EVIDENCE FOR AN IMMUNE RESPONSE IN MAJOR DEPRESSION: A REVIEW AND HYPOTHESIS

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Abstract


1. This paper reviews recent findings on cellular and humoral immunity and inflammatory markers in depression.

2. It is shown that major depression may be accompanied by systemic immune activation or an inflammatory response with involvement of phagocytic (monocytes, neutrophils) cells, T cell activation, B cell proliferation, an "acute" phase response with increased plasma levels...
of positive and decreased levels of negative acute phase proteins, higher autoantibody (antinuclear, antiphospholipid) titers, increased prostaglandin secretion, disorders in exopeptidase enzymes, such as dipeptidyl peptidase IV, and increased production of interleukin (IL)-1β and IL-6 by peripheral blood mononuclear cells.

3. It is hypothesized that increased monocytic production of interleukins (IL-1β and IL-6) in severe depression may constitute key phenomena underlying the various aspects of the immune and "acute" phase response, while contributing to hypothalamic-pituitary-adrenal-axis hyperactivity, disorders in serotonin metabolism, and to the vegetative symptoms (i.e. the sickness behavior) of severe depression.

Keywords: acute phase response, cellular and humoral immunity, depression, inflammation, interleukin-1β, interleukin-6, psychoneuroimmunology.

Abbreviations: adrenocorticotropic hormone (ACTH), albumin (Alb), angiotensin converting enzyme (ACE), acute phase (AP), acute phase protein (APP), α1-antitrypsin (α1AT), competing amino acids (CAA), corticotropin releasing hormone (CRH), dexamethasone suppression test (DST), dipeptidyl peptidase IV (DPP IV), haptoglobin (Hp), hemopexin (Hpx), hypothalamic-pituitary-adrenal (HPA), indoleamine dioxygenase (IDO), interleukin (IL), lymphocyte transformation tests (LTT), natural killer cell activity (NKCA), peripheral blood mononuclear cells (PBMC), retinol binding protein (RBP), serotonin (5-HT), transferrin (Tf), tryptophan (TRP).

1. Introduction

The last decade has produced a series of studies which indicate that there are reciprocal relationships between the immune system, resistance to physical illness and brain function in man (Ader, 1981). Recent developments in psychoneuroimmunology suggest that major depression and stressful life events may modify immune functions (Ader, 1981; Tecoma and Huey, 1985) and may effect susceptibility to physical illness (Gunderson and Rahe, 1974; Tecoma and Huey, 1985). Hence, the above studies support the view that psychological state may alter immune function and, consequently, lead to physical illness (Khansari et al., 1990).

The effects of mood state on immune function may be part of multiple and reciprocal neuroimmunoneuroendocrine feedback loops. Indeed, there is a shared communication between brain and immune function: the brain may affect the immune system through - amongst others - secretion of hormones, such as adrenocorticotropic hormone (ACTH) and, consequently, glucocorticoids, β-endorphin, prolactin, growth hormone, and through noradrenergic inputs (Riley, 1981; Berczi, 1986; Berkenbosch et al., 1986; Plotnikoff et al., 1986; Calabrese et al., 1987). The immune system may produce thymic, monocytic and lymphocytic constituents that may alter brain noradrenergic, serotonergic and endocrine function (Besedovsky et al., 1983; Miller and Norin, 1989).

2. Major Depression and Immunity

A substantial amount of research concerned with immunity in relation to depression has been conducted over the last decade; the findings may be categorized as follows:
Depression is accompanied by immunosuppression (Asnis and Miller, 1989; Kronfol et al., 1983; Schleifer et al., 1984). Kronfol et al. (1983) were the first to show that major depressed subjects exhibit blunted lymphoproliferative responses as indicated by lymphocyte transformation tests (LTT). These findings were replicated by several other groups (Schleifer et al., 1984; Maes et al., 1989; 1991a). These disorders have been ascribed to the fact that the absolute T helper lymphocyte cell counts were reduced in major depression (Schleifer et al., 1989; Keller, 1989). Schleifer et al. (1984) described lower numbers of T and B-cells, determined by means of rosette-formation procedures. However, using the same techniques, Sengar et al. (1982) were unable to find differences in the number of T and B cells between normal controls and depressed subjects. Recently, it has been shown that major depression is characterized by diminished natural killer cell activity (NKCA) (Irwin and Gillin, 1987). These findings have been replicated by other laboratories (Kronfol et al., 1989; Maes et al., 1992g). The above results suggest that major depression may be accompanied by ex vivo immunosuppression as assessed by means of LTT and NKCA.

Depression may be regarded from an autoimmune conceptual frame of reference. Von Brauchitsch (1972) was the first to report a higher incidence of antinuclear factor in endogenous depression. The presence of antinuclear autoantibodies was also shown by Deberdt et al. (1976) and Gastpar and Muller (1981). DeLisi et al. (1985) found antibrain antibodies in some patients with affective disorders.

Other findings may be interpreted as to indicate that severe depression is accompanied by an in vivo activation of cell-mediated immunity. Preliminary results of flow cytometry have shown that major depression is characterized by an increased CD4+/CD8+ (T helper/T suppressor) cell ratio (Tondo et al., 1988; Darko et al., 1988; Muller et al., 1989). It was observed that the higher CD4+/CD8+ ratio in depression was determined by an increased percentage of CD4+ cells (Muller et al., 1989; Darko et al., 1988) or by a lowered percentage of CD8- cells (Tondo et al., 1988). Some reports that have examined the peripheral blood leukocyte subset profile of major depressed patients found a higher number of leukocytes (Kronfol and House, 1989; Irwin et al., 1990b), neutrophils (Kronfol et al., 1983; Kronfol and House, 1989; Irwin et al., 1990a), and monocytes (Muller et al., 1989). The hypothesis that activation of cellular immunity may occur in major depression is further corroborated by the findings of increased plasma and urinary neopterin concentrations (Duch et al., 1984; Dunbar et al., 1992). Increased neopterin secretion is a very sensitive marker of activation of cell-mediated immunity (Wachter et al., 1992). Finally, there were several reports of increased secretion of constituents of activated
monocytes/macrophages, i.e. prostaglandins (e.g. PGE2) and thromboxane B2 (Lieb and Karmali, 1983; Calabrese et al., 1986; Linnoila et al., 1983; Abdulla and Hamadah, 1975). Smith (1991) has hypothesized that excessive secretion of cytokines (e.g. interleukin-1) by activated cells of the monocyte/macrophage lineage may trigger depression.

3. Aims and Results of the Present Studies

The present studies have been carried out in order to investigate the pathophysiology underlying the diminished ex vivo (i.e. LTT and NKCA) immune tests, and the status of cellular and humoral immunity in depression. As our preliminary results were indicative of in vivo systemic immune activation, and, consequently, opposite to the "immunosuppression" hypothesis, the authors decided to replicate the preliminary findings in large, well-controlled studies, and to investigate other characteristics of immune activation.

This research provided evidence that major depression, and in particular melancholia, is characterized by in vivo immune activation with involvement of phagocytic, T and B cells, acute phase proteins, exopeptidase enzymes, increased autoantibody titers, increased secretion of monocytic interleukins (Il's), such as Il-1β and Il-6, together with ex vivo downregulated NKCA and LTT. Excessive secretion of monocytic Il-1β and Il-6 are proposed as the causes of many of the above immune, inflammatory or autoimmune responses in depression. The most important findings are discussed in the following.

3.1. Leukocytes, T Cells and Major Depression

The authors have replicated that major depression is characterized by a significantly increased number of leukocytes (Kronfol and House, 1989; Irwin et al., 1990b), and have delineated that this phenomenon is determined by increased numbers of phagocytic cells, i.e. neutrophils and monocytes (Maes et al., 1992a; 1992h).

Our research (Maes et al., 1992e) has replicated previous findings of increased CD4+/CD8+ ratio in severe depression (Tondo et al., 1988; Darko et al., 1988; Muller et al., 1989). The melancholic patients presented with a significantly higher ratio (i.e. 2.78 ± 0.34) than normal controls (i.e. 1.88 ±0.24) (Maes et al., 1992e). A comparison with the reference range, established in the UCLA Medical Immunology Laboratory (Giorgi, 1986) shows that the ratio of those melancholic patients hovers somewhere between the 90 and 95 percentiles (Maes et al., 1992e). Recently, Charles et al. (1992) observed that the CD4+/CD8+ ratio was significantly and positively related to severity of illness. Like Muller et al. (1989), we have found that the increased ratio in depression is, in part, determined by increased absolute numbers and percentages of CD4+ cells (Maes et al., 1992e). The latter phenomenon, in turn,
was caused by an upregulation of CD4^+CD45RO^+ T memory cells. Like Tondo et al. (1988), we found that the increased ratio was, in part, related to a reduction in CD8^+ or a CD8^+-subset, i.e. CD8^+CD57^- T suppressor cells (Maes et al., 1992a; 1992e).

There was an imbalance between CD^+CD45RO^+ memory T cells and CD4^+CD45RA^+ virgin T cells resulting from an increase in clone size of the former (Maes et al., 1992a; 1992e). As the phenotypic change from CD4^+CD45RA^+ into CD4^+CD45RO^+ cells may occur after immune activation (Byrne et al., 1988; Clement et al., 1988), these results may refer to an activated state of T cells in major depression. The reduction in CD8^+ T suppressor cells may refer to a relative loss of immune suppression (Roitt et al., 1985). Therefore, the present results could also point toward a relationship between alterations in the above leukocyte subsets and the autoimmune response observed in some depressed subjects.

The author's laboratories have reported that major depression and in particular melancholia, is characterized by T cell activation. Indeed, this illness is accompanied by a significantly increased number and percentage of activated T lymphocytes, i.e. CD25^- (IL-2 receptor bearing cells) and HLA-DR^- T cells (Maes et al., 1992a; 1993f): II-2Rs are expressed on the cell membrane of activated T lymphocytes (Robb, 1985; Lowenthal et al., 1985; MacKeen et al., 1986), while the HLA-DR phenotype is expressed only on mature, activated peripheral T cells (Ko et al., 1979). Moreover, major depression is characterized by significantly higher circulating levels of soluble IL-2-receptors, another marker of T cell activation (Maes et al., 1991c). Recently, these findings were replicated by Nassberger and Traskman-Bendz (1993), who found increased plasma sIL-2R levels in depressed suicide attempters.

3.2. Interleukins and Major Depression

It has been suggested that disturbances in cytokine synthesis or secretion (e.g. II-1B, II-6) can best be studied under dynamic conditions by stimulating immunocompetent cells with polyclonal activators and that the pattern of cytokine production offers an index of in vivo cytokine secretion (De Groote et al., 1992). Therefore, the authors determined the secretion of II's in mitogen-stimulated peripheral blood mononuclear cells (PBMC) of depressed subjects and normal controls. We observed that major depressed patients, and in particular melancholics, exhibited a significantly higher production of II-1B and IL-6 in culture supernatant of mitogen-stimulated PBMC than normal controls (Maes et al., 1991b; 1993e).

Mitogen-induced lymphocyte transformation and production of IL-1B and sII-2R in supernatant after the administration of dexamethasone were significantly higher in depressed than in normal subjects (Maes et al., 1991b). These findings may suggest the existence of glucocorticoid resistance in lymphocytic function of depressives and may refer to the fact that
activated lymphocytes are less sensitive to glucocorticoid inhibition (Levine and Claman, 1970). We have argued that this glucocorticoid resistance in depression may be related to higher IL-1β, and IL-6 production (Maes et al., 1991b). These interleukins are known to counteract glucocorticoid suppressive effects upon cells of the monocytic and lymphocytic lineage (Bloemena, 1989; Nieto and Lopez-Rivas, 1989; Almawi et al., 1991). Another hypothesis is that the relative glucocorticoid resistance in lymphoproliferative responsivity in depression is related to decreased lymphocyte glucocorticoid receptor sites which may occur in that illness (Lowy et al., 1987; Gormley et al., 1985; Whalley et al., 1986).

3.3. B Cells, Autoimmunity and Major Depression

Our studies revealed that the number or percentage of various B cell subsets were significantly higher in depression, and in particular, in melancholia as compared with normal controls (i.e. HLA-DR+, CD19+, CD20+ and CD21+ B cells) (Maes et al., 1992a; 1992f). These results may indicate that major depression is accompanied by B cell proliferation.

Our laboratory has replicated the findings on higher antinuclear autoantibody titers in major depressed subjects (Deberdt et al., 1976; Gastpar and Muller, 1981) and reported increased activity of antiphospholipid (i.e. anticardiolipin, antiphosphatidylserine and antithromboplastin) autoantibodies in depression compared to normal controls (Maes et al., 1991c; 1993b). Joyce et al. (1992) found significantly higher plasma levels of immunoglobulin G in major depressed subjects than in normal controls or alcoholic patients. The above findings may indicate B cell proliferation and a mild autoimmune response in some major depressed patients.

3.4. Acute Phase Response and Major Depression

We have reported disorders in positive acute phase proteins (APPs) and in negative APPs or visceral proteins in major depression (Maes et al., 1991f; 1992b; 1992d). Major depression is associated with higher plasma levels of haptoglobin (Hp), ceruloplasmin (Cp), hemopexine (Hpx), and α1-antitrypsin (α1AT), and lower plasma levels of negative APPs such as transferrin (Tf), albumin (Alb), and retinol binding protein (RBP). Of the various APPs measured in our studies, the most prominent disorders were found in Hp plasma levels: up to 45% of the melancholic subjects showed Hp plasma levels that fell outside the reference range. Increased levels of α1-acid glycoprotein, another positive AP reactant (Nemeroff et al., 1990; Kehoe et al., 1991) and lower levels of serum Alb (Swartz, 1990) were also described in depression. These authors, however, did not interpret their findings in relation to a possible AP response in major depression. Our findings of increased APP levels in major depression are also replicated by Joyce et al. (1992).
It is known that elevated levels of positive APPs and a drop in visceral proteins are important indicators of acute or chronic inflammatory states (Kleesiek and Greiling, 1984; Romette et al., 1986; Mackiewicz et al., 1988). Consequently, these results together with the IL and prostaglandin findings may indicate that some major depressed subjects suffer from an inflammatory (the "acute" phase) response.

3.5. Peptidases and Major Depression

It has become clear that proteolytic enzymes are involved in activation, proliferation and communication between T cells and monocytes (Scharpé et al., 1990). Therefore, we investigated the serum activity of two exopeptidases involved in these immune functions.

First, major depression is characterized by lower serum dipeptidyl peptidase IV (DPP IV) activity (Maes et al., 1991d). A decreased DPP IV activity is also seen in inflammatory and autoimmune disorders (Maes et al., 1991d). The physiological role of this enzyme may encompass: (i) induction and activation of some cytokines, such as IL-2, which controls lymphocyte differentiation and proliferation (Schon et al., 1984; 1985; 1989). Therefore, decreased DPP IV activity may play a role in the diminished LTT in severe depression; (ii) DPP IV may cleave IL-1 (De Meester, 1992), and, consequently, lower DPP IV activity in major depression may be related to increased IL-1β secretion. On the other hand, a drop in serum DPP IV may be caused by an acute increase of lymphokines, which are the physiological substrates of DPP IV (Kubota et al., 1992).

Second, our laboratory found lower angiotensin converting enzyme (ACE) activity in melancholia (Maes et al., 1992c). ACE is a key enzyme in the renin-angiotensin system (RAS). RAS activity is generated through a cascade reaction: angiotensinogen is hydrolyzed in the circulation by renin to form AgI; ACE, in turn, removes a dipeptide from the C terminal end of AgI to form AgII (Deschepper and Ganong, 1988). ACE is a rather aspecific dipeptidyl carboxypeptidase that cleaves off C-terminal dipeptides from various substrates such as opioid peptides and inflammatory mediators (Ganten et al., 1981). Disorders in serum ACE activity are observed in many acute and chronic inflammatory disorders (Neels et al., 1984). Moreover, it has been shown that AgII stimulates the release of serotonin from synaptosomes, stimulates prostaglandin synthesis (Muller and Nistico, 1989), acts on central parts of HPA-axis inducing immediate dose related increments in ACTH (Muller and Nistico, 1989), and potentiates catecholamine (CA) release and synthesis in the central nervous system and SAS (Muller and Nistico, 1989; Carey et al., 1989). The above findings could prove that RAS takes part in the pathophysiology of melancholia through effects upon HPA-axis function, SAS activity, serotonin turnover, and immune system.
3.6. Sensitivity and Specificity of the Immune Variables

Table 1 lists the diagnostic performance of various immune parameters for melancholia versus normal controls. Listed are the sensitivity, specificity and predictive value (PV) for a positive test result and the relevant statistics (Maes et al., 1986). These figures have been published in our articles or were re-computed on the data sets described in these reports. The different indices of systemic immune activation are rather sensitive (62%-83%) and specific (≥90%) for melancholia compared with the normal state.

It should be emphasized that the depression-related changes in some of the above immune or inflammatory parameters are not comparable to those observed in immune disorders. For example, although our results point towards a higher expression of antiphospholipid antibodies during depression, a much lower incidence of positive patients than in classical autoimmune disorders, such as systemic lupus erythematosus, is found. Moreover, by using a conservative value for phospholipid positivity, the patients' autoantibody titers were, on the whole, within the normal range (Maes et al., 1993b). Also, the increase in the concentration of serum sIL-2Rs in depression is modest and not comparable to the much higher levels observed in some inflammatory disorders (Maes et al., 1991c). The increased CD4+/CD8+ ratio in depression is not as high as the values observed in, for example, rheumatoid arthritis (Caldwell et al., 1992). Hp plasma levels, on the other hand, are remarkably increased in major depression (Maes et al., 1992d; Joyce et al., 1992). The decrease in DPP IV is comparable to that seen in various autoimmune and inflammatory disorders (De Meester, 1992). Although it is difficult to compare in vitro interleukin secretion between different laboratories, it may be suggested that the higher secretion rates in melancholia of IL-1β and, in particular, IL-6 are comparable to those seen in inflammatory disorders such as rheumatoid arthritis (Zangerle et al., 1992).

3.7. Conclusions

Along the diagnostic spectrum (minor depression to major depression without melancholia to major depression with melancholia) there is a systemic activation of the immune system in parallel with the intensity of severity of illness. In depression per se (i.e. minor + major depression) there is an increase in number of leukocytes, monocytes, neutrophils, higher serum sIL-2R, increased CD4+/CD8+ ratio, higher percentage of CD4+ cells, lower percentage of CD8+ T suppressor cells, higher number of various B cell subsets, higher autoantibody titers and lower levels of negative APPs. Major depression per se is characterized by a recruitment of T memory cells, the appearance of previously unexpressed T cell surface markers, i.e. HLA-DR+, and the acquisition of IL-2 receptors on T cells, a clonal expansion of effector T and B cells, a higher expression of positive APPs, increased prostaglandin secretion, and lower serum
<table>
<thead>
<tr>
<th>Variables</th>
<th>Specificity</th>
<th>%</th>
<th>%</th>
<th>PV+ (%)</th>
<th>K</th>
<th>Statistic</th>
<th>P- Value</th>
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<tr>
<td>Increased 11-18 production in supernatant of mitogen-stimulated peripheral leukocytes</td>
<td>90.0</td>
<td>0.79</td>
<td>2.9</td>
<td>0.009</td>
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<tr>
<td>Increased CD4+, CD8*, CD4+, CD45- and lower CD8+ CD57 percentages</td>
<td>68.0</td>
<td>95.0</td>
<td>62.0</td>
<td>3.3</td>
<td>0.002</td>
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<tr>
<td>Increased CD25+ and HLADR+ T cell numbers</td>
<td>64.1</td>
<td>90.9</td>
<td>56.0</td>
<td>2.7</td>
<td>0.008</td>
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<tr>
<td>Higher serum levels of soluble IL-2 receptor</td>
<td>81.8</td>
<td>92.9</td>
<td>75.0</td>
<td>3.1</td>
<td>0.005</td>
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<tr>
<td>Higher CD19+, CD20+, CD21+ and HLADR+ B cell numbers</td>
<td>63.0</td>
<td>94.7</td>
<td>92.0</td>
<td>5.4</td>
<td>0.006</td>
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<tr>
<td>Higher antinuclear and anticardiolipin antibodies</td>
<td>81.8</td>
<td>92.9</td>
<td>94.1</td>
<td>5.3</td>
<td>0.005</td>
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<tr>
<td>Hyperhaptoglobinemia</td>
<td>67.0</td>
<td>95.8</td>
<td>100.0</td>
<td>3.4</td>
<td>0.005</td>
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<tr>
<td>Hyperhaptoglobinemia and hypotransferrinemia</td>
<td>81.8</td>
<td>92.0</td>
<td>93.0</td>
<td>3.1</td>
<td>0.005</td>
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<tr>
<td>Hypotransferrinemia and hypoalbuminemia</td>
<td>72.0</td>
<td>90.0</td>
<td>64.0</td>
<td>3.7</td>
<td>0.009</td>
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<tr>
<td>Blunted natural killer cell activity</td>
<td>72.7</td>
<td>92.0</td>
<td>90.4</td>
<td>2.5</td>
<td>0.001</td>
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The diagnostic performance was computed as previously described (Maes et al., 1986): sensitivity, specificity, predictive value for a positive test result (PV+), Cohen's \( \chi^2 \)-statistic with \( \mid r \) and exact \( p \)-value.
DPP IV activity. Melancholia, in turn, is characterized by more pronounced disorders in the various above immune variables and by increased II-1β and IL-6 production.

4. The Immune Response: Inferences and Hypotheses

4.1. Interleukins and the Immune Response

It may be hypothesized that increased II-1β and IL-6 production in severe depression underlie the systemic immune activation observed in that illness. II-1β and IL-6 are pleiotropic cytokines, which are considered to be major immune and inflammatory mediators (Durum and Oppenheim, 1989) that synergize strongly in T and B cell differentiation or proliferation (Dinarello, 1991; Durum and Oppenheim, 1989; Hirano, 1991; Wolvekamp and Marquet, 1990), i.e. they play a pivotal role in: (a) T cell activation and proliferation (Vink et al., 1990; Hirano, 1991), regulation of CD4, CD8, CD45, CD25, and CD57 expression on T cells (Brod et al., 1989; Ford et al., 1991); (b) B cell growth and differentiation (Splawski et al., 1990; Xia et al., 1989), and regulation of antibody production (Galanaud and Emilie, 1990); and (c) induction of prostaglandin secretion (Hauptmann et al., 1991; Fukunaga et al., 1991). Based on the above, it may be hypothesized that the depression-related disorders in cellular and humoral immunity and in prostaglandin secretion can be explained by II-6 and II-1β-related mechanisms.

4.2. Systemic Immune Activation and the Acute Phase Response

Another finding of our studies is the significant correlation between supernatant IL-6 production and the number of peripheral blood monocytes, on the one hand, and plasma levels of Hp (positively) and Tf (negatively), on the other (Maes et al., 1992b; 1993e). It is known that the monocytic production of IL-6 and IL-1β induces the synthesis of positively regulated APPs, such as Hp, α1-AT, and Hpx, whereas negatively regulated APPs, such as Alb and Tf decrease in response to IL-6 and IL-1β (Mayer et al., 1991; Castell et al., 1989; Heinrich et al., 1990). There is evidence that a combination of II-1 and IL-6 is required for regulation of APP synthesis (Durum and Oppenheim, 1989; Heinrich et al., 1990; Prowse and Baumann, 1989). Therefore, we may hypothesize that the AP response in depression can be explained by hypersecretion of II6 and II-1β.

Another finding of our studies is the significant positive relationship between Hp plasma levels and the various indices of systemic immune activation, i.e. increased numbers of leukocytes, monocytes, neutrophils, and activated T cells: up to 35% of the variance in Hp circulating levels could be explained by cellular indices of the immune response (Maes et al., 1994b). The above relationships may be explained by the fact that both components of the immune response (i.e. AP response and immune activation) are induced by II-1β and IL-6. In
conclusion, increased production of both IL-1β and IL-6 may constitute a common denominator of the alterations in APP synthesis, and activation or proliferation of the various immune cells.

The authors found that the higher Hp levels in depression are related to psychomotor retardation, anorexia, weight loss, anergy, loss of interest in work and activities, and sleep disorders (middle insomnia) and less diurnal variation (Maes et al., 1993d). Up to 31% of the variance in the Hp values could be explained by those symptoms. Consequently, the principal psychopathological correlates of increased Hp levels are the vegetative symptoms (i.e. sickness behavior) of the depressive syndrome, whereas no significant relationships were established either with affective symptoms (e.g. depressed mood, a distinct quality of mood, nonreactivity), cognitive disturbances (e.g. feelings of guilt, suicidal ideation) or symptoms indicative of anxiety (Maes et al., 1993d). We have argued that also the symptom profile of higher Hp levels in major depression (i.e. sickness behavior) may, in fact, be related to IL hypersecretion. Indeed, ILs produced during an immune challenge or given to volunteers or animals may induce a wide variety of behavioral effects: anorexia, weight loss (Klasing et al., 1988; Durum and Oppenheim, 1989; Gershenwald et al., 1990), reduction in horizontal and vertical locomotor activity in the rat (Otterness et al., 1991), motor depressant effects (Miller et al., 1991), and reduction of exploratory behavior in mice (Dunn and Welch, 1991). IL-1β has somnogenic effects and reduces wakefulness; higher concentrations, however, may suppress REM and non-REM sleep (Susic and Totic, 1989; Opp et al., 1991; Opp and Krueger, 1991; Kapas et al., 1991). In addition, IL-1β applied systemically may induce behavioral effects reminiscent of a fear reaction or a depressive-like syndrome (Zalcman et al., 1991; Dantzer and Kelley, 1989; Sparado et al., 1989). Although ILs are seemingly unable to cross the blood brain barrier, the median eminence/organum vasculorum laminae terminalis appears to be a site whereby peripheral ILs (e.g. IL-1β) can access or influence the brain (Matta et al., 1990; Stitt, 1985; Hashimoto et al., 1991). As a result, it may be hypothesized that increased IL production by cells of the monocytic lineage in major depression may constitute a common denominator for alterations in positive and negative APPs, activation of cellular and humoral immunity, and for the somatic component of depressive phenomenology.

4.3. Immune Activation and Hypothalamic-pituitary-adrenal-axis

The authors found a significant positive correlation between postdexamethasone (DST) cortisol values and IL-6 or IL-1β production in culture supernatant (Maes et al., 1993a; 1993e). Likewise, DST cortisol non-suppressors showed significantly higher IL-1β and IL-6 secretion than cortisol suppressors. The relationships between post-DST cortisol values and IL-1β or IL-6 secretion cannot be explained by effects of endogenous glucocorticoid hypersecretion, which
frequently occurs in major depression (Carroll, 1980; Maes et al., 1991e). Indeed, glucocorticoids are known to inhibit the production of both cytokines (Waage et al., 1990; Zanker et al., 1990; Snyder and Unanue, 1982).

There are, at least, two hypotheses that may explain the positive relationship between post-DST cortisol values and IL-18 or IL-6 secretion. First, a common mechanism, such as psychological or medical stress, may underlie both HPA-axis hyperactivity and increased monokine production (LeMay et al., 1990; Heinrich et al., 1990). Second, it is known that during an immune response the hypothalamic-pituitary-adrenal (HPA)-axis is activated in parallel with the intensity of the immune response (Sapolsky et al., 1987). Both IL-1 and IL-6 exert potent enhancing effects on HPA-axis by stimulating hypothalamic CRH (Navarra et al., 1991; Naitoh et al., 1988), pituitary ACTH (Woloski et al., 1985; Fukata et al., 1989), and adrenal steroidogenesis (Tominaga et al., 1991). IL-6 may, for example, stimulate the HPA-axis at concentrations known to occur in human plasma (Navarra et al., 1991) and sufficiently to exert its actions on immune cells (Carmeliet et al., 1991). Therefore, it may be hypothesized that the more generalized glucocorticoid resistance in depression (i.e. in HPA-axis and immune function) may in part be related to IL-18 and IL-6-related mechanisms. Moreover, it has been shown that the monokine-related stimulation of the HPA-axis during an immune response may result from increased serotonergic (5-HT) and catecholaminergic (CA) turnover (Dunn, 1988; Mohankumar et al., 1991; Weidenfeld et al., 1989; Dunn et al., 1989; Matta et al., 1990; Dunn and Welch, 1991). It is of interest to note that increased 5-HT and CA turnover are believed to play a role in HPA-axis overdrive in major depression (Maes et al., 1991e).

The authors have also investigated the effects of dexamethasone administration and endogenous cortisol secretion on various leukocyte subsets in depressed subjects (Maes et al., unpublished data). As expected, administration of dexamethasone resulted in a monocytopenic and lymphocytopenic effect, while the mean blood neutrophil pool and total number of leukocytes was significantly increased. These findings are in agreement with the established alterations in leukocytes after administration of a single dose of glucocorticoids (Bloemena, 1989; Berczi, 1986; Deinard and Page, 1974; Thompson and van Furth, 1973). However, DST cortisol nonsuppressors showed an increased "escape" of lymphocytes, CD4+, CD4+CD45RO+, CD8+, CD8+CD57- and CD8+CD57+ T cells from the suppressive effects of dexamethasone. These results suggest that some leukocyte subsets exhibit a relative glucocorticoid resistance in depressed HPA-axis nonsuppressors. This relative glucocorticoid resistance in, for example, CD4+ cells, may explain the findings that some depressed subjects exhibit a partial dexamethasone resistance in lymphoproliferative responses (Lowy et al., 1987; Maes et al., 1991b). There was a significant inverse relationship between 24 hr urinary cortisol excretion
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Evidence for an immune response in major depression and number or percentage of monocytes, lymphocytes, CD4+, CD4+CD45RA+, CD8+, CD8+CD57- T cells and CD20+ B cells. These results may suggest that endogenous cortisol hypersecretion in depression tends to downregulate the above leucocyte subsets. By inference, increased glucocorticoid secretion in depression may exert negative feedback effects on monocytoysis and upregulated expression of various T and B cell subsets. The results may also suggest that glucocorticoid hypersecretion is related to a lower number or percentage of CD8+CD57- (suppressor) T cells. T suppressor cells constitute an important component in the containment of autoreactivity and defects in these cells may be implemented in the development of autoimmune disorders (Roitt et al., 1985). The above results show that multiple and complex intertwined relationships between HPA-axis hyperactivity and systemic immune stimulation may participate in the pathophysiology of major depression.

4.4. Immune Activation and Serotonin

There is evidence that the plasma levels of L-tryptophan (L-TRP) and the ratio of L-TRP to the sum of amino-acids known to compete for the same cerebral uptake mechanism (i.e. competing amino acids, CAA) are lower in severely depressed subjects than in normal controls and minor depressives (DeMyer et al., 1981; Maes et al., 1987a; 1987b; Cowen et al., 1989). Brain 5-HT synthesis depends, in part, on the availability of L-TRP in the blood (Moir and Eccleston, 1968; Fernstrom and Faller, 1977), as indexed by total L-TRP plasma concentrations or the molar ratio of L-TRP to individual or grouped CAA (Fernstrom et al., 1973; Curzon and Sarna, 1984; Fernstrom, 1984; Moller et al., 1986). However, despite much research, the pathophysiology underpinning lower L-TRP availability in major depression has remained elusive (Maes et al., 1987c; 1990a; 1990b; 1990c).

As it has been shown that an immune response may be accompanied by a decreased availability of L-TRP to the brain, it may be hypothesized that lower L-TRP availability in major depression could be related to the immune activation in that illness (Maes et al., 1993c). This hypothesis is underscored by our findings that plasma L-TRP levels are significantly and negatively related to II-6 secretion, plasma levels of Hp and neopterin, and positively to DPP IV and Tf values; the L-TRP/CAA ratio was significantly and negatively related to plasma Hp and neopterin levels (Maes et al., 1993c; Maes et al., submitted).

There are at least three pathophysiological mechanisms that may contribute to immune activation-linked decrements in TRP availability: (i) Immune stimulation or administration of various cytokines may induce indoleamine 2,3 dioxygenase (IDO) resulting in TRP degradation to kynurenine (Brown et al., 1989; Carlin et al., 1989a; 1989b); (ii) an immune response has been shown to be accompanied by an increase in brain TRP concentrations and by an enhanced central 5-HT turnover, which may be secondary to increased uptake of TRP into the
brain (Dunn and Welch, 1991; Mefford and Heyes, 1990); (iii) the metabolic response to an immune challenge involves a series of reactions in protein metabolism such as a net flux of amino acids out of the muscle to other tissues, where they are reutilized for leukocyte activity and synthesis of APPs and secretory proteins (Moldawer et al., 1987; Wolvekamp and Marquet, 1990; Hasselgren et al., 1988; Heinrich et al., 1990; Blackburn et al., 1979).

4.5. Immune Activation and In Vitro Immune Tests

The authors have hypothesized that the ex vivo blunted LTT and NKCA may reflect, in part, the in vivo systemic immune activation observed in depression. For example, the authors found a significant negative relationship between NKCA and the absolute number of leukocytes, monocytes, neutrophils and activated T lymphocytes (i.e. HLA-DR+ T cells) in peripheral blood: an important part of the variance (±30%) in NKCA was found to be explained by the cumulative effects of number of monocytes and percentage of HLA-DR+ T cells (Maes et al., 1994a).

Various factors pertinent to systemic immune activation in depression could explain the findings of diminished ex vivo LTT or NKCA: (a) higher expression of some acute phase proteins which may act as immunosuppressive factors in the serum (Ikeda et al., 1987); (b) higher soluble IL-2-receptor (sIL-2R) secretion (q.v. Introduction), which could induce a state of relative IL-2 starvation by binding their ligand (IL-2) and limiting the amount of IL-2 necessary for immune cell proliferation and NKCA (Oppenheim et al., 1986; Rubin et al., 1985; Chopra et al., 1989); (c) increased prostaglandin secretion, which may suppress the ex vivo lymphoproliferative responses (Calabrese et al., 1986); (d) lower DPP IV activity which may play a role in the diminished LTT responses in depression (Maes et al., 1991d); and (e) overproduction of cytokines such as IL-1β which renders the immune cells refractory to respond properly to antigenic or mitogenic stimulation (Fuchs et al., 1989/1990). As a result, various products of the immune response could act as immunosuppressive agents counteracting the primary immune activation (Besedovsky et al., 1983; 1986). In addition, increased HPA-axis activity in depression may in part be related to systemic immune activation (q.v. 4.3.), while exhibiting immunosuppressive effects (Maes et al., 1989; Calabrese et al., 1986). In this respect, blunted ex vivo NKCA and LTT may well reflect these immunosuppressive effects of circulating factors related to the systemic immune response. Moreover, a secondary reduced NKCA may bring about a marked weakening of the body defenses against various injuries, such as viral infections and tumors, thereby increasing the immune challenge to the body.
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5. Hypotheses

Figure 1 summarizes the findings and shows a hypothetical model depicting the putative immune pathophysiology of an acute episode of severe unipolar depression: IL-1B and IL-6 hypersecretion may constitute key phenomena underlying immune activation (T-cell activation, B cell proliferation, neutrophilia), the "acute" phase response, prostaglandin secretion and sickness behavior (i.e. vegetative symptom cluster of depressive illness). Systemic immune activation may be causally related to the serotonergic pathophysiology of depression by lowering the availability of plasma L-TRP to the brain. In this model, diminished ex vivo immune tests, such as LTT and NKCA, may be regarded as being secondary to in vivo systemic immune activation. Multiple and complex intertwined relationships between HPA-axis hyperactivity and systemic immune stimulation may participate in the pathophysiology of major depression: hypersecretion of immune constituents may be related to HPA-axis hyperactivity; increased HPA-axis activity may exert negative (feedback) effects upon various aspects of immunity, such as number and function of monocytes (including IL-1B and II-6 production), T and B cells.

There are several hypotheses that may explain the increased secretion of ILs and the observed relationships between immune activation and HPA-axis hyperactivity in depression. (1) First, established "etiologic" factors of depression, such as medical (e.g. immune processes) or psychological stress, may simultaneously induce HPA-axis activity and production of monokines (e.g. II-6) by cells of the monocyte/macrophage lineage (Heinrich et al., 1990; LeMay et al., 1990; Smith, 1991). Increased production of cytokines may, subsequently, evoke the immune and inflammatory disorders described above. The in vivo activation of cellular immunity may then be regarded as a "built-in protection" against the possible deleterious effects of depression-related HPA-axis hyperactivity on immune function. (2) Immune activation may be the primary event through for example infectious, autoimmune or inflammatory disorders or psychological stressors. Consequently, HPA-axis hyperactivity in depression may in part be induced through stimulation by - amongst others - IL-1B and IL-6. This concept implies that the increased HPA-axis activity may protect the body from an overactivated immune system through immunosuppression. (3) Another thesis is that increased HPA-axis activity is the primary event which endangers some immune functions (e.g. T helper or suppressor cell function), thus weakening the resistance of the body to various injuries (e.g. autoimmune responses) which, consequently, may induce a secondary state of immune activation.

6. Concluding Remarks

The above studies are limited in so far that only conclusions can be drawn on the pathophysiology of an acute episode of unipolar major depression: as only cross-sectional studies on patients with an actual unipolar depressive episode were conducted, no conclusions
Fig. 1 The interleukin hypothesis of major depression. See text for explanation.
can be drawn whether immune activation, the 'acute' phase response, II hypersecretion or disorders in peptidases are state or trait markers of unipolar depression. In addition, it may not be concluded that these disturbances are related to the pathogenesis rather than to the pathophysiology of unipolar major depression. Although the results strongly indicate the presence of an AP response and increased II secretion in unipolar major depression, the presence of increased levels of, for example, plasma II-6 and other specific positive AP reactants, such as fibrinogen, would make this hypothesis more powerful. Further research in our laboratories will be directed to investigate the role of activation of systemic immune activation, the AP response, interleukin hypersecretion and peptidases in the pathophysiology or pathogenesis of severe unipolar and bipolar depression.

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