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The Role of Cytokines on the Aetiology of Depression

Eun-Yee Jung and Insop Shim*

Department of Integrative Medicine, The Catholic University of Korea
College of Medicine, Seoul 137-701, Korea

ABSTRACT

The increase in plasma concentrations of the pro-inflammatory cytokines observed in patients suffering from depression is known to be closely correlated with the severity of this psychiatric disorder, the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and the deficiency in serotonergic (5-HT) neurotransmission. Several medical conditions e.g. autoimmune disease such as rheumatoid arthritis (RA), cancer or hepatitis C therapies producing activation of the immune system are associated with psychological and neuroendocrine changes that resemble the characteristics of depression including depressed mood, appetite disturbance, sleep disturbance, psycho motor disturbance, fatigue, loss of energy, difficulty in thinking or concentrating, activation of the immune system, hyperactivity of HPA axis and monoaminergic alterations. Similarly, administration of pro-inflammatory cytokines in animals induces 'sickness behavior' which is a pattern of behavioral symptoms that are very similar to those of depression in humans. Furthermore, treatment of antidepressants in depression attenuates cytokine production and their action. Cytokine therapy itself alleviates symptoms of depression in medical conditions and animal experiments. These results indicate that activation of the immune system is associated with behavioral, neuroendocrine and neurochemical changes that resemble the characteristics of depression and suggest that pro-inflammatory cytokines are involved in the aetiology and pathophysiology of depression. In the present review, the current knowledge on the possible role of pro-inflammatory cytokines such as IL-1, TNF-α and IFN-γ in depression is discussed.

Key words: depression, pro-inflammatory cytokines, IL-1, TNF-α, IFN-γ

INTRODUCTION

The term of the “Psychoneuroimmunology” was introduced by Robert Ader in 1981 in order to define the interaction among behavioral, neural, endocrine, immune and psychological systems (Ader, 1981). In this respect, there has been increasing interest in the possible involvement of the immune system in psychiatric disorders such as depression (Kronfol et al., 1983; Maes, 1995, 1999; Nunes et al., 2002). Moreover, changes in the immune system can lead to profound alterations in psychological status such as mood and behavior. Therefore, changes in the immune system have been intensively investigated in depression (Kronfol et al., 1983; Maes, 1995, 1999; Nunes et al., 2002). The most important link between the immune system and depression is established by the cytokines which act as signalling molecules of the immune system. Cytokines increase central monoamine metabolism and are

*To whom correspondence should be addressed.
TEL: 82-2-590-2971, FAX: 82-2-592-6359
e-mail: ishim@catholic.ac.kr

potent activators of the hypothalamic-pituitary-adrenal (HPA) axis which are disturbed in depression (Kines and Maes, 2002). Considerable clinical and experimental data support the close relationship between cytokine and depression and much attention has focused on the role of cytokines in the aetiology and pathophysiology of depression (Connor and Leonard, 1998; Licinio and Wong, 1999; Maes, 1995, 1999). This review has paid attention to the possible role of pro-inflammatory cytokines such as IL-1, TNF-α and IFN-γ in depression.

CYTOKINE

Pro-inflammatory and anti-inflammatory cytokines

Initially, cytokines were discovered and described as proteins that were produced by activated monocyte, lymphocytes and macrophages in response to immune stimulation. Now, it is clear that these molecules do much more than only participate in the regulation of the immune responses and that are produced by various cell types including cells of the central nervous system (CNS) (astrocytes, microglia and even neurons) (Kines and Maes, 2002). However, their biological activities may vary in immune homeostasis in which two classification systems can be distinguished, pro-inflammatory and anti-inflammatory cytokines. Pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-2, IL-6, IL-8, tumor necrosis factor (TNF) and interferon-γ (IFN-γ) are involved in inflammatory reactions and they tend to stimulate or activate immunocompetent cells (Table 1). In contrast, anti-inflammatory cytokines inhibit inflammation and deactivate immune cells. Group of anti-inflammatory cytokine is IL-4, IL-10 and IL-13 (Table 1), which is a major deactivator of monocytes, lymphocytes and macrophages. Interleukin-1 receptor antagonist (IL-1Ra) is another anti-inflammatory cytokine that specifically antagonizes the activities of IL-1 (Abbas et al., 1996). These chemical messengers have profound effects on the CNS and endocrine functioning.

DYSREGULATION OF IMMUNE SYSTEM IN DEPRESSION

In depressed patients, characteristics of immune system include increases in the numbers of circulating lymphocytes and macrophages cells, and up-regulated serum levels following activation of the inflammatory response (Licinio and Woong, 1999; Maes, 1995, 1999). Higher serum concentrations of acute-phase proteins (APPs) and pro-inflammatory cytokines, such as IL-1, IL-2, IL-6 and IL-12 and IFN-γ were observed in patients suffering from depression, and these were highly correlated with the severity of this psychiatric disorder and HPA

Table 1. Selected cytokines and their characteristics

Cytokine	Producer cells	Category	Central expression of cytokine & receptor	References
IL-1	Macrophages	Pro-inflammatory	+/+	Breder et al., 1988; Rothwell et al., 1994
IL-2	T cells	Pro-inflammatory	+/+	Hanisch and Quirion, 1995
IL-4	T cells	Anti-inflammatory	+/?	Racke et al., 1995
IL-6	Macrophages, T cells	Pro-inflammatory	+/+	LeMay et al., 1990; Benveniste et al., 1990
IL-8	T cells	Either	+/+	Ehrlich et al., 1998
IL-10	Macrophages, T cells	Anti-inflammatory	+/+	Wong et al., 1997
IL-12	Macrophages, B cells	Pro-inflammatory	+/?	Elenkov et al., 1996; Stalder et al., 1997
IL-13	T cells	Anti-inflammatory	+/?	Wong et al., 1997
TNF-α	Macrophages, NK cells	Pro-inflammatory	+/+	Breder et al.,1993;
TNF-β	T cells, B cells	Pro-inflammatory	+/+	Bethea et al.,1992
IFN-α	Leukocytes	Pro-inflammatory	+/+	Licinio et al.,1998;
IFN-γ	T cells, NK cells	Pro-inflammatory	+/+	Lin et al.,1998

IL: interleukin, TNF: tumor necrosis factor, IFN: interferon, NK: natural killer (Adapted and modified from Kronfol and Remick, 2000; Schiepers et al., 2005).

axis hyperactivity (Maes et al., 1993, 1995, 1999; Kim et al., 2002; Nunes et al., 2002). Concerning the immune characteristics of depression, it should be noted that depression is a heterogeneous disorder, which implies that the various types of depression may not only be psycho-pathologically different, but might also differ from one another on the immunological level. For example, studies performed by Rothermundt et al. (2001a,b) have demonstrated that different immune patterns were shown in melancholic and non-melancholic major depression. Whereas cell counts of monocytes, leukocytes, lymphocytes and natural killer (NK) cells, as well as APP concentrations, were increased in the plasma of patients suffering from non-melancholic depression, normal or decreased cells and APP concentrations were detected in melancholic patients. Unfortunately, many studies use psychiatrically heterogeneous patient samples, thereby making it rather difficult to discriminate the different types of depression from an immunological perspective. As depression may be considered a genetic disorder, the genetics of the immune system in relation to depression should be investigated. It has been suggested that certain cytokine gene polymorphisms, e.g. of the genes encoding for TNF-α and IL-1, may confer a greater susceptibility to develop depressive illness (Jun et al., 2003; Fertuzinhos et al., 2004; Rosa et al., 2004).

BEHAVIORAL EFFECTS UNDERLYING CYTOKINE-INDUCED DEPRESSION

The major features of depression are depressed mood and loss of interest or pleasure in all and several associated symptoms including appetite disturbance, change in body weight, sleep disturbance, psychomotor disturbance, fatigue, loss of energy and difficulty in thinking or concentrating (Yirmiya et al., 2000). These behavioral features resemble the symptoms of the elicitation of certain behavioral characteristics by pro-inflammatory cytokines. Pro-inflammatory cytokines, such as IL-1, TNF-α, IFN-γ that are released during an infection, induce a set of feelings and behaviors that are called "sickness behavior". Studies with animals and humans have shown that the infusion of systemic or central cytokines induce sickness behavior symptoms including decreased appetite, anorexia, weight loss, fatigue, sleep disturbances, retardation of motor activity, reduced interest in the physical and social environment, impaired cognitive abilities, dysphoria, anhedonia and depressed mood (Yirmiya, 2000; Yirmiya et al., 2000; Dantzer, 2001). In human cytokine therapy, based on the administration of cytokines, is used for the treatment of several pathological conditions (Table 2). Cancer therapies, which often involve treatment with pro-inflammatory cytokines (mainly IFN-α, IL-2 and TNF-α), have been associated with flu-like and depressive symptoms, as well as signs of cognitive impairment (Meyers, 1999 -Table 2). Administration of IFN-α, which is primarily used in the treatment of chronic hepatitis C, for produced symptoms of cognitive impairment, anxiety, fatigue and depressed mood (Van Gool et al., 1999; Bonaccorso et al., 2000 -Table 2). The fact that the symptoms of sickness behavior almost immediately are disap-

Table 2. Neuropsychiatric side effects of immunotherapies based on the administration of pro-inflammatory cytokines

Immunotherapy	Clinical condition treated	Neuropsychiatric side effects
IL-1	Cancer	Cognitive impairment
IL-2	Cancer	Fatigue
	AIDS	Anhedonia
		Dysphoria
		Cognitive impairment
TNF-α	Cancer	Fatigue
		Anorexia
IFN-α	Cancer	Fatigue
	Chronic hepatitis C	Depressed mood
	Multiple sclerosis other viral infections	Anxiety
		Social withdrawal
		Irritability
		Anorexia
		Cognitive impairment (mental slowing, lack of concentration, memory impairment)
IFN-β	Multiple sclerosis	Fatigue
		Depressed mood
		Cognitive impairment
IFN-γ	Chronic granulomatous disease, AIDS	Fatigue, depression, cognitive impairment, psychosis, suicidal ideation

IL: interleukin, TNF: tumor necrosis factor, IFN: interferon (Adapted and modified from Kronfol and Remick, 2000; Schiepers et al., 2005).

peared after termination of cytokine administration, strongly suggests a causal role for cytokines in producing the depressive symptoms (Yirmiya, 2000). With respect to the role of pro-inflammatory cytokines in inducing the symptoms of sickness behaviour, Banks et al. (2003) have studied the effects of IL-1 on learning and memory, as disturbances in these cognitive processes appear to be largely dependent on the central action of this specific cytokine. The authors suggest that the memory-impairing effects of IL-1 may be mediated by the posterior division of the septum, as selective uptake of blood-borne IL-1α was observed in the brain area. In another study investigating the effects of IL-1 on cognitive functions in rats, Song (2002) found that the memory impairments following central administration of IL-1 may be related to IL-1-induced hypercortisolaemia, as the cognitive disturbances were reversed not only by IL-1ra, but also by a corticosteroid receptor antagonist. Indeed, elevated plasma concentrations of corticosteroids, e.g. during depression, have been found to cause memory deficits in humans (Luine, 1994; Newcomer et al., 1999). The demonstration that pro-inflammatory cytokines as immunemodulator are able to influence behavioral responses has raised the question about the link depressive disorders between cytokines.

POSSIBLE MECHANISMS UNDERLYING CYTOKINE-INDUCED DEPRESSION

Cytokines and monoaminergic alterations

Depression is characterized by disorders in norepinephrine (NE), 5-HT and dopamine (DA) neurotransmission as well as their receptor regulation (Ressler and Nemeroff, 1999, 2000; Gavin et al., 2000, Dursun et al., 2001). It has been hypothesized that immune activation may be causally related to these signalling disorders, as pro-inflammatory cytokines have been implicated in alterations in NE, 5-HT and DA in brain regions assumed to be involved in depression, including the hypothalamus, hippocampus, amygdala and prefrontal cortex (Dunn et al., 1999). Systemic administration of IL-1β stimulated one of the immediate early genes, c-fos, expression in several brain regions, including the paraventricular nucleus of the hypothalamus (PVN), bed nucleus of the stria terminalis, and central nucleus of the amygdala (Day et al., 1999; Ericsson et al., 1997; Xu et al., 1999). Moreover, this treatment increased NE activity within the PVN, medial basal and lateral hypothalamic nuclei (Kaur et al., 1998; Lacosta et al., 1998a,b; Dunn, 2001), and increased DA utilization within the hypothalamus and prefrontal cortex (Kabiersch et al., 1988; Masana et al., 1990) and 5-HT activity within the hypothalamus, prefrontal cortex and hippocampus (Carmelia et al., 1991; Zalcman et al., 1994; Brebner et al., 2000; Dunn, 2001). Paralleling the actions of systemic treatment, i.c.v. IL-1β increased hippocampal 5-HT release (Linthorst et al., 1995), while direct application of IL-1β into the rat anterior hypothalamus increased the release of NE, 5-HT and DA (Shintani et al., 1993). Similarly, when directly injected into the medial basal hypothalamus, IL-1β augmented 5-HT and DA release (Mohankumar and Quadri, 1993; Mohankumar et al., 1993), and local injection of IL-1β increased NE release within the medial prefrontal cortex (Kamikawa et al., 1998). Like IL-1β, systemic TNF-α administration also increased central monoamine activity, including NE and 5-HT activity within the PVN, central amygdala, locus coeruleus (LC) and prefrontal cortex (Hayley et al., 1999), and altered tryptophan (TRP) levels within the hippocampus and hypothalamus (Dunn, 2001; Leonard, 2001). Similarly, i.c.v. TNF-α stimulated amine, particularly within hypothalamic nuclei (Hayley et al, 1999) lowered activity of presynaptic 5-HT neurons and changed in 5-HT re-uptake from the synaptic cleft, as well as alterations concerning postsynaptic 5-HT receptors (Kubera and Maes, 2000). Synthesis of 5-HT is largely dependent on the availability of its precursor TRP to the brain. Cytokines, including IL-1, IL-2, IL-6 and IFNs, have been found to reduce TRP availability by activation of the TRP-metabolising enzyme indoleamine-2,3-dioxygenase (IDO). Thus, overstimulation of IDO by cytokines may lead to depletion of serum TRP, which is accompanied by a significant reduction of 5-HT synthesis (Heyes et al., 1992; Stone and Darlington, 2002; Myint et al., 2003). Indeed, IDO is induced both at the periphery and in the brain of cytokine-treated animals and intracerebroventricular injection of IFNα was found

to reduce brain levels of serotonin in several regions of the rat brain. Significant decreases in serum TRP concentrations were also found in cancer patients undergoing cytokine therapy (Capuron et al., 2002). The amplitude of TRP decreases was correlated with the severity of depressive symptoms. Given the data indicating that TRP depletion is associated with the development of depressive symptoms and associated behavioral disturbances in patients (Delgado et al., 1991; Moreno et al., 1999; Moore et al., 2000), it is possible that at least some of cytokine-induced depressive symptoms are mediated by IDO-induced TRP depletion. Furthermore, increased monoamine oxidase (MAO) activity results in lower concentrations of 5-HT and catecholamines (Wild and Benzel, 1994). Thus, besides directly attenuating 5-HT availability, IDO may also contribute to the monoaminergic disorders that are observed in depression in an indirect manner. From the above findings, it may be assumed that IDO represents a link between the immune system and the neurochemical alterations that are associated with depression (Castanon et al., 2002; Wichers and Maes, 2004). In addition to presynaptic serotonergic disturbances, which may be related to the enhanced activity of IDO, peripheral immune activation may also be involved in modifying the activity of the 5-HT transporter (Mossner et al., 1998) and/or the number or sensitivity of postsynaptic 5-HT receptors, including the 5-HT_{1A} and 5-HT_{2A} receptors (Abe et al., 1999). Such changes may influence 5-HT and might thus represent another possible cause of serotonergic depletion in depression (Kubera and Maes, 2000). Most of the studies described thus far have pointed to cytokine treatment provoking increase monoamine release. Thus, it appears that proinflammatory cytokines may induce depressive symptomatology, at least in part, through the modulation of monoaminergic neurotransmission (Bonaccorso et al., 2000).

Cytokines and prolonged HPA axis hyperactivity

Depression is often associated with HPA axis hyperactivity, which is characterized by hypercortisolaemia (Murphy, 1991). Whereas hyperactivity of the HPA axis may normally be controlled by means of an negative feedback mechanism, dysregulation of this feedback mechanism appears to occur in depressive disorders (Young et al., 1991). Pro-inflammatory cytokines are potent activators of the HPA axis (Sapolsky et al., 1987), and therefore play a critical role in activating the HPA axis in depression. Furthermore, there is evidence that cytokines counteract the negative feedback action of corticosteroids on the HPA axis, which leads to HPA axis dysregulation (Miller et al., 1999). The mechanism by which cytokines may disturb negative feedback of corticosteroids on the HPA axis, may involve the induction of corticosteroid receptor resistance in the hypothalamus and pituitary gland, brain areas that normally mediate HPA axis downregulation (Miller et al., 1999). Alterations in the functioning of these central corticosteroid receptors could then lead to decreased sensitivity of the hypothalamus and pituitary to elevated corticosteroids, thereby resulting in lack of negative feedback (Miller et al., 1999). Cytokine-induced activation of IDO may also be involved in the attenuation of negative feedback inhibition of circulating corticosteroids on the HPA axis, through production of the kynurenine metabolite QUIN. QUIN, which is a potent N-methyl-d-aspartate (NMDA) receptor agonist, is hypothesized to cause hippocampal atrophy and loss of corticosteroid receptors (Wichers and Maes, 2004). Thus, besides the induction of corticosteroid receptor resistance, increased QUIN may represent an additional mechanism by which cytokines may disrupt the negative feedback function of the HPA axis, thereby causing HPA axis hyperactivity (Wichers and Maes, 2004). Sensitisation to the effects of pro-inflammatory cytokines, e.g. IL-1 and IL-6, may also contribute to the occurrence of HPA axis hyperactivity.

TREATMENT OF CYTOKINE-INDUCED DEPRESSION

Antidepressants as immunomodulators

The data, depressive illness has been closely associated with increased levels of pro-inflammatory cytokines (Maes et al, 1999), suggests a key role for cytokines in pathophysiological characteristics of depression. If cytokines indeed are involved in the pathogenesis of depressive symptoms, it might be expected that antidepressants for the treatment of

depressive disorders would attenuate cytokine production and their action in clinical conditions and animal experiments. Accumulating evidence concerning the influence of antidepressants on cytokines in depressed patients and experimental animals and on in-vitro cytokine production has been shown that the antidepressant treatment usually normalizes immune activation that occur in depression.

From in vitro studies that when human monocytes are incubated with different classes of antidepressants together with lipopolysaccharide (LPS) the synthesis and release of IL-1, IL-2, IL6 and TNF-α is markedly inhibited (Xia et al, 1996). Furthermore, the enhanced synthesis of IL-1 and IL-2 from spleen cells that occurs in rats that had been subject to chronic mild stress is reversed following chronic treatment with imipramine (Kubera et al., 1996). In addition, another in vitro studies with human whole blood have reported that TCAs (e.g. imipramine and clomipramine) and SSRIs (such as citalopram and sertraline) are able to inhibit the production of the pro-inflammatory cytokines IL-1, IL-2, IL-6, TNF-α and IFN-γ, while stimulating the anti-imflammatory cytokine IL-10 (Kubera and Maes, 2000). Long-term administration of the tricyclic antidepressant (TCA) imipramine or the selective serotonin reuptake inhibitor (SSRI) fluoxetine in rats has been reported to attenuate LPS induced sickness behavior and neuroendocrine alterations (Yirmiya, 1996). Shen et al. (1999) reported that chronic treatment with the TCA desipramine inhibits the LPS-induced TNF-α production and potentiates the secretion of IL-10 in response to LPS administration. The desipramine pretreatment also attenuated the LPS-induced behavioural response. In contrast, chronic treatment with imipramine or fluoxetine had no effect on the LPS-induced splenic TNF-α and IL-1b mRNA expression, although fluoxetine was effective in attenuating some of the effects on behaviour and also on the LPS-induced activation of the HPA axis (Yirmiya et al., 2001). Maes et al. (1997) reported that treatment with fluoxetine and trazodone had no effect on serum IL-6 and IL-1Ra levels, which were increased in depression patients (Maes et al., 1997). The plasma level of IFN-γ was reported not to be different between healthy controls and depressed patients, and treatment with moclobemide for up to 3 months did not affect the IFN-γ concentration (Landmann et al., 1997). In contrast, two other studies found that antidepressant treatment significantly lowered the initially increased serum IL-6 concentrations in depressed patients (Sluzewskaet al., 1996; Frommberger et al., 1997; Kenis and Maes, 2002). In contrast with the above findings, which strongly suggest a role for antidepressants in the downregulation of immune activation and pro-inflammatory cytokine production, increases in IL-1 and IL-3 production have been detected after administration of clomipramine in depressed patients (Weizman et al., 1994). Discrepancies in study results may be related to differences in methodology, the heterogeneity of the study and the patient status regarding the use of antidepressants. Obviously, more studies are needed to fully clarify the influence of antidepressant treatment on cytokines. However, there is limited experimental and clinical evidence to suggest that antidepressants may attenuate cytokine-induced depressive symptoms by exerting negative immunoregulatory effects (indicated in the Table 3).

Possible mechanisms of immune modulation by antidepressants

From the point of view that antidepressants may alleviate depressive symptoms by modulating cytokine secretion in individuals suffering from depression, then which mechanisms may account for this action? Several possible mechanisms have been suggested. First, antidepressants may reverse cytokine induced alterations in central corticosteroid receptor expression and responsivity, thereby discontinuing cytokine induced corticosteroid receptor resistance in the hypothalamus and pituitary gland. By doing so, antidepressants may restore the corticosteroids-mediated negative feedback inhibition of the HPA axis, which causes HPA axis activity to return to normal (Barden, 1999; Castanon et al., 2002; Schiepers et al., 2005). First, most antidepressants induce changes in central monoaminergic signalling, which itself might modulate immune reactivity and central actions of cytokines (Castanon et al., 2002; Schiepers et al., 2005). Second, antidepressants may also reverse cytokine induced alterations in central corticosteroid receptor expression and responsivity, thereby discontinuing cytokine

Table 3. Summary of studies that examined cytokine levels on in vitro experiment and in human and animal experiments

Study	Type	Antidepressant	Cytokine examined	Effects	References
in vitro	T lymphocytes, monocytes in human	TCAs (clomipramine imipramine citalopram)	IL-1 IL-2 IL-6 TNF-α	Decreased	Xia et al., 1996
in vitro	Spleen cells in rat	Imipramine	IL-1 IL-2	Decreased	Kubera et al., 1996
in vitro	Whole blood in human	TCAs (clomipramine imipramine) SSRIs (citalopram sertraline)	IL-1 IL-2 IL-6 TNF-α IFN-γ IL-10	Decreased Increased	Kubera and Maes, 2000
Animal model	Spleen cells in rat	TCA (imipramine) SSRIs (fluoxetine)	IL-1β TNF-α	No effect	Yirmiya, 1996
Animal model	Stimulated with LPS	TCA (desipramine)	TNF-α IL-10	Decreased Increased	Shen et al., 1999
Animal model	Stimulated with LPS	TCA (imipramine) SSRIs (fluoxetine)	IL-1β TNF-α	No effect	Yirmiya et al., 2001
Depressed patients	Plasma cytokine level	Fluoxetine/trazodone	IL-6 IL-1Ra	No effect	Maes et al., 1997
Depressed patients	Plasma cytokine level	Moclobemide	IFN-γ	No effect	Landmann et al., 1997
Depressed patients	Plasma cytokine level	Various type	IL-6	Decreased	Frommberger et al., 1997
Depressed patients	Plasma cytokine level	Fluoxetine	IL-6	Decreased	Sluzewska et al., 1997
Depressed patients	Plasma cytokine level	Clomipramine	IL-1 IL-3	Increased	Weizman et al., 1994

IL: interleukin, TNF: tumor necrosis factor, IFN: interferon, TCA: Tricyclic antidepressants, SSRIs: selective serotonin reuptake inhibitors (Adapted and modified from Kenis and Maes, 2002).

induced corticosteroid receptor resistance in the hypothalamus and pituitary gland. By doing so, antidepressants may restore the corticosteroids-mediated negative feedback inhibition of the HPA axis, which causes HPA axis activity to return to normal (Barden, 1999; Castanon et al., 2002; Schiepers et al., 2005). A third mechanism by which antidepressants may indirectly attenuate the central effects of pro-inflammatory cytokines might reduce cytokine-induced NO and/or PGE2 production which are centrally produced by inflammatory cells in the CNS and by peripherally produced cytokines. Reducing NO and/or PGE2 secretion in the brain may therefore contribute to an attenuation of cytokine-mediated depressive symptomatology (Leonard, 2001; Castanon et al., 2002; Schiepers et al., 2005). Another mechanism by which antidepressants may reverse the central effects of cytokines, might be the inhibition of cytokine-induced IDO activation, as activation of IDO by cytokines enhances the catabolism of the 5-HT's precursor tryptophan (Konan and Taylor, 1996; Castanon et al., 2002; Schiepers et al., 2005). However, these mechanisms explain the role of antidepressants' immune modulation, the mechanisms of antidepressants on cytokine production and actions have to be further investigated. Whether antidepressants' immune effects are a side effect or a significant clinical activity still remains to be elucidated.

Cytokine therapy

If antidepressants indeed exert immunoregulatory effects, this may offer new perspectives for dealing with the side effects accompanied by cytokine therapies (or immunotherapy) in certain medical conditions (e.g. cancer or hepatitis C therapies). Treatment of antidepressants in patients treated with high doses of cytokines in cytokine therapy is able to prevent the occurrence of cytokine-induced depressive symptomatology (Capuron et al., 2002). So far, there is no treatment approach regarding

the administration of antidepressants to patients receiving cytokine therapy (Schiepers et al., 2005).

Anticytokine therapy

In several specific medical conditions such as e.g. rheumatoid arthritis (RA) or inflammatory bowel disease (IBD), cytokine inhibitors and cytokine antagonists may be useful for new treatment approach. Administration of TNF-α blockers, such as etanercept and infliximab (RemicadeR) to patients suffering from RA and IBD, respectively, was capable of attenuating depressive symptoms and accompanied immune activation in these medical conditions (Rogler and Andus, 1998; Weinblatt et al., 1999). Although to date the putative antidepressant effect of anticytokine therapy has not yet been investigated, antagonism of cytokine may reduce depressive symptomatology. Furthermore, the administration of anti-inflammatory cytokines, such as IL-4 and IL-10, which have a rather broad spectrum of action, may also be used in anticytokine therapies. However, detailed research is needed to be undertaken in order to establish the therapeutic value of cytokine inhibitors concerning the treatment of depressive disorders (Schiepers et al., 2005).

CONCLUSION

Depression is also characterized by specific alterations in the functioning of neurochemical and neuroendocrine systems including monoaminergic neurotransmission, the HPA axis and peripheral immune activation, through the release of pro-inflammatory cytokines. Although accumulating evidence supports a role for immune activation, through the production of pro-inflammatory cytokines, in the aetiology and pathophysiology of depression is still debatable. The question whether cytokines play a critical role in depressive illness or represent epiphenomenon without major significance should be established. Future research should also examine the effects of antidepressants on immune function and cytokine secretion, as well as the clinical effects of cytokine inhibitors and antagonists on the psychological and pathophysiological features of depression. However, cytokine's depression regulation has created new perspectives in the study of the psychological and pathophysiological mechanisms that are associated with depression, as well as the prospect for developing a new generation of antidepressants.

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