processive stressors. Interestingly, however, the effects of systemic stressors may be augmented if administered to animals that had been experiencing a processive stressor. Furthermore, cytokines may provoke the sensitization of neurochemical systems, thereby leading to exaggerated stress responses upon subsequent encounters with processive challenges. In the present review we describe several immediate and proactive neurochemical effects of cytokine activation [interleukin-1β and tumor necrosis factor-α(TNF-α)], particularly as they relate to stressor effects, and discuss some of the behavioral ramifications of the sensitization. In particular, it is hypothesized that the cytokine, TNF-α, sensitizes neural systems, thereby increasing vulnerability to the depressive effects of stressors or cytokine challenge. In effect, exposure to immunogenic challenges (e.g. viral and bacterial infections) that typically induce the release of TNF-α and other proinflammatory cytokines may impact upon the development of affective states.

Direct and Indirect Central Actions of Cytokines

Cytokines have been proposed as "immunotransmitters" that act as messengers between the immune system and the brain. Indeed, when administered systemically, cytokines such as interleukin-1β (IL-1β) stimulate *c-fos* expression in numerous brain regions important for autonomic and endocrine functions (Ericsson *et al.*, 1997; Day *et al.*, 1999; Xu *et al.*, 1999). Moreover, elevated circulating and central cytokine levels, as well as augmented basal and endotoxin-stimulated lymphocyte activity have been associated with brain injury and neurodegenerative diseases (Mogi *et al.*, 1994; Phelps *et al.*, 2001). However, the processes through which neuro-immune communication occurs are not fully understood, as cytokines are relatively large, hydrophilic polypeptides, that do not readily cross the blood brain barrier (BBB). Cytokine receptors are numerous at vascular regions, and circulating cytokines can interact with these receptors to generate secondary messengers within the brain (Laflamme and Rivest, 1999; Rivest, 2001). For instance, both IL-1β and TNF-α stimulate the expression of the inducible prostaglandin regulatory enzyme, cyclooxygenase-2 (COX-2), at brain microvessels (Lacroix and Rivest, 1998). As well, TNF-α increases protein levels of COX-2 and the release of prostaglandin in cultured bovine brain microvessel endothelial cells (Mark *et al.*, 2001). In addition, cytokines can affect CNS processes by stimulating afferent fibers of the vagus nerve which sends projections to the brainstem nucleus of the solitary tract (NTS) (Dantzer *et al.*, 1996; Maier and Watkins, 1998) provoking *de novo* cytokine synthesis within various brainstem and hypothalamic nuclei (Dantzer *et al.*, 1996). Furthermore, cytokines may stimulate specific brain nuclei, such as the parabrachial nucleus and the paraventricular thalamus, which then influence functioning of the central amygdala (Buller and Day, 2002). Regardless of the mechanisms involved, it does appear that systemic cytokine treatments will promote changes in brain neuronal activity and hence may affect behavioral output.

Beyond these indirect routes, the possibility cannot be ignored that cytokines may directly influence CNS functioning. One such mechanism is through saturable carrier mediated transporters that have been identified for IL-1β and TNF-α (Guiterrez *et al.* 1993; Plotkin *et al.*, 1996). For instance, following i.v. injection of radiolabeled murine TNF-α in mice, the cytokine was detected in the cortex, hippocampus, brainstem, hypothalamus and several other brain regions, in the absence of any breakdown in the BBB. In addition, it appeared that once critical levels of brain cytokines were present, further influx of the cytokine declined (Guiterrez *et al.*, 1993; Banks *et al.*, 2001). Interestingly, rate of cytokine entry, as indicated by the unidirectional influx rate (Ki), was greatest at the hypothalamus (1.73 ul/g/min) and was also influenced by the animal's age (Banks *et al.*, 2001). Moreover, cytokines may gain entry into the brain through circumventricular areas, which lack an efficient BBB (Banks, 2001). In this respect, passive diffusion of cytokines into the brain may occur at the organum vasculosum lamina terminalis (OVLT) and other circumventricular organs, and may reach various brain nuclei through volume diffusion (Laflamme and Rivest, 1999; Konsman *et al.*, 2000). Further, IL-1β or TNF-α themselves can disrupt the BBB (Quagliarello *et al.*, 1991; Merrill and Benveniste, 1996; Mayhan, 2002) making it still easier for these substances to gain entry to the brain.

Although the evidence suggesting that cytokines are constitutively expressed in the brain is somewhat controversial, a recent review on this subject concluded that the genes for IL-1β and TNF-α, as well as their accessory proteins are indeed expressed in neurones and glial cells in the normal (unchallenged) brain (Vitkovic *et al.*, 2000). While their basal levels are low, mRNA and/or protein for IL-1β, TNF-α, as well as their receptors, have been detected within neuronal cell bodies, microglia and astrocytes in a brain region-specific manner (Vitkovic *et al.*, 2000). For instance, TNF-α protein was detected within the hypothalamus, bed nucleus of the stria

terminalis and several brainstem nuclei (Breder *et al.*, 1993), while mRNA for the p55 receptor was especially evident in the leptomeninges and circumventricular organs (Nadeau and Rivest, 1999). The detection of IL-1β protein within the normal brain has likewise been reported in the hypothalamus of human and rat tissue using several detection methods (immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), immunoassay) (Lechan *et al.*, 1990; de Cunha *et al.*, 1993; Hagan *et al.*, 1993; Quan *et al.*, 1996; Nguyen *et al.*, 1998). The central expression of these cytokines may be increased by stressors, as well as by various immunological and neurological insults, including systemic or central LPS administration, viral infection, brain injury, cerebral ischemia and seizure (Sato *et al.*, 1997; Nguyen *et al.*, 1998; Rothwell, 1999; Turrin *et al.*, 2001).

Once present in the brain, cytokines may elicit a functional response by binding to specific receptors (Kinouchi *et al.*, 1991; Cunningham and De Souza, 1993; Laflamme and Rivest, 1999). *In vitro* findings demonstrating that TNF-α and IL-1β modulate the activity of neuronal Ca^{2+} and other ion channels (Tancredi *et al.*, 1992; Pita *et al.*, 1999; Koller *et al.*, 2001) raising the possibility that cytokines and classical neurotransmitters may have neuronal and functional outcomes dependent upon similar basic cellular processes. In fact, reciprocal interactions between cytokines and neurotransmitters likely play a role in normal as well as pathological behavioral and neurological states (De Simoni and Imeri, 1998). For instance, intra-hippocampal injection of IL-1β was reported to induce impairment of working memory that was reversible by the NMDA partial agonist, D-cycloserine, and the cholinesterase inhibitor, physostigmine, implicating altered glutamatergic and cholinergic neurotransmission in the effects of IL-1β on memory (Matsumoto *et al.*, 2001). It was further reported that IL-1β interfered with the development of long term potentiation through either its inhibitory effects on glutamatergic neurotransmission, or through stimulation of stress-activated kinases (c-jun N terminal kinase (JNK), p38) (Vereker *et al.*, 2000). It ought to be considered, as well, that cytokines may influence neurotransmitter functioning through their stimulation of local glial cells (most notably microglia) to release a host of inflammatory factors (platelet activating factor, complement, oxidative species).

NEUROCHEMICAL EFFECTS OF STRESSORS AND CYTOKINES

HPA Activation in Response to Cytokine Challenge

Stressors and proinflammatory cytokines share several common neurochemical outcomes. Most prominently, such treatments elicit marked HPA activation as reflected by increased *c-fos* expression in corticotropin releasing hormone (CRH)-immunoreactive neurones within the paraventricular nucleus of the hypothalamus (PVN), and increased PVN mRNA levels for the immediate early gene, nerve growth factor inducible-B (NGFI-B), as well as increasing CRH mRNA and levels of plasma ACTH and corticosterone (Rivest and Rivier, 1994; Brebner *et al.*, 2000; Dunn, 1995; 2001). It does not appear that peripheral immune activation is necessary for increased *c-fos* expression within PVN neurones expressing CRH as such an outcome was elicited by either intravenous or intracerebroventricular (icv) IL-1β administration (Ericsson *et al.*, 1994) and icv IL-1β treatment elevated *c-fos* expression within the supraoptic nucleus and CRH mRNA within the PVN (Vellucci *et al.*, 1995). Paralleling these findings, systemic and central IL-1β administration increased the expression and release of CRH and arginine vasopressin (AVP) secretion from PVN neurones of the hypothalamus (Tilders *et al.*, 1993; Rivier, 2001) and direct infusion of IL-1β into the median eminence (site of CRH terminals from neurones originating within the PVN) increased AVP and CRH secretion (Watanobe and Takebe, 1993). Thus, IL-1β resulted in increased ACTH secretion from the pituitary corticotrophes (Watanobe and Takebe, 1993), and such effects were attenuated by CRH antagonists (Rivier, 2001) as well as by lesions of the PVN (Rivest and Rivier, 1991). Like IL-1β, treatment with IL-6 or TNF-α increased HPA activity (Ando and Dunn, 1999; Hayley *et al.*, 1999; Brebner *et al.*, 2000; Zhou *et al.*, 1996), and ACTH and corticosterone secretion provoked by TNF-α were blocked by CRH antiserum (Bernardini *et al.*, 1990).

Typically, factors that influence immune activity (and cytokine release), such as infection, have their effects over sustained periods of time. Likewise, when cytokines are used for immunotherapeutic purposes, as in the case of IL-2 and interferon-α treatment of certain cancers and hepatitis C, these agents are administered for sustained periods. Patients undergoing such treatments often display numerous adverse neuropsychological, neurologic and psychiatric disturbances, including depression, of sufficient severity to necessitate discontinuation of treatment (Capuron *et al.*, 2001). Interestingly, it has been reported that the selective serotonin reuptake inhibitor, paroxetine, attenuated the depressive-like effects associated with interferon-α treatment of malignant melanoma (Musselman *et al.*, 2001). Moreover, several studies demonstrated altered circulating cytokine levels in depressed patients, although normalization of cytokine levels and their soluble receptors does not necessarily follow antidepressant treatment (Maes, 1999; Griffiths *et al.*, 2000; Nishida *et al.*, 2002). Given the possible influence of sustained cytokine elevations in the provocation of depressive affect, surprisingly little information is available concerning the effects of chronic cytokine administration on neurochemical and mood-related processes. Likewise, there are limited data available concerning the effects of antidepressants on inflammatory processes, although it was shown that antidepressants reduce proinflammatory (TNF-α, IFN-γ) and increase anti-inflammatory cytokine production (IL-10) in

response to endotoxin treatment (Kenis and Maes, 2002). Interestingly, application of traditional stressors, such as footshock or restraint, also induce the central expression of cytokines (Nguyen *et al.*, 1998); however, it remains to be determined whether antidepressant treatments would impact upon these changes. Thus, a major focus of the present review was to assess the temporal and brain region specific patterns of neurochemical changes elicited by proinflammatory cytokine administration. In as much as stressors promote the sensitization of neurochemical processes so that later challenges provoke exaggerated neurochemical and behavioral responses, attention is also given to the relatively protracted effects of a single administration of the proinflammatory cytokine, TNF-α.

Central Neurochemical Effects of Cytokine Challenge

Psychogenic stressors have long been known to affect neurotransmitter activity, including the functioning of norepinephrine (NE), dopamine (DA) and serotonin (5-HT) in brain regions thought to be important for depressive illness (Anisman *et al.*, 1991). Similarly, several cytokines affect monoamine activity within such regions, and have the potential to elicit depressive-like symptoms. Of course, this does not imply that the behavioral effects of cytokines fully mimic the symptoms presented in clinically depressed patients, nor that the neurochemical changes associated with cytokine challenges are precisely the same as those that occur in depression. Indeed, depression is a multifaceted disorder and some symptoms (e.g. fatigue, loss of appetite) may be provoked by cytokines, while others (e.g. cognitive deficits) may not be as readily induced. Yet, it may be the case that the superimposition of a cytokine challenge given a backdrop of a chronic stressor (or conversely a stressor superimposed on an activated immune system) may promote a behavioral and neurochemical profile reminiscent of affective disorders.

Consistent with the view that cytokines induce stressor-like effects, and also those thought to be associated with depression, systemic administration of IL-1β, TNF-α as well as the bacterial endotoxin, lipopolysaccharide (LPS) increased NE and/or 5-HT activity within the PVN or whole hypothalamus (Lacosta *et al.*, 1998; ,1999; Hayley *et al.*, 1999; Brebner *et al.*, 2000; Dunn, 2001). As well as the hypothalamic monoamine changes, IL-1β increased 5-HT activity at extrahypothalamic sites, such as the prefrontal cortex and hippocampus (Brebner *et al.*, 2000; Dunn, 2001). As shown in Fig. 1 (Brebner *et al.*, 2000), like psychogenic and neurogenic stressors, subpyrogenic doses of IL-1β influenced 5-HT utilization (reflected by increased accumulation of the metabolite, 5-HIAA) within the PVN, central amygdala, and medial prefrontal cortex. Likewise, *in vivo* studies indicated that systemic IL-1β increased hypothalamic NE release as well as that of 5-HT at the nucleus accumbens and the hippocampus (Merali *et al.*, 1997; Song *et al.*, 1998; Dunn, 2001). When centrally administered, IL-1β increased hypothalamic release of NE, 5-HT and DA, as well as that of NE and 5-HT within the prefrontal cortex and hippocampus, respectively (Mohankumar and Quadri, 1993; Shintani *et al.*, 1993a,b; Linthorst *et al.*, 1995; Kamikawa *et al.*, 1998). Of particular significance regarding the intersection of stressors and cytokine actions is that pretreatment with the IL-1 receptor antagonist, IL-1Ra, blocked the hypothalamic NE alterations and the plasma ACTH increases ordinarily induced by a stressor (Shintani *et al.*, 1995). The latter findings not only show a parallel between the treatment effects, but also suggest that cytokines may have regulatory actions with respect to the impact of traditional stressors.

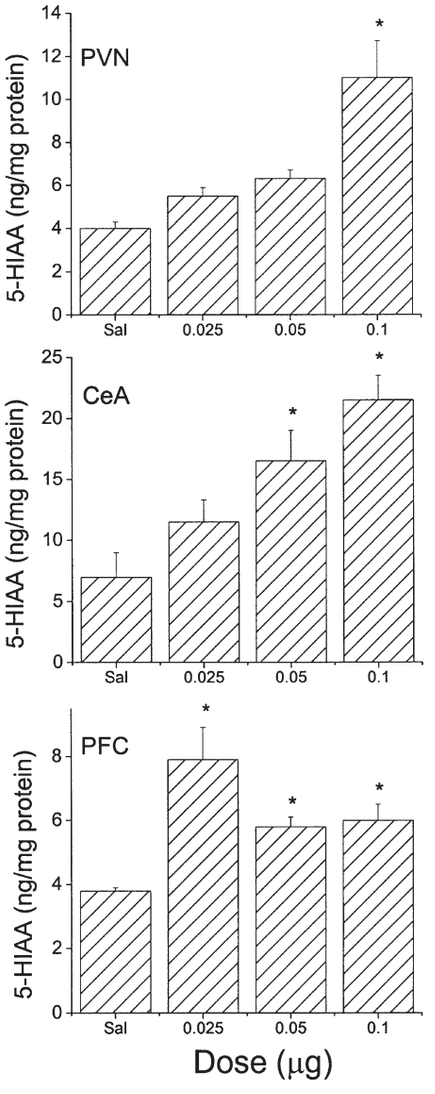

FIGURE 1 Mean (±SEM) levels of the 5-HT metabolite, 5-HIAA (5-hydroxyindole acetic acid), within the paraventricular nucleus (PVN), central amygdala (CeA) and prefrontal cortex (PFC) of mice 60 min following intraperitoneal administration of saline (Sal) or various doses (μg/mouse) of IL-1β treatment ($n = 10$/group). *$p < 0.05$ vs. saline. Modified from Brebner et al. (2000).

The data concerning the effects of TNF-α on central monoamine activity are not nearly as extensive as those

concerning IL-1β. Nevertheless, it has been shown that systemic TNF-α administration increased NE activity within the PVN, central amygdala, dorsal hippocampus and locus coeruleus, while 5-HT utilization was increased within the PVN, medial prefrontal cortex, hippocampus and central amygdala (Ando and Dunn, 1999; Brebner *et al.*, 1999; 2000; 2002a; Cho *et al.*, 1999; Hayley *et al.*, 1999). *In vivo*, icv TNF-α administration increased plasma corticosterone, but did not influence hippocampal 5-HT release (Pauli *et al.*, 1998). However, we observed that hippocampal 5-HT utilization measured in post-mortem tissue was increased following systemic cytokine treatment (Hayley *et al.*, 2001a). Whether the between laboratory differences were related to dosage, species, route of administration, or other factors remains to be determined.

A crucial role for the amygdala in processing stressful stimuli has long been proposed, and amygdala activation may also be involved in the response to cytokines and other immunogenic stimuli. Specifically, like stressors, IL-1β increased CRH mRNA expression at the amygdala and bed nucleus of the stria terminalis (Sawchenko *et al.*, 1996; Lee and Rivier, 1998). Moreover, just as anxiety may be elicited by central CRH administration (Davis, 1992; LeDoux, 2000), IL-1β or TNF-α may provoke anxiogenic-like effects, although this has only been evaluated in a limited number of situations (Connor *et al.*, 1998). Further, there is reason to suppose that distinct stressor-responsive brain circuits mediate different phases of the anxiogenic response. While the basolateral amygdala may play a prominent role in the initial processing of fearful stimuli, the central nucleus may be more important for the generation of behavioral outputs to contend with the challenge (Davis, 1992). The effects of stressors relative to those of cytokine treatments need to be established with respect to their effects on these different populations of amygdaloid neurones.

Additive or Synergistic Effects of IL-1β, IL-6, TNF-α and Stressors

Agonistic or antagonistic effects have been observed in response to different cytokines, and in some instances cytokines were shown to produce synergistic actions (i.e. actions beyond the additive effects of the individual cytokines) (Turrin and Plata-Salaman, 2000). For instance, IL-1β and TNF-α synergistically reduced sexual behavior, body weight and food consumption, intake of highly palatable substances, and circulating ACTH and/or corticosterone levels (Perlstein *et al.*, 1993; van der Meer *et al.*, 1995; Sonti *et al.*, 1996; Avitsur and Yirmiya, 1999; Brebner *et al.*, 2000). Limited information, however, is available concerning the potential synergistic effects of these cytokines on central neurotransmitter activity, although it was reported that IL-1β and TNF-α did not synergistically affect brain monoamine activity (Brebner *et al.*, 2000). However, as the latter studies involved single doses of cytokines and analyses performed in postmortem tissues of mice at a single time point following treatment, it is premature to assume that synergistic effects would not appear under other conditions. In fact, while IL-1β was found not to affect DA activity within the nucleus accumbens (an effect ordinarily elicited by neurogenic stressors) (Lacosta *et al.*, 1998), *in vivo* analyses indicated that systemic LPS administration markedly influenced accumbal DA and 5-HT functioning (Borowski *et al.*, 1998). At this juncture data are unavailable regarding central neurotransmitter changes using multiple doses or isobolographic analyses, and hence conclusions regarding potential synergies need to be considered cautiously.

Given that cytokines and stressors activate several common neuronal processes, the possibility was considered that they would have additive or synergistic effects. Indeed, cytokines and stressors may synergistically stimulate central monoamine functioning. In particular, as depicted in Fig. 2, among IL-1β treated rats a mild stressor (air puff) markedly increased NE and 5-HT activity at the hippocampus and nucleus accumbens (Merali *et al.*, 1997; Song *et al.*, 1998). As well, in rats exposed to a chronic stressor regimen in which different stressors were applied over more than 2 months, later IL-1β administration induced more pronounced sickness than among acutely stressed or non-stressed mice (Tannenbaum *et al.*, 2002).

Summarizing, stressors and cytokines may act synergistically with respect to behavioral outputs as well as central monoamine functioning. In light of such findings, it would seem appropriate to consider that similar processes might be operative in patients undergoing immunotherapy. As indicated earlier, IL-2 and IFN-α are used therapeutically, but the side effects (including depression) may be particularly pronounced limiting the use of the treatment (Pizzi *et al.*, 2002). In addition to these effects, patients are certainly also undergoing considerable distress, owing to the physical discomfort, life changes, fear of the future and feelings of loss of control associated with the disease. Thus, it ought to be considered that the evolution of the symptoms reflect the conjoint actions of the cytokine and the persistent stressor experience.

SENSITIZATION

Stressor Effects

In addition to their immediate effects, stressors and certain pharmacological agents (e.g. catecholamine stimulants) may prime biological systems so that an enhanced response is elicited by later exposure to the same or somewhat different challenges (sensitization) (Kalivas and Stewart, 1991; Anisman *et al.*, 2001). In the case of HPA activity, Tilders and his associates (de Goeij *et al.*, 1991; 1992; Bartanusz *et al.*, 1993; Schmidt *et al.*, 1995; Tilders and Schmidt, 1999), demonstrated that stressors provoke

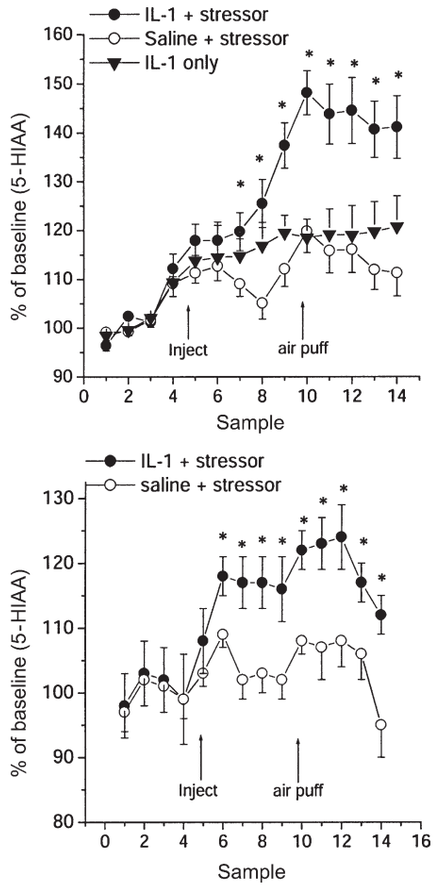

FIGURE 2 Extracellular 5-HIAA (±SEM) within the nucleus accumbens (top) and hippocampus (bottom) of rats as a percent of baseline levels. Samples were collected over 30 min periods. In the top panel (nucleus accumbens) rats had received intraperitoneal IL-1β (1.0 μg/rat) or saline ($n = 8$/group) after four dialysate samples, which served as the baseline, were collected. Thereafter, five dialysate samples were collected, after which the vehicle treated rats and one group of IL-1β treated rats were exposed to a stressor (a series of 5 air-puffs) and five further dialysate samples were collected. In the hippocampal study (lower panel) rats were treated with IL-1β (1.0 μg/rat) or saline, and then all animals were exposed to the stressor as described above. *$p < 0.05$ relative to saline-treated rats. Modified from Merali et al. (1997).

a phenotypic change in the co-localization of the hypothalamic neuropeptides, AVP and CRH, such that increased co-expression of AVP occurs within CRH terminals in the external zone of the median eminence (ZEME), coupled with an increased proportion of CRH/AVP co-producing neurones within the mediodorsal PVN (De Goeij *et al.*, 1992). As AVP and CRH synergistically stimulate ACTH release from the pituitary corticotrophes, the increased co-expression of these neuropeptides would be expected to enhance ACTH and corticosterone secretion upon subsequent challenges (Schmidt *et al.*, 1996).

In addition to the neuroendocrine processes, stressor-induced sensitization of NE activity, as indicated by increased release, has been demonstrated within the hypothalamus, hippocampus and amygdala, and DA release within the prefrontal cortex is likewise influenced by previous stressor experiences (Anisman *et al.*, 1993; Gresch *et al.*, 1994; Finlay *et al.*, 1997). It is of particular significance that cross-sensitization can be induced wherein exposure to a particular stimulus may enhance the response to a subsequently applied stimulus of a different form, including pharmacological challenges (Robinson *et al.*, 1987; Kalivas and Stewart, 1991; Anisman *et al.*, 1993; van Dijken *et al.*, 1993; Finlay *et al.*, 1997; Tilders and Schmidt, 1999).

As in the case of acute insults, chronic stressors proactively influence responses to later stressors (Irwin *et al.*, 1986; Nisenbaum *et al.*, 1991; Anisman *et al.*, 1993; Jedema *et al.*, 1999). Exposure to intermittent cold or repeated restraint augmented the effects of subsequent restraint, in terms of enhanced HPA activity and *c-fos* immunoreactivity within several stressor-sensitive brain regions (Bhatnagar and Dallman, 1998). Chronic exposure to a series of different stressors also sensitized *in vivo* dopamine release from the frontal cortex (Cuadra *et al.*, 1999). At this point it is not known what effects are provoked in animals exposed to an extended series of stressors (of sufficient severity and frequency to promote allostatic load) and then later introduced to a stressor once again. However, as repeated perturbations of stressor-sensitive systems may eventually result in adverse behavioral and physiological repercussions (McEwen, 2000), it would not be surprising to find that reexposure following such a regimen would readily re-induce these adverse outcomes. It is important, however, to underscore that stressors do not invariably have sensitizing actions, and it is not uncommon for adaprtation to be evident, particularly with the repeated application of the same stressor.

Cytokine-induced Sensitization: HPA Activity

Just as stressors may instigate sensitized neurochemical systems (de Goeij *et al.*, 1992; Schmidt *et al.*, 1996), both IL-1β and TNF-α engender such effects. Interestingly, however, the sensitization was found to develop with the passage of time following the initial treatment (Tilders *et al.*, 1993; 1994; Schmidt *et al.*, 1995; Hayley *et al.*, 1999). Specifically, several days after acute IL-1β treatment, an increase of AVP stores was apparent within CRH terminals of the ZEME (de Goeij *et al.*, 1992; Bartanusz *et al.*, 1993; Schmidt *et al.*, 1995). This effect peaked 7–11 days after treatment, and did not return to control levels until several weeks later (Schmidt *et al.*, 1995). If animals received a second injection of IL-1β, circulating ACTH and corticosterone levels were elevated (Schmidt *et al.*, 1995), suggesting that the increased co-storage of AVP and CRH, and their subsequent release upon cytokine challenge, provoked the exaggerated corticosterone response.

Although acute IL-1β ordinarily provokes sickness behaviors, such as ptosis, piloerection, soporific effects, fatigue, curled body posture, anorexia and anhedonia (Konsman *et al.*, 2002), acute TNF-α at moderate doses

does not provoke these symptoms. However, TNF-α provoked a time-dependent sensitization wherein later reexposure to the cytokine (at a still lower dose) provoked profound sickness behaviors coupled with elevated plasma corticosterone (Fig. 3). These symptoms as well as the corticoid elevations were not evident when reexposure occurred 1–7 days following initial treatment, but were pronounced upon re-exposure 2–4 weeks following initial cytokine treatment (Hayley *et al.*, 1999; 2002a,b). The fact that this effect appeared using both hTNF-α and mTNF-α is consistent with the view that the sensitization was not simply a reflection of an immunological sensitization involving cross-species cytokine effects. Furthermore, as mTNF-α acts upon both the p55 and p75 receptors, and the recombinant human form (hTNF-α) selectively binds to the p55 receptor in the mouse (Brouckaert *et al.*, 1992), it seems likely that the p75 receptor is not necessary for the development of the sensitized response. Of course, this does not rule out the possibility that the sensitization of sickness reflects a shock reaction engendered by the cytokine or other immunogenic components such as the bovine serum albumin (and TNF-α as an adjuvant) used as a carrier protein for the cytokine. Regardless of the case, as will be discussed shortly, the central neurochemical sensitization effects associated with the cytokine treatment are independent of the sickness behavior and appear to be mediated by central processes.

Commensurate with the effects of stressors and IL-1β, systemic TNF-α administration elicited time-dependent phenotypic changes within CRH neurones terminating in the external zone of the median eminence (Hayley *et al.*, 2001a). A single dose of TNF-α provoked a shift towards increased AVP/CRH co-immunoreactive terminals within this site (see Fig. 4). This effect increased with the passage

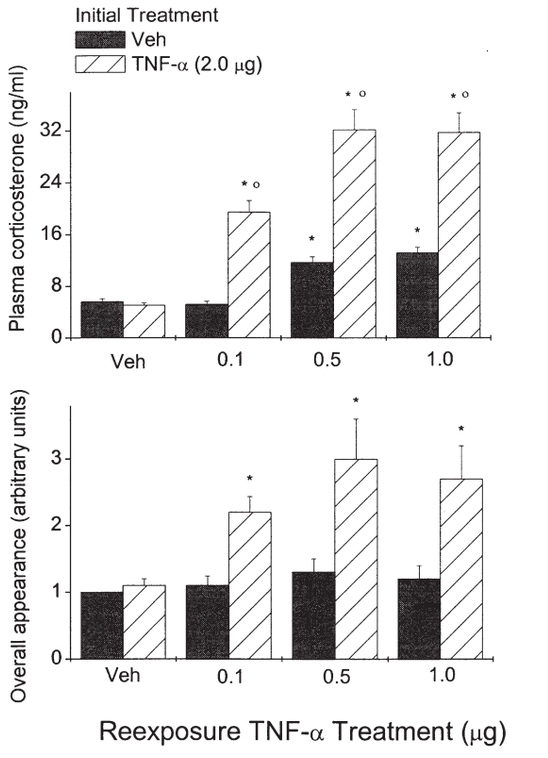

FIGURE 3 Mean (±SEM) plasma corticosterone concentrations (top) and ratings of illness as reflected by overall appearance (e.g. ptosis, piloerection, curled body posture; bottom) as determined using a 4-point scale. Mice ($n = 10$/group) were pretreated with saline (gray bars) or mTNF-α (2.0 μg; i.p.; hatched bars) and 28 days later exposed to saline or mTNFα (0.1, 0.5 or 1.0 μg; i.p.). Behavioral and hormonal measures were made at 60 min following the second injection. $^{*}P < 0.05$ relative to mice treated with saline on two occasions, $^{\circ}P < 0.05$ relative to animals pretreated with saline that subsequently received a single acute injection of mTNF-α. Modified from Hayley *et al.*, (2002).

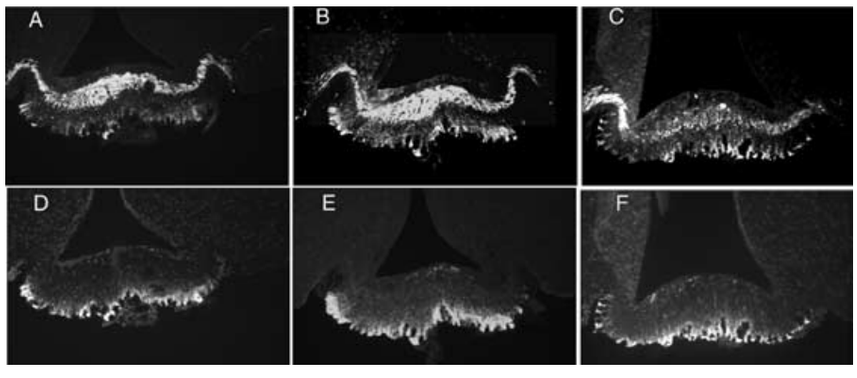

FIGURE 4 Immunoreactivity for AVP and CRH within the median eminence of mice treated with saline on two occasions 7 days apart (left), TNF-α (4.0 μg) 7 days earlier (middle) or TNF-α (4.0 μg/mouse; i.p.) 14 days earlier (right). The top panels depicts AVP immunoreactivity, as labeled using Texas Red, while the bottom panels show CRH positive terminals (visualized using the FITC fluorophore), within the same double labeled section. Reexposure to the cytokine 1 or 28 days after initial TNF-α treatment was without effect, and the data for these time points are not shown in the photomicrographs. Enhanced AVP and CRH immunoreactivity was evident within 7 and 14 days after a single TNF-α injection, (B,C and E,F, respectively). However, AVP-ir, within the interval zone of the median eminence, was somewhat diminished after the 14 day interval (C). ($n = 6$/group). Magnification × 20. $n = 5$/group. From Hayley *et al.* (2001a,b).

of time, such that the relative density (arbitrary units) of AVP and CRH was increased at 7 (143 ± 18, 148 ± 23, respectively) and 14 (104 ± 5, 81 ± 21) days following initial cytokine treatment, relative to saline treated mice (80 ± 19, 50 ± 11), but normalized after 28 days (84 ± 20, 47 ± 14). Given that the corticosterone release was augmented in mice re-exposed to the cytokine 28 days after pretreatment, but not after earlier intervals (Hayley *et al.*, 1999), it is unlikely that the altered median eminence AVP/CRH-ir plays a primary role with respect to the sensitization of the corticosterone response. It is tempting to suggest that since the cytokine induces sensitization of sickness behavior (Hayley *et al.*, 1999), the elevated corticosterone was secondary to the stress associated with illness or related factors (e.g. activation of acute phase proteins, histamine). However, it was observed that the development of the illness and the enhanced corticosterone levels were, in fact, independent of one another (e.g. corticosterone elevations could readily be induced at doses that did not elicit sickness).

It is likely that the TNF-α induced sensitization of corticosterone and sickness behavior involved peripheral processes (e.g. direct glandular actions), as icv infusion of the cytokine did not provoke signs of illness, irrespective of dosage or re-exposure regimen employed. Moreover, the cytokine provoked only a modest increase of plasma corticosterone after acute icv infusion, an effect that was considerably less pronounced than that observed following intraperitoneal (ip) treatment with the cytokine (Hayley *et al.*, 2002a). As well, contrary to the pronounced corticosterone sensitization engendered by ip TNF-α, re-exposure to icv TNF-α at 1, 7 or 28 days following initial central infusion of the cytokine did not induce a sensitization with respect to circulating corticosterone. Taken together, these data raise the possibility that the protracted effects of TNF-α on HPA activity and sickness behavior depends upon the actions of the cytokine on some yet unidentified sites outside the brain (e.g. lymphoid or endocrine organs or circulating immune cells), which may in turn, stimulate central processes.

Consistent with this position, the symptom profile elicited upon TNF-α reexposure at 14–28 days following initial cytokine treatment was reminiscent of a shock reaction. Ordinarily, during an acute phase reaction blood volume and pressure decline, and the distribution of blood may be altered with preferential pooling in certain visceral or limb regions (Hardaway, 2000). One of the key mediators of such a shock reaction is the monoamine, histamine, which is found in abundance within circulating mast cells as well as the CNS (leptomeninges and thalamus) (Silverman *et al.*, 2000). However, histamine is also produced by neurones located within the tuberomammillary nucleus of the posterior portion of the hypothalamus (Schwartz *et al.*, 1991; Brown *et al.*, 2001) and like other monoamines, sends widespread projections to various cortical and subcortical brain regions affecting behavioral outputs, including arousal, feeding (Doi *et al.*, 1994; Masaki *et al.*, 2001), and depressive-like behaviors (e.g. diminished active responding in a forced swim test) (Giovannini *et al.*, 1999; Perez-Garcia *et al.*, 1999). Accordingly, TNF-α may sensitize CNS functioning through the stimulation of either neurones or mast cells, which may be present in diverse brain regions.

We have routinely observed that upon re-exposure to TNF-α 28 days after an initial cytokine treatment, pronounced reddening of the tail, ears and nose occurred (cyanosis; indicating increased accumulation of blood cells and inflammation), coupled with a marked reduction of blood volume and pressure, as well as signs of hypothermia (see also Hayley *et al.*, 2002b). In as much as TNF-α influences mast cell histaminergic activity, which might be involved in the provocation of a shock reaction (Brown *et al.*, 2001), we assessed the impact of H_1 and H_2 antagonists on the behavioral and corticosterone variations associated with acute TNF-α treatment as well as reexposure to the cytokine. When administered either singly or conjointly, the H_1 and H_2 antagonists, diphenhydramine and cimetidine, did not appreciably influence the acute effects of mTNF-α on plasma corticosterone or sickness. However, the co-administration of these antihistamines prevented the sickness and corticosterone sensitization ordinarily provoked by re-exposure to the cytokine after a 28 day interval (Hayley *et al.*, 2002b). However, much higher doses of these antihistamines were required to attenuate the sickness than the corticosterone variations. These findings are consistent with the proposition that the response to mTNF-α reflects an acute phase response, mediated by histaminergic processes.

Cytokine-induced Sensitization of Central Processes: *c-fos* Activation

The administration of IL-1β promotes the expression of Fos-ir within parvocellular (Rivest and Rivier, 1994) and magnocellular PVN neurones (Chang *et al.*, 1993). Moreover, when administered icv, IL-1β induced the transcription factor, nuclear factor kappa B (NFκB), within the basolateral amygdala as well as several vascular associated sites, while *c-fos* immunoreactivity was elevated within hypothalamic nuclei (PVN, supraoptic nucleus) and in the central amygdala (Konsman *et al.*, 2000). This pattern of *c-fos* upregulation was indistinguishable from that observed after ip TNF-α treatment in our laboratory (Hayley *et al.*, 2001a). Interestingly, while ip TNF-α administration elicited a modest effect on immunoreactivity for the Fos protein at these sites, upon cytokine reexposure 7 or 14 days afterward, *c-fos*-ir was markedly increased (Hayley *et al.*, 2001a). The elevation of *c-fos*-ir elicited by TNF-α re-exposure may reflect intracellular changes primed by the initial cytokine administration, as TNF-α has been shown to influence synaptic transmission and to modulate Ca^{2+} currents in hippocampal and sympathetic neurones (Soliven and Albert, 1992).

In addition to the increased *c-fos*-ir within the central amygdala, re-exposure to the TNF-α markedly increased CRH-ir within the central amygdala, but such an outcome was evident irrespective of whether re-exposure occurred 1, 7, 14 or 28 days after initial treatment. Further, unlike the hypothalamic changes which evolved simply with the passage of time (i.e. cytokine reexposure was not necessary to elicit the increased CRH-ir), the variations within the amygdala required that the cytokine be re-administered. Given that c-fos-ir peaked 14 days after TNF-α, whereas CRH-ir peaked at 7 days, the *c-fos*-ir likely involves factors other than, or in addition to CRH. Furthermore, given the time course for the amygdala variations, it is clear that these central changes are independent of those associated with the sickness and HPA variations associated with re-exposure to the cytokine. Thus, while the latter effects may reflect an acute phase response, the amygdala variations involve alternate processes.

It has been argued that activation of CRH within the central amygdala and the bed nucleus of the stria terminalis contributes to anxiety and responses to fear-related stimuli (Lee and Davis, 1997). While these behavioral effects appear to be independent of HPA activation, they may involve interactions between CRH and noradrenergic projections between the amygdala and the bed nucleus of the stria terminalis as well as the locus coeruleus (Van Bockstaele *et al.*, 1998). In as much as proinflammatory cytokines and endotoxin challenges have been reported to increase anxiety in animals and in humans (Anisman and Merali, 1999; Reichenberg *et al.*, 2001), these data raise the possibility that such effects involve processes akin to those associated with stressor-provoked fear and anxiety.

Cytokine-induced Sensitization of Central Processes: Monoamine Variations

As indicated earlier, systemic TNF-α markedly influences monoamine activity within several brain regions (Ando and Dunn, 1999; Hayley *et al.*, 1999; Brebner *et al.*, 2000). In addition, re-exposure to the cytokine increased turnover of NE, DA and 5-HT in a region-specific, time-dependent fashion (Hayley *et al.*, 1999; 2002a). Importantly, these time-dependent brain neurochemical alterations were not congruent with the HPA changes, and thus these also involve different mechanisms. Specifically, within the PVN, TNF-α induced a modest sensitization of NE activity, as indicated by accumulation of the metabolite, MHPG, that was evident when the cytokine was readministered 28 days after initial treatment (Hayley *et al.*, 1999). In contrast, at other brain sites, such as the medial prefrontal cortex and central amygdala the utilization of NE (as reflected by increased MHPG accumulation) was evident when the reexposure treatment was applied after 1 day, but not at lengthier intervals. Interestingly, the sensitization of 5-HT activity within the central amygdala and prefrontal cortex, as reflected by accumulation of 5-HIAA, was apparent upon reexposure to the cytokine after intermediate intervals (7–14 days) (Hayley *et al.*, 1999).

In contrast to the effects of systemic administration, when mTNF-α was administered icv, there was no indication of a sensitization effect developing with respect to either sickness behaviors or HPA activity. However, central infusion of the cytokine promoted the sensitization of brain monoamine utilization such that re-exposure to the cytokine augmented NE and DA utilization within the PVN and ME/ARC relative to that evident in acutely treated animals (see Fig. 5). Likewise, among mice that had initially received ip mTNF-α subsequent icv cytokine administration elicited increased 5-HT and DA activity within the ME/ARC. These effects were restricted to hypothalamic nuclei (with the exception of augmented NE activity within the locus coeruleus) (Hayley *et al.*, 2002a). This contrasts with the mesolimbic sensitization effects associated with systemic administration of the cytokine (Hayley *et al.*, 1999; 2001a). Of course, direct comparisons between the effects of the two routes of administration are complicated by the fact that one cannot readily equate the icv and ip doses used. Yet, it ought to be considered that when the cytokine is administered via the ip route, numerous processes may be affected (e.g. vagal afferents, adrenal) which are not influenced by icv administration. Thus, while behavioral effects related to hypothalamic functioning (e.g. fever, feeding) may be associated with increased central TNF-α administration, peripheral factors may account for some of the effects of systemically administered cytokines.

It will be recognized that in the present review cytokine treatments were generally found to elicit an increase in the turnover of monoamine functioning, and yet depressive illness has typically been considered to be a result of diminished monoamine activity (Nemeroff, 1998). We suggested previously (Anisman *et al.*, 2002) that this mismatch may actually be a reflection of the fact that most studies that evaluated the neurochemical effects of cytokines have involved acute treatments. It has been suggested, at least in the case of stressors, that sustained, chronic, unpredictable challenges may favor the development of pathology to a greater degree than acute insults (McEwen, 1998; Anisman *et al.*, 2002). In a like fashion, it might be expected that chronic cytokine treatments would likewise promote neurochemical alterations more in line with those thought to subserve depression (e.g. diminished 5-HT functioning). At this juncture, however, there are insufficient data available concerning the impact of chronic cytokine treatment on neuroendocrine and central neurotransmitter functioning. Likewise, there are limited data concerning the proactive effects of chronic cytokine treatments on subsequent neurochemical activity in response to different challenges. The lack of information regarding the impact of chronic cytokine activation is of particular note given that immune activation stemming from bacterial or viral insults, as

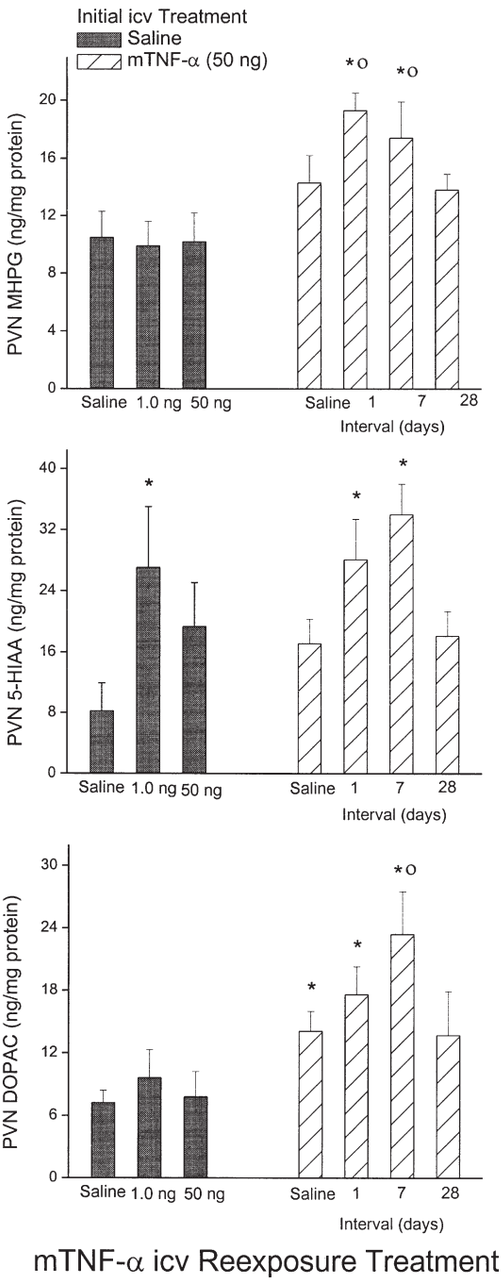

FIGURE 5 Concentrations of the NE, 5-HT and DA metabolites, 3-methoxy-4-hydroxyphenethyleneglycol (MHPG; top), 5-HIAA (middle) and 3,4-dihydroxyphenylacetic acid (DOPAC; bottom), respectively, within the PVN (mean ± SEM) among mice that received icv mTNF-α treatments. Mice ($n = 8$/group) were pretreated with either saline (gray bars) or mTNF-α (50 ng; icv; hatched bars). After a 28 day interval, saline pretreated animals received a second injection of the vehicle or mTNF-α (1.0 or 50 ng; icv) (left bars). Animals initially treated with mTNF-α were reexposed to the cytokine either 1, 7 or 28 days later (1.0 ng; icv), or received saline 28 days following the initial injection (right bars). $^{*}P < 0.05$ relative to saline only treated mice, $^{\circ}P < 0.05$ relative to mice receiving saline pretreatment followed by acute TNF-α one hour prior to decapitation. From Hayley et al. (2002).

well as cytokine immunotherapy, involve sustained and persistent alterations of cytokine activity. Clearly, to evaluate the influence of cytokine treatments on depressive-like states it may be more productive to assess the impact of chronic activation of the inflammatory response system or repeated cytokine administration.

CONCLUSIONS

Numerous challenges, including stressful and immunological stimuli, may prime biological systems so that augmented responses are elicited upon later challenges with either the same or somewhat different stimuli. In addition to having immediate effects, cytokines appear to exert long lasting behavioral and neurochemical consequences. Indeed, like stressors, a single exposure to TNF-α primes CNS activity, such that later reexposure to the cytokine provoked profound alterations of sickness, HPA activation and brain monoamine utilization. Such effects may stem from increased receptor sensitivity or the augmented release of various endogenous factors, such as other cytokines, prostaglandins or acute phase proteins. In this respect, enhanced co-activity of these factors would be expected synergistically to influence central processes.

The mechanisms responsible for the development of the sensitization remain to be established. However, it is clear that multiple sensitizing effects are elicited by various treatments. This is not altogether surprising as cytokines have multiple effects involving different processes; witness for instance the findings that IL-1β-induced anorexia and anhedonia are independent of one another (Merali *et al.*, 2002) as are the fever and affective responses elicited by this cytokine (Konsman *et al.*, 2001). In the case of TNF-α, it seems that the sensitized sickness and corticosterone responses are independent of one another, although they may both involve a histamine-mediated component (Hayley *et al.*, 2002b). Both of these effects, however, appeared to be unrelated to the central monoamine changes observed. Indeed, icv treatment with TNF-α induced the sensitization of monoamine functioning, but not that of illness or corticosterone alterations. Moreover, the central sensitizing effects of TNF-α were modifiable by variations of macrophage functioning, and histamine appeared to contribute to the peripheral sensitization associated with the cytokine (Hayley *et al.*, 2001b; 2002b). Finally, although LPS induced macrophage release of TNF-α, it is clear that these two treatments induced different types of effects. The LPS treatment engendered a sensitization that was marked at short intervals, while TNF-α induced a sensitization that progressed with the passage of time (Hayley *et al.*, 2001b).

Brain levels of various cytokines are markedly upregulated in a number of neurological conditions (e.g. multiple sclerosis and cerebral infections), in response to traumatic events (e.g. head injury or stroke), as well as in response to stressful stimuli. Moreover, increased circulating levels of IL-1β and TNF-α, as well as IL-2, are often associated with depressive conditions (Maes, 1999; Griffiths *et al.*, 2000). It is unclear, however, whether the emergence of the depression is secondary to

variations of cytokine functioning, or whether cytokine alterations simply represent an epiphenomenon (bystander effect) associated with the mood disorders. As some of the depressive effects attributable to LPS treatment are modifiable by antidepressant medication (Yirmiya *et al.*, 1999), as are the depressive actions associated with interferon-α immunotherapy (Musselman *et al.*, 2001), it is tempting to argue that cytokines play a role in the emergence of the affective condition. Yet, it has been demonstrated that the elevated cytokine levels associated with depressive illness do not necessarily normalize with the alleviation of symptoms following successful pharmacotherapy (Maes, 1999). Thus, the precise relationship between cytokines and depressive illness remains to be elucidated. This notwithstanding, the fact that cytokines may increase the neurochemical responses to later stressors, and stressors may act as a provocative agent for the induction of depression, the possibility needs to be considered that cytokines indirectly increase vulnerability to affective illness. Indeed, it has even been suggested that protracted alterations of HPA functioning stemming from early-life stressor or immunological challenges may contribute to the organism's subsequent ability to contend with environmental challenges, and hence may contribute to the development of stressor-related psychopathology (Meaney *et al.*, 1996; Heim *et al.*, 1997; Shanks *et al.*, 2000).

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