MINIREVIEW

DEPRESSION, STRESS AND IMMUNOLOGICAL ACTIVATION: THE ROLE OF CYTOKINES IN DEPRESSIVE DISORDERS

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Summary

Traditionally, both stress and depression have been associated with impaired immune function and increased susceptibility to infectious and neoplastic disease. However over the last number of years a large body of evidence suggests that major depression is associated with signs of immunological activation. Moreover it has been suggested that cytokine hypersecretion may be involved in the etiology of depressive disorders. The present article reviews the evidence from both clinical and experimental studies which implicates immunological activation and particularly hypersecretion of cytokines in the onset and maintenance of depressive illness. Both clinical and experimental studies indicate that stress and depression are associated with increased circulating concentrations of cytokines such as IL-1β, IL-6 and γ-IFN and positive acute phase proteins, and hyperactivity of the HPA-axis. In addition, it has been reported that immunological activation induces "stress-like" behavioural and neurochemical changes in laboratory animals. Although for many years it has been suggested that stress acts a predisposing factor to depressive illness, the precise mechanisms by which stress-induced depressive symptoms occur are not fully understood. Nevertheless, behavioural changes due to stress have often been explained in terms of changes in neurotransmitter function in the brain. In the present article increased cytokine secretion is implicated as a mechanism whereby stress can induce depression.

Key Words: psychoneuroimmunology, stress, depression, immunity, cytokines, autoimmunity, reward, anhedonia, neurotransmitters, behavior, animal models

Depression of mood is experienced by most people at one time or another. When mild, it is a passing feeling with no serious consequences. However, depressive illness involves an accentuation of intensity of otherwise normal emotions and can be so severe that it can be regarded as an illness.
causing severe distress, disruption of life and, if left untreated, can be potentially fatal. In addition to the abnormal severity of mood disturbance, the psychopathological state involves a combination of other features such as loss of motivation and an inability to experience pleasure (anhedonia), loss of self esteem, feeling of worthlessness and extreme pessimism, sleep disturbance, appetite disturbance and loss of energy, psychomotor disturbances (retardation or agitation), autonomic nervous system and gastrointestinal disturbances, impairment of reality (hallucinations, delusions or confusion) and suicidal tendencies. We are aware that depression is by no means a homogeneous disorder, but is in fact a complex phenomenon which has many subtypes, and probably more than one aetiology. However, for the purposes of the present article the term depression, or depressive illness is used throughout merely as a convention.

The concept of an inter-relationship between the psychological state and immune status can be traced back to ancient history. In 200 AD Galen wrote that melancholic women are more susceptible to breast cancer than sanguine women (1). Later in 1951, the British clinician George Day, cited unhappiness as a cause of lowered resistance in patients with active tuberculosis (2). Over the last fifteen years it has become apparent that the central nervous system (CNS) and immune systems are intimately connected (for review see Ref. 3) and more importantly that functional bidirectional communication exists between these two systems (4). It is now believed that the nervous, endocrine and immune systems are so intimately linked that they should be regarded as a single network rather than three separate systems. The study of interactions between these systems has given rise to the new discipline of psychoneuroimmunology, a term first coined by Ader and colleagues in 1981 (5). Since this time there has been an explosion of research in this discipline, with the number of neuroimmunology presentations at the Society of Neuroscience Annual Meeting going from zero in 1983 to approximately 125 in 1993 (6).

It is now widely accepted that psychological stress and psychiatric illness can compromise immune function (7). In addition, it is well established that soluble mediators released by immune cells can affect central nervous system (CNS) function and produce alterations in behaviour. In addition to the behavioural changes that are evident in depressed patients, many endocrine and immune abnormalities have also been identified. Most of the initial research that examined the effect of depression on immunity indicated that there were depressive effects on many aspects of immune function. Thus some studies reported impaired zymosan-induced neutrophil phagocytosis (8,9), mitogen-stimulated lymphocyte proliferation (10,11) and natural killer cell (NK-cell) activity (12,13) in depressed patients. Despite the numerous reports documenting a suppression of various indices of immune function in depression, contradictory studies have been reported in which researchers failed to detect any significant alteration in some of these immune parameters in depressed patients (14,15,16). It has been suggested that these inconsistencies were as a result of, among other things, evaluation of various forms of depression (unipolar patients displayed more immune alterations than bipolar patients), varying illness severity (suppression of immune function was positively correlated with illness severity), also, studies which examined immune correlates in relatively young outpatients with milder symptoms of depression found that lymphocyte function was not altered compared to control subjects (for a review see ref. 17).

In addition to the immunological alterations reported in patients suffering from major depression, a number of studies have examined indices of immune function in individuals who have been exposed to stressful life events such as academic examinations, divorce and bereavement. Exposure to such stressful life events was reported to cause impairments in various aspects of cellular immune function such as lymphocyte and NK-cell activity (18,19,20,21,22,23). There is also evidence to suggest that the severity of the immune changes observed in an individual as a result of exposure to stressful life events is inversely correlated to the ability of the individual to cope with the stressful event. For
example, those who cope experience less immune alterations than those who are unable to cope (24,25,26).

Despite these initial findings of immunosuppression in both depressed patients and subjects exposed to stressful life events, other studies have indicated that immune activation could also be present in depressed patients (27), and recently it has been suggested that such immune activation may play a role in the onset of depressive symptoms (27,28). Traditionally, major depression was viewed as a disorder which occurred as a result of abnormalities in central monoaminergic neurotransmitter systems (primarily the noradrenergic and serotonergic systems), and that such neurotransmitter changes gave rise to the behavioural sequelae and the reported alterations in endocrine and immune function. However, in recent times it has been suggested that the behavioural deficits, central monoamine abnormalities and hypothalamic-pituitary-adrenal axis (HPA axis) activation seen in depressed patients may in fact be secondary to alterations in immune function, at least in some cases of depression (27,28).

The aims of the present review are to examine the evidence from both experimental and clinical studies that implicate immunological activation and more specifically hypersecretion of cytokines in the onset of depressive illness.

The Role of Immunological Activation as a Causal Factor in Depressive Illness

The macrophage theory of depression was formulated by Smith in 1991 (28). This hypothesis proposes that excessive secretion of macrophage cytokines such as interleukin (IL) -1, tumour necrosis factor-α (TNF-α), and interferon-α (IFN-α) are a cause of some cases of major depression. To date, there are several lines of evidence that arise from both clinical and experimental studies to support this hypothesis. However before describing the experimental evidence for a role of cytokines in the onset of depressive symptoms, the mechanisms by which cytokines can affect brain function will be first outlined.

How do Cytokines Alter CNS Function?

Cytokines are a heterogeneous group of polypeptide hormones which were first identified as soluble mediators within the immune system, and have been associated with the activation of the immune system and with inflammatory responses. With regard to the role of specific cytokines within the immune system, cytokines are pletrophic molecules (ie) each acts on a variety of different target cells, often to produce quite different effects. Cytokines operate within a complex network and may act either synergistically or antagonistically and can influence the production of other cytokines from other cell types. It is beyond the scope of this review to discuss the roles of the many cytokines (17 interleukins, TNFs, IFNs and other growth factors) in the immune system. However this complex cytokine network has been extensively described elsewhere (29,30). In addition to the immune system, cytokines and their receptors have recently been located in many other tissues including the peripheral and central nervous systems (31). Receptors for IL-1, IL-2, IL-6 and TNF-α and some other growth factors have been localised in rodent brain with highest densities in the hippocampus and hypothalamus (32). Cytokines are synthesised and have been co-localised with their receptors within the CNS (33). Histochemical studies using rodent and human tissue have revealed that IL-1, IL-6 and TNF-α are expressed in neurons and glial cells within the CNS under non-inflammatory conditions, albeit in small quantities (34). After infection or trauma, cytokines are expressed in much larger quantities and excessive secretion of cytokines is thought to be involved in many pathological processes within the CNS (34). However despite a vast amount of research, the physiological roles of specific cytokines within the brain are not fully understood.
How do Peripherally Released Cytokines Act on the CNS?

In addition to cytokines produced within the CNS, peripherally produced cytokines can also affect the brain. However, the means by which cytokines produced in the periphery communicate with the brain is still a controversial issue. Cytokines are large (17-51 kD) hydrophillic molecules (30) and their size and structure is such that passive diffusion across the blood brain barrier (BBB) is unlikely (32). Currently, it is postulated that cytokines produced in the periphery act on the brain predominantly at the circumventricular organs, particularly via the organum vasculosum of the laminae terminalis (OVLT). The circumventricular organs are parts of the brain at which there is no functional BBB (32). At the OVLT cytokines are believed to bind to glial cells, which in turn produce cytokines and other mediators such as prostaglandins, particularly prostaglandin E$_2$ (PGE$_2$). Indeed, in rats it has been demonstrated (by means of in vivo microdialysis) that peripheral IL-1p administration elevates PGE$_2$ concentrations in many brain structures. This is maximal and most rapid at the OVLT and the medial preoptic area, and interestingly this central increase in PGE$_2$ precedes the onset of fever (35). The role of PGE$_2$ in the signalling mechanism for IL-1 and other cytokines is further strengthened by virtue of the fact that many cytokine and endotoxin induced neurochemical (36,37) and behavioural (38,39,40) responses are attenuated by cyclooxygenase inhibitors such as indomethacin. In addition, it has been reported that peripheral administration of bacterial lipopolysaccharide (LPS) induces the expression of mRNA for IL-1p, IL-6 and TNF-α within the CNS (41), suggesting that not only can peripherally produced cytokines act on the CNS but that they also induce the production of cytokines within the brain which can directly modulate CNS function. In fact it has been proposed that circulating IL-1 acts on cyclooxygenase containing neurons within the OVLT to produce local prostaglandin secretion, the local diffusion of prostaglandins into the hypothalamic area act on IL-1 containing neurons in this region causing IL-1 to be released from neuronal terminals (42). Thus it has been suggested that peripheral IL-1 induces the synthesis and release of IL-1 within the brain (42).

Other studies have reported that not only does IL-1 act at the OVLT, but that it can cross the BBB via an active transport mechanism (43,44). In addition, an active transport mechanism for TNF-α has been described (45). Nevertheless the concentrations of these cytokines crossing the BBB by such active transport mechanisms may be so low as to be physiologically insignificant (32). However, it has been suggested that such active transport mechanisms may be an important route of entry when plasma concentrations of cytokines are very high (43,44).

In addition to the hypothesis that peripherally produced cytokines affect CNS function via the circumventricular organs, there is also evidence suggesting the existence of neurally mediated mechanisms of communication between peripherally produced cytokines and the CNS (41). This hypothesis of communication between peripherally produced cytokines and the CNS via a neural pathway is supported by the fact that subdiaphragmatic vagotomy attenuated endotoxin induced depressive effects on behaviour, c-fos expression in the CNS and IL-1β mRNA expression in the hypothalamus (41). In addition, subdiaphragmatic vagotomy has been reported to block HPA-axis activation produced by peripheral IL-1β and TNF-α administration (46,47), and hypothalamic noradrenaline depletion produced by peripheral IL-1β administration (46).

Thus cytokines can affect CNS neurotransmission, via cytokine receptors located within the CNS. Therefore, mechanisms exist by which immune mediators can alter monoaminergic and peptidergic neurotransmission within the CNS and possibly induce depressive symptoms.
**Clinical Studies**

**Signs of Immunological Activation are Evident in Depressed Patients**

In addition to the initial findings of immunosuppression in depressed patients which have been already outlined, more recent research into the psychoneuroimmunology of depression has concentrated on the analysis of blood leucocyte subpopulations and the measurement of humoral factors such as cytokines, soluble cytokine receptors and acute phase proteins (APPs) in plasma/serum from depressed patients or in leucocyte culture supernatents after mitogenic stimulation.

Depression is associated with an increase in plasma concentrations of the complement proteins C3 and C4 and immunoglobulin (IgM) (48). In addition, Song and co-workers, (1994) reported increases in plasma concentrations of positive APPs haptoglobin, α1-antitrypsin, α1, and α2 macroglobulin in depressed patients (48). These findings were consistent with earlier reports of increases in complement and positive acute phase proteins in depressed patients (10,49), whereas negative APP concentrations were reduced in depressed patients (27).

Recently, increased concentrations of IL-6, soluble IL-6 receptor (sIL-6R), soluble IL-2 receptor (sIL-2R), IL-1, IL-1 receptor antagonist (IL-1ra) and γ-IFN have been reported to occur in depressed patients (50-52,53,54), and many of these alterations were accompanied by increased positive acute phase protein concentrations (54). In addition, increased monocyte phagocytosis has been observed in depressed patients, an effect that is reversed upon successful antidepressant treatment, suggesting that increased monocyte phagocytosis is a state marker of depression (55). Similarly, Griffiths et al., (1996) (56) reported that increased serum IL-β concentrations in depressed patients returned to normal in those patients who responded to a 12 week course of sertraline. Also, elevated serum IL-6 and α1-acid glycoprotein concentrations observed in a group depressed patients were normalised following chronic fluoxetine treatment (57), thus suggesting that like increased macrophage phagocytosis, increased concentrations of IL-1, IL-6 and α1-acid glycoprotein may be state markers of depression and may be causally involved in the onset of depressive symptomology. In this regard there is evidence suggesting that signs of immunological activation such as increased serum IL-6 and positive APP concentrations are more evident in patients suffering from treatment resistant depression, compared to those showing a positive response to antidepressant treatment (58,59). Seidel et al., (1995) reported a significant increase in mitogen-stimulated γ-IFN and sIL-2R production from PBMC cultures and elevated serum APP concentrations in depressed patients, which were maximal during the acute phase of the illness, and returned to control levels over a six week hospitalisation period during which time a concomitant decrease in HAM-D scores was apparent (60). However, in contrast to the studies conducted by Maes et al., (50,53) that found significant elevations in IL-1β and IL-6 in depressed patients, the study by Seidel and coworkers (60), reported that only a slight but non-significant increase in mitogen-stimulated PBMC production of these cytokines was evident in depressed patients. In stark contrast to the findings already outlined, Weizman and coworkers, (1994) reported that IL-1β, IL-2 and IL-3 production from mitogen-stimulated PBMC cultures was significantly reduced in depressed patients, when compared to age and sex matched controls (61). Furthermore, the reduced cytokine secretion in these depressed patients was normalised following four weeks of clomipramine treatment (61). The reason for this discrepancy between studies is not apparent, and clearly further studies with larger sample sizes need to be conducted to evaluate both circulating cytokine concentrations and ex vivo mitogen-stimulated cytokine production in various subtypes of depressed patients.

Studies employing flow cytometric analysis have revealed that depressed patients have an increased number of T-helper (CD4+), T-memory (CD4+,CD44RO+), activated T-cells (CD25+ T-cells and HLA-DR+ T-cells) and B-cell subsets indicating the presence of immunological activation in these
patients (27). However, recently it has been reported that depressed patients display increased serum anti-serotonin antibody titers (62,58) and increased serum antibodies against gangliosides which are part of the serotonin receptor (58). Furthermore, the presence of such antibodies was associated with much more intense features of immunological activation indicated by increased IL-6 and positive APP concentrations (58). Such a prevalence of anti-serotonin, and anti-serotonin receptor antibodies may indicate the presence of an autoimmune reaction against some components of the serotonergic system in depressed patients.

Although many discrepancies exist between the clinical studies conducted to date, a large volume of data has been generated which for the most part indicates that signs of immunological activation (elevated cytokine and positive APP concentrations) are evident in depressed patients. Nonetheless, relatively few of these studies have examined the effect of antidepressant treatment on the observed changes. However, the few studies which have evaluated the effect of antidepressant therapy suggest that signs of immunological activation are state, and not trait markers of depression (55,56,57). It remains to be seen if altered concentrations of cytokines, soluble cytokine receptors and APPs are specific to particular subtypes of depression and other conditions in which stress plays a major role. In this regard, it is of interest that a recent study reported that increased serum IL-1β concentrations were present in patients suffering from typical depression, but absent from patients suffering from atypical depression with increased neurovegetative symptoms (56).

Cytokines and HPA-Axis Activity in Depressed Patients

Hypersecretion of corticotropin-releasing factor (CRF) has been previously implicated to play a role in the pathophysiology of depressive illness (63). In addition, HPA-axis activation and consequently hypercortisolaemia is a common abnormality reported in a large proportion of depressed patients (64). Interestingly, in depression there seems to be a defect in the inhibitory feedback mechanism of cortisol on CRF secretion, thereby facilitating the maintenance of elevated cortisol levels (64).

As mentioned previously increased plasma cytokine concentrations have been reported to occur in depressed patients (50,51,52,53). Moreover, a positive correlation between monocyte production of IL-1β and increased serum cortisol concentrations has also been reported (53). It is well established that HPA axis activation is elicited by exogenous cytokine (IL-1, IL-6 and TNF-α) administration to rodents (65,66,67). Therefore it is not unreasonable to suggest that the hypercortisolemia observed in depressed patients may have resulted from a hypersecretion of CRF induced by pro-inflammatory cytokines such as IL-1 or IL-6.

A Paradoxical Co-existence of Hypercortisolemia and Elevated Cytokine and APP Concentrations is Evident in Depressed Patients - What Does it Mean?

The co-existence of hypercortisolemia and elevated circulating cytokine and acute phase protein concentrations in patients suffering from depressive illness is some what of a paradox, as it is well established that in normal circumstances glucocorticoids feedback on activated immune cells and have a tonic inhibitory action on the synthesis and release of pro-inflammatory cytokines (68,69). For example, glucocorticoids have been shown to selectively inhibit transcription of the IL-1β gene and also to decrease the stability of IL-1β mRNA in a human promonocytic cell line (69). The inhibitory effect of glucocorticoids on macrophage cytokine secretion is also evident from the fact that in laboratory animals both stressor-induced glucocorticoid release (70) and exogenous glucocorticoid administration (71) blocks endotoxin induced febrile response. However, it is obvious that in patients suffering from depressive disorders this inverse relationship between circulating glucocorticoid and cytokine concentrations does not exist. In the same way as there seems to be a defect in the inhibitory feedback mechanism of cortisol on CRF secretion in depressed patients (64), there also appears to be a defect in the inhibitory feedback action of glucocorticoids on cytokine secretion by immunocytes,
thereby allowing the co-existence of elevated circulating concentrations of both cortisol and cytokines. It is possible that such a defect in the feedback inhibitory mechanism of cortisol on central glucocorticoid receptors to prevent excessive CRF release, and on glucocorticoid receptors in immunocytes to restrain excessive cytokine secretion, may be a core defect in the aetiology of depressive disorders. Consequently the question must be posed as to how such a defect in glucocorticoid feedback occurs at a cellular level?, and how does successful antidepressant treatment normalise this defect? Recently, prereceptor metabolism of glucocorticoids by the enzyme 11-β-hydroxysteroid dehydrogenase has been reported as novel control mechanism of glucocorticoid action (72). Future research should examine the activity of this enzyme in tissue from depressed patients, as increased prereceptor glucocorticoid metabolism represents a potential cellular mechanism by which a defect in glucocorticoid feedback may occur in depressed patients. In this regard, the effect of antidepressant treatment on this enzyme activity should also be examined. In addition, the results of a recent study suggest that antidepressants may facilitate glucocorticoid-mediated feedback inhibition on the HPA-axis by facilitating glucocorticoid receptor (GR) translocation from the cytoplasm to the nucleus and to enhance GR-mediated gene transcription (73).

Independently of the effects of CRF on the HPA-axis, increased CRF secretion may also play a role in the behavioural abnormalities associated with both depressive disorders and anxiety disorders (74). Therefore cytokine-induced CRF hypersecretion in the absence of a normal glucocorticoid feedback mechanism may be responsible for both the persistent hypercortisolism, and behavioural dysfunction observed in depressed patients.

Other Evidence Which Implicates Hypersecretion of Cytokines in the Aetiology of Depressive Illness

In addition to the studies which report increased cytokine and positive acute phase protein concentrations in depressed patients, other evidence implicates hypersecretion of cytokines in the aetiology of depressive illness.

A large number of previously psychiatrically healthy individuals treated with exogenous cytokines such as IL-2, IFN-α and TNF-α develop depressive like symptoms such as depressed mood, increased somatic concern and stress reactions, cognitive impairment and difficulties with motivation and flexible thinking (75,76,77,78,79). The fact that these symptoms become apparent very quickly after cytokine administration, and usually disappear shortly after the termination of treatment implies that cytokines may play a causal role in producing such symptoms. Such depressive symptoms appear to be due to the biochemical changes induced by cytokine treatment rather than psychological reactions to the illness for which the agents are being administered (75). However, one must remember that the doses of cytokines administered to patients in these studies far exceeds normal physiological concentrations, and this is a factor that should be considered when implicating elevated endogenous cytokine secretion as a causal factor in the development of depressive symptoms.

Studies examining changes in various psychological parameters that accompany the onset of, or even the recovery from, infection in humans report that the most consistent psychological disturbance is depression (80). It has also been reported that a high incidence of depressive disorders is evident in individuals suffering from autoimmune diseases such as multiple sclerosis (81), rheumatoid arthritis (82), allergies (83) and systemic lupus erythematosus (84); such findings are of interest as it is known that cytokines are overexpressed in autoimmune disease (85). However, it may be the case that depressive symptoms are more prevalent in patients suffering from such disorders due to factors such as changes in their lifestyle due to the disease state or the experience of chronic pain as a result of the disease.
The occurrence of depressive disorders is twice as prevalent in women as it is in men. Interestingly, it has been reported that women also exhibit higher levels of immune activation than men (86). In addition, childbirth causes a profound increase in cytokine secretion (87) and it has been suggested

![Diagram of bidirectional interactions between the immune system and the CNS in depression.](image-url)

**FIG. 1.**

Bidirectional interactions between the immune system and the CNS in depression. Abbreviations: ACTH: Adrenocorticotropic; Adr: Adrenaline; APP: Acute phase protein; CD25: Interleukin-2 receptor; CD 56: Natural killer cell marker (isoform of N-CAM); CRF: Corticotropin releasing factor; DA: Dopamine; 5-HT: Serotonin; HLA-DR: Human Leucocyte Antigen; IFN: Interferon; IL: Interleukin; NA: Noradrenaline; NK-cell: Natural killer cell; PGE₂: Prostaglandin E₂.
that such an increase in cytokine secretion may play a role in the onset of postnatal depression in susceptible individuals (88).

Although the association between the winter season and depression has been known for many years, the concept that for some patients, depressive episodes are linked to annual changes in sunlight has only recently been the subject of research (89). Evidence suggests that patients respond to treatment with high intensity light and it has also been found that such patients can be effectively treated with antidepressants. The production of two cytokines, IFN-α and IFN-γ, has been reported to be increased in winter compared to summer (90); such an increase in these cytokine concentrations may therefore have a role to play in the aetiology of seasonal affective disorder.

Taking all this evidence into account, it is not unreasonable to suggest that increased cytokine (IL-1β, IL-6, IFN-γ) secretion due to environmental or internal stressors, or due to an underlying disease state, may play a role in the onset and maintenance of at least some cases depressive illness.

**Experimental Studies**

Much research has been devoted to examining the effects of immunological activation with lipopolysaccharide (LPS), sheep erythrocytes (SRBC) and various cytokines on neurochemical, behavioural and endocrine parameters in rodents. Moreover, it has been suggested that immunological activation may be perceived by the CNS as a stressor and that in fact the immune system may act as a sensory organ for non-cognitive stimuli such as tumours, bacteria and viruses (91,92). In this Section, many of the observed neurochemical, behavioural and endocrine alterations induced by immunological activation are delineated. In addition, the role of cytokines as mediators in the stress response and the induction of depressive-like symptoms are discussed.

**Immunological Activation Produces Stress-like Changes in Central Neurotransmission**

It is well established that both psychological and physiological stressors produce alterations in noradrenergic, serotonergic and dopaminergic function in rodents (for a review see ref. 91). Many studies in rodents have reported that administration of SRBC, LPS and cytokines produced alterations in monoamine neurotransmitter systems which are reminiscent of those engendered by stress (93,94,95). In addition, administration of an immunological challenge was reported to increase hypothalamic unit electrical activity in rodents (96). It is also of interest that an acute systemic injection of either IL-1β or IL-6 produces an enhancement of stressor-induced monoamine alterations (97,98), suggesting that cytokines may increase susceptibility to stressor-induced monoamine changes.

**SRBC**

Alterations in monoamine concentrations and turnover are evident in various brain structures following immunological challenge. Some authors have reported a decreased noradrenaline concentration in the whole hypothalamus at the peak of the immune response to SRBC in rats (99). Carlson and co-workers (100) reported that the there was a decrease in noradrenaline in the paraventricular nucleus (PVN) of the hypothalamus but not in any other hypothalamic nuclei at the peak of the immune response to SRBC while Zalcman and colleagues, (1991) (101) reported increased noradrenaline utilisation in the hypothalamus, locus coeruleus and hippocampus and increased dopamine turnover in mesocortical regions in response to SRBC administration. These alterations coincided with the time of peak immune response. More recently, using in vivo microdialysis, Lacosta and co-workers, (1994) reported increased in vivo dopamine release in the nucleus accumbens in
response to a challenge with SRBC (94). Furthermore this increase in dopamine release coincided with the time of maximal antibody production. It has been reported that there was increased in vivo 5-HT release in the frontal cortex 3 days after SRBC administration. Moreover, this effect was completely blocked by treatment with the immunosuppressive agent cyclosporin A (102), thereby demonstrating that the neurochemical changes were as a direct result of immune system activation.

**LPS**

Several studies have examined the neurochemical changes following the administration of bacterial LPS by both post mortem tissue analysis and in vivo microdialysis. In vivo, LPS undergoes phagocytosis by macrophages via an endotoxin receptor CD14 (103); these macrophages subsequently synthesise and secrete IL-1, IL-6, TNF-α and other cytokines (93). Therefore LPS induced alterations are mediated by cytokines. Increases in noradrenaline turnover, 5-HT turnover and tryptophan concentrations have been reported in numerous brain structures following peripheral endotoxin administration in mice, with dopamine turnover affected to a lesser extent (93). More recent studies utilising in vivo microdialysis in rats have reported increased release of noradrenaline and 5-HT in the hippocampus (104) and increased noradrenaline and dopamine release in the hypothalamus and prefrontal cortex in response to LPS administration (36). In addition, it was recently observed that peripheral LPS administration increased in vivo dopaminergic and serotonergic neurotransmission in the nucleus accumbens (105). It has also been reported that LPS-induced neurochemical changes were either completely blocked (36,106,37) or attenuated (107) by pretreatment with the cyclo-oxygenase inhibitor indomethacin, indicating that prostaglandins may mediate the neurochemical effects of LPS.

**Cytokines**

In addition to the effects of an immunological challenge on CNS neurotransmission, exogenous cytokine administration also produces changes in monoaminergic function. These changes include increases in noradrenaline and serotonin turnover, and in tryptophan in many brain regions (66,67,108,109). In addition, we recently reported increased hypothalamic dopaminergic activity in response to ICV administration of IL-1β, IL-2, IL-6 and TNF-α in the rat (110). Other studies have utilised in vivo microdialysis or push-pull perfusion to examine cytokine-induced changes in the interstitial concentrations of monoamines and their metabolites in different nuclei within the CNS after both systemic (97, 98) and central (95,104,111,112) administration. These studies have illustrated that both systemic and central cytokine administration can cause increases in interstitial concentrations of noradrenaline, dopamine and serotonin and their metabolites in different structures in the rat brain such as the hypothalamus (112,95), hippocampus (104,111,113) and nucleus accumbens (97,98). To date, IL-1β has been the most studied cytokine with respect to in vivo neurotransmitter release. However a recent study reported a profound increase in serotonergic neurotransmission in the hippocampus in response to ICV IL-2 administration. However, TNF-α administered by the ICV route failed to significantly alter hippocampal serotonergic function (113). Other studies have shown that systemic IL-6 administration produced an increase in noradrenergic and serotonergic neurotransmission in the nucleus accumbens, whereas IL-2 did not (98). In fact Anisman et al., (1996) demonstrated that systemic IL-2 administration inhibited in vivo dopamine efflux at the nucleus accumbens in rats (114).

**Both Immunological Activation and Stress Produce Many Depressive-like Behavioural Changes in Rodents**

Numerous animal models of depression involve the study of abnormal behaviours which are precipitated by stress. A consequence of stress seen in many models is a reduction in performance of
reward behaviour. A reduction in the activity of reward systems is central to a number of theories of depression (115) and a failure to respond to pleasurable events (anhedonia) is a major diagnostic feature of endogenous depression (116). In addition, it has been suggested that stress acts as a predisposing and precipitating factor in the onset of affective illness, especially depression (117,118,119).

In addition to the behavioural changes elicited by exposure to stress it has been reported that exogenous administration of SRBC, LPS or cytokines to rodents produces many behavioural symptoms which are qualitatively similar to those observed in depressed patients, such as anhedonia (80,120), appetite disturbance (6,121), anxiety (84,110,122) reduced social exploration (104,123,124,125) and cognitive dysfunction such as memory impairment (126,127).

Both stress and immunological activation provoke alterations in responding for brain stimulation reward

Many studies have examined the potential effects of stressors on motivational and reward processes by assessing responding for brain stimulation reward in various regions of the mesocorticolimbic dopaminergic system. In this paradigm animals (mice or rats) that are exposed to inescapable footshock stress, exhibit a marked and long lasting anhedonia as indicated by reductions in responding for electrical brain stimulation when electrodes are placed in the nucleus accumbens (nAcb), medial forebrain bundle (MFB), mesocortex or ventral tegmental area (VTA) (128,129,130). By contrast, performance was unaffected by escapable footshock stress. It has been suggested that this behaviour may provide an index of reductions in motivational or reward processes engendered by exposure to a stressor, and therefore may be taken to approximate one of the key symptoms of depression, namely that of anhedonia (128,131). Such stressor-induced reductions in responding for brain stimulation reward are reversed by chronic desipramine treatment (132,133).

More recently it has been reported that an antigenic challenge with SRBC's produced time dependent alterations in responding for rewarding brain stimulation from the nucleus accumbens which were qualitatively similar to those engendered by stressor exposure (134). Moreover, these disturbances in responding for brain stimulation reward coincided with the time of peak immune response and with maximal dopamine efflux in this brain region (94,135). As cytokines are thought to mediate many of the effects of an immune challenge on the CNS, the effect of systemic cytokine administration on responding for electrical brain stimulation was examined. Systemic IL-2 administration produced a prominent disruption in responding for rewarding brain stimulation from the medial forebrain bundle (MFB) in the rat (114,135), IL-1β produced a disruption which was less profound and more transient, whereas IL-6 was without effect on this response (135). These results indicate that IL-2, and to a lesser extent IL-1β, cause a disruption in reward mechanisms. However, the effect of antidepressant treatment on these alterations induced by an immune challenge with SRBC or cytokine administration have not yet been examined.

Both stress and immunological activation produce "anhedonic-like" symptoms in the sucrose/saccharin consumption paradigm in rodents

Exposure of rodents to either chronic mild stress (CMS) (136) or the more severe chronic unpredictable stress protocol described by Katz, (1981)(137) produces a reduction in sucrose consumption compared to non-stressed controls, and it has been reported that this deficit can persist for many weeks following cessation of the stress (136). Such stressor-induced reductions in sucrose consumption have been interpreted to represent anhedonia (136), which is one of the core symptoms of major depression (116). The reduction in sucrose consumption in the stressed rats can be reversed by chronic antidepressant treatment with imipramine (138), maprotiline and fluoxetine (139). In addition, dopamine agonists have been found to reverse CMS induced anhedonia suggesting a role for the dopaminergic system in the anhedonic symptoms (140,141).
More recently it has been reported that peripheral administration of bacterial lipopolysaccharide (LPS) to rats (80), and cDNA for IL-6 incorporated in an adenovirus vector to mice (120), produces similar reductions in the consumption of a sweet solution (sucrose or saccharin) to those observed in stressed animals. In addition, one of the major behavioural alterations in autoimmune MRL-1pr mice that hypersecrete IL-6 (120) is depressive-like behaviour, as indicated by excessive immobility in the forced swim test (84) and an anhedonic response in the sucrose consumption paradigm (142). Chronic, but not acute, treatment with imipramine reverses the reduction in saccharin consumption produced by LPS administration in rats (80). However the effect of antidepressant treatment on cytokine induced alterations remains to be examined. To date, imipramine is the only antidepressant which has been examined with regard to LPS-induced behavioural changes and it will be of interest to access the specificity of other clinically effective antidepressants on such behavioural effects. In addition, the effect of other cytokines such as IL-1, IL-2, TNF-α and IFN-γ need to be evaluated in the sucrose consumption paradigm.

Both stress and immunological activation produces appetite disturbance in rodents

It has been reported that stress decreases food intake and bodyweight gain in rats, and that these effects are dependent on stressor intensity (143). It has also been reported that administration of both LPS and various cytokines reduces food intake in laboratory animals by a centrally mediated mechanism (6,121). To date, both ICV and peripheral administration of LPS has been reported to dose dependently reduce food consumption in rats (144). Both ICV and peripheral administration of IL-1β also causes a suppression of food intake (145,146). In addition, when IL-1β is infused directly into the ventromedial hypothalamus a suppression of food intake is also observed (147). It has also been reported that when IL-1β is electrophoretically applied in the lateral hypothalamic area it specifically suppresses the neuronal activity of glucose sensitive neurons in this region (148). A similar effect has been observed when TNF-α was applied in the same manner (148). ICV administration of IL-6, TNF-α, IL-8 and IFN also produce a suppression of food intake in rodents (121,149). The peripheral administration of IL-6 and TNF-α also suppresses food intake but much larger doses are required for an effect to become apparent (121). To date, only one study has evaluated the effect of antidepressant treatment on the anorexic effects of immunological activation in rats; chronic imipramine treatment produced a modest but significant attenuation of LPS-induced suppression of food intake and reduction in bodyweight gain (79).

Immunological activation produces anxiogenic-like behaviour in rodents

Recently both peripheral administration of LPS and IL-1β produced anxiogenic-like behaviour in the light/dark box and elevated plus maze tests of anxiety in mice (122). In addition, ICV administration of both IL-1β and TNF-α to rats produced anxiogenic-like behaviour in the elevated plus maze test, with IL-6 producing a slight but non-significant anxiogenic response (110). However the non-inflammatory cytokine IL-2 did not alter elevated plus maze behaviour (110). It is of interest that a strain of mice that develop auto-immune systemic lupus erythematosus and also hypersecrete the proinflammatory cytokine IL-6 (120) display anxiogenic-like behaviour in the elevated plus maze (84,85). In addition, normal mice that were injected with IFN displayed anxiety on the plus maze (85). As of yet, it is not clear whether the altered plus maze behaviour observed after cytokine administration or in animals which constitutively hypersecrete various cytokines represents a true anxiogenic effect, since the effects of anxiolytic agents, such as benzodiazepines, on reversal of these anxiogenic-like effects have not yet been assessed. Afterall, it is possible that the animals may simply feel strange, and the observed effects may be secondary to such a factor.

In addition to the effects of LPS and cytokines in these tests of anxiety, these immunomodulators also reduce social exploration in a novel environment and induce freezing behaviour which resembles that seen in stressed rats (104,123,124,125). While most behavioural data is on the effects of IL-1β, recently it has been reported that both IL-1β and IL-2 administered ICV produced reduced locomotor
activity in rats whereas ICV administration of TNF-α did not (113). In addition, it has been reported that autoimmune MRL-1pr mice which constitutively overexpress IL-6 (120) display hypoactivity in a novel open-field environment (84).

**Both stress and immunological activation produce alterations in memory and long term potentiation (LTP)**

It has been reported that chronic stress in rats produced a reversible impairment in spatial memory performance in the eight arm radial maze test (150). Other researchers found that exposure to stress impaired working (hippocampal dependent) memory, but not reference (hippocampal independent) memory in rats (151). However, in other studies it was reported that stressor exposure enhanced memory in rodents (152,153). It is also of interest that stress has been shown to impair LTP, a process involved in memory consolidation (154). Recently exogenous IL-1β administration in mice blocked the acquisition of spatial learning in the Morris water maze test (127). In another study peripheral administration of both LPS and IL-1β severely disrupted the acquisition of a task involving cognitive processing in the rat (126). Both LPS and the cytokines IL-1, IL-2, IL-6, IFN and TNF have also been implicated as inhibitors of LTP (155,156,157,158,159). Therefore, in addition to the alterations in memory and LTP induced by exposure to stress, immunological activation also produces impairments in memory.

**Effects of Immunological Activation on the HPA-Axis Activity in Rodents**

It is well established that activation of the hypothalamic pituitary adrenal axis (HPA-axis) and consequential corticosterone secretion occurs as a result of exposure to both physical and psychological stressors (160,161,162). In addition, hypersecretion of cortisol is evident in clinically depressed patients (64). It is of interest that HPA-axis activation also occurs as a consequence of immunological activation with systemic administration of LPS (93,103) and SRBC (163). In addition, both systemic (65,67,87,93,164) and central (110,164,165) cytokine administration can activate the HPA-axis. It is well established that IL-1 stimulates the secretion of CRF from the cells of the paraventricular nucleus in the hypothalamus (166,167) thereby stimulating the HPA-axis and the secretion of ACTH and ultimately glucocorticoids. Other cytokines such as IL-2 (168,169), IL-6 (67,170) and TNF-α (164) have also been reported to stimulate HPA-axis activity but with less potency that IL-1.

It is also of interest that in a recent study, systemic IL-6 administration synergistically increased circulating concentrations of both ACTH and corticosterone in response to a mild stressor in rats (171), suggesting that elevated circulating levels of this pro-inflammatory cytokine can increase HPA-axis reactivity to a mild emotional stressor.

**Does CRF mediate the effects of cytokines on the brain?**

In addition to the effects of hypothalamic CRF on HPA-axis activity, it has been reported that CRF may play an important role in the co-ordination of the stress response (172). For instance, central administration of CRF to rodents produces both neurochemical and behavioural alterations which resemble those observed in response to stress and these effects are independent of HPA-axis activation (173). Exogenous CRF administration to rodents produces hypoactivity and freezing behaviour in a novel environment (174), anxiogenic responses in the elevated plus maze test (175), a suppression of food intake (176) and reduced sexual behaviour (177).

The role of CRF in the stress response was strengthened by the fact that many stress-induced behavioural effects can be antagonised by pretreatment with the CRF antagonist α-helical CRF (176,178,179,180,181). Central CRF administration activates the sympathetic nervous system and consequently elevates plasma catecholamine concentrations, blood pressure and heart rate (182,183).
Furthermore stress-induced increases in plasma adrenaline and ACTH concentrations have also been reversed by pretreatment with \( \alpha \)-helical CRF (184,185).

Neurochemical changes observed in response to central CRF administration include increased release (186) and turnover (172) of noradrenaline and dopamine in various brain regions. CRF also produced a profound increase in extracellular 5-HIAA concentrations in the medial prefrontal cortex and medial hypothalamus in vivo (186), which may indicate increased 5-HT release in these brain regions. In addition to the effects of central CRF administration on neurotransmitter release it has been reported that intraperitoneal CRF administration increases both cortical and hypothalamic noradrenaline and dopamine release and interstitial levels of 5-HIAA (186). These alterations in monoamine neurotransmitter turnover and release observed after CRF administration are similar to those observed after exposure to stress. However, to our knowledge the effect of \( \alpha \)-helical CRF on stress-induced activation of monaminergic systems has not been evaluated. The fact that cytokines produce stress-like behavioural and neurochemical changes in rodents and also stimulate CRF secretion posed the question; Does cytokine-induced CRF release mediate cytokine-induced behavioural and neurochemical changes? To date it has been reported that central administration of \( \alpha \)-helical CRF or CRF neutralising antibodies markedly attenuated IL-1\( \beta \) induced suppression of food intake (187) and exploratory behaviour (188) suggesting that these effects are mediated by IL-1\( \beta \)-induced CRF release. However, Bluthe and coworkers, (1989) found that pretreatment with \( \alpha \)-helical CRF did not block the decrease in food motivated behaviour induced by IL-1 administration (189), suggesting that this IL-1-induced response was not mediated by central CRF release. Similarly, in a recent study it was observed that ICV administration of the pro-inflammatory cytokine TNF-\( \alpha \) provoked anxiogenic-like behaviour in the elevated plus maze test of anxiety in rats, without increasing HPA-axis activity. Thereby suggesting that the observed anxiogenic actions of TNF-\( \alpha \) may be mediated by a mechanism(s) independent of hypothalamic CRF release (110).

**Both Stress and Central Cytokine Administration Suppress Cellular Immune Function**

Many reports indicate that exposure of laboratory animals to stress suppresses cellular immunity. Studies have reported a reduction in NK-cell activity, neutrophil phagocytosis and mitogen stimulated lymphocyte proliferation in response to stress (162,190,191,192). In addition stressor-induced changes in leucocyte subsets have been reported in rats, such as increased neutrophils and reduced lymphocytes in the peripheral blood (190,193).

Recently it has been reported that ICV IL-1\( \beta \) administration to rats produces stress-like alterations in aspects of cellular and humoral immunity. ICV administration of IL-1\( \beta \) produced a suppression of blood and splenic NK-cell activity, PHA-induced lymphocyte proliferation and IL-2 production (165). Both HPA-axis activation and activation of the sympathetic system contributed to these immunosuppressive effects (194). In addition, ICV IL-1\( \beta \) administration has been shown to reduce splenic macrophage IL-1\( \beta \) production (195). In a recent study we demonstrated that central IL-1\( \beta \) administration produced a reduction in splenic Con A-induced lymphocyte proliferation whereas IL-2, IL-6 and TNF-\( \alpha \) did not (110). It is of interest that a similar suppression of cell mediated immunity to those induced by both stress and central IL-1\( \beta \) is observed in clinically depressed patients.

Beside the effects on cell mediated immunity, it has been reported that ICV IL-1\( \beta \) administration reduced the IgG response to kehole limpet haemocyanin, suggesting that centrally administered IL-1\( \beta \) also suppresses humoral immunity (196). Increased CRF release has been implicated in the mediation of the immunosuppression induced by both stress and central cytokine administration (194,197,198).
Could Stress-induced Cytokine Secretion be Responsible for the Induction of Depressive Symptoms?

Classically stress is defined as a threatening of homeostasis to which the organism, in order to survive, responds with a large number of adaptive responses. It has been suggested that stress acts as a predisposing and precipitating factor in the onset of affective illness, especially depression (117,118,119) and that an individual's ability or lack of ability to cope with stress may be a predisposing factor to psychiatric illness. There is general agreement that the likelihood of suffering from a depressive episode is increased five or six fold in the six months following stressful life events such as bereavement, divorce, moving house etc. There is also evidence to suggest that exposure to chronic low grade stress may be a predisposing factor in depression (199).

It is notable that cytokines are secreted in response to stress in rodents (200,201,202,203). Both physical and psychological stress has been reported to increase plasma IL-6 concentrations (200,201,203). With regard to the mechanism of stressor-induced IL-6 secretion, it of interest that adrenaline administration to rats induces a rapid increase in plasma IL-6 concentrations, an effect that is blocked by pretreatment with the β-adrenoceptor antagonist I-propranolol (204). This suggests that stressor-induced increases in plasma IL-6 concentrations may be mediated by increased sympathetic activity and concomitant release of adrenaline from the adrenal medulla. It is also of interest that exposure to acute stress has been reported to induce increases in positive APP concentrations in rats (205). It seems possible that such a stressor-induced elevation in positive APPs is an IL-6 mediated response (30,206). In contrast to these findings, a recent study reported that 2 hr after exposure to 15 min of restraint stress, plasma IL-1β concentrations were not significantly different between stressed and unstressed mice (207). However, this is not entirely surprising as Takaki and coworkers (1994) demonstrated that 2 hr following a 30 min restraint stress, stressor-induced increases in plasma IL-6 concentrations had returned to basal values (201). Therefore, to date most of the data concerning the stimulatory effects of stress on cytokine release bears on IL-6, and data concerning other proinflammatory cytokines such as IL-1β and TNF-α is limited, inasmuch as stressor-induced effects on plasma levels of these cytokines has not been thoroughly examined in a time-course fashion.

In addition to stressor-induced effects on plasma cytokine concentrations, other studies have focused on the effect of stress on brain cytokine, and cytokine mRNA levels (202,207,208). In this regard, it was reported that exposure to acute restraint stress induced IL-1β mRNA expression in the rat hypothalamus (208). More recently Shintani et al., (1995) demonstrated that exposure to acute restraint stress increased IL-1β concentrations in the hypothalamus as assessed by a thymocyte proliferation assay (202). While pretreatment with IL-1ra blocked stress-induced HPA-axis activation and in vivo monoamine alterations in the hypothalamus (202), suggesting that stressor-induced IL-1β secretion was responsible for the observed HPA-axis activation and neurotransmitter release. However, Goujon and coworkers, (1995) reported that in mice exposed to 15 min of restraint stress, mRNA expression of IL-1α, IL-1β, IL-6 and TNF-α was either reduced, or was not significantly altered in a number of brain regions including the hypothalamus (207). In light of these conflicting findings, further studies are required to extensively characterise the effects of stress on cytokine activity within the brain.

Interestingly, it has been recently reported that exposure of mice to acute swim stress causes an increase in the permeability of the blood brain barrier (BBB) which may thereby provide an opportunity for peripheral immune cells and cytokines to enter the central nervous system and alter brain function (209). In addition, it is possible that stress-induced changes in the structure of the BBB may play a role in the susceptibility to both psychiatric and neurological disorders such as depression and multiple sclerosis.
In light of the evidence outlined from both clinical and experimental studies, it is not unreasonable to suggest that increased cytokine secretion due to environmental or internal stressors, or due to an underlying disease state, may play a role in the induction and maintenance of depressive symptoms in susceptible individuals.

Effects of Antidepressants on Cytokine Release

If excessive cytokine release in vivo either as a result of stress or an underlying disease state, plays a causal role in the development of depressive symptoms, one might expect that antidepressant treatment would impair the release of cytokines from peripheral immune cells or cells with in the brain. In this regard a recent study reported that incubation of monocytes with the antidepressants clomipramine, imipramine or citalopram in vitro produced a marked inhibition of LPS induced IL-1β, TNF-α and to a lesser extent IL-6 secretion (210); IL-2 and IFN-γ release from T-cells was also inhibited by preincubation with these antidepressants (210). However, to date the effects of acute or chronic antidepressant treatments on LPS or stress-induced cytokine secretion has not been examined in vivo. Nonetheless a recent study in rabbits reported that chronic treatment with the tricyclic antidepressant amitriptyline, blocked the LPS-induced febrile response in a dose-dependent manner (211). Whether chronic amitriptyline treatment inhibited LPS-induced cytokine release, or inhibited the effect of the released cytokines on central neurotransmission is not clear, and requires further investigation. In this regard, studies which examine the effect of antidepressant treatment on behavioural and neurochemical changes elicited by exogenous cytokine administration are necessary, so as to determine whether antidepressant treatment alters the CNS response to cytokines released either in response to stress or due to an underlying disease state.

It is also noteworthy to mention that a recent study reported that chronic, but not acute, treatment with a variety of psychotropic drugs including the antidepressants imipramine, fluvoxamine and maprotiline produced a profound increase in IL-1ra mRNA expression in rat brain (212). These increases in IL-1ra mRNA expression were evident in a number of brain regions such as the hypothalamus, hippocampus, frontal cortex and brain stem. In addition, increased IL-1ra mRNA was accompanied by increased IL-1β mRNA expression, however the increases in IL-1ra were of a much greater magnitude than that of IL-1β mRNA (212). Therefore, in the light of these findings, it is not unreasonable to suggest that antidepressants may alleviate depressive symptoms by inhibiting cytokine secretion from immune cells in vivo or by increasing brain concentrations of IL-1ra the endogenous antagonist of IL-1 receptors and thereby blocking the action of IL-1 and possibly other cytokines on the CNS. Moreover, these increases in IL-1ra mRNA expression are seen after chronic antidepressant treatment (28 days), whereas after subacute administration (4 days) the increases were much less profound (212). This time profile of IL-1ra expression in response to antidepressant treatment closely parallels the time required for the onset of therapeutic efficacy of all the antidepressants used to date. In addition, another study reported that the antidepressant rolipram suppressed the production of several cytokines by autoreactive T-lymphocytes and also prevented the development of autoimmune encephalomyelitis (213), suggesting that one of the actions of antidepressants in vivo may be to inhibit cytokine secretion by either direct action on immune cells or alternatively by a centrally mediated mechanism. As previously outlined, stressor-induced increases in plasma IL-6 concentrations appear to be mediated by increased sympathetic activity and concomitant release of adrenaline from the adrenal medulla. Therefore, another possible mechanism by which antidepressants could modulate stressor-induced cytokine secretion is by reducing stressor-induced sympathetic activation.

Cytokine Antagonists in Animal Models of Depression

In light of the report that pretreatment with IL-1ra blocked acute stress-induced HPA-axis activation and in vivo monoamine changes in the hypothalamus (202), the effect of IL-1ra and other cytokine
antagonists (anticytokine antibodies) on stressor-induced behavioural dysfunction needs further evaluation in animal models of depression (for example, chronic mild stress-induced anhedonia, stressor-induced alterations in brain stimulation reward and the forced swim test). Such an investigation may give an insight into the role that stressor-induced cytokine secretion plays in the induction of behavioural alterations in these models. In this regard, the role of stressor-induced cytokine secretion in the development of depressive-like behavioural symptoms has been examined in the learned helplessness model, Maier and Watkins (1995) reported that treatment with the interleukin-1 receptor antagonist (IL-1ra) prevented the development of learned helplessness in rats (214). These data suggests that stressor-induced IL-1 release may be one of the primary events in the induction of the associated behavioural deficits seen in the learned helplessness model of depression. It should also be noted that administration of a non-peptide CRF receptor antagonist CP-154,526 also prevented the development of learned helplessness in rats (215). This is of great interest as some IL-1-induced behavioural alterations are mediated via central CRF release (187,188). Based on the evidence that stressor-induced cytokine secretion may precipitate some of the behavioural alterations provoked by stress, the effect of antidepressant treatment on stressor-induced cytokine release in vivo should be evaluated to see if antidepressant treatment reduces stressor-induced cytokine secretion.

Changes in both cellular and non-cellular immunity have been reported in the olfactory bulbectomized (OB) rat model of depression. In this model there is a hyperactivity of monocyte phagocytosis (216,217) and increased serum acute phase protein concentrations (218,219). Moreover, the alterations in acute phase proteins are normalised following chronic antidepressant treatment (219). Such increases in monocyte phagocytosis and positive acute phase protein concentrations suggest that there is a hyperactivity of monocyte function and possibly cytokine secretion in this model. Therefore the administration of IL-1ra and other cytokine antagonists to the OB rat may help to delineate the role played by cytokine hypersecretion in the neurochemical and behavioural changes observed.

**Acute Versus Chronic Immunological Activation**

To date, the majority of experimental studies performed which report stress-like effects of cytokines on neurotransmitters, behaviour and the HPA-axis, have been restricted to the acute administration of these immunological mediators. In future research there is a necessity to examine the effects of chronic immunological activation using repeated cytokine administration, on behaviour, neurochemistry and HPA-axis activity in rodents. It has already been demonstrated that acute pretreatment with cytokines (IL-1β and IL-6) produces an enhancement of stressor-induced monoamine changes in rats (97,98), suggesting that cytokines produce an increased susceptibility to stressor-induced monoamine, and possibly behavioural alterations, however the effect of repeated cytokine administration on stressor-induced effects remains to be examined. Therefore, the behavioural and neurochemical effects of chronic immunological activation is an important research area which has been so far overlooked in preclinical studies, as after all, the effects seen in patients with depressive disorders are of a chronic nature. With regard to any future studies which may examine the effects of repeated cytokine administration in rodents, researchers must ensure that the cytokines administered are not immunogenic (ie) That they are not recognised as a foreign antigen by the subjects used in the study. Consequently, in studies carried out in rats, rat cytokines should be used and in studies carried out in mice, mice cytokines should be used etc. For this same reason, it would not be possible to use repeated LPS administration as a model for chronic immunological activation, as LPS itself is immunogenic and would be immunoneutralised by anti-LPS antibodies after repeated administration. Finally, it would be of interest to evaluate the effect of antidepressant treatment on the depressive-like behavioural alterations reported in cytokine hypersecreting mice, which develop systemic lupus erythematosus (84,85,120).
Conclusion

Both clinical and experimental studies indicate that stress and depression are associated with increased plasma cytokine and acute phase protein concentrations and HPA-axis activation. In addition, it has been reported that immunological activation induces "stress-like" behavioural and neurochemical changes in laboratory animals. It is suggested that hypersecretion of cytokines due to stress or due to an endogenous trigger factor may induce depressive symptoms. In addition, central CRF release has been implicated as a mediator of at least some cytokine-induced behavioural and neurochemical changes. Future research should examine the effect of antidepressant treatment on cytokine hypersecretion in depressed patients and in animal models of depression. Due to the chronic nature of depressive disorders there is a need to place a greater emphasis on the effects of chronic immunological activation on behaviour and neurotransmitter function in rodents.

There is already a substantial body of evidence to suggest that changes in the immune system play a major role in the aetiology of depression and that cytokines are crucially involved in the neurochemical, behavioural and endocrine changes that characterise the condition. Future studies should help to clarify the causal link between the central actions of cytokines and depression.

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