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Activation of the inflammatory response system: A new look at the etiopathogenesis of major depression

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Abstract Major depression is accompanied by various direct and indirect indicators of a moderate activation of the inflammatory response system (IRS). Increased production of proinflammatory cytokines, such as interleukin-1 (IL-1), IL-6 and interferon (IFNγ), may play a crucial role in the immune and acute phase response in depression. Lower serum zinc and changes in the erythron are indirect indicators of IRS activation in depression. The reciprocal relationships between IRS activation and hypothalamic-pituitary-adrenal (HPA)-axis hyperactivity, alterations in HP thyroid (HPT)-axis function and the availability of tryptophan to the brain led us to hypothesize that these neuroendocrine changes in depression are indicators of IRS activation and that a combined dysregulation of the IRS, the turnover of serotonin (5-HT) and the HPA-axis is an integral component of depression. The IRS activation model of depression provides an explanation for the psychosocial (external stress) as well as organic (internal stress) etiology of major depression. Antidepressive treatments with various antidepressive agents, including SSRIs, tricyclic and heterocyclic antidepressants, have in vivo and in vitro negative immunoregulatory effects, suggesting that their antidepressant efficacy may be attributed, in part, to their immune effects.

NEL REVIEW

1. Introduction

Current models concerning the biological pathophysiology of depression emphasize the role of brain monoaminergic neurotransmitters, such as serotonin (5-HT) and catecholamines, and hypothalamic-pituitary-adrenal (HPA)-axis hyperactivity. The contemporary models of depression do not incorporate the activation of the inflammatory response system (IRS), even though immune functions may powerfully influence behavior, serotonergic and catecholaminergic metabolism in the brain and HPA-axis activity (Connor and Leonard 1998; Maes 1993, 1995, 1997; Maes and Smith 1997; Maier and Watkins 1995). The hallmarks are in vivo stimulation of some aspects of cell-mediated immunity, the presence of an acute phase (AP) response and increased production of pro-inflammatory cytokines.

2. Indicators of IRS activation in depression

2.1. Cell-mediated immunity

Indicators of IRS activation in major depression are confirmed findings of increased numbers of leukocytes, monocytes, neutrophils and increased secretion of neopterin and prostaglandins. Flow-cyto-metry shows an increased $CD4^+/CD8^+$ T cell ratio and increased numbers of activated T cells, such as $CD25^+$ and $HLA\text{-}DR^+$ T cells, in depression (Maes 1997; Maes et al. 1992a; Maes et al. 1993d; Seidel et al. 1996). Increased concentrations of the soluble interleukin-2-receptor (sIL-2R) point also toward T cell activation in depression (Maes et al. 1995a). Other authors reported increased concentrations of prostaglandin E2 (PGE2) in serum, cerebro-spinal fluid (CSF) and mitogen-stimulated culture supernatant (Song et al. 1998), increased serum or urine secretion of neopterin, a very sensitive marker of activation of cell-mediated immunity (Bonaccorso et al. 1998; Maes et al. 1994d) and increased serum concentrations of elastase (Deger et al., 1996).

2.2. Acute phase response

Indicators of an AP response in major depression are the confirmed findings on changes in serum concentrations of positive and negative AP proteins (APPs). Major depression is characterized by increased serum levels of positive AP proteins, such as haptoglobin (Hp), α1-antitrypsin, ceruloplasmin, α1-acid glycoprotein, C-reactive protein, hemopexin and α1-antichymotrypsin; and by a downregulation of the synthesis of negative APPs (visceral proteins), such as albumin (Alb), retinol binding protein and transferrin (Tf) (Maes et al. 1991b, 1992b, 1992c, 1994a, 1995b, 1997b; Song et al. 1994; Swartz 1990; Hornig-Rohan et al. 1996; Joyce et al. 1992; Sluzewska et al. 1996b) (Table 1).

Table 1. The acute phase response in major depressed patients. This table shows the increase and/or decrease in serum concentrations of positive and negative acute phase proteins (APPs), respectively, in depressed patients compared with normal controls.

	Increases in positive APPs	Decreases in negative APPs
Maes et al. 1992b		transferrin albumin
Maes et al. 1992c	α1-antitrypsin haptoglobin ceruloplasmin	retinol binding protein
Maes et al. 1991c		albumin transferrin
Schwartz 1990		albumin
Joyce et al. 1992	haptoglobin α1-antitrypsin α1-antichymotrypsin immunoglobulin G	albumin
Song et al. 1994	haptoglobin α1-antitrypsin haptoglobin	albumin
Hornig-Rohan et al. 1996	C-reactive protein	
Sluzewska et al. 1996b	α1-acid glycoprotein	

2.3. Cytokines and the IRS

In depression, there are several reports that the secretion of proinflammatory cytokines, either in serum or in culture supernatant may be increased, i.e. interleukin-1β (IL-1β), IL-6 and interferon-γ (IFNγ) (Frommberger et al. 1997; Maes et al. 1995a, 1997a; Sluzewska et al. 1996a; Maes et al. 1991a, 1993a, 1993c, 1994d). Since proinflammatory cytokines induce IRS activation and an AP response and since we found significant and positive correlations between cytokine production, e.g. IL-6 and indicators of immune activation, such as increased numbers of peripheral blood mononuclear cells (PBMC) and APPs, we have suggested that IRS activation in depression is caused by an increased production of the proinflammatory cytokines, IL-1β, IL-6 and IFNγ (Maes 1993, 1995, 1997; Maes et al. 1992a, 1993d).

3. Indirect indicators of IRS activation in major depression

If there is an IRS activation in major depression, it was anticipated to find other indicators of IRS activation, such as lower serum zinc (Zn), and specific alterations in the erythron.

3.1. Zinc and depression

Zn is a trace element and an important cofactor for various enzymes (zinc metalloenzymes). Zn is needed for DNA synthesis, conformation of protein, stabilization of membranes, protection of membranes against lipid peroxidation and as a free ion within the cell (Solomons 1988). Early clinical manifestations of human Zn deficiency are behavioral disturbances, such as depression, anorexia, dysphoria, impaired taste, impaired cognitive functions and immune deficiencies (Solomons 1988). There are two factors which can explain lower serum Zn in depression. First, because IRS activation results in decreased serum Alb concentrations and Alb is the major Zn binding protein, there is potentially less Zn binding protein available, which could in part explain lower serum Zn (Goldblum et al. 1987). Second, lowered serum Zn during IRS activation may be secondary to sequestration of the intracellular heavy metal binding protein metallothionein in the liver, which, in turn, may be related to an increased production of the proinflammatory cytokines, IL-1 and IL-6 (Cousins and Leinart 1988). In depression, there were highly significant relationships between serum Zn and the $CD4^+/CD8^+$ T cell ratio (negative), and total serum protein, serum Alb and Tf (all positive) (Maes et al. 1994c, 1997c).

3.2. Alterations in the erythron and depression

It has been shown that patients with major depression have significantly lower serum iron (Fe) and Tf, and a significantly lower number of red blood cells (RBC), lower hematocrit (Htc) and hemoglobin (Hb), and a significantly increased number of reticulocytes than normal controls (Maes et al. 1996b; Vandoolaeghe et al. 1999). We observed that serum Fe, Tf and ferritin were significantly related to other well-established inflammatory markers of major depression. For example, serum Fe was significantly related to serum Alb and Zn (positively) and to the α1-globulin fraction (negatively). Serum Tf was significantly related to serum Alb and Zn and serum ferritin was significantly inversely related to serum Zn. Significant relationships were reported between the erythron variables and indicators of IRS activation. For example, in depression, there are significant and positive correlations between serum Zn and number of RBC, Htc, Hb (all positive), and serum ferritin (negative), and between serum Alb and RBC, Htc and Hb (all positive). There are also significant correlations between serum Zn and Fe and serum Tf (positive), serum Alb and Fe (positive), serum Alb and Tf (positive) and the α_1-globulin fraction and Fe (negative). Finally, there were significant and positive correlations between the number of reticulocytes and number of leukocytes and neutrophils and the α_1-globulin fraction (Maes et al. 1996b; Vandoolaeghe et al. 1999). The alterations in Fe metabolism and in the erythron reported in depression may be related to increased production of cytokines, such as IL-1β and IL-6, which frequently occurs in that illness. The latter may effect Fe metabolism and the erythron through increased storage of Fe, reduced release of Fe from the reticuloendothelial cells, increased Fe incorporation into ferritin, increased ferritin synthesis, failure to deliver Fe to the erythron and a reduction in erythrocyte life span (review: Maes et al. 1996b).

4. Neuroendocrine disorders in major depression and IRS activation

As described above, IRS activation not only involves specific immune and metabolic alterations, but also neuroendocrine changes such as HPA-axis hyperactivity, and alterations in HP-thyroid (HPT) axis function and in the peripheral and central turnover of serotonin (5-HT).

4.1. Neuroendocrine effects of cytokines

Cytokines have been shown to stimulate the release of HPA-axis hormones, eventually leading to the secretion of excessive amounts of glucocorticoids.

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Increased glucocorticoid production then acts as a negative feedback mechanism which tends to suppress exaggerated immune or inflammatory reactions caused by proinflammatory cytokines (Navarra et al. 1991; Sapolsky et al. 1987; Miller et al. 1997). A wide spectrum of alterations in HPT-axis function has been observed in patients with IRS activation or systemic nonthyroidal illnesses, caused by infection, sepsis, or injury (Kushner 1982). Abnormal low total T3 or T4, lowered basal TSH, increased free T4 concentrations and decreased plasma T4-binding prealbumin levels may be observed in those conditions. Proinflammatory cytokines have profound effects on the peripheral and brain serotonergic systems. Immune stimulation and administration of various cytokines, such as IFNγ and IL-2, may induce indoleamine-2,3-dioxygenase (IDO) which results in an increased catabolism of tryptophan. Plasma concentrations of tryptophan and the ratio of tryptophan to the sum of amino-acids known to compete for the same cerebral uptake mechanism (i.e. competing amino acids, CAA) are lower in major depressed patients than in normal volunteers. Brain 5-HT synthesis depends, in part, on the availability of plasma tryptophan, as indicated by total tryptophan plasma concentrations or the molar ratio of tryptophan to the grouped CAA (Maes and Meltzer 1995; Song et al. 1998).

4.2. Neuroendocrine function, cytokines and depression

Major depression is accompanied by HPA-axis hyperactivity, HPT-axis alterations, such as lower basal TSH concentrations and serotonergic disturbances. The most consistently reported signs of HPA-axis hyperactivity in major depression are endogenous hypercortisolemia and escape from suppression by dexamethasone, i.e. the 1 mg dexamethasone suppression test (review: Maes et al. 1993a). The most consistent sign of HPT-axis dysfunction in depression is lower basal TSH. There is evidence that disorders in the central and peripheral neurotransmission of serotonin (5-HT) are implicated in the pathogenesis or pathophysiology of major depression (Maes and Meltzer 1995). Therefore, we have hypothesized that, if major depression is indeed characterized by IRS activation, the glucocorticoid resistance in depression, lower serum basal TSH concentrations and lower availability of tryptophan to the brain may be related to indicators of IRS activation. In accordance with this hypothesis we found the following. i) In depressed patients, there is a significant positive correlation between IL-1β production and post-DST cortisol values, and a significant positive correlation between baseline plasma cortisol and IL-6 concentrations (Maes et al. 1993a, 1993c). ii) In depression, basal TSH was significantly and negatively related to Hp values, whereas in normal controls a trend toward a positive correlation between both factors was found. iii) Lower availability of plasma tryptophan to the brain was significantly correlated to serum IL-6, serum Hp, the α2 globulin fractions, neopterin and the $CD4^+/CD8^+$ T cell ratio (inversely) and to serum Alb, Fe, Tf and Zn (all positively) (Maes et al. 1994b, 1997d).

5. Cytokines and the etiology of major depression

5.1. Proinflammatory cytokines induce depression-like effects

IRS activation not only encompasses a broad array of immune, metabolic and neuroendocrine alterations, but also specific behavioral changes, i.e. sickness behavior. Sickness behavior consists of anorexia, weight loss, sleep disorders, suppression of social, locomotor and exploratory behavior and anhedonia, the vegetative symptoms of major depression (Anisman et al. 1998; Dantzer et al. 1998; Linthorst and Reul 1998; Maier and Watkins 1995, 1998). Proinflammatory cytokines, such as IL-1, IL-6 and IFN are key mediators of sickness behavior.

In major depression, we found significant relationships between indicators of IRS activation and the vegetative symptoms of depression. Increased plasma Hp concentrations in depression were significantly and positively related to vegetative symptoms, such as psychomotor retardation, anorexia, weight loss, anergy, loss of interest in work and activities and middle insomnia (Maes et al. 1993b). 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. 1993b). In other studies, psychomotor retardation, anorexia and middle insomnia were highly significantly related to serum Alb or the α1 and α2 globulin fractions, while serum Zn was significantly and inversely related to psychomotor retardation only. Therefore, we have hypothesized that the somatic dimension (the vegetative symptoms) of major depression may, in fact, be related to IRS activation, through hypersecretion of proinflammatory cytokines (Maes et al. 1993b).

5.2. External stress, cytokines and the etiology of depression

Major depression has a multicausal etiology, whereby internal (organic factors) as well as external (psychosocial) stressors are considered to play a pivotal role in the etiology of depression. Recently, we found that academic examination stress in university

students significantly increases the stimulated production of proinflammatory cytokines, such as IL-6, TNFα and IFNγ, and that of the negative immunoregulatory cytokine IL-10 (Maes et al. 1998c).

We found that the response to psychological stress in humans consists of two different profiles of cytokine production, i.e. a first characterized by a higher IFNγ/IL-10 response (labeled IFNγ reactors) and a second characterized by a higher IL-10 than IFNγ response (labeled IL-10 reactors). IFNγ reactors, but not IL-10 reactors, show significant stress-induced increases in anxiety and depression ratings. Therefore, it could be hypothesized that external stressors are perceived by the immune system and, through secretion of proinflammatory and negative immunoregulatory cytokines, take part in an integrated psychoneuroendocrine homeostatic response (Maes et al. 1998b).

5.3. Internal stress, cytokines and the etiology of depression.

Important epidemiological features of major depression are the higher incidence of major depression in the medically ill or in "organic" conditions and in women, and the increasing rates of depression this century. The IRS activation model is consistent with each feature.

The high occurrence of major depression in the medically ill is clearly consistent with the IRS activation model of depression (Maes 1997; Maes and Smith 1998). Indeed, internal stressors, such as infection, injury, autoimmune disease, toxins, cancer, myocard infarction, dementia, stroke, and the postpartum period are well-documented causes of immune activation, including increased cytokine secretion, as well as being causes of depression. The elevated rate of depression in women is consistent with the greater immune responsivity in females and the immune activating effects of sex hormones (Ahmed et al. 1985; Knapp et al. 1992; Washburn et al. 1965). Also the increased incidence rate of major depression since 1913 may be explained by the IRS activation model of depression. This increased incidence parallels the increasing ratio of ω6 to ω3 fatty acids in Western diets the last century. A high dietary ω6/ω3 fatty acid ratio may increase the secretion of proinflammatory cytokines (review: Maes et al. 1996a; Maes and Smith 1998).

6. Antidepressant treatments, cytokines and depression

6.1. In vivo effects of antidepressants.

If increased production of proinflammatory cytokines is at all involved in the etiology of depression, one would expect that the various antidepressive treatments have negative immunoregulatory effects. It is generally believed that tricyclic antidepressants have immunosuppressive effects ex vivo as well as in vivo (Miller and Lackner 1989). Subchronic treatment with fluoxetine, a selective serotonin reuptake inhibitor (SSRI), may normalize initially elevated serum Il-6 levels in major depression (Sluzewska et al. 1995). Subchronic treatment with psychotropic medications, such as lithium, tricyclic antidepressants and fluoxetine is able to suppress the acute phase response in major depression (Maes et al. 1997b). The above results show that, in vivo, antidepressants have antiinflammatory effects through downregulation of proinflammatory cyto-kines and upregulation of negative immuno-regulatory cytokines, such as IL-10, and receptor antagonists, such as the IL-1 receptor antagonist.

6.2. In vitro effects of antidepressants.

In vitro it has been shown that antidepressants, such as clomipramine, imipramine and citalopram significantly suppress the secretion of IL-1β and TNFα by

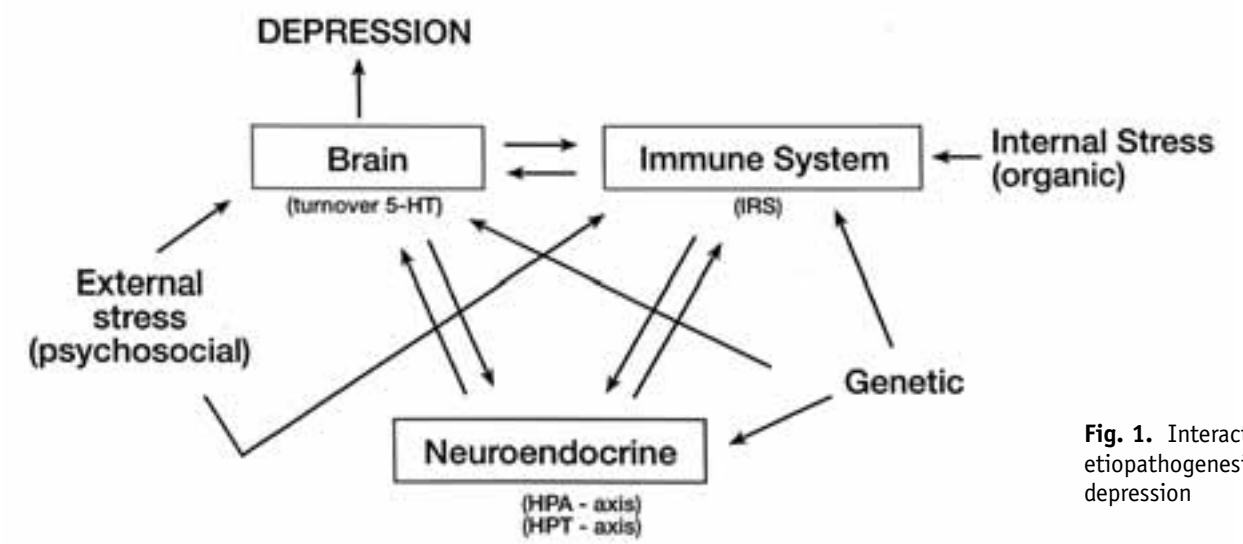

Fig. 1. Interactions on the etiopathogenesis of major depression

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stimulated monocytes (Xia et al. 1996). Our laboratory found that clomipramine, sertraline and trazodone, at concentrations in the range of the therapeutic plasma concentrations achieved during clinical treatment, had a significant suppressive effect on the IFNγ/IL-10 ratio, which was attributable to a suppression of the stimulated production of IFNγ and a significant stimulatory effect on IL-10 production (Maes et al. 1998a). Thus, antidepressive agents, including SSRIs, tricyclic and heterocyclic antidepressants, may have negative immunoregulatory effects, since they significantly suppress the IFNγ/IL-10 ratio. Since antidepressants decrease the IFNγ/IL-10 ratio and since IFNγ has depressogenic properties and since IFNγ production is increased in depression and in stress-induced depressive and anxious states, it may be speculated that antidepressants exert some of their antidepressant effects through their negative immunoregulatory capacities.

7. Conclusion

The IRS model of depression provides a model to account for the organic (internal stressors) as well as the psychosocial (external stressors) etiology of major depression, whereby both types of stressors cause depression, through IRS activation with increased secretion of proinflammatory cytokines. The findings may be consistent with the hypothesis of a combined 5-HT, IRS and HPA-axis dysfunction as an integral component of depression (Figure 1).

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