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SPECIAL SECTION

Cytokines as a stressor: implications for depressive illness

Hymie Anisman[1], Shawn Hayley[1], Nicolas Turrin[1] and Zul Merali[2]

[1] *Institute of Neuroscience, Carleton University, Ottawa, Ontario, Canada*
[2] *School of Psychology and Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada*

Abstract

Stressful events have been implicated in the provocation of depressive illness. Inasmuch as immunological challenge, and particularly cytokine administration, engender neuroendocrine and central neurochemical changes reminiscent of those provoked by psychogenic stressors, it was suggested that immune activation may also contribute to affective illness. The present report provides a brief overview of the neurochemical sequelae of acute and repeated interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α) and IL-2 treatment, describes some of the synergisms associated with these treatments, as well as their potential interactions with psychogenic stressors. In addition, a discussion is provided concerning the fact that cytokines, like stressors, may have time-dependent proactive effects, so that re-exposure to the treatments provoke greatly augmented neurochemical changes (sensitization). Given that the effects of cytokines are evident within hypothalamic, as well as extrahypothalamic sites, including various limbic regions, it is suggested that cytokines may impact on emotional changes, including depression.

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Introduction

Stressful events, coupled with the inability to cope adequately with such insults, may be fundamental in the provocation of affective disorders (Griffiths et al., 2000), and may exacerbate or promote physical pathologies, including those related to cardiovascular illness and immune dysfunction (Herbert and Cohen, 1993). The findings that communication may occur between the immune and central nervous systems (Blalock, 1984) prompted the proposition that depression may be influenced by immunological processes, just as psychological stressors have such an effect. While several potential routes of communication exist between the immune and central nervous systems, it has been suggested that cytokines, signalling molecules of the immune system, may act as immunotransmitters (Dunn, 2001). In this respect, cytokines engender central neurochemical changes, much like those elicited by psychological stressors (Anisman and Merali 1999; Dunn, 1993; 2001), thereby promoting affective disorders (Leonard, 2001; Maes, 1999). In addition to their indirect effects, central expression of several cytokines may be elicited by stressors, various insults related to brain injury, and by endotoxin challenge, and may thus impact on mood states. The present review will argue that:

(1) Immune challenge (and particularly cytokine release), like stressful events, provokes central neurochemical changes that favour the development of affective disturbances.
(2) Affective disturbances are more likely to emerge if an immune insult is superimposed on a background of stressful events (synergistic effects).
(3) Stressors and cytokines may promote the sensitization of central neurochemical processes, and may thus proactively influence the response to subsequently encountered insults.

Address for correspondence: Dr H. Anisman, Life Science Research Building, Carleton University, Ottawa, Ontario K1S 5B6, Canada.
Tel.: (613) 520-2699 *Fax*: (613) 520-4052
E-mail: hanisman@ccs.carleton.ca

Relation between stressors and affective state

Depressive illness has been associated with antecedent stressful life events (Abramson et al., 1978; Brown and Harris, 1978; Brown et al., 1987; Monroe and Depue, 1991; Paykel, 2001), including not only major traumas, but also the accumulation of slight stressors (Kanner et al., 1981). While the development of depression may stem from the cognitive disturbances

associated with stressful events or failure experiences (Abramson et al., 1978), it is equally possible that the affective illness follows from the stressor-elicited neurochemical alterations (Anisman et al., 1991; Weiss and Simson, 1989).

The impact of stressor experiences appears to be dependent upon experiential factors, the individual's ability to cope with the stressor through behavioural means, and by the characteristics of the stressor itself (e.g. severity, chronicity, predictability). Among other things, these factors may influence the appraisal of the stressor and the behavioural response to it (Lazarus, 1993), as well as neurochemical functioning (Anisman et al., 1991). Additionally, the individual's stressor history (including early life trauma) may affect the subsequent response to a stressor, thereby influencing vulnerability to illness (Brown and Harris, 1989; Roy, 1985). In this respect, it was suggested (Post, 1992) that the neurochemical substrates of the illness may evolve over time following stressor exposure and over repeated illness episodes (sensitization effects). Thus, while early depressive episodes may be associated with stressful events, once the neurochemical systems are sensitized, even inocuous events may elicit adverse outcomes (Kendler et al., 2000; Lewinsohn et al., 1999; Solomon et al., 2000). As will be described shortly, stressors and cytokine treatments share several common effects, including the sensitization of neurochemical systems. In light of the parallel effects of these treatments, the possibility ought to be considered that activation of the inflammatory response system might also influence affective consequences of later stressor encounters.

Stress, depression and neurochemical status

Depression has been attributed to a variety of neurochemical disturbances, including alterations of norepinephrine (NE), dopamine (DA) and serotonin (5-HT), or their receptors (Maes and Meltzer, 1995; Schatzberg and Schildkraut, 1995) as well as various hormonal alterations (Plotsky et al., 1995). Coupled with the disparate symptoms of the illness and the variability in response to treatments, it is likely that depression is a biochemically heterogeneous disorder, wherein the substrates for the illness varies across individuals.

It appears that aversive events induce several of the central neurotransmitter alterations (e.g. variations of NE, DA and 5-HT turnover and levels, as well as receptor regulation) thought to subserve the depressive syndrome. Moreover, many of the variables considered important in promoting human depression (e.g. stressor controllability, predictability, chronicity), influence stressor-provoked amine alterations in animals (Anisman et al., 1991; Weiss and Simson, 1989). These neurochemical changes may be of adaptive significance, in that they may blunt the psychological or physical impact of stressors, facilitate responses to deal with the challenge (Anisman et al., 1991), and stimulate processes which prevent excessive physiological activation (Munck et al., 1984). With continued exposure to a stressor, compensatory increases of amine synthesis may ensue, and concentrations of the amine may be increased (Anisman et al., 1991; Deutch and Roth, 1990; Herman and Cullinan, 1997; Irwin et al., 1986; Puglisi-Allegra et al., 1991). Despite the presumed adaptive consequences of the enhanced neuronal functioning, it is thought that under such conditions the wear and tear on the system may become excessive (e.g. allostatic load), increasing vulnerability to pathology (McEwen, 1998). In this respect, it may be particularly appropriate to evaluate the impact of chronic, unpredictable stressors (including psychogenic, neurogenic and systemic insults) on depressive states.

Cytokines as neuromodulators

Although cytokines are relatively large molecules, they may gain access to the brain and have direct actions on CNS processes. In particular, interleukin-1β (IL-1β) (Banks et al., 1989) and tumour necrosis factor-α (TNF-α) (Gutierrez et al., 1993) have saturable carrier-mediated transport mechanisms, which pump these cytokines into the brain. Further, entry into the brain may occur at circumventricular areas, which lack an efficient blood–brain barrier (BBB) (Banks et al., 1989; Quagliarello et al., 1991), ultimately reaching various brain nuclei through a process of volume diffusion (Konsman et al., 2000; Laflamme and Rivest, 1999; Lee et al., 1998). Interestingly, IL-1β and TNF-α themselves may disrupt the BBB (Quagliarello et al., 1991), thereby increasing accessibility of the CNS. Parenthetically, the view was also expressed that cytokines may affect the BBB by the induction of adhesion molecules, such as ICAM-1 and VCAM-1 in the brain endothelium and astrocytes, which may guide inflammatory leucocytes into the brain parenchyma (Merrill and Benveniste, 1996). Moreover, cytokines and stressors may increase BBB permability by increasing the expression of vasoactive and inflammatory factors, such as cyclooxygenase-2 (COX-2; rate-limiting enzyme for the synthesis of the pyrogenic, prostaglandins) and histamine at cerbrovascular sites (Esposito et al., 2001; Mark et al., 2001). Additionally, stressors may influence the trafficking of cytokines into the brain parenchyma;

as such challenges may also alter BBB permeability (Esposito et al., 2001). Once present within the brain, cytokines can provoke a functional response by binding to specific receptors at hypothalamic and extra-hypothalamic brain regions (Cunningham and De Souza, 1993; Kinouchi et al., 1991; Laflamme and Rivest, 1999; Schobitz et al., 1994) or by other processes that stimulate neurotransmitter functioning. Indeed, both IL-1 and TNF-α may have functions similar to classical neurotransmitters through their modulation of neuronal Ca^{2+} channels and activation of intracellular second-messenger systems (Tancredi et al., 1992).

In response to systemic insults, cytokines and other immune factors (such as endotoxin) can bind to the endothelium of the brain microvasculature, which will in turn produce signalling mediators, such as histamine, nitric oxide (NO), nuclear factor kappa B (NFκB; a signal transduction protein common to many cytokines, including IL-1β and TNF-α) and COX-2 (Chao et al., 1995; O'Connor and Coogan, 1999; Rivest et al., 2000). Indeed, TNF-α was reported to increase histamine, NFκB and COX-2 expression as well as prostaglandin release at cerebral endothelial capillaries (Blais and Rivest, 2001; Igaz et al., 2001; Mark et al., 2001). These mediators may be responsible for the altered synthesis/activity of other cytokines, neurotransmitters and hormones as well as central metabolic processes. For instance, elevated central prostaglandins may stimulate hypothalamic–pituitary–adrenal (HPA) activity and provoke febrile responses (Parsadaniantz et al., 2000; Roth et al., 2002). Additionally, through induction of these factors, and perpetuation of the inflammatory response, pro-inflammatory cytokines may influence cellular plasticity and neurodegeneration. In fact, chronic stressors have recently been suggested to promote neurodegeneration through activation of a TNF-α cascade involving increased NFκB expression and downstream activation of NO (Madrigal et al., 2002).

In addition to direct actions, cytokines may influence CNS processes indirectly through stimulation of afferent fibres of the vagus nerve (Dantzer et al., 1996; Maier and Watkins, 1998; Watkins et al., 1995). Receptors for IL-1 are present on the nodose ganglion which sends afferent projections to the brainstem nucleus tractus solitarius (NTS), and following cytokine or endotoxin challenge, c-*fos* expression is elevated in these regions (Ek et al., 1998; Gaykema et al., 1998). It appears that activation of vagal branches may stimulate the de-novo synthesis of cytokines within brainstem and hypothalamic nuclei (Dantzer et al., 2001; Gaballec et al., 1995; Hopkins and Rothwell, 1995).

Central cytokine distribution and the impact of varied challenges

Although their levels in brain are admittedly low under basal conditions, cytokines and their receptors are endogenous to the brain, having been identified within neuronal cell bodies, microglia and astrocytes (Cunningham and De Souza, 1993; Kinouchi et al., 1991; Laflamme and Rivest, 1999; Nistico and De Sarro, 1991). Levels of cytokines and their receptors are influenced by various stressors as well as by immunological and neurological insults. For instance, IL-1β protein levels were increased in several brain regions in response to stressors (Nguyen et al., 1998, 2000). Moreover, elevated IL-1β, IL-6 and/or TNF-α mRNA was observed in the CNS following immobilization stress (Minami et al., 1991; Yabuuchi et al., 1996), systemic lipopolysaccharide (LPS) administration (Ban et al., 1992; Breder et al., 1994; Buttini and Boddeke, 1995; Gaballec et al., 1995; Gatti and Bartfai, 1993; Laye et al., 1994; Liu et al., 1996), central LPS injection (De Simoni et al., 1995; Quan et al., 1994; Rajora et al., 1997), viral infection (Sato et al., 1997), brain injury, tumours, cerebral ischaemia and seizure (Buttini et al., 1994; Giulian and Robertson, 1990; Hopkins and Rothwell, 1995; Ilyin et al., 1999; Minami et al., 1990; Rothwell and Hopkins, 1995; Taupin et al., 1993; Yabuuchi et al., 1993). Further, peripherally administered cytokines may even stimulate their own expression within the brain, thus potentially placing these molecules in the vicinity of their receptors (Butinni and Boddeke, 1995; Cunningham and De Souza, 1993). Parenthetically, it will be recognized that some of the aforementioned insults were essentially of an acute nature, while others involved chronic repercussions. At present, insufficient information exists concerning the relative effects of acute and chronic stressors on central cytokine activity.

Elevated central cytokine levels in response to insults have been associated with neurological and behavioural changes, including somnolence (Krueger et al., 1998), cognitive disturbances (Fiore et al., 1996), and disruptions of eating as well as cachexia (Plata-Salamán, 1998). Similarly, these signs are evident in response to exogenous central cytokine application. The severity of these signs depends on the nature, chronicity and magnitude of the challenge, all of which will influence central levels of cytokines.

In considering the central actions of the pro-inflammatory or stimulatory cytokines, it should be considered that anti-inflammatory or inhibitory signals are also present, including IL-4, IL-10 (Szczepanik et al., 2001), IL-1 receptor antagonist (IL-1Ra) (Licinio and Wong, 1997) as well as soluble receptors for IL-1β

(Colotta et al., 1994) and TNF-α (Shohami et al., 1999). It is not the level of pro-inflammatory cytokine, per se, that determines the impact of cytokine activation in the brain, but the balance between the pro- and anti-inflammatory signals (Licinio and Wong, 1997; Plata-Salaman et al., 1998). Additionally, since most stimulatory cytokine receptor-bearing cells need only a few ligands to become biologically active, a substantial accumulation of their inhibitory counterparts will be needed to suppress the activating signal. In effect, when evaluating immune insults, it ought to be considered that the magnitude and chronicity of the challenge will impact on the neurological manifestations associated with cytokine activation. Highly toxic challenges (e.g. LPS) and chronic ailments (e.g. tumours) will shift the balance toward the pro-inflammatory cytokines and promote more detrimental consequences (Plata-Salaman et al., 1998), while milder and acute challenges (e.g. single, low doses of a cytokine) will shift the balance toward the anti-inflammatory cytokines and have more subdued repercussions.

Cytokine-induced activation of the HPA axis

Like stressors, various immunogenic and cytokine challenges (e.g. LPS and IL-1β) stimulate HPA activity (Brebner et al., 2000; Del Rey and Besedovsky, 1992; Dunn, 1992; Turnbull and Rivier, 1999). Systemic and intracerebroventricular (i.c.v.) IL-1β administration increased c-*fos* expression within the paraventricular nucleus (PVN) of the hypothalamus corticotropin-releasing hormone (CRH) neurons (Ericsson et al., 1994; Vellucci et al., 1995) and increased the expression of CRH and arginine vasopressin (AVP) secretion in PVN neurons of the hypothalamus (Lee and Rivier, 1994; Mandrup-Poulsen et al., 1995; Tilders et al., 1993). Moreover, IL-1β infusion into the median eminence (site of CRH terminals from neurons originating within the PVN) increased AVP and CRH secretion and provoked elevated plasma adrenocorticotropic hormone (ACTH) and corticosterone levels (McCoy et al., 1994; Watanobe and Takebe, 1993). Predictably, CRH antagonists attenuated the IL-1β-induced ACTH changes (Saperstein et al., 1992). While, the effects of IL-1β on HPA activity have primarily been assessed in acute preparations, continuous systemic infusion (via osmotic minipumps) of this cytokine over 1 wk provoked a persistent increase of plasma ACTH and corticosterone levels (Sweep et al., 1992). Moreover, as will be discussed later, acute and chronic systemic IL-1β administration may result in a long-lasting increase of CRH and AVP co-expression within the external zone of the median eminence, and thus may have protracted repercussions with respect to the impact of later challenges (Tilders and Schmidt, 1998). Finally, in addition to IL-1β, HPA activity was increased by other pro-inflammatory cytokines, including IL-6 and TNF-α (Bernardini et al., 1990; Brebner et al., 2000; Dunn, 2001; Hayley et al., 1999; Rothwell and Hopkins, 1995; Zhou et al., 1996), and these effects were blocked by CRH antiserum (Bernardini et al., 1990; Turnbull et al., 1997).

Central neurochemical effects elicited by activation of the inflammatory response system or cytokine challenge

Although the central neurotransmitter effects of various cytokines have been assessed, greatest attention has been devoted to the impact of IL-1β. Following its systemic administration, IL-1β stimulated c-*fos* expression in several stressor-sensitive brain regions, including the PVN, bed nucleus of the stria terminalis, and central nucleus of the amygdala (Day et al., 1999; Ericsson et al., 1997; Xu et al., 1999). Moreover, this treatment increased NE activity within the PVN, medial basal and lateral hypothalamic nuclei (Dunn, 2001; Kaur et al., 1998; Lacosta et al., 1998a,b), and increased DA utilization within the hypothalamus and prefrontal cortex (Kabiersch et al., 1988; Masana et al., 1990) and 5-HT activity within the hypothalamus, prefrontal cortex and hippocampus (Brebner et al., 2000; Carmelia et al., 1991; Dunn, 2001; Zalcman et al., 1994). In vivo, systemic IL-1β administration increased hypothalamic NE and 5-HT release from the nucleus accumbens and the hippocampus, respectively (Merali et al., 1997; Smagin et al., 1996; Song et al., 1999).

Paralleling the actions of systemic treatment, i.c.v. IL-1β increased hippocampal 5-HT release (Linthorst et al., 1995), while direct application of IL-1β into the rat anterior hypothalamus increased the release of NE, 5-HT and DA (Shintani et al., 1993). Similarly, when directly injected into the medial basal hypothalamus, IL-1β augmented 5-HT and DA release (Mohankumar and Quadri, 1993; Mohankumar et al., 1993), and local injection of IL-1β increased NE release within the medial prefrontal cortex (Kamikawa et al., 1998).

Like IL-1β, systemic TNF-α administration also increased central monoamine activity, including NE and 5-HT activity within the PVN, central amygdala, locus coeruleus and prefrontal cortex (Hayley et al., 1999), and altered tryptophan levels within the hippocampus and hypothalamus (Dunn, 2001; Leonard, 2001). Similarly, i.c.v. TNF-α stimulated amine turnover, particularly within hypothalamic nuclei (PVN and

median eminence/arcuate nucleus) (Hayley et al., In Press).

Most of the studies described thus far have pointed to cytokine treatment provoking increase monoamine release. Yet, it will be recognized that depressive illness has typically been considered to reflect a down-regulation of monoamine functioning. However, two issues need to be considered in relating the effects of cytokine treatments to depression. First, in addition to affecting monoamine release, it was reported that, in vitro, IL-1 provokes activation of the 5-HT transporter, thus enhancing reuptake of 5-HT from the synaptic cleft (Ramamoorthy et al., 1995). Thus, the availability of 5-HT may be diminished, depending on the cytokine dosage.

Secondly, the aforementioned studies assessed the consequences of acute cytokine administration. There is presently insufficient information available concerning the impact of chronic cytokine treatment on neuroendocrine and central neurotransmitter functioning, and limited data are available concerning the proactive effects of cytokines on neurochemical activity. This is particularly critical, as immune activation stemming from bacterial or viral insults, as well as cytokine immunotherapy, involve sustained and persistent alterations of cytokine activity. Thus, to obtain a more realistic index of the effects relevant to depression, it may be more productive to assess the impact of chronic activation of the inflammatory response system or repeated administration of cytokines. It has been shown that sustained systemic or i.c.v. IL-1β administration provokes marked and persistent HPA activation (Sweep et al., 1992; Van der Meer et al., 1996) while chronic central IL-1β administration promotes activation of hypothalamic–pituitary–gonadal axis (Rivest et al., 1993). Indeed, chronic IL-1β administration promoted sustained variations of CRH, CRH receptors and pro-opiomelanocortin gene expression coupled with elevated secretion of ACTH, β-endorphin and corticosterone (Parsadaniantz et al., 1997). Importantly, it was also shown that continuous intravenous infusion of IL-1β not only augmented c-*fos* expression within specific hypothalamic nuclei (PVN and supraoptic nucelus), but also provoked such effects within the central amygdala. While the hypothalamic effects were attenuated by pretreatment with a cyclo-oxygenase inhibitor, this was not the case within the central amygdala (Niimi et al., 1996). Thus, hypothalamic and amygdala alterations likely involve different mechanisms. At any rate, the finding that chronic cytokine treatments may have protracted repercussions is consistent with the elevated HPA activity evident in some forms of depression. However, it is still not certain what immediate or protracted effects are induced by chronic cytokine treatments on the activity of monoamines that are believed to contribute to affective illness.

Owing to the redundancies and pleiotropic nature of cytokine networks, it is important not only to consider their individual effects, but also to determine the interactive effects of cytokines on central processes. In particular, cytokines may act in a synergistic fashion, such that their co-administration results in effects greater than the sum of their individual effects. In fact, co-administration of either TNF-α and IL-1β or IL-6 and IL-1β provoked a synergistic increase of HPA, but not central monoamine, activity (Brebner et al., 2000; Perlstein et al., 1993; Zhou et al., 1996). Interestingly, cytokines and stressors may also have synergistic effects, as observed with respect to the in-vivo release of 5-HT from mesolimbic brain sites (Merali et al., 1997). In particular, it has been shown that the increased in-vivo NE and 5-HT release within the hippocampus and nucleus accumbens elicited by IL-1β was greatly augmented following the application of a mild stressor (air puff) (Merali et al., 1997; Song et al., 1999). Moreover, in chronically stressed animals the administration of LPS promoted a greater IL-1 response, although this effect was not necessarily accompanied by elevated ACTH or corticosterone secretion (Mekaouche et al., 1994). Nevertheless, it seems reasonable to suppose that synergisms may occur between stressor and cytokine treatments, as they do between different cytokines, so that the response of endogenous neurochemical systems will be exaggerated. Incidentally, it might be noted at this juncture that the behavioural effects of cytokine treatments may be altered by environmental stimuli, particularly those contextual cues that involve a stressful component. For instance, reactivity in response to the T-cell superantigen, staphylococcal enterotoxin B, was enhanced by exposure to novel stimuli (Kawashima and Kusnecov, 2002), and IL-2 similarly provoked behavioural activation in response to a novel stimulus (Zalcman et al., 1998, Zalcman, 2001), and increased locomotor activity under anxiety-provoking conditions (on a plus maze) (Petitto et al., 1997). Similarly, the sickness-inducing effects elicited by cytokines, such as IL-1, may not be evident in novel environments, particularly when this environment was stressful (Lacosta et al., 1999). Thus, we argued that while cytokines could produce marked illness, in a novel environment that may signal danger, animals do not have the luxury of expressing sickness behaviours. In a like fashion, one can imagine that the anhedonic or depressogenic action of cytokines may be context-dependent.

As indicated earlier, it has been proposed that depressive mood results when monoamine utilization exceeds synthesis, resulting in insufficient amine concentrations to meet demands exerted by new or ongoing stressors. In a similar fashion, it ought to be considered that following chronic activation of the inflammatory response system the effects of stressors may be augmented, and moreover in chronically stressed animals the central effects of cytokine or immune challenges may be appreciably enhanced, thereby favouring the development of mood disturbances.

The role of cytokines in the stress response: immune activation as a stressor

As already indicated, 'processive' stressors (i.e. psychogenic or neurogenic stimuli or events that involve appraisal processes or higher order sensory cortical processing) share several effects with those elicited by systemic (metabolic) insults, such as bacterial or viral infection (Herman and Cullinan, 1997). While, different neural circuits are activated in response to processive and systemic stressors, these insults trigger some common end points, such as HPA activation. It was suggested that while processive stressors engender such outcomes via activation of limbic mechanisms, systemic stressors may have more direct effects through actions at the hypothalamus (Herman and Cullinan, 1997). Indeed, exposure to a novel environment (processive stressor) increased c-*fos* mRNA within limbic regions (e.g. lateral septum and medial amygdaloid nucleus) to a much greater extent than did inhalation of ether vapours (systemic stressor), although both stressors had comparable effects within the hypothalamus (Emmert and Herman, 1999). Further, while footshock and cytokine challenge were both shown to increase c-*fos* within the PVN, catecholamine denervation was only effective in attenuating the effects of the cytokine treatment (Li et al., 1996). Similarly, the HPA-stimulating effects of IL-1β were attenuated by ablation of aminergic fibres originating from the medulla or removal of the area postrema (a brainstem, circumventricular organ) (Ericsson et al., 1994; Lee et al., 1998). Interestingly, Shintani et al. (1995) demonstrated that pretreatment with IL-1Ra, blocked the hypothalamic NE alterations and the plasma ACTH increases induced by immobilization, suggesting that cytokines may play a role in the regulation of the stress response elicited by processive types of stressors.

In relating the effects of stressors and cytokines to emotional states, it is important to consider the effects on limbic regions that have been implicated in anxiety and depression (e.g. the amygdala and prefrontal cortex). It appears likely that different nuclei of the amygdala, and particularly CRH neuronal activity within these sites, contributes to the maintenance of anxiety (LeDoux, 2000). In this respect, the basolateral nucleus of the amygdala may play a prominent role in the initial processing of fearful stimuli, while the central nucleus may be more important for the generation of behavioural outputs to contend with the challenge (Davis, 1992). Consistent with a role of IL-1β in promoting anxiety-related responses (Anisman and Merali, 1999), it was reported that as in the case of psychogenic stressors, IL-1β increased CRH mRNA expression at the amygdala and bed nucleus of the stria terminalis (Day et al., 1999; Lee and Rivier, 1998; Makino et al., 1999; Sawchenko et al., 1996). Moreover, lesions of the central amygdala attenuated the plasma corticosterone and ACTH responses elicited by IL-1β, supporting the possibility that amygdaloid–PVN communication may be important in regulating cytokine-elicited HPA responses (Xu et al., 1999).

While these data point to the similarity between the effects of stressors and immunogenic stimuli, it seems that stressors and cytokines may activate different regions of the amygdala. Ericsson et al. (1994) reported profound c-*fos* activation of the central amygdala in response to footshock, while systemic IL-1β provoked the strongest effect within the medial nucleus. Little information exists concerning the role of the medial amygdala in the response to cytokines, relative to those elicited by stressors; however, it was suggested that the medial nucleus may play a more important role than the central nucleus in the neuroendocrine response to restraint stress (Dayas et al., 1999). Given that cytokines and stressors may contribute differentially to amygdaloid stimulation, these challenges may affect different phases of anxiety/fear responses.

Although cytokines influence amygdala neuronal activity, there is limited information concerning the anxiogenic effects of cytokine treatments. The i.c.v. administration of IL-1β or TNF-α elicited anxiogenic-like effects, but this has been evaluated in only a limited number of situations (Connor et al., 1998). Moreover, it is not clear that the anxiety-like effects associated with IL-1β treatment stemmed from the central actions elicited by the cytokine, and instead may have been secondary to the malaise engendered by the treatment.

Cytokine and stressor sensitization effects

In addition to their immediate behavioural and neurochemical effects, stressful events may influence the organism's responses to later challenges. In fact, a variety of stressors, including immunological stimuli,

prime biological systems so that an augmented response is elicited by later exposure to the same or somewhat different challenge (sensitization) (Anisman et al., 2001; Tilders and Schmidt, 1998). As indicated earlier, the development of a stressor-elicited sensitization effect is believed to have important repercussions for behavioural pathology, particularly with respect to the recurrence of depression (approx. 30–50% of patients suffer recurrence within 1 yr). Given that cytokines may induce neurochemical effects similar to those provoked by processive stressors, it ought to be considered that cytokine alterations (and sensitization to the effects of cytokines) might similarly contribute to depressive episodes.

Stressor effects

Stressor-provoked sensitization effects have been demonstrated with respect to NE activity within the hypothalamus, hippocampus and amygdala, and DA utilization within the prefrontal cortex (Anisman et al., 1991; Finlay et al., 1997; Jordan et al., 1994). Also, cross-sensitization has been demonstrated wherein exposure to a particular stimulus enhances the response to a subsequently applied stimulus of a different form, including pharmacological challenges (Anisman et al., 1993; Finlay et al., 1997; Flores et al., 2000; Gresch et al., 1994; Hayley et al., 1999; Tilders and Schmidt, 1998). Like acute challenges, chronic stressors influence responses to subsequent stressor encounters. In animals exposed to a chronic cold stressor regimen, later application of tail shock augmented NE release within the hippocampus and prefrontal cortex and DA release from cortically projecting neurons (Gresch et al., 1994; Jedema et al., 1999; Nisenbaum and Abercrombie, 1992).

As in the case of amine variations, stressors may have protracted effects on HPA functioning. It has been suggested that such changes stem from phenotypic alterations of CRH terminals within the median eminence, wherein co-localization of AVP and CRH occurs (Bartanusz et al., 1993). Specifically, a chronic stressor regimen has been shown to provoke a progressive increase of AVP stores in these CRH terminals (Bartanusz et al., 1993; de Goeij et al., 1992a,b; Schmidt et al., 1995). As CRH and AVP synergistically stimulate pituitary ACTH release, the neuroendocrine response to subsequent challenges ought to be increased.

Cytokine sensitization: HPA effects

Cytokines, such as IL-1β and TNF-α, provoke behavioural and neurochemical sensitization effects, just as traditional stressors do. These cytokines provoke the sensitization of HPA activity such that later re-exposure to the cytokine resulted in augmented neuropeptide and hormonal activity. Interestingly, the emergence the sensitization was dependent on the passage of time following the initial challenge (Hayley et al., 1999, 2001a; Schmidt et al., 1995). In particular, while the cytokines increased the co-localization of CRH and AVP within the median eminence, this outcome only became apparent 4 d after IL-1β administration and peaked 1–2 wk following the treatment (Schmidt et al., 1995). A second administration of IL-1β (11 d after the initial challenge) elevated plasma ACTH and corticosterone levels (Schmidt et al., 1995), suggesting that the cytokine provoked a functionally hyper-responsive HPA axis.

Systemic administration of TNF-α also induced a time-dependent sensitization of HPA activity. However, the temporal profile of induction of the hypothalamic peptide immunoreactivity did not parallel the expression of the corticosterone sensitization. Specifically, while median eminence CRH and AVP immunoreactivities were maximally elevated 7–14 d following the initial TNF-α injection, the neuropeptide expression was comparable to baseline by 28 d (Hayley et al., 2001a). However, re-exposure to TNF-α 28 d following initial administration of the cytokine provoked a pronounced sensitization of corticosterone release, an effect that was absent at earlier re-exposure intervals (1, 7 and 14 d) (Hayley et al., 1999). Thus, factors in addition to hypothalamic CRH and AVP may influence the TNF-α-induced hormonal sensitization. For instance, the cytokine may have had direct actions upon the adrenal or pituitary gland, both of which contain high TNF-α receptor densities (Kobayashi et al., 1997). Similarly, other peripherally acting inflammatory factors (e.g. histamine) may mediate some of the sensitizing effects of TNF-α. Indeed, we recently observed that systemic antihistamine treatment (H1 and H2 antagonists) ameliorated both the corticosterone and sickness sensitization effects of TNF-α (Kelly et al., 2001). As well, in animals treated with TNF-α, later i.c.v. re-exposure to the cytokine did not sensitize HPA activity, irrespective of whether the initial injection was centrally or peripherally administered, suggesting that peripheral factors and/or targets are involved (Hayley et al., 2002).

It is important to note that mice displaying the TNF-α-induced HPA sensitization also showed signs of marked illness (e.g. ptosis, piloerection, lethargy, cyanosis of the extremities) (Hayley et al., 2001b). Although it is tempting to speculate that stress or other factors associated with the illness may be related to the provocation of the corticosterone sensitization, we

observed that that the two processes were independent of one another (Hayley et al., 2001b).

Cytokine sensitization: central monoamine alterations

In addition to the immediate neurotransmitter effects, re-exposure to TNF-α augmented monoamine activity in a region-specific and time-dependent fashion (Hayley et al., 1999, 2002). Within the PVN, TNF-α induced a sensitization of NE activity, which followed a time-course similar to that observed with respect to the corticosterone and sickness sensitization effects, becoming progressively more pronounced at longer intervals following initial cytokine treatment (Hayley et al., 1999). In contrast, the sensitization of NE activity within the prefrontal cortex and central amygdala was evident at 1 d following the initial treatment with the cytokine, but not at longer intervals. However, a TNF-α provoked sensitization of 5-HT activity was apparent within the central amygdala and prefrontal cortex upon re-exposure to the cytokine after an intermediate interval (7–14 d) following pretreatment (Hayley et al., 1999), paralleling the increased CRH–AVP co-localization within the median eminence (Hayley et al., 2001a).

Although i.c.v. TNF-α did not sensitize corticosterone activity, this treatment did elicit a sensitization of NE and DA utilization within the PVN and median eminence/arcuate nucleus complex (ME/ARC). Moreover, mice that initially received intraperitoneal (i.p.) mTNF-α and later challenged via i.c.v. administration with this cytokine displayed greatly increased 5-HT and DA activity within the ME/ARC, as well as augmented NE activity within the locus coeruleus. Interestingly, unlike the effects of peripheral cytokine administration, when administered i.c.v., the sensitization occurred largely within hypothalamic nuclei (Hayley et al., 2002).

Cytokines and depression

Major depression in humans, particularly in patients presenting with severe melancholic illness, has been associated with variations of immune functioning, including a reduction of mitogen-stimulated lymphocyte proliferation and reduced natural-killer (NK) cell activity (Herbert and Cohen, 1993; Irwin, 1999; Maes, 1995, 1999). Contrary to the position that depression was associated with the suppression of non-specific immunity, the view was advanced that affective disturbances may be secondary to activation of the inflammatory immune response (Licinio and Wong, 1997; Maes, 1995, 1999). In this respect, depressed patients were found to present with signs of immune activation reminiscent of an acute phase response, including increased plasma concentrations of complement proteins, C3 and C4, IgM, and positive acute phase proteins, haptoglobin, α_1-antitrypsin, α_1 and α_2 macroglobulin, whereas negative acute phase proteins were reduced (Maes, 1999; Nieto et al., 2000; Rothermundt et al., 2001; Sluzewska, 1999). Further, major depressive illness was accompanied by elevated activated T cells ($CD_{25}+$ and HLA-DR+), secretion of neopterin, prostaglandin E2 and thromboxane (Maes, 1995, 1999). Parenthetically, although cortisol has often been shown to be immunosuppressive, the changes in immune cell populations are correlated with elevated urinary cortisol levels (Maes et al., 1994). Interestingly, in a dexamethasone suppression test, non-supressors were also resistant to the immune effects of dexamethasone (Maes et al., 1994), suggesting that the absence of negative feedback by cortisol on the HPA axis in depression could extend to the dysregulation in the levels of immune markers observed in the condition.

Commensurate with the view that cytokines are fundamental in depression, it was reported that severe affective illness was accompanied by elevated circulating cytokines or their soluble receptors, including IL-2, soluble IL-2 receptors (sIL-2R), IL-1β, IL-1Ra, IL-6, soluble IL-6 receptors (sIL-6R), and γ-interferon (γ-IFN) (Berk et al., 1997; Frommberger et al., 1997; Maes, 1995, 1999; Mullar and Ackenheil, 1998; Nassberger and Traskman-Bendz, 1993; Sluzewska et al., 1995; Smith, 1991; Song et al., 1994) as well as increased production of IL-1β, IL-6 and TNF-α in response to mitogen challenge (Anisman et al., 1999a,b; Maes, 1995, 1999). Interestingly, with alleviation of depression in response to antidepressant treatment, normalization was evident with respect to levels of IL-1β, IL-6 and α_1-acid glycoprotein (Frommberger et al., 1997; Sluzewska et al., 1995), whereas no such changes were apparent concerning the up-regulated production of sIL-2R, IL-6 and sIL-6R in major depression (Maes, 1999). Similarly, antidepressant treatment did not diminish the elevated serum levels of the IL-6, or that of anti-inflammatory cytokines, IL-10 and IL-1Ra (Kubera et al., 2000). In effect, these cytokines may act simply as trait markers of the illness (Anisman et al., 1999b; Maes, 1999), although it ought to be considered that sustained treatment may be necessary to achieve normalization of cytokine functioning.

The aforementioned studies, in the main, are correlational, and thus it cannot be determined whether the cytokine elevations are secondary to the illness (i.e. being directly or indirectly brought on by the depression), or contribute to the provocation of the disorder. Yet, it has been reported that in humans undergoing

immunotherapy high doses of IL-2 and IFN-α induce neuropsychiatric symptoms, including depression. As such, these data imply that the affective changes were related to the cytokine treatment (Capuron et al., 1998; Caraceni et al., 1992; Denicoff et al., 1987; Maes et al., 2001; Meyers and Valentine, 1995). Importantly, it was reported (Musselman et al., 2001) that depressive symptoms provoked by IFN-α were attenuated by treatment with the selective serotonin reuptake inhibitor, paroxetine. Together, these findings provide good reason to suspect an aetiological role for cytokines in depressive illness. Yet, it is important to consider that the populations being assessed in the latter studies were undergoing considerable strain (e.g. the distress regarding their illness), and hence depression may reflect the interactive effects of the distress and the cytokine treatments.

TNF-α signalling and depression

Recent clinical studies have suggested that elevated circulating TNF-α or its p55 receptor may be associated with psychiatric illness (Maes, 1999) and such an effect could come about by virtue of the cytokine's effects on central monoamine turnover (Ignatowski et al., 1997). Indeed, antidepressant medication has been reported to alter levels of TNF-α in brain regions such as the hippocampus and locus coeruleus (Ignatowski et al., 1997). Commensurate with the proposition that TNF-α may be involved in stressor- or depressive-like states, we found that TNF-α sensitized expression of the immediate early gene, c-*fos*, in several stressor-sensitive brain regions. Specifically, re-exposure to the cytokine 7 or 14 d following its initial i.p. pretreatment resulted in a pronounced increase of Fos immunoreactive protein within the PVN, supraoptic nucleus and central amygdala.

The fact that TNF-α sensitized 5-HT activity within stressor-sensitive brain regions (Hayley et al., 1999, 2002) may reflect cytokine-provoked neuroplastic changes, which may be reminiscent of those thought to characterize clinical depression (Altar, 1999; Manji et al., 2001). Further to this point, recent studies suggest that major affective disorders probably involve alterations in pathways typically activated by cytokines (Chen et al., 2001). In particular, the mitogen-activated protein (MAP) kinase pathway, which is involved in cytokine signalling [e.g. IL-6, brain-derived neurotrophic factor (BDNF)], as well as pathways involving the cAMP response-binding element (CREB) factor, which has important neuroplastic effects, are both proposed to play a role in the long-term neurochemical changes evident in depression (Guillin et al., 2001). Indeed, while stressors (which may be associated with the provocation of depression) reduce the expression of neurotrophic products of these pathways, antidepressants stimulate these trophic factors. For instance, chronic antidepressant treatments increased the central expression of cAMP and CREB and some of their target genes, including the neurotrophic cytokine, BDNF (Vaidya and Duman, 2001). Moreover, stressor-induced reductions of central BDNF levels were ameliorated by antidepressant pretreatment (Vaidya and Duman, 2001). Supporting a direct beneficial role for neurotrophic cytokines in depression, infusion of either BDNF or the closely related neurotrophin-3 (NT-3) into the dentate gyrus produced an antidepressant effect, as assessed in animal models of depression (forced swim and learned helplessness), that was comparable to that provoked by traditional chemical antidepressants (Shirayama et al., 2002). In human post-mortem studies, increased hippocampal BDNF expression was associated with chronic antidepressant regimens (Chen et al., 2001). Thus, it may be useful to consider alternate antidepressant treatments that affect BDNF or other trophic factors that may engender a certain degree of protection or resiliency of monoaminergic cells in the face of everyday stressors. In particular, it is significant that the recent report by Shirayama et al. (2002) indicated that a *single* bilateral infusion of BDNF had antidepressant effects similar to that provoked by a chronic antidepressant regimen. The possibility exists that traditional antidepressants come to exert their beneficial effects only after neutrophic factors and related messenger pathways have been sufficiently 'primed'. If this is the case, then alternate neurotrophic antidepressants may circumvent the problem of long-term daily administration required for traditional antidepressant efficacy.

Stimulation of these cAMP and MAPkinase-dependent pathways can also induce the anti-apoptotic factor, bcl-2, which has been suggested to have beneficial actions in depressive disorders (Chen et al., 2000; Manji et al., 2001), just as it has a neuroprotective role in neurodegenerative states (Guillin et al., 2001). With respect to cytokines and depression, it appears that TNF-α provokes bcl-2 expression, as well as pro-apoptotic factors, suggesting that a delicate balance between the expression of death regulatory signals may ultimately determine the consequences of the cytokine, with respect to cellular survival and resiliency. It may be the case that TNF-α priming induces changes in these intracellular pathways (e.g. phosphorylation states) that 'set the stage' for the aberrant neurochemical responses to subsequent challenges that impinge upon this sensitized system.

Conclusions

It seems likely that behavioural and neurochemical plasticity is essential for an animal to cope with environmental demands. Various challenges, including stressful and immunological stimuli, may provoke central neurochemical alterations that may be of adaptive significance. Yet, some of these effects may also increase vulnerability to behavioural disturbances, particularly mood disorders. Further, it appears that both stressors and activation of the inflammatory response system may prime biological systems so that augmented responses are elicited upon later challenges with either the same or somewhat different stimuli (Tilders and Schmidt, 1998). As a result, these treatments do not only have immediate repercussions, but may exert long-lasting neurochemical consequences, which may impact on behavioural processes.

Several sources of evidence are, in fact, consistent with the supposition that activation of the inflammatory response system contributes to depression. For instance, depressive illness has been associated with increased levels of several cytokines and their soluble receptors (Maes, 1999), endotoxin challenge elicits signs of depression in both animals and human studies (Reichenberg et al., 2001; Yirmiya et al., 1999), and such effects in animals are attenuated by tricyclic antidepressant treatments (Shen et al., 1999; Yirmiya et al., 1999). Similarly, immunotherapy (IL-2 and IFN-α) has been shown to elicit depressive symptoms (Capuron et al., 2001) that are attenuated by antidepressant medication (Musselman et al., 2001). Clearly the behavioural tests are still somewhat limited, but coupled with the neurochemical findings, a prima-facie case exists supporting a cytokine link in the aetiology of some instances of depression. Of course, it ought to be underscored that while activation of the inflammatory response system may favour the development of depressive symptoms, this does not necessarily imply that instances of depression necessarily involve immune activation.

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