Cytokines as mediators of depression: What can we learn from animal studies?

Adrian J. Dunn, Artur H. Swiergiel, Renaud de Beaurepaire

Abstract

It has recently been postulated that cytokines may cause depressive illness in man. This hypothesis is based on the following observations: 1. Treatment of patients with cytokines can produce symptoms of depression; 2. Activation of the immune system is observed in many depressed patients; 3. Depression occurs more frequently in those with medical disorders associated with immune dysfunction; 4. Activation of the immune system, and administration of endotoxin (LPS) or interleukin-1 (IL-1) to animals induces sickness behavior, which resembles depression, and chronic treatment with antidepressants has been shown to inhibit sickness behavior induced by LPS; 5. Several cytokines can activate the hypothalamo–pituitary–adrenocortical axis (HPAA), which is commonly activated in depressed patients; 6. Some cytokines activate cerebral noradrenergic systems, also commonly observed in depressed patients; 7. Some cytokines activate brain serotonergic systems, which have been implicated in major depressive illness and its treatment. The evidence for each of these tenets is reviewed and evaluated along with the effects of cytokines in classical animal tests of depression. Although certain sickness behaviors resemble the symptoms of depression, they are not identical and each has distinct features. Thus the value of sickness behavior as an animal model of major depressive disorder is limited, so that care should be taken in extrapolating results from the model to the human disorder. Nevertheless, the model may provide insight into the etiology and the mechanisms underlying some symptoms of major depressive disorder. It is concluded that immune activation and cytokines may be involved in depressive symptoms in some patients. However, cytokines do not appear to be essential mediators of depressive illness.

Keywords: Cytokines; Depression; Interleukin-1; Interferon; Norepinephrine; Serotonin; HPA Axis; Sickness behavior; Animal models

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1. Introduction

In recent years, it has been postulated that depression may be caused by cytokine secretion associated with activation of the immune system. This hypothesis was proposed initially because the incidence of immune abnormalities is higher in depressed patients than in the general population, and because depression is a common side effect of cytokine therapy. The hypothesis gained momentum when it was shown that immune activation and administration to animals of endotoxin (lipopolysaccharide, LPS) or the cytokine, interleukin-1 (IL-1), could induce a behavioral pattern resembling that commonly observed in sick animals, including man. This behavioral pattern has become known as sickness behavior. There are many similarities between sickness behavior and the symptoms of depression. Thus it was suggested that cytokines could induce depression, or indeed were the cause of depression. The hypothesis has come to be called the cytokine hypothesis of depression, although proponents differ on whether cytokines are a cause of major depressive disorder, or the cause.

1.1. Origins of the cytokine hypothesis

The cytokine hypothesis of depression posits that depression is caused by the actions of cytokines. Cytokines are proteins and glycoproteins secreted by immune cells that function as signals among and between immune cells. They are the hormones of the immune system. It is now known that cytokines have effects on cells outside the immune system, and that non-immune cells can synthesize and secrete cytokines. Thus cytokines can be regarded as classical hormones that can function locally or systemically to orchestrate immune responses, and can also coordinate immune responses with those of other physiological systems in the body, including the nervous system.

The cytokine hypothesis of depression derives from both clinical and experimental observations. The clinical observations were made on patients treated with interferons (IFN’s) and interleukin-2 (IL-2). Such patients often displayed influenza-like symptoms and nonspecific neuropsychiatric symptoms, some of which are characteristics of depression. However, the initial interest was not focused on depression, although depression is a relatively common side-effect. Immune abnormalities in depressed patients have been widely reported for more than 30 years. The earliest studies suggested deficient immune function in depressed patients, but the results were inconsistent and highly variable (see Weisse, 1992). Subsequent studies indicated that depressed patients often exhibited immune activation, and that depression was more frequent in patients with diseases having an immunological component (Kronfol, 2002). However, the results were quite varied; immune function in depressed patients was decreased in some aspects, but activated in others.

The interest in an immune system involvement in depression intensified around 15 years ago with the juxtaposition of the above observations on immune abnormalities in depressed patients with the effects of immune challenges in animals. In the animal studies, it was shown that administration of LPS or IL-1 induced a behavioral syndrome that became known as ‘sickness behavior’ (Kent et al., 1992). Smith first suggested that depression was associated with increased secretion of cytokines (especially IL-1) by macrophages (Smith, 1991). He noted that administration of IL-1 mimicked not only some of the behavioral characteristics of depression, but also activated the hypothalamo-pituitary-adrenocortical axis (HPAA). This macrophage theory of depression attracted immediate attention, because it was compatible with a number of earlier findings in depressed patients.

2. Experimental evidence for the cytokine hypothesis of depression

The experimental evidence for the cytokine hypothesis of depression is summarized in Table 1. Each of these points will be reviewed in turn, focusing on the evidence from animal models.

2.1. Responses to cytokine treatment in man

Cytokines have been shown to be effective in the treatment of medical conditions, such as hepatitis C, multiple sclerosis, some infections, leukemia, Kaposi’s sarcoma, melanoma, myeloma, renal carcinoma and other forms of cancer. The cytokines most commonly used are IFNα, IFNβ, IFNγ and IL-2. Each of these cytokines has been reported to produce side effects such as asthenia, myalgia, confusion and influenza-like symptoms. Depression is most commonly associated with treatment with IFNα and IL-2, and occasionally with IFNβ but not with IFNγ (Valentine et al., 1998; Gohier et al., 2003).
Table 1
Experimental evidence cited for a cytokine hypothesis of depression

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Principal cytokines implicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of patients with cytokines induces symptoms of major depressive disorder</td>
<td>IL-2, IFNα</td>
</tr>
<tr>
<td>Activation of the immune system is observed in many depressed patients. This may be reflected in elevated circulating concentrations of cytokines</td>
<td>IL-6</td>
</tr>
<tr>
<td>Depressive disorders occur more often in medical disorders involving immune dysfunction than those that do not</td>
<td>IL-1</td>
</tr>
<tr>
<td>Activation of the immune system, and administration of LPS or cytokines to animals induces sickness behavior, which resembles major depressive disorder. Chronic treatment with antidepressants inhibits LPS-induced sickness behavior</td>
<td>IL-1, IL-6, TNFα, IFNα</td>
</tr>
<tr>
<td>Cytokines can activate the HPA axis. Elevated plasma cortisol is commonly observed in depressed patients</td>
<td>IL-1</td>
</tr>
<tr>
<td>Cytokines activate brain noradrenergic systems. Elevated NE and its catabolites are commonly observed in the CSF of depressed patients</td>
<td>IL-1, TNFα</td>
</tr>
<tr>
<td>Cytokines activate brain serotonergic systems. A abnormalities of brain serotonin have been implicated in major depressive disorder and its treatment</td>
<td>IL-1, IL-6, TNFα</td>
</tr>
</tbody>
</table>

The evidence has been reviewed recently by de Beaurepaire et al. (2005) and will only be summarized here. The incidence of depression associated with cytokine therapy is highly variable, ranging from 0 to 45% in different studies. The reasons for this are multifaceted. They are in part related to the disease under treatment and the cytokines and doses used, but are also related to the assessment measures, the patient’s psychiatric history, and the choice of comparison (control) subjects (de Beaurepaire et al., 2005).

In most cases, the depressive symptoms can be treated effectively with antidepressants. Interestingly, however, antidepressants are sometimes more effective on the mood symptoms, and not on the neurovegetative symptoms, like anorexia, psychomotor retardation and sleep disorders (Miyaoka et al., 1999; Musselman et al., 2001a; Capuron et al., 2002), whereas it is the latter that are the focus of most of the animal studies.

2.2. Immune activation in depressed patients

Immune function in depressed patients has been the subject of study for around half a century. Interestingly, the early studies indicated a tendency to decreased immune function in depressed patients (Weisse, 1992), whereas the more recent studies have emphasized immune activation (see review de Beaurepaire et al., 2005). According to the reviews of Maes (1995) and Kronfol (2002) major depression appears to be associated with increased plasma concentrations of positive acute-phase proteins (haptoglobin, ceruloplasmin, C-reactive protein, hemopexine, α1-antitrypsin, and α1-acid glycoprotein), and with lower plasma concentrations of negative acute-phase proteins (transferrin, albumin, and retinol-binding protein). Increases of acute-phase proteins associated with decreases in negative acute-phase proteins are considered to be indicative of an inflammatory state. Thus, it has been postulated that chronic depression is associated with chronic inflammation (Maes, 1995). Consistent with this are the reports that depressed patients display elevated concentrations of inflammatory markers, such as prostaglandins (Lieb et al., 1983) and complement (Kronfol and House, 1989). Maes suggested that the chronic inflammatory state he believes underlies depression can be explained by increased production of cytokines by circulating monocytes and macrophages (Maes, 1995). In his review, Kronfol cites reports of increased circulating leukocytes (Kronfol and House, 1989) (see below), activated T-cells (Maes et al., 1992), and elevated plasma concentrations of cytokines (Kronfol, 2002). Other studies have focused on the ability of immune cells obtained from patients to produce cytokines in vitro (Maes, 1999; Anisman et al., 1999). Such assays have been argued to provide functional measures of immune activity, but the biological significance of such ex vivo measures is not at all clear. Also, neopterin, considered to be a marker of activation of cell-mediated immunity, was increased in the plasma and urine of depressed patients (Duch et al., 1984; Dunbar et al., 1992). However, other authors have failed to find evidence for immune activation in depressed patients (Landmann et al., 1997; Natelson et al., 1999).

Several studies have focused on the possible elevation of cytokines in depressed patients. IL-1β, interleukin-6 (IL-6) and the IFN's have been reported to be increased in the plasma of depressed patients (Maes et al., 1993a,b, 1994). Increases of plasma IL-1β reported in some studies (Griffiths et al., 1997; Owen et al., 2001) were not replicated in others (Brambilla and Maggioni, 1998). Some have reported higher IL-6 concentrations in cancer patients with depression (Musselman et al., 2001b), but others found only normal concentrations of circulating cytokines in psychiatric patients, including those diagnosed with depression (Haack et al., 1999). One recent study indicated increases in IL-1β and decreases in IL-6 in the cerebrospinal fluid (CSF) of depressed patients (Levine et al., 1999). In this study, the increase in IL-1β correlated with the severity of the depression.

A recent meta-analysis of the clinical data on immune abnormalities in depressed patients by Zorrilla et al. (2001) found that patients with major depression exhibited: an overall leukocytosis, manifested as a relative neutrophilia...
and lymphopenia; increased CD4/CD8 ratios; increased circulating haptoglobin, prostaglandin E$_2$ (PGE$_2$) and IL-6 concentrations; reduced natural killer (NK)-cell cytotoxicity; and reduced lymphocyte proliferative responses to mitogens. Interestingly, plasma concentrations of IL-1, the only cytokine that clearly induces depression-like symptoms in animals, were not consistently altered. The authors commented that ‘the degree of heterogeneity of the studies’ results raises questions about their robustness’. They also noted that among these biological markers, only three were associated with chronic stress: increased CD4/CD8 ratios, reduced mitogen-induced proliferative responses, and reduced NK cell cytotoxicity (Zorrilla et al., 2001).

Pollmacher et al. noted that certain cytokines (most notably IL-1β) are undetectable in human plasma under normal physiological conditions as well as during experimental endotoxemia (Pollmacher et al., 2002). They also pointed out that the physiological fluctuations of the detectable cytokines (IL-6 and tumor necrosis factor α, TNF α) are very poorly characterized in normal and pathological states, and the alterations of circulating cytokines observed in the depressed (as well as in immune-related medical conditions) are extremely modest compared with the concentrations of circulating cytokines that occur during cytokine treatments. These observations pose important issues for proponents of a simple cytokine hypothesis of depression. It is also clear that the immune activations observed in depressed patients are not of the magnitude observed when sickness behavior is induced by IL-1, LPS or infections with pathogen (see below). Another important caveat is that depression may occur in response to an undetected medical condition that itself results in immune activation.

Overall the evidence for an activation of immune responses in patients with major depressive disorder is not very consistent (de Beaurepaire et al., 2005; Zorrilla et al., 2001), although there are trends to leukocytosis, increased CD4/CD8 ratios, elevated plasma concentrations of haptoglobin, IL-6 and PGE$_2$ and decreased NK cell activity and lymphocyte proliferative responses. It is clear that immune activation does not occur in all depressed patients.

2.3. Depression in immune-related medical conditions

As indicated above, there is some evidence for a higher incidence of immune activation in depressed patients. If immune activation were a direct cause of depression, it should be possible to obtain evidence for this by assessing symptoms of depression and immune states in different medical conditions. Depression should be more prevalent in patients that suffer from medical conditions associated with immune activation, and it should be possible to correlate the symptoms of depression with evidence of immune activation (such as circulating cytokines) in those conditions.

Depression has been reported to be more common in non-infectious diseases associated with a chronic activation of the immune system, such as multiple sclerosis (Minden and Schiffer, 1990), allergy (Marshall, 1993), rheumatoid arthritis (Dickens et al., 2002), and stroke (Schwartz et al., 1993). In these diseases, the immune abnormalities precede the development of depression (Foley et al., 1992). Nevertheless, data on the correlations between depression and immune activation or plasma concentrations of cytokines in patients with autoimmune diseases or chronic infections or inflammation are few and conflicting (see Pollmacher et al., 2002).

A complicating factor is that depression may also have a higher prevalence in diseases characterized by a loss of immune function, although the loss of some immune mechanisms in these diseases is often accompanied by increases in others, for example in asthma or in stroke. If depression were accompanied by the loss of immune mechanisms of defense, diseases that develop because of a loss of these mechanisms should have a higher incidence in depressed patients. Thus, for example, a higher prevalence of infections and cancers should occur in depressed patients. Some epidemiological evidence indicates that this may be true, but there are major methodological problems, and the biological mechanisms are very uncertain (see Kronfol, 2002).

2.4. Sickness behavior and depression

The concept of sickness behavior was defined by Ben Hart in a classic review (Hart, 1988). Sick animals, including humans, exhibit decreases in a number of activities, most notably feeding, exploration and sexual activity. They also exhibit increased body temperature (i.e. fever) and increased sleep. Contrary to the prevailing opinion that the behavior of sick animals was a nonspecific malaise, Hart argued that it was ‘not a maladaptive and undesirable effect of illness but rather a highly organized strategy that is at times critical to the survival of the individual if it were living in the wild state’. The behavioral responses were important in facilitating recovery from the illness, and defending the animal against pathogens and predators. The fever was thought to increase the efficacy of the host’s immune system, and in some cases to decrease the proliferation of pathogens. The behavioral responses were considered to drive the animal to hide, and remain safe, while the immune system cleared invading pathogens and aided the repair of damaged tissue. This revolutionary hypothesis immediately gained widespread support. Hart also recognized that endotoxin and IL-1 induced behavioral patterns that resembled very closely those present in sick animals. Most authors have supported and applauded his insight.

The term ‘sickness behavior’ was coined in a subsequent review (Kent et al., 1992), in which it was argued that the relationships between sickness behavior and LPS and IL-1 suggested that the symptoms of sickness might be treated with antagonists of the immune activation, such as cytokine antagonists. The link to depression was made in Smith’s ‘macrophage theory of depression’ (Smith, 1991) in
A diagnosis of depressive disorder requires symptoms 1 or 2, plus four of 3–9 for a period of two weeks or more. References are included only when they are not cited in the text.
of DA in hedonia, the effect of IL-2 would be consistent with the reduction in apparent DA release, although the latter has only been reported after acute injection of IL-2 (Anisman et al., 1996). Similar effects of IL-2 were observed in mice stimulated in the ventral tegmental area. In this case icv application of IL-2 (5 ng) elevated the frequency required to elicit self-stimulation from the dorsal, but not the ventral A10 region (Hebb et al., 1998). Taken together these results suggest that IL-2, but not IL-1 and IL-6, can have long-lasting anhedonic effects in rats and mice.

There has been less research on cognitive behavior. Certainly, sick animals may show cognitive deficits, for example, in learning and memory tasks (see examples in Dantzer et al., 2001; Larson and Dunn, 2001), but several of the above characteristics of sickness behavior, could explain the apparent cognitive deficits. Major cognitive deficits are not often observed in depressed patients, and when they are, they are generally mild, normally restricted to some cognitive bias (McKenna et al., 2000). Clinical research has shown that cytokine administration (IFNα and IL-2) in cancer patients can affect cognitive functions, with effects reminiscent of the dysfunctions observed in neurodegenerative diseases (Meyers, 1999).

Several observations are not compatible with a simple model of cytokine-induced depression. For example, IL-1 antagonists, such as the IL-1-receptor antagonist (IL-1ra) can effectively prevent the effects of IL-1, but the effects of LPS are only partially prevented, and those of influenza virus are only slightly attenuated (Swiergiel et al., 1997b). Also, LPS induces hypophagia in IL-1-knockout mice (Fantuzzi and Dinarello, 1996) and in IL-6-knockout mice (Swiergiel and Dunn, 2003). It must be concluded that, whereas IL-1 is sufficient to induce sickness behaviors, it is not necessary, and that other factors must contribute to the behavioral responses. Therefore, the mechanisms involved
in the expression of sickness behavior are complex and must involve multiple mechanisms. It is certainly possible that these mechanisms involve cytokines other than IL-1, but no cytokine that induces sickness behavior as effectively as IL-1 has yet been identified.

A popular version of the cytokine hypothesis of depression proposes a role for cytokines within the brain. According to this model, immune activation in the periphery can induce the synthesis or appearance of cytokines and their receptors in the brain parenchyma. This could be regarded as a local inflammation within the brain. The major route by which this is believed to occur involves stimulation of afferents of the vagus nerve (Watkins et al., 1995; Bluthé et al., 1996) affecting cells in the brain stem, which in turn project to the forebrain. The hypothesis states that it is the cytokines induced within the brain that are responsible for the depressive symptoms (Lasic and Wong, 1999). The major cytokine implicated has been IL-1.

This is a novel and an intriguing idea, but more substantial evidence will be necessary to establish such a mechanism. The experimental data cited to support this hypothesis are the induction of the appearance of IL-1 in various regions of the brain, and the ability of intracerebrally administered IL-1 antagonists to prevent the effect of the peripheral treatments. Most of the studies indicating induction of IL-1 in the brain have involved peripheral administration of very high doses of LPS. Many of them have reported only the presence in the brain of mRNA for IL-1 and/or the IL-1 Type I receptor (Layé et al., 1994; Wong and Lasic, 1994; Wong et al., 1997), and many of those have used non-quantitative techniques. Demonstration of the presence of the mRNA only indicates the propensity for the synthesis of the proteins, and in the case of IL-1, only the synthesis of its precursor, pro-IL-1β, which must be cleaved by interleukin-1 converting enzyme (caspase 1) to produce active IL-1β. Quan et al. (1998) showed that administration of LPS (2.5 mg/kg ip) to rats induced the mRNA for IL-1 in the pituitary and the circumventricular organs (CVO’s), i.e. outside the blood-brain barrier. Small amounts of mRNA for IL-1β were found in the brain, but most was present in microglia, thought to be derived from macrophages that penetrated the endothelia and/or accessed the brain via the CVO’s (Quan et al., 1998).

Whether or not active IL-1 occurs in the normal brain is controversial. As indicated above, most of the evidence indicates that IL-1β appears in the brain after high doses of LPS and is largely localized in glia. An early immunohistochemical study indicated the presence of IL-1 in post mortem human brain (Breder et al., 1988), and immunohistochemical findings have subsequently been reported from the rat (Lechan et al., 1990) and the pig (Molenar et al., 1993). The anatomical distributions of the IL-1 expression differed somewhat among the individual human brains in the human study, and there was little concordance among the anatomical distributions observed in human, rat and pig. Van Dam et al. (1995) observed immunoreactivity for IL-1 in microglia in rat brain and sparsely in astroglia after peripheral administration of a high dose of LPS (2.5 mg/kg ip or intravenously (iv)). This result is consistent with those of Quan et al. (1994) using an immunoassay for IL-1 after a similar dose of LPS.

A more recent study on the brains of multiple sclerosis patients and controls also found IL-1β-like immunoreactivity primarily in microglia, especially in the sclerotic plaques (Huizinga et al., 2000). However, IL-1β-like immunoreactivity was also found in neuronal cell bodies in the hypothalamus particularly in the paraventricular nucleus, but also in several other hypothalamic nuclei and in certain neuronal fibers. The neuronal IL-1β immunoreactivity was dramatically reduced in the brains of multiple sclerosis patients. Curiously, all of the IL-1β-positive neurons also contained oxytocin, although only about one-third of the oxytocin neurons contained IL-1β. None of the corticotropin-releasing factor (CRF)- or vasopressin-positive neurons contained IL-1β immunoreactivity. Huizinga et al. (2000) considered whether the association of IL-1β with oxytocin neurons could be artifactual reflecting another protein with similar antigenic properties, although it occurred with three different antibodies to IL-1β. Any association of IL-1β in oxytocin-containing neurons with sickness behaviour requires explanation.

Several studies from Maier’s group have used ELISA’s to demonstrate the presence of IL-1 in the brain, especially in the hippocampus, following a variety of treatments including LPS and various stressors (see Watkins et al., 1995). However, in none of these studies was the purported IL-1 purified, even partially, prior to the assay, so we cannot be certain that the apparent immunoreactivity truly reflected IL-1, especially because the amounts of IL-1 reported were around the limits of the sensitivity of the assays. However, in one study, Quan et al. (1996) employed a bioassay to demonstrate the activity of partially purified IL-1 in the brains of untreated rats. Classical criteria for the identification of hormones and neurotransmitters require more rigorous techniques, involving extensive purification of the candidate molecule, and demonstration of its identity using both immunological and bioassays. However, to date, not even a Western blot has been published to demonstrate the existence of IL-1 in the brain. Moreover, it cannot be excluded that the presence of the limited amounts of IL-1 in these reports reflects local pathologies. The IL-1 may well have been present in microglia involved in the phagocytosis of dead cells or cellular components.

There are similar problems with the studies purporting to demonstrate the presence of IL-1 receptors in the brain. An early study claimed widespread binding of [125I]IL-1 (mouse) to slices of rat brain (Farrar et al., 1987). Careful studies by Haour et al. (1992) and Takao et al. (1992) found that the majority of IL-1 binding in the rat and the mouse brain was associated with the cells in the endothelia, which may explain the earlier results of Farrar et al. (1987). Neither group found any evidence for binding of IL-1 in
the brain parenchyma of the rat, although both observed limited binding in the hippocampus of the mouse. It is possible that there are so few IL-1 receptors in the rat and mouse brain that they could not be detected by these binding techniques. It is thought that the presence of a very small number of IL-1 receptors on a cell may be sufficient to induce biologic responses (Karakauer and Oppenheimer, 1999). Nevertheless, it is clear that the existence of IL-1 receptors in the brain parenchyma is limited at best. Other studies have identified mRNA for the IL-1 Type 1 receptor in the brain (Wong and Licinio, 1994; Y abuuchi et al., 1994; Ericsson et al., 1995). However, the presence of mRNA is insufficient to prove the existence of functional receptors, for which other proteins, such as the IL-1 receptor accessory protein, are required.

The major evidence cited to indicate a role for cytokines in the brain is based on the use of intracerebral injections of IL-1ra (Dantzer et al., 1999; Pugh et al., 1999; Borsody and Weiss, 2004). Such data are useful and suggestive of a role for IL-1, but much more evidence will be needed to define and establish a physiological role for IL-1 in the brain, not the least in depression.

2.4.1. Effects of antidepressant treatments on sickness behavior

Depression in humans responds reasonably well to antidepressant drugs. Antidepressants also have useful anti-stress effects (Strohle and Holsober, 2003), but they are not particularly effective in alleviating the feeling of being sick. In a creative series of studies, Yirmiya used ingestion of a saccharin solution by rats as a measure of hedonia (Yirmiya, 1996). He showed that treatment of rats with LPS, which is a potent stimulator of the production and secretion of the pro-inflammatory cytokines, IL-1, IL-6, TNFα and IFNγ, decreased the frequency with which rats pressed a bar to obtain the saccharin solution. This response was considered to reflect anhedonia, a cardinal symptom of depression. This hypothesis was tested by treating the rats chronically (for 3–5 weeks) with the classic tricyclic antidepressant, imipramine, which inhibits the reuptake of both norepinephrine (NE) and serotonin (5-hydroxytryptamine, 5-HT). This treatment prevented the induction by LPS of the ‘anhedonia’ in the rats. Similar results were obtained by Shen et al. using the NE-selective reuptake inhibitor, desmethylimipramine (Shen et al., 1999), and by Yirmiya using the 5-HT-selective reuptake inhibitor (SSRI), fluoxetine, although in the latter case, the prevention was less complete (Yirmiya et al., 2001). However, Shen et al. observed no such effect of the SSRI, paroxetine, nor of the 5-HT and NE reuptake inhibitors, venlafaxine (Shen et al., 1999). Thus the effect of antidepressants appears to be less evident with the SSRI’s than with the tricyclic antidepressants (Yirmiya et al., 1999; Shen et al., 1999). However, the atypical antidepressant, tianeptine was effective chronically but not acutely (Castanon et al., 2003). We failed to observe any effect of chronic imipramine or venlafaxine, on the inhibitory effect on LPS on the drinking of sweetened milk in mice (Dunn and Swiergiel, 2001). Yirmiya has also indicated a failure to observe an effect of antidepressants on LPS-induced saccharin-drinking in mice (Yirmiya et al., 1999). From the above cited studies, it appears that the effect of chronic antidepressant treatment is observed most often with LPS, is less evident with IL-1, and the effects on LPS are evident in rats and not in mice. Other evidence suggests that antidepressants may affect the induction of IL-1 production by LPS (Yirmiya et al., 1999; Castanon et al., 2003; Connor et al., 2000), and reflect a peripheral rather than a central mechanism. A peripheral mechanism of action for antidepressants is highly unlikely, so that Yirmiya’s exciting initial observation has failed to provide strong support for an IL-1 hypothesis of depression.

A nother important aspect of sickness behavior is that it does not appear to be stereotyped but is adaptive. This means that the specific expression of sickness behaviors can vary according to the needs of the organism (see Larson and Dunn, in press) For example, although hypophagia is a typical symptom of sickness behavior, it may not be expressed if the food supply is limited, or the animals are food-deprived (McCarthy et al., 1986; Kent et al., 1994; Larson et al., 2002). It may also be diminished if there is only one source of food (Aubert et al., 1997a). Priorities for food and warmth may also be altered (Aubert et al., 1997b). A nother example is sexual activity, which is inhibited by IL-1 and LPS in females, but not in males (Avitsur et al., 1998). This presumably reflects the obvious danger for the sick gravid female and her offspring, but is not a threat for the male.

In sum, although there are many similarities between sickness behavior and the behavior of patients suffering from major depressive disorder, there are many aspects in which the sickness behavior model does not resemble the human syndrome. Furthermore, it has been shown that in experimental endotoxemia, the fever and corticosterone responses occur at a time when there are no detectable increases in circulating endotoxin or cytokines (Campisi et al., 2003). These discrepancies suggest that cytokines may not be necessary for the activation of the endocrine and sickness responses, nor for major depressive disorders.

2.5. HPAA activation by cytokines: the relationship to depression

The potent activation of the HPAA by IL-1 (Besedovsky et al., 1986) was a seminal discovery because it extended the concept of stress to immune activation. In this sense, the immune system acts a sensor of invading pathogens, signalling the brain of a threatening environmental event (Blalock, 1984). It is highly significant that the major mechanism by which immune stimuli activate the HPAA is the same as that involved in the responses to psychological and physical stressors, namely activation of CRF-containing neurons in the paraventricular nucleus of the hypothalamus,
and subsequent secretion of anterior pituitary ACTH (although there is evidence that IL-1 may activate the HPAA by multiple mechanisms (see Silverman et al., 2003; Dunn, 2005). Interestingly, there is little evidence for habituation (desensitization) of the HPAA response to IL-1, although there is rapid tolerance to the responses to LPS (Fan and Cook, 2004).

The HPAA-activating effect of IL-1 is shared by other cytokines, most notably, IL-6 and TNFα, but the latter are markedly less potent than IL-1, and may have limited physiological significance, except perhaps in the absence of IL-1 (Silverman et al., 2003; Dunn, 2005). Treatment with antibodies to IL-6 and studies in IL-6-knockout mice indicate that IL-6 contributes only modestly to the elevation of plasma ACTH and corticosterone by LPS in mice (Wang and Dunn, 1999; Swiergiel and Dunn, 2003) However, because plasma concentrations of IL-6 can be dramatically elevated by infections and other pathologies in which the HPAA is activated, IL-6 may contribute to this activation (Silverman et al., 2004) Depending on the physiological conditions, IL-6 apparently has the ability to activate the HPAA via the hypothalamus, the pituitary and the adrenal cortex (Silverman et al., 2003; Silverman et al., 2004; Dunn, 2004; Dunn, 2005).

Administration of IFNα and IFNγ, but not IFNβ causes marked activation of the HPAA in man (e.g. Shimizu et al., 1996; Capuron et al., 2003). However, curiously, IFNγ elevates cortisol, but has little effect on ACTH (Holsboer et al., 1988). There appear to be marked species differences, because administration of relatively high doses of IFNα (human or mouse) to mice did not alter plasma corticosterone (Dunn, 1992, 2005). In rats, both peripheral (ip) and intracerebroventricular (icv) administration of hIFNα induces decreases in plasma ACTH and corticosterone (Saphier, 1989; Saphier et al., 1993), although one study showed modest increases in ACTH and corticosterone following iv rat IFNα (Menzies et al., 1996).

In depressed patients, activation of the HPAA is perhaps the most consistent biological marker, yet it occurs in only 50–70% of patients. A similar proportion of depressed patients are abnormal in the dexamethasone suppression test and the CRF challenge tests (Strohle and Holsboer, 2003). Smith cited the ability of IL-1 to activate the HPAA as support for a cytokine hypothesis of depression (Smith, 1991). It is relevant that the HPAA activation by IL-1 can be dissociated from its behavioral effects. Inhibitors of the enzyme cyclooxygenase (COX) more or less prevent several behavioral responses to IL-1 (Swiergiel et al., 1997a; Dunn and Swiergiel, 2000), but the HPAA activation is affected only after iv injection of IL-1, and in the early phase after ip injections (Dunn and Chuluyan, 1992). The role of CRF also differs in the HPAA and the behavioral responses. It appears to be involved in the HPAA responses to IL-1, because antibodies to CRF prevent IL-1-induced HPAA activation in rats and mice (Dunn, 1993; Turnbull and Rivier, 1999). Also, HPAA activation is insusceptible in CRF-knockout mice (Mugila et al., 2000; Dunn and Swiergiel, 1999), while the hypophagic responses to IL-1 and LPS are normal (Dunn and Swiergiel, 1999).

The principal factors mitigating against a hypothesis of IL-1-induced HPAA activation in depression is the failure to observe consistent elevations of plasma concentrations of IL-1 in depressed patients, and the fact that one third or more of depressed patients do not exhibit HPAA activation, or other abnormalities of HPAA function.

2.6. Brain catecholaminergic activation induced by cytokines: relationship to depression

In mice and rats, central noradrenergic systems are markedly activated by IL-1 as indicated by classical neurochemical studies showing increases in the NE catabolite, 3-methoxy,4-hydroxyphenylethylenglycol (MHPG) (Dunn, 1988; Dunn, 2001; Kabiersch et al., 1988). The noradrenergic activation is not uniform, the ventral system (ventral noradrenergic ascending bundle, VNAB) being activated substantially more than the dorsal system. Consistent with this, reductions in the hypothalamic content of NE have also been observed in rats (Flesher et al., 1995). Microdialysis studies in rats have indicated a similar activation (Shintani et al., 1993; Smagin et al., 1996; Wieczorek and Dunn, 2003). There is no evidence for noradrenergic activation associated with IL-6 (Wang and Dunn, 1998), although TNFα has such an effect in mice at high doses (Ando and Dunn, 1999). The latter could be attributed to TNFα-induced IL-1 secretion.

In contrast to these robust effects of IL-1 on NE, this cytokine does not consistently affect dopamine (DA) metabolism, although small increases are occasionally observed (Dunn, 2001). IL-6 and TNFα have not been reported to affect DA. However, IL-2 (1 μg ip) induced a marked reduction in microdialysate concentrations of DA from the nucleus accumbens of the rat (Anisman et al., 1996). The latter result is consistent with the increase in thresholds for ICSS observed in rats following similar treatments with IL-2, indicative of anhedonia (see above).

Reports of the effects of interferons on brain catecholamines have been quite varied (see also Schaefer et al., 2003). Shuto et al. found that chronic (but not acute) administration of hIFNα (15×10⁶ Units ip) induced small decreases in whole brain (minus cerebellum) DA and its catabolite, 3,4-dihydroxyphenylacetic acid (DOPAC), but there were no changes in the DOPAC:DA ratio nor in NE (Shuto et al., 1997). They also reported a decrease in the apparent turnover of DA, assessed by blocking its synthesis with α-methyl-p-tyrosine. Kumai et al. reported that repeated subcutaneous treatment (7 days) with hIFNα increased the DA and NE contents of the cortex, hypothalamus and medulla, but not of the hippocampus or thalamus (Kumai et al., 2000). We observed no effects of a single ip injection of mouse IFNα (1000 or 10,000 U/mouse) on DA, NE or any of their metabolites (Dunn, 2001). On the other hand, a single icv injection of IFNα (200 or
2000 U of hIFN αA/D) was reported to decrease frontal cortical NE (Kamata et al., 2000). However, in yet another study, 1000 U hIFN α injected icv increased apparent DA turnover (DOPAC:DA ratio) in the hippocampus (primarily caused by a substantial decrease in DA), although no such effect was observed in the prefrontal cortex or striatum (De La Garza and Asnis, 2003).

Many studies have indicated hypersecretion of brain NE in depression, principally assessed by increased CSF or urinary concentrations of the NE catabolite, MHPG (3-methoxy,4-hydroxyphenylethylenglycol), but also by direct measurement of CSF NE (Wong et al., 2000). Thus an IL-1-mediated elevation of cerebral NE activity could be taken as evidence for a role of IL-1 in depression, although as in the case of the HPAA activation, the failure to observe consistent elevations of plasma IL-1 in depressed patients tempers this evidence.

2.7. Cytokines, depression and serotonin

Currently, the prevailing hypothesis is that depression is caused by some disorganization of brain serotonergic systems, perhaps a deficiency in serotonergic neurotransmission. This hypothesis is based largely on the observation that many effective antidepressants affect serotonergic transmission. Also, serotonin receptor abnormalities are found in the brains of depressed patients (for reviews, see Bell et al., 2001; Coppen and Wood, 1978; Wichers and Maes, 2004). Antidepressants are presumed to work by normalizing a defect in brain serotonergic transmission through plastic changes or neurotrophic effects (Manji et al., 2001).

An interesting mechanism by which infections might induce depression, relates to the metabolism of tryptophan and 5-HT). Infections, especially viral ones, induce IFN γ, which is a potent inducer of indoleamine 2,3-dioxygenase (IDO) in macrophages and certain other cells. IL-2 and IFN α have similar effects on IDO, but to a lesser extent. This enzyme degrades tryptophan, so that infections are typically associated with decreases in plasma tryptophan. IDO enables the conversion of tryptophan to kynurenine, and the production of neopterin, both of which are elevated in the plasma of infected subjects. The resulting catabolism of tryptophan decreases its circulating concentrations.

Lower plasma concentrations of tryptophan have been associated with depression (Coppen and Wood, 1978), but low plasma tryptophan is not a particularly reliable biologic marker for depressive illness (Bell et al., 2001). It has been postulated that such a decrease may limit the availability of tryptophan to the brain, thus limiting serotonin synthesis, and precipitating depression (Wichers and Maes, 2004). Such a mechanism for the induction of depression has not been adequately demonstrated, but lowering plasma tryptophan can precipitate a relapse in depressed patients treated with SSRI’s (Delgado et al., 1994, 1999), but not in those treated with desmethyli mipramine (whose primary mechanism of action is thought to be inhibition of NE uptake) (Delgado et al., 1999) or cognitive therapy (O’Reardon et al., 2004). It appears that medicated patients are more likely to experience relapse following tryptophan depletion than unmedicated patients (Moore et al., 2000). Tryptophan depletion may also induce depression in susceptible individuals (Bell et al., 2001). There is also evidence that individuals who exhibit mood changes in response to rapid tryptophan depletion may be at risk for depression (Moreno et al., 2000).

There is some limited support for this mechanism from animal studies. Repeated tryptophan depletion of rats increased anxiety-like behavior in the open field and immobility in the forced swim test (thought to reflect depression-like behavior, see below), but did not alter behavior in the Morris water-maze (Blokland et al., 2002). However, acute tryptophan depletion did not alter the behavior of rats in the open-field test, the home cage emergence test, and the forced swim test, but decrements were observed in an object recognition test (Lieben et al., 2004).

IL-1, IL-6 and TNF α have been shown to activate brain serotonergic systems, increasing brain tryptophan concentrations and the metabolism of 5-HT as indicated by increases in the brain concentrations of its catabolite, 5-hydroxyindoleacetic acid (5-HIAA) (Dunn, 2001; Zalcman et al., 1994; Clement et al., 1997). Apparent 5-HT release by peripherally administered IL-6 has also been indicated by microdialysis and in vivo chronoamperometry (Zhang et al., 2001). The acute effects of IL-1 and IL-6 appear to increase the available tryptophan in the brain, perhaps enhancing serotonergic activity, which could be considered to have an antidepressant effect. The problem for a hypothesis that cytokines induce depression by activating serotonin is that such an effect is apparently in the wrong direction, because SSRI’s also induce increased extracellular 5-HT. This could perhaps be explained if the chronic effects of the cytokines differed from the acute ones. The effects of chronic administration of the cytokines on serotonin metabolism have not been studied extensively, but one report indicated that repeated TNF α administration increased its effects on 5-HT (Hayley et al., 2002). IL-1β has also been reported to activate the serotonin transporter, which could decrease extracellular 5-HT (Morikawa et al., 1998).

There are few data on the effects of IFN’s on brain 5-HT. A single icv injection of 200 or 2000 U of hIFN α was reported to decrease the 5-HT content of the frontal cortex, and both 5-HT and 5-HIAA were decreased in the midbrain and the striatum of rats (Kamata et al., 2000). However, we observed no effects of ip human or mouse IFN α on 5-HT or 5-HIAA in mice at doses (400–16,000 U/mouse) that induced behavioral changes (Dunn, 2001). However, in another study a single icv injection of IFN α (1000 U) increased 5-HIAA:5-HT ratios in the prefrontal cortex, but not in the striatum or the hippocampus of rats (De La Garza and Asnis, 2003).
and Asnis, 2003). This latter effect appeared to be prevented by diclofenac pretreatment.

Therefore, there are several hypothetical mechanisms by which cytokines could act on brain serotonergic systems and thus contribute to the pathophysiology of depression. However, relationships between these potential mechanisms and depression remain to be demonstrated in depressed patients.

3. Effects of immune activation and cytokines in classical tests of depression

The cytokine hypothesis of depression would be strengthened if immune stimulation or cytokine administration proved positive in classical models of depression. Generally, these models are based on the assumption that a particular behavioral pattern resembles a human depressive symptom, and/or it is selectively sensitive to clinically effective antidepressant treatments. The most recent reviews indicate that there are some half dozen rodent models of depression (Cryan et al., 2002; Cryan and Mombereau, 2004; Porsolt, 2000). The two tests most commonly used are the forced swim test (FST), and the tail suspension test (TST).

3.1. The Porsolt or forced swim test

The forced swim test introduced by Porsolt et al. (1977a) is by far the most frequently used. The test involves placing a rat or a mouse in a tall cylinder of water from which it cannot escape, so that it must swim or float to survive. In the original form of the test, rats were placed in the cylinder of water on the first day for 15 min. It has been suggested that this session may be necessary for the rats to learn that escape is impossible (Borsini and Meli, 1988). The rats are tested again 24 h after the first trial after potential antidepressant treatments. In its original form, drugs or other treatments were administered immediately after the session on the first day, and then again five hours and one hour before the test on the second day (Porsolt et al., 1977a). However, Porsolt subsequently showed that many antidepressant treatments tested positively with only one or two of the three treatments, although in many cases the three-treatment regimen was more effective (Porsolt et al., 1978). The key parameters affected by antidepressants are the time spent immobile (floating) and the latency to stop active swimming (struggling) or attempting to escape. Antidepressants increase the latency to float and decrease the floating time; whereas chronic stress and certain other treatments considered depressogenic increase the time spent floating. This test has been shown to work for most antidepressant treatments, including atypical antidepressants, such as the monoamine oxidase inhibitors (MAOIs) and electroconvulsive therapy (ECT) (Cryan and Mombereau, 2004; Porsolt, 2000), although the SSRI’s are less effective and some are ineffective. Thus the test has been validated pharmacologically, even though the drug treatments work after one, two or three treatments, rather than the chronic treatments required in depressed patients. Porsolt also developed a test for use in mice, but in this test the mice are forced to swim only once, usually with the antidepressant treatments applied shortly before the test. Immobilization is scored during the last 4 min of the 6-minute test (Porsolt et al., 1977b). However some researchers have employed a 2-day test in mice like that in rats.

Surprisingly, there are few data in the literature on the effects of cytokines or immune stimulation using the FST. In an early report, del Cerro and Borrell found that IL-1 (5 U) administered icv reduced floating in rats by more than two-fold (del Cerro and Borrell, 1990), an apparent antidepressant effect. In direct contradiction to these results, Huang and Minor reported (in abstract form only) that icv injection of 2 ng of IL-1β significantly increased floating in rats in the FST, and that this response was prevented by icv administration of 6 µg of IL-1ra or by ip caffeine, the latter implicating adenosine receptors (Huang and Minor, 2000).

As discussed above, patients medicated with IFNα may display depressive symptoms that can be successfully treated with antidepressants (Musselman et al., 2001a). Makino et al. reported that recombinant human IFNα (60,000 U/kg iv) increased floating in the FST in rats, without altering locomotor activity (Makino et al., 2000a). Human IFNα-2, and IFNα-2b also increased floating in the FST in mice (Makino et al., 1998). Curiously, this effect was observed only with human IFNα, hIFNβ and hIFNγ, and mouse IFNα, IFNβ and IFNγ were all ineffective. Pretreatment with naloxone, but not indomethacin prevented the FST response to hIFNα (Makino et al., 2000b). We have observed consistent increases in floating in the FST in rats injected icv with 150 or 1500 U rat IFNα (Dunn and Swiergiel, unpublished observations). In preliminary results in mice, we have also observed increased floating times following icv administration of mIFNα (500–5000 U) (Dunn and Swiergiel, unpublished observations).

Several other reports pertain indirectly to a role of cytokines in behavior in the FST. Tannenbaum et al. showed that chronic stress increased sickness scores and the duration of floating in the FST, and although they reported that chronic stress augmented the sickness behavior induced by ip IL-1β, they did not report the effects of IL-1β in the FST (Tannenbaum et al., 2002). Deak et al. showed that exposure to the FST did not alter the concentrations of IL-1 measured in the brain or in peripheral tissues, and concluded that the production of IL-1 in the brain was unlikely to play a role in the behavioral consequences of the forced swim (Deak et al., 2003).

A potential role for IL-6 was demonstrated by Sakic et al. (2001) who observed that a spontaneous increase in serum interleukin-6 (IL-6) concentrations in lupus-prone (MRL-lpr) mice coincided in time with increased immobility in the FST. Also, sucrose intake was decreased when IL-6 was over-expressed systemically in healthy mice,
suggesting that sustained elevation of plasma IL-6 might affect other behaviors. High circulating concentrations of IL-6, were achieved in mice by infecting them with Ad5mIL6 adenovirus. This treatment reduced exploration of a novel object, as well as food, water, and sucrose intake, that is, resembling changes observed in sickness. Furthermore, in lupus-prone mice the presence of CD45-positive cells (leukocytes) in the choroid plexus and in the brain parenchyma correlated positively with floating in the FST (Farrell et al., 1997). These results suggest that immune system alterations may affect the behavior in the FST. However, elevations of IL-6 are commonly associated with sickness, but whether or not the IL-6 is responsible for the symptoms has not been established. It is significant that IL-6 administration has not been shown to induce any sickness behaviors (Blüthé et al., 1998; Swiergiel and Dunn, 1999).

Comparing results derived from sickness behavior studies and the FST requires careful interpretation. If sickness behavior is considered adaptive, its functional adaptive behavioral equivalent in the FST may be an increased floating (usually interpreted as an increase in behavioral despair), as opposed to active swimming that could be considered maladaptive (Nishimura et al., 1986). An appropriate response to LPS or IL-1 would be to increase flotation, not because it produces depression, but because it is an appropriate strategy for survival. Thus the biological significance of the effects of immune challenges, LPS or cytokines in behavioral patterns observed in the FST remains unclear.

3.2. Tail suspension test (TST)

The tail suspension test, the second most widely used test for depression, is conceptually similar to the FST. This test is most commonly used in mice, because it is very difficult to implement in rats. The animal is suspended by its tail and the latency to cease struggling and the duration of passive immobility are scored. The duration of immobility displayed by the suspended animals is reduced by antidepressant treatments (Cryan et al., 2002; Cryan and Mombereau, 2004). The TST has the advantage of eliminating confounding effects of thermal effects of the swimming (Cryan and Mombereau, 2004). Nevertheless, the FST and TST may differ in the biological substrates underlying the observed behaviors (Cryan and Mombereau, 2004). Lines of helpless mice responding to antidepressants, have been developed by selective breeding for responses in the TST (Vaugeois et al., 2004).

Relatively few data are available on the effects of immune activation or cytokines on responses in the TST. Y amano et al. reported that YM 643 (2×10^5–2×10^6 U iv), a consensus IFNα, and sumiferon (2–20×10^6 U), a natural IFNα, administered iv, increased immobility time in the TST in mice (Y amano et al., 2000). Icv and repeated subcutaneous injections were also effective. Peripheral pretreatment with imipramine or CP-154,526 (a CRF1 receptor antagonist), but not with naloxone or indomethacin, reversed the IFN-induced immobility and it was concluded that the IFNα induced depression-like behavior by acting centrally (Y amano et al., 2000). Y amano et al. suggested that IFNα induced depression via IL-1β release, which in turn was responsible for the CRF secretion. In preliminary studies, we have also observed increases in the time spent immobile in the TST after icv mIFNα (500–5000 U/mouse) (Dunn and Swiergiel, unpublished observations).

A summary of the biological effects observed in depression and in animal models is provided in Table 4. Even though the data are incomplete, the table clearly indicates the existence of common features between depression and sickness behavior, as well as some aspects of chronic stress in animals.

3.3. Involvement of cytokines in other models of depression

There are very limited data on the involvement of cytokines in other models of depression. In the chronic mild stress (CMS) model for depression, K ubera et al. showed that 3 weeks of CMS increased the ability of splenocytes to produce IL-1 and IL-2, an effect that was partially prevented by chronic treatment with imipramine (K ubera et al., 1996; K ubera et al., 1998). A decrease in NK cell activity was also observed (Kubera et al., 1998). Mormède et al. (2003) observed decreases in body weight after 21 days of CMS, but these were not accompanied by changes in the hematocrit or plasma concentrations of corticosterone. However, the consumption of sucrose was decreased, consistent with an anhedonic effect. Spleen cells did not display any changes in the production of IFNγ or IL-6. However, the mRNA’s for IL-1β and IL-6 were decreased in the liver, while they were increased in the hypothalamus (Mormède et al., 2003).

A number of immune abnormalities have been observed in the rat olfactory bulbectomized model (see Leonard and Song, 2002). In the only published study involving cytokines, the serum concentrations of IL-1β and TNFα were increased by LPS administration, but this response was decreased by bulbectomy (Connor et al., 2000). Treatment with desmethylimipramine decreased the responses in both bulbectomized and control rats. These changes paralleled the increases in plasma corticosterone.

3.4. Usefulness of the cytokine-induced sickness behavior model for the study of depression

The value of animal models of human diseases is to provide insight into the mechanisms involved in the diseases, which may suggest potential therapies that can then be tested in the models. Because such models will normally involve artificial interventions, it is important to use them intelligently. Thus if cytokine administration is used to induce a model for depression, then the introduction of appropriate cytokine antagonists should prevent
the symptoms in the model. However, unless cytokines are the cause (or a cause) of major depressive disorder, cytokine antagonists are unlikely to be effective clinically. Moreover, provided they are safe and non-toxic, the cytokine antagonists could be tested directly in patients, negating the need for the model. The model could be used to assess the toxicity of the treatments or the efficacy of chronic treatment, but such tests would normally employ standard tests for toxicity and not use the disease model. If cytokine antagonists are not effective in the clinical situation, there would be no need to test them in the animal model, and the model would have little value. Models are most useful if they are based on the etiology of the human disease, or to test a proposed underlying mechanism.

It is unlikely that treatments effective in the model will work if the method used to induce the model is unrelated to the basic mechanism(s) of the disease. A example of the successful use of an animal model is the development of treatments for attention deficit hyperactivity disorder (ADHD). When it was observed that methylphenidate (an amphetamine-like drug that stimulates DA release) paradoxically reversed the hyperactivity observed in 6-hydroxydopamine-treated rats (Shaywitz et al., 1976), it was reasoned that it might counter the hyperactivity observed in children with ADHD. Such treatment has proven very effective in humans (Shaywitz et al., 2001). In this case, the model was useful most probably because ADHD in children involves an abnormality in brain catecholamine systems. But not all models have proven so useful. For example, the olfactory bulbectomy model mimics depression in several tests, and the effects respond appropriately to very many treatments effective in depressed patients (see Cryan et al., 2002; Cryan and Mombereau, 2004; Kelly et al., 1997). Nevertheless, although the model is of considerable scientific interest, it has failed to provide insight into the mechanism of depression and has so far failed to inspire useful clinical therapies.

Needless to say, we do not yet know the value of the cytokine-induced sickness behavior model of depression, but we do have some insight into what will probably not work. For example, there is general agreement that many behavioral responses to IL-1 are largely prevented by inhibition of COX, a key enzyme for the production of prostaglandins and other eicosanoids (Swiergiel et al., 1997a; Uehara et al., 1989; Bluthé et al., 1992). This observation led Charlton (2000) (and subsequently others) to propose that COX inhibitors (the non-steroidal anti-inflammatory drugs (NSAID’s), such as aspirin, indomethacin and ibuprofen) should have antidepressant activity. However, depressed patients have frequently taken NSAID’s, but there is no good evidence for any antidepressant activity. Reference to the animal data indicates something of the problem. Whereas COX inhibitors more or less prevent several sickness behaviors induced by IL-1, they are much less effective against LPS, and have virtually no effect against more complex immune challenges, such as influenza virus infection or tumors (Swiergiel et al., 1997a; McCarthy and Daun, 1993; Jain et al., 2001).

4. Conclusions

The above review indicates some associations between the appearance of cytokines and major depressive disorder. However, no clear causal relationship has been established. Administration of certain cytokines to humans (especially IFN-α and IL-2) induces symptoms of depression in some patients, but such responses occur in only a minority of patients, and many other neuropsychiatric symptoms may also be induced. Immune activation appears more frequently in depressed patients than in the general population, but is not observed in all depressed patients. It is possible that the immune activation may reflect other medical conditions, which may themselves induce depression. Alternatively, depression may ensue when a patient hears a diagnosis with a poor prognosis. Nevertheless, it is possible that excessive production of cytokines may induce symptoms of depression in some patients.

Although there is some evidence that depressed patients exhibit elevated plasma concentrations of cytokines, such effects are not observed consistently. Elevations are not observed in all depressed patients, and when they do occur they are frequently quite small. IL-1 is the major cytokine known to induce depression-like symptoms, but the evidence for elevations of this cytokine in depressed patients is sparse. The only cytokine consistently elevated in the plasma of depressed patients is IL-6. Plasma concentrations of IL-6 are frequently elevated during infections and other pathological conditions (and following some forms of stress), Thus there is unlikely to be any specific relationship between plasma IL-6 and depression. Moreover, in most studies in which IL-6 was administered to rats and mice, it failed to induce sickness behavior.

Sickness behavior induced by immune stimulation or IL-1 has many similarities with the behavior of depressed patients. However, there are important differences, for example, in the effects on body temperature, in the sensitivity to pain, and in the specific changes in sleep patterns. Therefore, it may be premature to consider experimentally induced sickness behavior as a true model for depressive illness. Nevertheless, certain aspects of depression may be studied in this way, if the results are interpreted conservatively. Nevertheless, experiments in which animals were treated chronically with antidepressant drugs have failed to provide strong support for the idea that such treatments work by antagonizing the actions of cytokines.

The cytokine hypothesis is not in conflict with earlier hypotheses of depression, such as those involving hyperactivity of the HPAA, or CRF, or of noradrenergic systems, because IL-1 activates the HPAA and brain noradrenergic systems. Also, CRF appears to be involved in the HPAA
responses to IL-1, because antibodies to CRF prevent IL-1-induced HPAA activation in rats and mice, and HPA responses to IL-1 are minuscule in CRF knockout mice. A cytokine hypothesis could also be consistent with a serotonin hypothesis of depression, because IL-1, IL-6 and TNFα have each been shown to affect brain serotoninergic transmission. However, IL-1, IL-6 and TNFα administered acutely appear to increase 5-HT release, which would achieve an effect similar to that induced by the many commonly used antidepressants that inhibit 5-HT re-uptake, so that these cytokines ought to have antidepressant effects.

Although drugs that inhibit serotonin reuptake are the most useful currently available for the treatment of depression, there is no strong direct evidence that abnormalities in 5-HT cause depression. More research on the effects of antidepressants on the immune system would be useful. In particular, the associations of abnormalities in tryptophan and serotonin with pathogen infection, with immune activation, and with depression, are potentially very significant, and require further investigation.

These observations do not exclude a role for cytokines in inducing depression. It is certainly possible that increased cytokine production may induce depression in some patients, and certain cytokines may contribute to a variety of neuropsychiatric symptoms in patients with a variety of diseases. Nevertheless, one can conclude with some confidence that the actions of cytokines cannot account for all cases of depression. It is also possible that by activating the HPAA axis, and central CRF, noradrenergic and serotoninergic mechanisms, cytokines may complement (or even synergize with) other factors that induce depression.

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