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Review

# Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression

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ABSTRACT

This paper reviews that cell-mediated-immune (CMI) activation and inflammation contribute to depressive symptoms, including anhedonia; anxiety-like behaviors; fatigue and somatic symptoms, e.g. illness behavior or malaise; and mild cognitive impairment (MCI). These effects are in part mediated by increased levels of pro-inflammatory cytokines (PICs), e.g. interleukin-1 (IL-1), IL-6 and tumor necrosis factor (TNF)α, and Th-1-derived cytokines, such as IL-2 and interferon (IFN)γ. Moreover, new pathways, i.e. concomitants and sequels of CMI activation and inflammation, were detected in depression: (1) Induction of indoleamine 2,3-dioxygenase (IDO) by IFNγ and some PICs is associated with depleted plasma tryptophan, which may interfere with brain 5-HT synthesis, and increased production of anxiogenic and depressogenic tryptophan catabolites. (2) Increased bacterial translocation may cause depression-like behaviors by activating the cytokine network, oxidative and nitrosative stress (O&NS) pathways and IDO. (3) Induction of O&NS causes damage to membrane ω3 PUFAs, functional proteins, DNA and mitochondria, and autoimmune responses directed against intracellular molecules that may cause dysfunctions in intracellular signaling. (4) Decreased levels of ω3 PUFAs and antioxidants, such as coenzyme Q10, glutathione peroxidase or zinc, are associated with an increased inflammatory potential; more oxidative damage; the onset of specific symptoms; and changes in the expression or functions of brain 5-HT and N-methyl-D-aspartate receptors. (5) All abovementioned factors cause neuroprogression, that is a combination of neurodegeneration, neuronal apoptosis, and lowered neurogenesis and neuroplasticity. It is concluded that depression may be the consequence of a complex interplay between CMI activation and inflammation and their sequels/concomitants which all together cause neuroprogression that further shapes the depression phenotype. Future research should employ high throughput technologies to collect genetic and gene expression and protein data from patients with depression and analyze these data by means of systems biology methods to define the dynamic interactions between the different cell signaling networks and O&NS pathways that cause depression.



**Contents**



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## 1. Introduction

There is evidence that unipolar depression is associated with a chronic, low grade inflammation and cell-mediated immune (CMI) activation (Maes et al., 1990, 1991, 1992). Since these first results (1990–1992), many papers have been published on inflammatory and CMI biomarkers in depression as evidenced by the publication of two meta-analyses which underscored that depression is associated with signs of inflammation (Dowlati et al., 2010) and T cell activation (Liu et al., 2011). Moreover, new pathways, i.e. concomitants and sequels of CMI activation and inflammation, were discovered in depression, e.g. activation of indoleamine 2,3-dioxygenase (IDO) (Maes et al., 1993a, 1994); increased translocation of gram-negative bacteria (Maes et al., 2008); decreased antioxidant levels and increased oxidative and nitrosative stress (O&NS) pathways (Maes et al., 2000b, 2011a; Bilici et al., 2001); lowered levels of zinc (Maes et al., 1997b) and ω3 polyunsaturated fatty acids (PUFAs) (Maes et al., 1999a); and damage to mitochondria (Gardner and Boles, 2011).

Parallel to the progress made in the field of inflammation and CMI activation, new findings showed progressive neuroanatomical dysfunctions in depression, such as neurodegeneration, increased neuronal apoptosis, reduced neurogenesis and lowered neurotrophic factors as well as a neurocognitive decline in depression (Duman and Monteggia, 2006; Maes et al., 2009c; Catena-Dell'Osso et al., 2011). Neuroprogression is a new label that was introduced to denote the abovementioned progressive neuroanatomical and neuronal dysfunctions (Berk et al., 2011).

The main aims of this paper are to explain how the various inflammatory and CMI pathways as well as their sequels and concomitants contribute to the pathophysiology of unipolar depression and may be associated with the onset of depression; and how all those factors act in concert to cause the neuroprogressive aberrations described in depression. Towards this end we will briefly review the CMI and inflammatory findings in clinical depression and the body of evidence that CMI activation, including increased production of interferon-γ (IFNγ) and interleukin-2 (IL-2); and pro-inflammatory cytokines (PICs), such as IL-1β, IL-6 and tumor necrosis factor-α (TNFα), may cause depressive-like behaviors, including melancholic symptoms (anhedonia); anxiety; fatigue and somatic symptoms; and neurocognitive symptoms as well. The symptomatology of human depression is indeed very complex and consists of different, albeit overlapping symptom dimensions: (a) the melancholic dimension, characterized by a distinct quality of depressed mood (anhedonia), non-reactivity, early morning awakening, anorexia, body weight loss, and cognitive and psychomotor disturbances; (b) the anxiety dimension, with tension, anxious behavior, and respiratory, genito-urinary and autonomic symptoms; (c) the fatigue and somatic dimension, with aches and pain, muscular tension, fatigue, concentration difficulties, failing memory, irritability, irritable bowel, headache, and a flu-like malaise; and (d) neurocognitive disorders, including mild cognitive impairment (MCI) (Maes, 2009).

To comprehend the mechanisms that may explain the effects of CMI activation and inflammation we will focus on the new pathways, i.e. the sequels and concomitants of CMI activation and inflammation, that underpin the pathophysiology of depression and that in concert with the aforementioned cytokines contribute to the pathology of depression. We will describe how all these events together contribute to the neuroprogressive processes in depression. For a description of the various pathways involved in bipolar depression we refer the readers to a recent review in the same journal (Berk et al., 2011).

## 2. Cell-mediated immunity and inflammation in unipolar depression

### 2.1. Cell-mediated immune activation and inflammation

CMI is that component of the immune system that involves interactions between different immune cells, including T lymphocytes and macophages/monocytes and that does not involve complement, the acute phase response or antibodies. Once triggered, T cells are activated, acquire receptors, e.g. the IL-2 receptor

(IL-2R or CD25) and produce T cell derived cytokines, such as IFNγ and IL-2, which will activate monocytes/macrophages (Wachter et al., 1992). The latter in turn will produce cytokines, such as IL-1β, that exert a positive feedback loop on T cells. During that process, the IL-2R subunit is released from T cells into the serum (Caruso et al., 1993), while IFNγ-activated monocytes produce neopterin, a sensitive biomarker for CMI activation. IL-12, another cytokine that is involved in CMI activation, is produced by monocytes/macrophages, dendritic cells, and antigen-presenting cells, and triggers T cells to produce more IFNγ (Trinchieri, 2003). T cells are further differentiated into Th-1, Th-2, Th-3, Th17, Th22, Treg, Tr1, etc. Th-1 cells mainly produce IL-2 and IFNγ; Th-3 cells produce transforming growth factor-(TGF)β, a cytokine that has immunosuppressive effects; while most Th subpopulations produce the anti-inflammatory cytokine IL-10 albeit in different amounts (Sabat, 2010).

Inflammatory reactions consists of cellular, cytokine and complement cascades and an acute phase response (Burdette et al., 2010). Primary mediators of inflammation are macrophage-derived cytokines, e.g. IL-1β and TNFα. These cytokines activate nuclear factor κB (NFκB), which in turn increases the production of IL-6 and IL-8, and induce T cells to produce IFNγ. PICs enhance the production of positive acute phase proteins (APPs), e.g. haptoglobin and C-reactive protein, and downregulate the production of negative APPs, e.g. albumin and transferrin (Maes, 1993). During inflammation the body mounts a counter anti-inflammatory responses syndrome (CARS), which tends to dampen the primary inflammatory response. The increased synthesis of the IL-1 receptor antagonist (IL-1RA), which blocks the activities of IL-1, is one characteristic of this CARS (Burdette et al., 2010).

### 2.2. Findings in depression

In 1990, increased serum sIL-2R levels and an increased expression of T cell activation markers, e.g. IL-2R, were reported in depression, suggesting CMI activation (Maes et al., 1990). Recently, we reviewed the body of evidence that depression is accompanied by T cell activation as indicated by increased serum sIL-2R and sCD8 levels (Maes, 2011); increased numbers of activated T cells bearing the IL-2R activation marker; an increased production of IFNγ (Maes et al., 1992, 1994; Seidel et al., 1995); increased IFNγ/IL-4 and IFNγ/TGFβ ratios (Myint et al., 2005; Kim et al., 2007; Song et al., 2009a); and a relative resistance to the activities of glucocorticoids in immune cells (Maes, 2011). These results show that depression is accompanied by a Th-1-like shift away from Th-2 and Th-3-like cells. Other findings, such as increased production of neopterin and IL-12, indicate an activated state of macrophages/monocytes associated with CMI activation.

Three major findings show that depression is an inflammatory disorder. Firstly, key inflammatory cytokines, such as IL-1β, IL-6 and TNFα, are consistently increased in the blood or the brain of depressed patients (Maes et al., 1991; Maes, 1995; Mikova et al., 2001; Dean et al., 2010). Secondly, depression is accompanied by an AP response as shown by increased serum levels of positive APPs, such as haptoglobin, $\alpha_1$-antitrypsin, $\alpha_1$-acidglycoprotein, ceruloplasmin, and the electrophoretically separated $\alpha_1$- and $\alpha_2$-globulin fractions (Maes, 1993; Joyce et al., 1992; Song et al., 1994; Sluzewska et al., 1996, 1997), and decreased levels of negative APPs, such as albumin and transferrin (Maes, 1993; Song et al., 1994). Thirdly, higher plasma C3C and/or C4 concentrations were observed in depressed patients (Song et al., 1994; Maes et al., 1997a; Berk et al., 1997). Finally, depression is accompanied by an increased synthesis of the IL-1RA (Maes, 1995).

There are significant positive correlations between serum neopterin, on the one hand, and serum sIL-2Rs, a biomarker of T cell activation and IL-2 production (Maes, 2011); and PICs, including IL-1 and TNFα, on the other (Maes et al., in press). This suggests that in depression, IFNγ has stimulated monocytic cells to secrete more neopterin, and that depression is accompanied by a pathological, intertwined upregulation of CMI activation and inflammation.

### 2.3. PICs and T cell cytokines may contribute to depression

#### 2.3.1. PICs may contribute to depressive symptoms

There is some evidence that administration of PICs is associated with the onset of depressive and anxiety-like symptoms, fatigue and MCI. Different models show that increased IL-6 levels are associated with depression-like behaviors and anxiety. In humans, typhoid vaccination induces increased IL-6 levels that are associated with prolonged reaction times and increased neural activity within the substantia nigra, suggesting that plasma IL-6 mediates psychomotor retardation (Brydon et al., 2009). Infecting healthy MRL++, C3H.SW and Balb/C mice with adenovirus vector carrying cDNA for murine IL-6, a model that causes subchronic elevations in IL-6, induces depressive-like behavior (Sakić et al., 1997, 2001). Salome et al. (2008) found that stimulated plasma IL-6 was significantly higher in high anxiety behavior rats than in rats with lower anxiety levels. In male Sprague-Dawley (SD) rats, IL-6 administration in the amygdala and hippocampus increased the immobility time in the forced swim test (FST) (Wu and Lin, 2008). In BALB/c mice, peripheral administration of PICS, such as IL-6, increased locomotion and grooming and the time spent in ambulatory exploration, digging and rearing (Zalcman et al., 1998).

Animal models of depression show that increased IL-1β levels are associated with melancholic and depression-like behaviors; anxiety-like behaviors; fatigue; and memory impairment. Rats subjected to chronic mild stress (CMS) display elevated circulating levels of IL-1 (Kubera et al., 1996). Increased hippocampal levels of IL-1β in the CMS model in the rodent is associated with the onset of depression-like behaviors including sucrose reference and social exploration (Goshen et al., 2008). Anisman et al. (2008) found that systemic IL-1β administration increased sickness behavior. In rats, intracerebroventricular (icv) IL-1β administration causes depression- and anxiety-like behaviors, stress and memory impairment. Anisman and Merali (1999) reported that systemic administration of IL-1β elicits anxiety, anorexia and sickness behavior. Administration (icv) of IL-1 provoked anxiogenic effects in the elevated plus maze, while spatial memory was impaired by subchronic icv administration of IL-1 (Song et al., 2006). Central administration of IL-1β significantly elevates conditioned fear memory in the rat as assessed by a passive avoidance task (Song et al., 2003b). Acute and chronic administration of IL-1β (intraperitoneally, ip) significantly increase the latency of escape to a foot shock (Bonaccorso et al., 2003). Anhedonic behavior caused by chronic stress exposure was attenuated following inhibition of the IL-1 receptor or using IL-1 receptor null mice (Koo and Duman, 2008). When IL-1RA is administered icv before inescapable shock the subsequent enhancement of fear conditioning is blocked (Maier and Watkins, 1995). Arakawa et al. (2009) found that infusions of IL-1RA blocks the reduction of social investigation induced by foot shock, suggesting that IL-1 plays a key role in mediating behavioral responses to external stressors. Importantly, icv administration of IL-1β induced two different behavioral responses, i.e. a sickness response (reduced locomotor activity, lethargy, reduced body weight) and a stress- or anxiety-like response (Song et al., 2003a,b). There are also data showing that IL-1 plays a role in immunologically mediated fatigue (Sheng et al., 1996; Cavadini et al., 2007). Thus, injection of Corynebacterium parvum antigen to C57BL/6 mice causes an increased expression of IL-1 and TNFα mRNA in the brain and fatigue (Sheng et al., 1996, 2001). The fatigue symptoms that are associated with recovery from muscle damage are

associated with brain macrophage activation and increased IL-1β production (Carmichael et al., 2010).

Systemic administration or microinjections of TNFα into the anterior hypothalamus provokes anxiogenic and anorectic actions, signs of illness and somatic symptoms (Anisman and Merali, 1999; Jiang et al., 2008). TNFα and IL-1β synergistically disrupt behaviors, such as consumption of chocolate milk (reflecting anorexia and/or anhedonia) (Brebner et al., 2000). Connor et al. (1998) observed that TNFα and IL-1β (icv) elicit anxiogenic responses in the elevated plus maze test. Brain TNFα concentrations induced by systemic administration of lipopolysaccharides (LPS) may remain elevated for 10 months and activate brain microglia and consequently, induce chronic neuroinflammation that is associated with the onset of sickness behavior and depressive-like symptoms (Qin et al., 2007). Etanercept, a p75 TNF receptor/Fc fusion protein that blocks TNFα functions, neutralizes IL-1β-mediated sickness behavior, including reduced open-field activity and glucose consumption, suggesting that increased levels of peripheral cytokines, such as TNFα, mediate the malaise that occurs in inflammatory disorders of the central nervous system (Jiang et al., 2008). One of the fatigue and somatic symptoms of depression, i.e. a "a flu-like malaise" probably reflects the sickness behavior that is induced by the abovementioned cytokines. TNFα may also cause other somatic symptoms, such as "autonomic symptoms" through its effects on autonomic functions (Hermann and Rogers, 2008).

#### 2.3.2. T cell derived cytokines may contribute to depressive symptoms

In patients with cancer treated with IL-2-based immunotherapy (subcutaneous) there is a rapid development of depressive symptoms (Capuron et al., 2001). The side effects of IL-12-based immunotherapy (subcutaneous) in patients with AIDS-related Kaposi syndrome include not only flu-like symptoms, but also depression (Little et al., 2006). In animals, peripheral or central administration of IL-2, elicits anhedonia, anorexia, cognitive disturbances, and sickness behavior although markedly less than that produced by monocytic cytokines (Anisman et al., 2005). In CD-1 mice, continuous infusion of IL-2 over 7 days reduced the consumption of chocolate milk and locomotor activity (Sudom et al., 2004). Chronic systemic IL-2 administration to mice induced modest reductions in exploration and impaired Morris water-maze performance, while these effects were not associated with sickness behavior (Lacosta et al., 1999). In another study in mice, IL-2 administration elicited significant increases in the number of free rears and non-ambulatory exploration and exploration of novel stimuli (Zalcman et al., 1998). Administration (ip) of IL-2 in the mouse enhanced the amnesic effect of scopolamine (Bianchi and Panerai, 1993). In rats, spinal injection of IL-2 increases the responses to stimulation of the hindpaws and yields biphasic effects on thermal responses, suggesting that IL-2 participates in hyperalgesia (Cata et al., 2008). Stimulation of IL-2 production with staphylococcal enterotoxin B significantly causes anorexic effects related to anxiety-like processes (Kusnecov et al., 1999; Kusnecov and Goldfarb, 2005). In the CMS model of depression in Wistar rats, an increased production of IL-2 by splenocytes was found (Kubera et al., 1996).

In C57BL/6 mice sustained IFNγ production induces signs of the autoimmunity-associated behavioral syndrome, e.g. emotional reactivity and motivated behavior (Kwant and Sakic, 2004). These authors found that increased systemic IFNγ reduces the responses to the sucrose preference test, food and water intake, and body weight. In mice, repeated administration of murine-recombinant IFNγ (ip) decreased spontaneous locomotor activity and induced an increased weight (Weinberger et al., 1988). One dose of human recombinant IFNγ (icv) was able to decrease 2-h food intake (Plata-Salaman, 1992). In the golden hamster, administration (icv) of IFNγ suppresses locomotor activity and modifies the circadian clock probably through effects at the IFNγ receptors in the suprachiasmatic nucleus (Boggio et al., 2003). In patients with chronic fatigue syndrome (CFS), increased circulating levels of IFNγ, or activation of IFNγ-induced pathways are associated with chronic fatigue and pain following parvovirus B19 infection (Kerr et al., 2001; Bellmann-Weiler et al., 2008). All in all, these data show that T cell activation is involved in the onset of depressive-like behaviors, including anhedonia, anorexia, psychomotor disorders, anxiety, fatigue and memory disturbances.

#### 2.3.3. Limitations of translational research

A first limitation of the above models of depression is that they select one or two aspects of one of the different symptom dimensions of depression. For example, a reduction in the intake of sweetened milk in the rodent is employed as a model for anhedonia (Jancsar and Leonard, 1981). An increase in sensitivity in environmetal stressors is thought to reflect anxiety-like behavior and therefore is employed as a template for human anxiety (Song and Leonard, 1994). These symptoms in the rodent and their associated pathways are then 'extrapolated' to organic substrates in the depressed patient. Inevitably, this leads to selective information and hampers interpretation of the 'big clinical picture' in depression consisting of different symptom profiles.

A second limitation is that the inflammatory pathways also trigger a symptom complex, called sickness behavior, including lethargy; anorexia; weight loss; sleepiness; hyperalgesia; reduction of locomotor activity, exploration and grooming; failure to concentrate and anhedonia (Holmes and Miller, 1963; Hart, 1988; Maier et al., 1993; Kelley et al., 2003; Yirmiya, 1996; Johnson, 2002; Qin et al., 2007). This behavioral complex and the pathophysiology behind it enhances recovery following viral and bacterial infections (Hart, 1988; Johnson, 2002). The "behavioral" similarities between sickness behavior and the vegetative or somatic symptoms of depression and the associations of these symptoms to inflammatory responses in depressed patients were first described by Maes et al. (1993b). It could be argued that most abovementioned "inflammatory models of depression" may not differentiate well between sickness behavior and depression. However, key symptoms of simple major depression and melancholic depression, such as a "flu-like malaise" and some associated "fatigue and somatic" symptoms may reflect sickness behavior responses in some depressed individuals (Maes, 2009). All in all, the translational experiments discussed above may have identified pathways that contribute not only to the fatigue and somatic symptom complex of depression, but also to the melancholic (anhedonia), anxiety and MCI symptom profiles.

A third limitation of most experiments listed above is that they do not provide mechanistic explanations how cytokines may cause depression but merely report that peripheral and central administration of PICs and T cell cytokines may cause depressive-like behaviors. Although there are effects of those cytokines increasing noradrenaline and 5-HT levels in some brain regions and decreasing noradrenaline in other regions these data are not consistent with the monoamine hypotheses of depression, which considered that a lowered 5-HT and noradrenergic turnover may be etiological factors in depression (Zalcman et al., 1994). Morever, these cytokine-induced behavioral responses can occur without effects on the noradrenergic or serotonergic activities (Connor et al., 1998).

#### 2.3.4. Effects of antidepressants on inflammatory processes and cell-mediated immunity

The evidence that CMI activation and inflammation play a role in depression is further corroborated by findings that antidepressants attenuate both inflammatory and CMI processes. Thus, subchronic treatment of depressed patients with antidepressants normalizes

the increased plasma levels of APPs, like CRP and haptoglobin, and C3C and C4 (Seidel et al., 1995; Maes et al., 1997a). Tricyclic antidepressants (TCAs) block the ex vivo monocytic production of IL-1β, TNFα and IL-6 (Xia et al., 1996). It should be stressed, however, that the effects of antidepressants on IL-6 levels or production are not concordant (Sluzewska et al., 1996; Kubera et al., 2000b, 2004, 2005). In responders to treatment, amitriptyline, a TCA, significantly reduced plasma TNFα concentrations (Lanquillon et al., 2000). In animal models of depression, antidepressants have been shown to attenuate depressive-like symptoms and the associated production of PICs, e.g. IL-1β and TNFα (review: Kubera et al., 2011; Yirmiya et al., 2001). In brain cell cultures, the production of IL-1β, IL-6 and TNFα is suppressed by TCAs and selective serotonin reuptake inhibitors (SSRIs) (review: Kubera et al., 2011).

Treatment with antidepressants significantly attenuates the increased production of IFNγ in depressed patients (Seidel et al., 1995). TCAs block the ex vivo production of IFNγ and IL-2 in human lymphocytes (Xia et al., 1996). Not only TCAs, but also SSRIs; reversible inhibitors of monoamine oxidase A (RIMAs), "noradrenergic" antidepressants; and even atypical antidepressants, such as tianeptine, suppress IFNγ production or increase the production of IL-10 (Maes et al., 1999c; Kubera et al., 2001; Kenis and Maes, 2002). These findings are corroborated by a report by Myint et al. (2005) who found that antidepressant treatment decreased the IFNγ/IL-4 ratio. In animal models of depression, antidepressants attenuate the production of IL-2 and IFNγ and/or increase the production of IL-10 (Kubera et al., 2000a,c). In rats with experimental autoimmune neuritis, Zhu et al. (1998) found that TCAs reduce Th-1 cells that produce IFNγ. In depressed patients, subchronic antidepressant treatment attenuates the initially increased IL-12 levels (Kim et al., 2002). Moreover, antidepressants increase TGFα and thus reduce the IL-12/TGFα ratio (Lee and Kim, 2006; Sutcigil et al., 2007). All in all, antidepressants suppress CMI activation and induce a shift away from Th-1 cells towards Th-2, Th-3, Tr1 and/or Th22 cells.

#### 2.3.5. Conclusions

The abovementioned results in the rodent show that PICs, such as IL-1, IL-6 and TNFα, and cytokines produced during CMI activation, i.e. IFNγ and IL-2, all at around 50 μg/kg, may induce depressive-like symptoms in animals, e.g. melancholic, anxiety, neurocognitive and fatigue and somatic symptoms. We know that IFNγ, IL-2 or IL-1 can initiate the synthesis and release of other pro-inflammatories and that those pro-inflammatory mediators impact on the brain, causing neuroinflammation, and contribute to the pathological changes that are reflected in the different symptom clusters of depression. Another question remains whether data obtained in cytokine treated patients may be extrapolated to endogenous depression. The therapeutic doses employed in non-depressed patients being treated for hepatitis C or cancer with cytokines, such as IL-2 and IFNα, are much higher than the concentrations that are observed in depressed patients and even at these high concentrations only cause depressive-like symptoms in 30–50% of the patients. In any case, studies in clinical depression demonstrate that a cascade of inflammation and CMI activation occurs in depression and that those pathways are associated with the cardinal symptoms of depression. The changes in cytokine levels in depressed patients that occur at much lower blood concentrations presumably reflect the vulnerability of depressed patients to inflammatory changes that may be initiated by other factors, including psychological stressors and many medical conditions (Maes et al., 2011c). Predisposing factors are decreased peptidase levels and genetic polymorphisms in inflammatory and CMI-related genes (Maes, 1995, 2011; Maes and Bonaccorso, 2004). In the next sections we will discuss new pathways related to the effects of those cytokines that may explain the onset of depressive symptoms, e.g. their effects on IDO, the 5-HT transporter (5-HTT or SERT), and neuroprogression. We will also discuss new inflammatory/CMI pathways that were discovered in clinical depression and that are associated with the onset of depressive-like symptoms, e.g. increased bacterial translocation, oxidative and nitrosative stress (O&NS), decreased levels of antioxidants, and lowered ω3 polyunsaturated fatty acid levels (PUFAs). Fig. 1 shows the causal pathways from inflammation and CMI activation to depressive symptoms.

## 3. Cytokine-induced changes in 5-HT metabolism

### 3.1. Cytokine-induced changes in 5-HT receptors

Aberrations in the metabolism of 5-HT are involved in the pathophysiology of depression, e.g. changes in 5-HT mediated second-messenger signaling and changes in SERT, 5-HT2 and 5-HT1A receptors and a lowered availability of plasma tryptophan (the precursor of 5-HT) to the brain (Maes and Meltzer, 1995; Plein and Berk, 2000; Plein et al., 2000). SERT regulates the synaptic availability of 5-HT in the CNS and is therefore employed as the major target of currently available antidepressant drugs. A functional SERT is expressed on astrocytes and microglia. Prolonged treatment with IL-1β, TNFα, IL-6 and LPS upregulates SERT mRNA and protein levels. Zhu et al. (2006) established that both TNFα and IL-1β produce a rapid catalytic activation of SERT, depending on p38 MAPK activation. This upregulation is proposed as one of the mechanisms by which inflammation can trigger despair-like behaviors (Tsao et al., 2008; Zhu et al., 2005, 2006, 2010). In the poly I:C-induced fatigue rats, expression of SERT increased, while extracellular concentration of 5-HT in the medial prefrontal cortex decreased, probably on account of the enhanced expression of SERT (Katafuchi et al., 2006). These findings define the elements of a cytokine-modulated pathway for SERT activation having the potential to diminish extracellular (synaptic) 5-HT levels. In addition, inflammation as induced by LPS administration also increases 5-HT2A receptor expression in midbrain and decreases 5-HT1A receptor expression in the cortex in adult mice (Kulikov et al., 2010).

### 3.2. Cytokine-induced activation of indoleamine 2,3-dioxygenase (IDO)

#### 3.2.1. Findings in clinical depression

A lowered availability of plasma tryptophan to the brain is consistently reported in depression (Maes and Meltzer, 1995). During CMI activation, IFNγ not only induces GTP-cyclohydrolase I, but also indoleamine 2,3-dioxygenase (IDO; EC 1.13.11.52) (Werner-Felmayer et al., 1989). IDO is an IFNγ-inducible enzyme that activates the catabolism of tryptophan thus leading to the synthesis of tryptophan catabolites (TRYCATs) and nicotinamide. IDO is expressed in macrophages and dendritic cells, astroglia and microglia and in many organs, such as the kidney, lung, spleen, and duodenum (Takikawa et al., 1984; Moroni et al., 1991). Following activation of IDO plasma tryptophan is depleted and various TRYCATs are formed from tryptophan. Kynurenine, kynurenic acid, xanthurenic acid, and quinolinic acid are the most important TRYCATs for depression research (Maes et al., 2011e). Some of these TRYCATs, e.g. kynurenine and quinolinic acid, have detrimental effects, e.g. they are anxiogenic and depressogenic and induce neurotoxic effects. Other TRYCATs, like kynurenine acid, have neuroprotective effects. IDO is not only induced by IFNγ but also by TNFα, IL-2 and IL-1β (at least synergistically) (Oxenkrug, 2007), prostaglandin PGE2, oxidative stress, and LPS (Maes et al., 2011e). IDO can be inhibited by anti-inflammatory cytokines, such as IL-4, IL-10 and TGFβ (Yuan et al., 1998). Already in 1993–1994 it was shown that lower plasma tryptophan levels in depression are

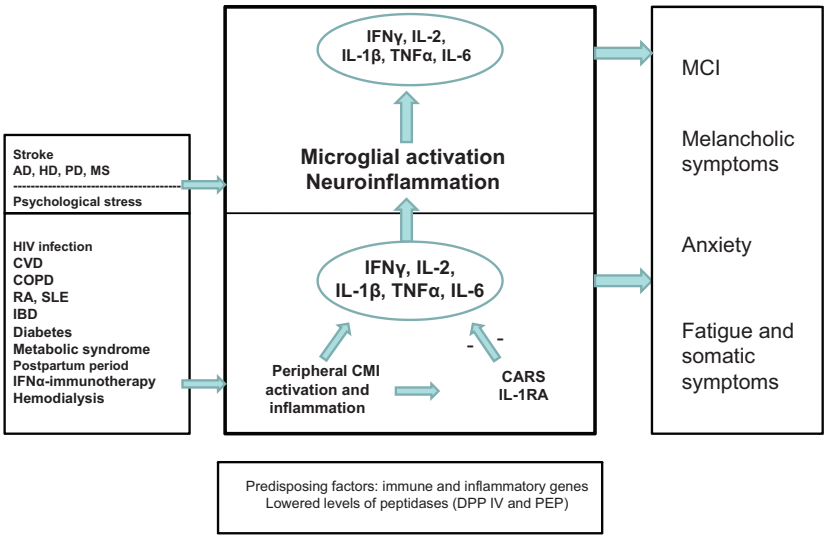


**Fig. 1.** Causal pathways from (neuro)inflammation to depressive symptoms.
The primary events in depression are cell-mediated immune (CMI) activation with increased production of interferon-γ (IFNγ) and interleukin-2 (IL-2), and an inflammatory response with increased production of IL-1β, IL-6 and tumor necrosis factor-α (TNFα). A counter anti-inflammatory responses system (CARS) is activated that tends to downregulate the primary immune response. Increased levels of the IL-1 receptor antagonist (IL-1RA) and T cell exhaustion by increased T cell cytokines are part of this CARS. Peripheral inflammation and CMI activation are translated to the brain to cause neuroinflammation and microglial activation (review: Maes et al., 2011c). All abovementioned cytokines are known to induce depression-like behaviors, subdivided into four main symptom domains, i.e. melancholic symptoms (anhedonia, anorexia, weight loss, and psychomotor retardation); anxiety-like behaviors; fatigue and somatic symptoms (fatigue, hyperalgesia, a flu-like malaise); and mild cognitive impairment (MCI). Trigger factors of depression are known to cause inflammation and CMI activation and/or neuroinflammation (Maes et al., 2011c): (a) systemic disorders, such as cardiovascular disorder (CVD), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), HIV infection, diabetes and the metabolic syndrome; (b) neurodegenerative and neuroinflammatory disorders, e.g. Alzheimer (AD), Huntington (HD) and Parkinson's disorder (PD), multiple sclerosis (MS) and stroke; and (c) conditions that are known to cause peripheral inflammation and CMI activation, e.g. the postnatal period, hemodialysis, IFNα-induced depression; and psychological stressors. Single nucleotide polymorphisms in inflammatory and T cell genes and lowered activity of peptidases, including dipeptidyl peptidase IV (DPP IV) and prolyl endopeptidase (PEP) increase the vulnerability to develop depression (Maes, 2011; Maes and Bonaccorso, 2004).

associated with increased neopterin, IL-6 and acute phase protein levels, suggesting that increased IFNγ production had induced both GTP-cyclohydrolase I and IDO (Maes et al., 1993a, 1994, 1996) and thus that the lowered levels of plasma tryptophan result from IDO activation (Maes et al., 1993a, 1994).

We now discuss the findings on TRYCATs in depression. Hoes (1979) found an increased excretion of xanthurenic acid in 24 h urine following ingestion of 5 g tryptophan in patients with anxiety, but not depression. Møller et al. (1982) and Maes et al. (1986) were unable to find increased xanthurenic acid or kynurenine after tryptophan loading in depressed patients. In patients with acute 'endogenous' anxiety disorders increased plasma kynurenine was found and upon remission these levels normalized (Orlikov et al., 1990). Increased levels of TRYCATs are detected in melancholic depression in adolescents (Gabbay et al., 2010). In depressed patients, Myint et al. (2007) found lower levels of the protective TRYCAT kynurenic acid as compared to kynurenine. The levels of the detrimental TRYCATs are related to residual depressive symptoms that have remained after antidepressant treatment (Mackay et al., 2006). In patients with coronary artery disease and malignant diseases, significant associations were found between higher levels of detrimental TRYCATs and the severity of depressive symptoms (Swardfager et al., 2009; Brandacher et al., 2006). Recently, we reported that the protective TRYCAT kynurenic acid was significantly decreased while the kynurenine/kynurenic acid ratio was significantly increased in depressed patients with somatic complaints (somatization) but not in depressed patients without somatic complaints (Maes et al., 2011b). Taken together, there is some evidence that depression and in particular depression with somatic symptoms is characterized by IDO activation and as a consequence lowered plasma tryptophan and a relative increase in detrimental TRYCATs.

### *3.2.2. How cytokines may contribute to depression through IDO activation*

When IDO is activated by cytokines, mainly IFNγ, but also IL-6 and TNFα, LPS, and oxidative stress (see following sections), the TRYCAT pathway is induced causing two mechanisms that play a role in the onset of depression.

- Firstly, IDO activation causes a lowered plasma tryptophan availability to the brain and, consequently, lower brain contents of tryptophan and 5-HT (Moir and Eccleston, 1968). Acute depletion of plasma tryptophan through depletion techniques (administration of tryptophan-free amino acid drinks coupled with ingestion of large concentrations of amino acids that compete for the same amino acid transporter) may lower brain 5-HT synthesis and has consistent mood-lowering effects in subgroups of remitted depressed patients (Van der Does, 2001). Depletion of plasma tryptophan not only plays a role in mood but also in the onset of somatic symptoms. For example, tryptophan depletion elicits increased distress, visceral perception, pain responses, autonomic stress responses, nausea, headache, etc. (review: Maes et al., 2011b).
- Secondly, induction of IDO elevates the production of detrimental TRYCATs, such as kynurenine and quinolinic acid. In fact, in some models the production of TRYCATs is more closely related to the onset of depression than the depletion in plasma tryptophan (Maes et al., 2011e). For example, in the early puerperium, IDO activation and TRYCAT production are significantly associated with the onset of affective symptoms (Maes et al., 2002). The development of depressive symptoms during IFNα-based immunotherapy is strongly associated with IDO activation and the production of detrimental TRYCATs (Maes et al., 2001; Bonaccorso et al., 2002). Raison et al. (2010) observed that the development of depressive symptoms during IFNα-based

immunotherapy is associated with increased levels of detrimental TRYCATs, like kynurenine and quinolinic acid. Recent studies of the Dantzer group have apparently separated the initial sickness behavior symptoms caused by LPS activation of PICs and the chronic depressive phase associated with the activation of IDO by bacille Calmette-Guérin (BCG). Thus, in WT mice, inoculation with BCG evokes depression-like behavior, which is accompanied by an increased expression of IDO, IFNγ, IL-1β and TNFα (O'Connor et al., 2009a,b).

Based on the abovementioned findings in the puerperium and IFNα-induced depression, a shift in the 5-HT hypothesis of depression was posited away from tryptophan and 5-HT depletion towards the effects of detrimental TRYCATs (Maes et al., 2002; Bonaccorso et al., 2002; Wichers and Maes, 2004; Myint and Kim, 2003; Wichers et al., 2005). The theory that IDO activation is related to depression is further developed in the "new 5-HT hypothesis of depression" (Maes et al., 2011e). Fig. 2 shows the causal pathways from CMI activation and inflammation to 5-HT disorders and depression.

The detrimental effects of TRYCATs encompass the following:

(a) Kynurenine and quinolinic acid induce anxiety-like (Lapin, 1996; Vécsei and Beal, 1990) and depression-like (O'Connor et al., 2009b) effects in animal models. In humans, a significant association between caffeine-induced kynurenine and anxiety was observed (Orlikov and Ryzov, 1991). Moreover, kynurenine contributes to pain and gut motility, while kynurenic acid has antinociceptive and analgesic effects and inhibits intestinal hypermotility (review: Maes et al., 2011b). Kynurenic acid is the only endogenous N-methyl-D-aspartate (NMDA) receptor antagonist, which activation may result in excitotoxic nerve cell loss (Swartz et al., 1990; Sapko et al., 2006). This suggests that peripheral TRYCATs may play a role in the somatic symptoms of depression.

(b) Kynurenine, kynurenic acid and xanthurenic acid are immunosuppressive and, therefore, exert a negative feedback on inflammatory responses and may downregulate the initial CMI activation and inflammation in depression (Maes et al., 2007a). Quinolinic acid, on the other hand, has pro-inflammatory effects and increases the IFNγ/IL-10 production ratio (Maes et al., 2007a). This may lead to toxic effects because IDO activation in the presence of microglia may cause an increased production of quinolinic acid originating from the kynurenine produced by astroglia, which lack kynurenine hydroxylase (Guillemin et al., 2000). During IDO activation, quinolinic acid may prevail in the brain thus aggravating the inflammatory response (Maes et al., 2007a).

(c) While activation of the IDO pathway has antioxidant capacities, the TRYCATs produced during IDO activation may have antioxidant or pro-oxidant capacities. The latter may play a role in pathophysiological conditions, like neurodegenerative disorders. For example, 5-hydroxyanthranilic acid, 3-hydroxykynurenine, 3-hydroxyanthranilic and quinolinic acid generate O&NS and damage including lipid peroxidation (review: Maes et al., 2011e).

(d) Some TRYCATs have detrimental effects on mitochondria and energy metabolism and thus may induce mitochondrial symptoms, to be discussed later. For example, kynurenic acid, 3-hydroxyanthranilic acid and/or 3-hydroxykynurenine impair adenosine triphosphate (ATP) production and/or reduce the respiratory control index and ADP/oxygen ratio in mitochondria (Schuck et al., 2007; Baran et al., 2003).

(e) One of the TRYCATs, quinolinic acid, is a strong agonist of the NMDA receptor (Müller and Schwarz, 2007). Therefore, CMI activation may not only cause a serotonergic deficiency, but also NMDA receptor activation, a phenomenon that may play a role in depression (Tokita et al., 2011). In this respect it is interesting to note that infusions with ketamine, a NMDA receptor antagonist, produce rapid antidepressant effects even in patients with treatment resistant depression (TRD) (Messer et al., 2010). A single infusion of ketamine improves suicidal ideation in TRD patients within 40 min that remains improved up to 4 h after infusion (DiazGranados et al., 2010). Ketamine is not only a NMDA receptor antagonist but also an anti-pro-inflammatory agent that blocks exacerbations of systemic inflammation (Loix et al., 2011). Ketamine also concentration-dependently inhibits LPS-induced IO&NS processes, such as IL-1β and NO release in primary cultured microglia (Chang et al., 2009). This suggests that the rapid antidepressant effects of ketamine may result from its NMDA receptor antagonist and anti-inflammatory effects.

## 4. Immune responses against bacterial translocation in the peripheral blood

### 4.1. Increased immune responses against LPS in depression

In the gut, epithelial cells surround the gut wall and form a tight junction barrier that segregates the luminal bacteria, including gram-negative commensal bacteria, from the interstitium. Inflammatory processes may cause a loosening of the tight junction barrier through the effects of NFκB (Al-Sadi and Ma, 2007; Ma et al., 2005); IL-1β, IL-6, TNFα, and IFNγ (Clark et al., 2005; Chavez et al., 1999); increased O&NS and a reduction in antioxidants (Wu et al., 2004b). The subsequent loosening of the spaces between the epithelial cells may lead to an increased translocation of gram-negative, commensal bacteria from the intestinal lumen through the epithelial mucosa into the lamina propria and the mesenteric lymph nodes (MLN) (Berg and Garlington, 1979; Wiest and Garcia-Tsao, 2005). In the MLN, a site of antigen presentation, the commensals may activate immune cells which can explain why the gut can become a cytokine-releasing organ even in the absence of an inflammatory lesion. From the MLN, the bacterial translocation of gram-negative commensals or LPS, a component of the outer membrane of gram-negative bacteria, may spread systemically when there are defects in the local or systemic immune defenses (Wiest and Garcia-Tsao, 2005). This mechanism, called leaky gut, may drive gut-derived inflammation (Wischmeyer, 2006).

Depression is accompanied by increased IgM and IgA-mediated immune responses against the LPS of *Hafnia alvei*, *Pseudomonas aeruginosa*, *Morganella morganii*, *Pseudomonas putida*, *Citrobacter koseri*, and *Klebsielle pneumoniae* (Maes et al., 2008). If only the IgA, and not the IgM, antibodies would be increased one could conclude that the the immune response is confined to the mucosal immune system without systemic involvement (Fanous et al., 2007). The increased levels of the IgM and IgA antibodies, however, indicate the presence of a systemic immune response against the LPS from various gram-negative bacteria. Since depression is also accompanied by gut inflammation and increased small intestine bacterial overgrowth (Maes et al., personal data), these findings indicate the presence of an increased gut permeability and bacterial translocation.

### 4.2. Bacterial translocation may contribute to depressive symptoms

First, the bacterial translocation occurring secondary to systemic inflammation, CMI activation and O&NS could intensify and perpetuate the primary inflammatory and CMI response

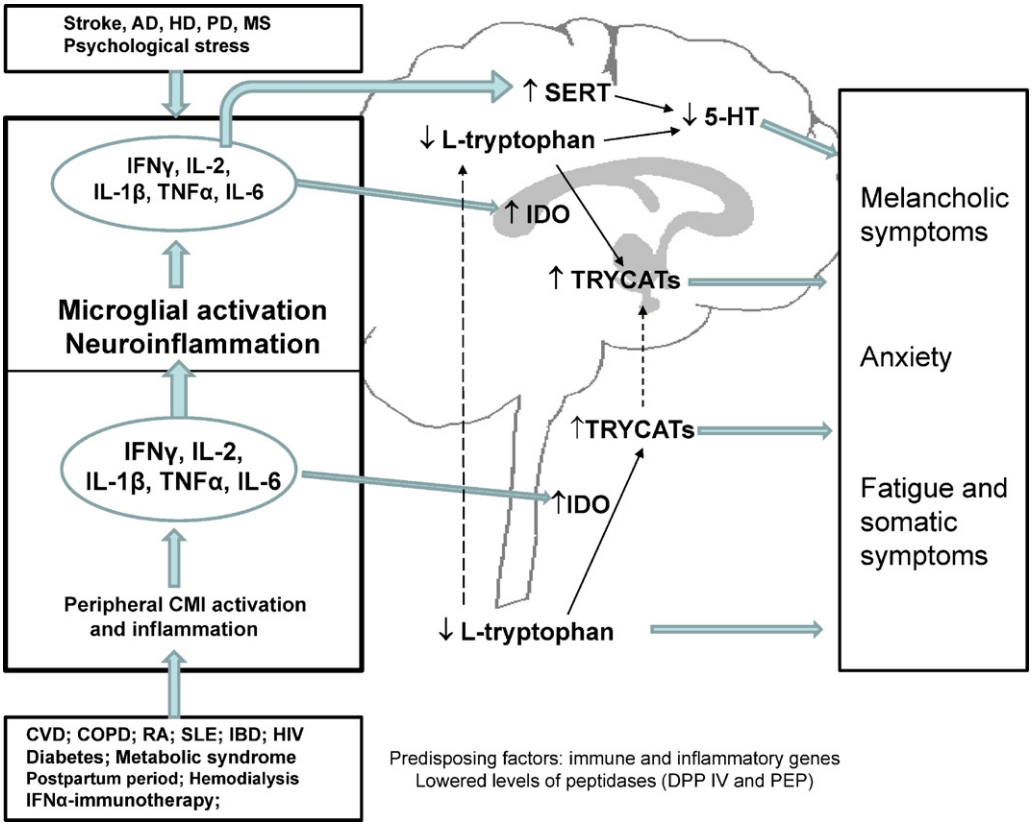


**Fig. 2.** Causal pathways from (neuro)inflammation to disorders in 5-HT metabolism and depressive symptoms.
Interconnections between peripheral cell-mediated immune (CMI) activation characterized by increased interferon-γ (IFNγ) and interleukin-2 (IL-2); and inflammation characterized by increased interleukin-1β (IL-1β), IL-6 and tumor necrosis factor-α (TNFα) and IL-6; and two serotonin (5-HT) pathways. A first is induction of indoleamine 2,3-dioxygenase (IDO) by IFNγ and, synergistically, by IL-2, TNFα and IL-1β. IDO activation causes depletion of L-tryptophan and thus 5-HT, which may cause melancholic symptoms; anxiety; and somatic symptoms; and increased production of tryptophan catabolites (TRYCATs) some of which have anxiogenic and depressogenic effects. A second pathway is upregulation of the 5-HT transporter (SERT) by IL-1β, TNFα, and IL-6, which has the potential to diminish synaptic 5-HT and thus to trigger despair-like behaviors.
Trigger factors of depression are known to cause inflammation and CMI activation and/or neuroinflammation (Maes et al., 2011c): (a) systemic disorders, such as cardiovascular disorder (CVD), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), HIV infection, diabetes and the metabolic syndrome; (b) neurodegenerative and neuroinflammatory disorders, e.g. Alzheimer (AD), Huntington (HD) and Parkinson's disorder (PD), multiple sclerosis (MS) and stroke; and (c) conditions that are known to cause peripheral inflammation and CMI activation, e.g. the postnatal period, hemodialysis, IFNα-induced depression; and psychological stressors. Single nucleotide polymorphisms in inflammatory and T cell genes and lowered activity of peptidases, including dipeptidyl peptidase IV (DPP IV) and prolyl endopeptidase (PEP) increase the vulnerability to develop depression (Maes, 2011; Maes and Bonaccorso, 2004).

because once the commensals are translocated into the MLN they may mount an immune response. Second, as explained above it is also possible that the bacterial or LPS translocation may spread systemically and thus that LPS is translocated into the blood or other organs. Thirdly, bacterial translocation may be the consequence of local gut inflammation, related for example to inflammatory bowel disease or chronic alcohol abuse and as such function as a cause for 'secondary' depression.

It is known that LPS is able to elicit depressive- and anxiety-like behaviors, fatigue and MCI. For example, LPS administration suppresses food consumption, body weight, social interaction and activity in the open-field test and elicits anhedonia (Yirmiya, 1996; Plata-Salamán and Borkoski, 1993; Bluthé et al., 1994; De La Garza et al., 2005). LPS is also able to elicit anxiety-related behaviors, including reduced exploratory behavior and social interactions (Engeland et al., 2003). Certainly, it is not always possible to decipher whether the anxiogenic and depressogenic effects of LPS are genuine or related to illness (Swiergiel and Dunn, 2007). Nevertheless, Frenois et al. (2007) reported that there is a dissociation between LPS-induced sickness behavior and LPS-induced depressive-like behaviors by testing mice at different time points after LPS administration.

LPS may induce the production of macrophage-derived pro-inflammatory cytokines by binding to specific receptors, the CD14-Toll-like receptor-4 (TLR4) complex. TLRs are expressed by peripheral blood mononuclear cells, microglia, astrocytes and neurons. TLRs recognize PAMPs (pathogen associated molecular patterns), such as LPS. Therefore LPS recognition induces an innate immune response that proceeds through activation of NFκB and mitogen-activated protein kinases (MAPK). This mechanism explains why repeated LPS instillations in the nasal cavities can provoke transcriptional regulation of TNFα in different brain regions (Tonelli et al., 2008).

While LPS induces depression- and anxiety-like behaviors, psychosocial stressors modulate the effects of LPS. Thus, social stress elicits higher TLR expression on the surface of splenic macrophages (Bailey et al., 2007). Chronic unpredictable stress aggravates LPS-induced NFκB activation in the frontal cortex and hippocampus (Munhoz et al., 2006). TLR4-deficient mice show lower inflammatory responses and lipid peroxidation in the brain, and a better behavioral outcome in response to immobilization stress (Caso et al., 2008). Thus, in depression, there may be an interaction

between the effects of LPS derived from leaky gut and psychological stress-induced upregulation of TLRs.

## 5. Oxidative and nitrosative stress (O&NS)

### 5.1. Activated O&NS pathways in depression

Inflammatory and CMI responses are accompanied by increased production of radical oxygen (ROS) and radical nitrogen species (RNS). PICs, such as IL-1 and TNFα, enhance the effects of ROS including hydrogen peroxide, while neopterin enhances iNOS gene expression causing increased nitric-oxide production (Maes et al., in press). O&NS processes react with proteins, fatty acids, DNA, including mitochondrial DNA (mtDNA), causing damage to these molecules and the tissues to which they belong. O&NS processes may change the functions and chemical structure of membrane fatty acids (by oxidative processes) and functional proteins (by oxidative and nitrosative processes). When these modified epitopes or neoepitopes become immunogenic, the immune system mounts an autoimmune response against the neoepitopes thereby further damaging the fatty acids or protein structures (Maes et al., 2012a).

There is now evidence that clinical depression and animal models of depression are accompanied by O&NS (review: Maes et al., 2011a) as evidenced by: increased plasma levels of peroxides and xanthine oxidase (Maes et al., 2010; Herken et al., 2007); increased xanthine oxidase activity in post-mortem brain tissue of patients with recurrent depression (Michel et al., 2008); increased lipid peroxidation, as indicated by increased levels of malondialdehyde (MDA), a byproduct of polyunsaturated fatty acid peroxidation and arachidonic acid (Khanzode et al., 2003; Ozcan et al., 2004; Gałecki et al., 2009a,b; Sarandol et al., 2007); increased plasma levels of 8-iso-prostaglandin F2, a bioactive product of free radical-catalyzed peroxidation of arachidonic acid (Dimopoulos et al., 2008); and increased 4-hydroxynonenal (4-HNE), a major aldehyde product generated by lipid peroxidation of omega-6 PUFAs like arachidonic acid and linoleic acid, in the anterior cingulate cortex of bipolar patients (Wang et al., 2009). Damage to DNA in depression has been observed in studies measuring 8-hydroxy-2′-deoxyguanosine (8-OHdG), a mutagenic DNA lesion, in the serum (Forlenza and Miller, 2006; Maes et al., 2009a) and peripheral leukocytes (Irie et al., 2005). Telomere shortening (Simon et al., 2006) and an increased frequency of DNA damage (Andreazza et al., 2007) have been detected in patients with affective disorders. Finally, depression is accompanied by increased autoimmune reactions against neoepitopes as evidenced by increased plasma concentrations of IgG autoantibodies against oxidized low density lipoproteins (LDL) and IgM-mediated immune responses directed against phosphatidyl inositol (Pi) and anchorage molecules, including palmitic and myristic acid (Maes et al., 2007b, 2012a).

There are sufficient data in men and animals to conclude that psychosocial stressors may induce O&NS pathways. Acute and chronic immobilization stressors in the rodent provoke iNOS and ONOO-expression in the brain (Olivenza et al., 2000; Madrigal et al., 2001). Attenuation of iNOS reverses the onset of depressive-like and anxiety behaviors induced by acute and chronic stressors (Sevgi et al., 2006; Mutlu et al., 2009).

There is evidence that antidepressants may attenuate activated O&NS pathways in clinical depression and animal models of depression (Maes et al., 2011a). For example, treatment with antidepressants reduces increased MDA levels, suggesting that these drugs attenuate lipid peroxidation (Khanzode et al., 2003; Bilici et al., 2001; Gałecki et al., 2009b). Restraint stress causes increased MDA and protein carbonyl accumulations in the brain, which were both normalized upon treatment with antidepressants (Zafir et al., 2009).

### 5.2. Activated O&NS pathways may contribute to depressive symptoms

Activated O&NS pathways may contribute to depression through a number of mechanisms.

- Activated O&NS pathways cause damage to membrane ω3 PUFA contents, and other membrane fatty acids, including oleic and palmitic acid. This damage in turn may cause alterations in cell membrane structure and viscosity and thus in receptor expression, including that of 5-HT receptors (Maes et al., 1999a).
- Lipid peroxidation may interfere with specific binding of 5-HT to membranes through effects of MDA causing irreversible decreases in Bmax of 5-HT and spiperone binding (Muakkassah-Kelly et al., 1982).
- O&NS processes may cause damage to DNA, mitochondria and proteins, which frequently occur in depression (Maes et al., 2011a; Gardner and Boles, 2011).
- O&NS pathways may damage functional intracellular signaling molecules involved in the pathophysiology of depression. One example is the autoimmune response mounted against oxidatively-damaged Pi in depression (Maes et al., 2007b). The latter may have detrimental consequences for proper functioning of the cells. Pi is converted to phosphatidylinositol-4,5-bisphosphate (PIP2), which is the direct precursor of important second-messenger molecules, i.e. inositol-1,4,5-triphosphate (IP3), diacylglycerol and phosphatidylinositol-3,4,5-triphosphate (PIP3). This complex plays a key role in modulating intracellular calcium levels; cell survival, growth and proliferation; phosphorylization of cellular proteins; and protein kinase C (PKC) activation. Pi functions as a lipid messenger from the plasma membrane to the nucleus and is needed for a proper functioning of 5-HT.
- IDO uses superoxide anion radical (SAR) as a co-substrate (Kobayashi et al., 1989). When IDO is activated and when there is excessive oxidative stress IDO may contribute to elimination of SAR. Thus, an excess in oxidative stress may cause superinduction of the IDO pathway (Daley-Yates et al., 1988).
- In human depression and CFS it is observed that O&NS damage to DNA, proteins and fatty acids is significantly correlated to fatigue, muscular pain and aches, a flu-like malaise, etc. (Maes et al., 2007b) and that in CFS incremental exercise associates O&NS with alterations in muscle membrane excitability (Jammes et al., 2005). In exercising humans, administration of N-acetylcysteine, an antioxidant that stimulates glutathione homeostasis, delays muscle fatigue (Matuszczak et al., 2005). Treatment with carnitine reduces O&NS and chronic inflammation in cancer and hemodyalisis patients thereby reducing fatigue (Laviano et al., 2006). There is also abundant evidence that in animal models experimentally induced activation of O&NS pathways is associated with the onset of fatigue and somatic symptoms and that blocking these O&NS pathways may reverse or prevent these F&S symptoms (Gupta et al., 2009; Singh et al., 2002). These findings suggest that O&NS damage is a causal factor in fatigue and somatic symptoms.

## 6. Antioxidants

### 6.1. Decreased antioxidant levels in depression

Antioxidants, antioxidant enzymes and some proteins tightly regulate ROS and RNS by scavenging or binding ROS/RNS or decreasing ROS/RNS production. Coenzyme Q10, vitamins C and E, and glutathione are important antioxidants. Superoxide dismutase (SOD) and glutathione peroxidase (GPX) are examples of

antioxidant enzymes that neutralize peroxides and superoxide. APPs, such as haptoglobin and albumin, function as antioxidants by binding ROS and RNS. Tryptophan and tyrosine residues have important antioxidant activities in lipid bilayers and protect cell membranes from oxidative damage (Moosmann and Behl, 2000). Tryptophan (Reiter et al., 1999) and 5-HT (Wrona and Dryhurst, 1991) act as radical scavenging antioxidants and prevent oxidative damage. When there are imbalances between antioxidant defenses and ROS/RNS, the protection against the detrimental effects of ROS/RNS is impaired allowing O&NS to damage lipids, proteins and DNA. The brain is characterized by a high metabolic rate and lower antioxidant levels and is therefore very vulnerable to O&NS.

Maes et al. (2000b) reviewed that depression is characterized by a lowered antioxidant status, as exemplified by lower serum levels of antioxidants, such as zinc, albumin, tryptophan, and tyrosine. Since then, many reports were published on associations between depression and lower antioxidant levels: vitamin E (Maes et al., 2000b; Owen et al., 2005; Tsuboi et al., 2006); coenzyme Q10 (Maes et al., 2009b); glutathione (GSH) (Kodydková et al., 2009) and GPX (Kodydková et al., 2009; Ozcan et al., 2004). These findings also explain why the total antioxidant capacity (TAC) is significantly decreased in patients with depression (Cumurcu et al., 2009; Gałecki et al., 2009a,b). Lowered antioxidant defenses are consistently reported in animal models of depression (review: Maes et al., 2011a).

In humans and animals there is evidence that antidepressants may increase lower antioxidant levels (Maes et al., 2011a). Ozcan et al. (2004) found that antidepressant treatments normalized GPX activity. Ex vivo tests showed that long-term treatment (24 h) significantly enhanced mRNA levels of antioxidant enzymes, including GPX (Schmidt et al., 2008). In rats subjected to CMS, different types of antidepressants increase brain GPX activity (Eren et al., 2007a,b). In rats, subchronic treatment with sertraline, a SSRI, improved toxin-induced decreases in glutathione levels (Kumar and Kumar, 2009). Treatment with antidepressants normalizes reduced brain glutathione caused by restraint stress (Zafir et al., 2009).

### 6.2. Lower antioxidant levels may contribute to depressive symptoms

Lower antioxidant levels may contribute to depression through a number of mechanisms:

(a) The reduced anti-oxidative capacities of the blood and especially the brain cause a decreased protection against ROS/RNS and inflammation. For example, coenzyme Q10 is not only a strong antioxidant, but also an anti-inflammatory agent that targets NFκB-gene expression; pro-inflammatory cytokines, such as TNFα; and LPS-induced inflammatory reactions (Schmelzer et al., 2008; Abd El-Gawad and Khalifa, 2001; Sugino et al., 1987). IDO-induced depletion of tryptophan and 5-HT, two antioxidants, may increase the oxidative potential in patients with depression. Thus, the deficiency in antioxidants in depression may predispose the patients towards greater IO&NS responses (Maes et al., 2011a).

(b) Decreases in specific antioxidants, e.g. coenzyme Q10, may be associated with the onset of F&S symptoms. For example, fatigue, myalgia and neurocognitive disorders are associated with low coenzyme Q10 levels in mitochondrial disorders, like Prader–Willi syndrome, Friedrich's ataxia, Steinert's myotonic dystrophy, and cardiac disorders, skeletal muscle dysfunctions, and cancers (Maes et al., 2009b). Statins may induce fatigue, myalgia and neurocognitive symptoms through coenzyme Q10 depletion, symptoms that are reversed by coenzyme Q10 supplementation (Langsjoen et al., 2005). The causation of symptoms is not only related to its protective properties against the production of free radicals, but also to the effects of coenzyme Q10 on the electron transport chain within the mitochondria and the synthesis of ATP (Butler et al., 2003; Crane, 2001). Therefore, the lower coenzyme Q10 syndrome in depression may be associated with mitochondrial dysfunctions including decreased activities of the mitochondrial respiratory chain and damage to mtDNA (Maes et al., 2011a).

Selected antioxidants have antidepressant effects in clinical and animal depression. Berk et al. (2008) reported that in depression N-acetyl-cysteine (NAC) significantly augments the clinical efficacy of antidepressants. NAC administration significantly reduces the immobility time in male Wistar rats (Ferreira et al., 2008). In the forded swimming test, Ebselen (2-phenyl-1,2-benzisoselenazol-3[2H]-one), a substance that mimics GPX activity (Müller et al., 1984), has antidepressant effects that are not associated to noradrenergic or dopaminergic systems (Posser et al., 2009). The effects of Ebselen may be explained since Ebselen is a strong antioxidant and anti-inflammatory substance (Satoh et al., 2004) that prevents the activation of immobilization stress-induced IO&NS pathways, such as increased IL-1 and COX-2 production (Lee et al., 2006). Curcumin or curcuma longa, a strong antioxidant and anti-inflammatory substance, attenuates depressive-like behavior in rat models of depression and this effect is associated with reduced NFκB and IFNγ-induced IDO expression (Zhang et al., 2008a; Xu et al., 2007). Flavonoids, like liquiritin, block CMS-induced depressive behaviors (increases in immobility time and decreases in sucrose consumption) and normalize O&NS pathways (increased MDA production) (Zhao et al., 2008). Epigallocatechin-3-gallate, the major constituent of green tea, attenuates activation of the IO&NS pathways, including increased TNFα production, in the brain of mice subjected to the forced swim test of Porsolt (Sachdeva et al., 2010).

## 7. Serum zinc

### 7.1. Lowered zinc in depression

Zinc is a trace element that is needed for the confirmation of polysomes during protein synthesis, and the stabilization of membranes. Zinc functions as an important cofactor for several pathways and enzymes, like metalloenzymes and zinc-dependent enzymes. Zinc has a key role in signal transduction and gene expression, including that of cytokine genes, and plays a key role in synaptic plasticity and glutaminergic neurons (Maes et al., 1997b; Szewczyk et al., 2011). During inflammatory reactions, serum zinc is decreased as a consequence of the sequestration of zinc-metallothionein from the circulation and increased synthesis in the liver of metallothioneins, which are induced by IL-1β and IL-6 (Bremner and Beattie, 1995). Decreased serum zinc during inflammation is associated with increased zinc contents in the liver, where zinc is used for the increased synthesis of APPs (Dunn and Cousins, 1989; Lowe et al., 1991). Zinc deficiency, in turn may impair cell-mediated and humoral immunity (Prasad et al., 1993).

There are now many studies showing that depressed patients have significantly lower serum zinc levels than normal controls (McLoughlin and Hodge, 1990; Maes et al., 1997b; Nowak et al., 1999). Lowered serum zinc occurs in antepartum and postpartum depressive symptoms (Wojcik et al., 2006) and is related to the severity of depression and treatment resistance to antidepressants (Maes et al., 1997b; Nowak et al., 1999). Maes et al. (1997b, 1999b) were the first to report that the lowered serum zinc levels are associated with signs of CMI activation and inflammation, e.g. with (a) the $CD4^+/CD8^+$ T cell ratio (negative), serum albumin and

transferrin (positive); (b) increased neopterin concentrations (negative); and (c) serum IL-6 (negative).

### 7.2. Lower zinc may contribute to depressive symptoms

In humans, hypozincemia is associated with depression, dysphoria, anorexia, impairment of taste and smell, and impaired neurocognitive function (Solomons, 1988; Aggett and Harris, 1979). In the rat, zinc-deficient diets provoke anhedonia, as measured by a preference for saccharin-sweetened water, and anxiety-like behaviors (Tassabehji et al., 2008). Dietary zinc deficiency elicits depressive-like behaviors in the forced swim and tail suspension tests, and anxiety-related behaviors in the novelty suppressed feeding test (Whittle et al., 2009). In patients and animal models of depression, treatment with zinc has antidepressant effects and enhances the effects of antidepressants (Siwek et al., 2008; Szewczyk et al., 2011, 2002, 2009). In some, but not all, studies successful antidepressant treatment normalizes lower serum zinc (Maes et al., 1997b; Schlegel-Zawadzka et al., 2000).

The depressogenic effects of lowered zinc levels and the clinical efficacy of zinc in treating depression may be explained by the anti-oxidative properties of zinc, and its effects on 5-HT and PUFA metabolism, cortisol, the NMDA receptor complex and neurogenesis (Maes et al., 1999b; Siwek et al., 2008). Thus, chronic zinc deprivation may result in an increased sensitivity to O&NS, while zinc administration increases the antioxidant capacity (Powell, 2000). Synaptic zinc functions as a natural allosteric modulator of 5-HT$1_A$ receptors and may modulate hippocampal functions via effects on 5-HT metabolism (Barrondo and Sallés, 2009). Lowered serum Zn may cause a depletion of the long-chain ω3 PUFAs in depression because desaturase enzymes require Zn as cofactor (Maes et al., 1999a). Zinc has an acute inhibitory effect on cortisol secretion (Brandão-Neto et al., 1990). Zinc deficiency increases cytosolic $Ca^{2+}$ concentrations through increased glutamate release and enhanced activity of NMDA, which may cause excitotoxic damage (Szewczyk et al., 2011). Zinc is a potent inhibitor of the NMDA receptor complex and selectively blocks central neuronal excitation of this receptor (Christine and Choi, 1990). The neurogenic effects of zinc are reviewed in one of the following sections.

## 8. Mitochondrial functions

### 8.1. Dysfunctional mitochondria in depression

Mitochondria produce most of the energy for the cell, stored as ATP, through β-oxidative processes. The latter constantly generate ROS/RNS that may damage mtDNA and lipid membrane structures of mitochondria. Specific antioxidants, such as coenzyme Q10, lipoic acid and GPX protect the mitochondria, including mtDNA, against these damaging effects (Chaturvedi and Beal, 2008; Liu, 2008).

Depression is accompanied by mitochondrial disturbances, such as deletions of mtDNA (Shao et al., 2008; Gardner et al., 2003; Suomalainen et al., 1992) and lower activities of respiratory chain enzymes and ATP production (Gardner et al., 2003). Findings in the brain of depressed patients encompass altered translational mitochondrial structures in the frontal and prefrontal cortices (Whatley et al., 1996; Karry et al., 2004); mitochondrial-located proteins in the anterior cingulate cortex (Beasley et al., 2006); nDNA-encoded mitochondrial mRNA and proteins in the cerebellum (Ben-Shachar and Karry, 2008); and decreased gene expression of mtDNA-encoded transcripts in frontal cortex (Shao et al., 2008). Virtually all depressed individuals with somatic complaints had lowered ATP production rates in biopsied muscles (Gardner and Boles, 2008a,b).

Recently, it was described that the mitochondrial defects that are observed in depression may be caused by inflammatory and activated O&NS pathways (Maes et al., 2011a; Gardner and Boles, 2011). Indeed, ROS – that are byproducts of respiratory chain activity in the mitochondria – are increased in depression, while antioxidants, such as coenzyme Q10 and GPX, that normally confer protection of mitochondria against the damaging effects of ROS, are reduced in depression. Therefore, depressed patients are predisposed towards mitochondrial dysfunctions including aberrations in mtDNA. Moreover, increased levels of LPS in depression could contribute to mitochondrial dysfunctions, because LPS affects mitochondrial bioenergetics (Hunter et al., 2007).

### 8.2. Mitochondrial dysfunctions may contribute to depression

Patients with mitochondrial disorders show a high frequency of affective disorders. Thus, the lifetime diagnosis of depression in patients with mitochondrial disorders is 54% and that of panic disorder 11% (Fattal et al., 2007). Adolescents with mitochondrial disorders suffer significantly more from depression than adolescents without mitochondrial disorders (Koene et al., 2009). Depression can be the only manifestation of mitochondrial disorders (Gardner and Boles, 2011). Somatic symptoms, such as chronic fatigue (75%) and headache (82%), myalgia, tinnitus, gastro-intestinal symptoms, blurred vision, etc., often accompany mitochondrial disorders. mtDNA sequence variants associated with mitochondrial dysfunctions have been shown to increase the odds to develop depression (Boles et al., 2005; Burnett et al., 2005). Administration (ip) of imipramine stimulates state 3 and 4 respiration rates (Katyare and Rajan, 1995). Nortriptyline is a strong inhibitor of mitochondrial permeability transition (MPT), which causes mitochondrial dysfunctions and acute neuronal death (Zhang et al., 2008b).

Different mechanisms explain why mitochondria play a role in the onset of depression. Firstly, a deficiency in ATP production could well explain why those individuals are at an increased risk of developing peripherally and centrally mediated fatigue and somatic symptoms. High energy levels are also required for brain functions, such as signal transduction, synaptic remodeling, and the maintenance of the transmembrane potential. Mitochondrial dysfunctions may contribute to decrease metabolism as measured by SPECT scan alterations in psychiatric disorders (Gardner and Boles, 2011). Secondly, decreased ATP production may cause neuronal dysfunctions and even "cellular energetic depression (CED)" leading to activation of the apoptotic cell death program, by releasing cytochrome c (Seppet et al., 2009).

## 9. Omega-3 PUFAs

### 9.1. Lower omega-3 PUFAs in depression

There is now evidence for lowered ω3 PUFA contents, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the serum, red blood cell (RBC) membrane, fat tissues and the brain of depressed patients, while no changes in ω6 PUFA contents are found (Maes et al., 1999a; Peet et al., 1998; Mamalakis et al., 2006; Lin et al., 2010). Epidemiologic studies show that a low dietery intake of EPA and DHA is associated with higher prevalence rates of depression and postpartum depression (Hibbeln, 1998, 2002). Depletion of ω3 PUFAs in depression is – in part – a consequence of increased damage by oxidative stress (Peet et al., 1998; Maes et al., 1999a) and inflammatory responses through reduced zinc, which is an important cofactor in the synthesis of PUFAs (Maes et al., 1999a).

### 9.2. Lower omega-3 PUFA levels may contribute to depression

Depletion of ω3 PUFAS may be causally related to the onset of depressive behavior. ω3 deficient diets in the rodent, which cause a depletion of ω3 PUFAs, e.g. DHA, in the brain cell membrane (Bourre et al., 1993), also cause behavioral changes, such as alterations in operant and passive avoidance behaviors (Umezawa et al., 1995). Depletion of ω3 PUFAs in rhesus monkeys is associated with increased behavioral reactivity to stress (Reisbeck et al., 1990).

EPA, as a monotherapy, has beneficial effects in patients with TRD (Puri et al., 2002). A meta-analysis of the placebo controlled, double-blind trials of ω3 PUFAs in depression showed that EPA has significant antidepressant activity (Lin and Su, 2007). More recent studies show that ω3 PUFAs significantly improve depressive symptoms in patients with major depression (Lespérance et al., 2011) and in elderly depressed females (Rondanelli et al., 2010). In animal models, such as the forced swimming test in rats, ω3 PUFAs have antidepressant effects (Huang et al., 2008). ω3 PUFAs improve the immobility and swimming behavior significantly more than control, while the efficacy of fluoxetine and ω3 PUFAs combined is significantly greater than that of fluoxetine alone (Lakhwani et al., 2007). In the forced swim test in rats, dietary ω3 PUFA supplementation significantly reduced immobility when treated during 30 days, but not for less than 10 days (Carlezon et al., 2005).

A first mechanism that may explain the association between depleted ω3 PUFAs and depression and the clinical efficacy of ω3 PUFAs is that ω3 and ω6 PUFAs modulate immune functions. ω3 PUFAs, like EPA, attenuate PGE2 synthesis and the production of monocytic and T cell cytokines, including IL-1, IL-6, TNFα and IFNγ (review: Maes et al., 1999a). ω6 PUFAs and in particular arachidonic acid (AA) have pro-inflammatory effects: ω6 PUFAs are precursors of prostaglandins, such as PGE2, and increase the production of IL-1, TNFα and IL-6. The depletion of ω3 PUFAs and the relatively higher ω6 contents in depression may cause an increased production of PICs and T cell cytokines and therefore take part in the immune pathophysiology of depression (Maes et al., 1999a, 2000a). In this regard, subjects with low ω3 PUFA levels show a significantly higher stress-induced production of PICs, such as TNFα and IFNγ, as compared with subject with higher ω3 levels (Maes et al., 2000a). These greater inflammatory responses are associated with higher anxiety and perceived stress ratings (Maes et al., 1998).

Song et al. (2004) have investigated some of the possible mechanisms of action of EPA. In these studies it was shown that ethyl-EPA (1%), administered for 8 weeks in the diet of rats, significantly attenuated the acute and sub-acute (3 days) effects of icv administered IL-1β (10 μg). IL-1β also impaired working memory, increased the serum corticosterone and prostaglandin E2 concentrations, and reduced the release of the anti-inflammatory cytokine IL-10 from whole blood cultures. These effects were blocked by ethyl-EPA thereby demonstrating the anti-inflammatory and anti-stress effects of EPA. The results were confirmed in a subsequent study that, in addition, demonstrated that ethyl-EPA reversed the changes in the turnover of brain noradrenaline, 5-HT and dopamine caused by IL-1β in several brain regions (Song et al., 2008). A second mechanism is that ω3 PUFAs determine cell membrane fluidity and the quaternary structure of membrane lipids and proteins (Maes et al., 1999a; Beltz et al., 2007). The microstructure of the neuronal membrane can be adversely affected by changes in the composition of the PUFAs thereby leading to abnormal signal transduction. Moreover, membrane fatty acids partly determine 5-HT turnover, e.g. 5-HT release and reuptake; the activity of tryptophan hydroxylase, the rate limiting enzyme in 5-HT synthesis; brain concentrations of 5-HT and 5-hydroxyindolacetic acid, a 5-HT metabolite (Block and Edwards, 1987; Mullen and Martin, 1992; Crane and Greenwood, 1987). A dietary deficiency in ω3 PUFAs is associated with increased MAO-B activity and increased density of brain 5-HT2 receptors (Delion et al., 1996, 1997).

## 10. The neuroprogressive hypothesis of depression

### 10.1. Neuroprogression in depression

There is now evidence that neuroprogression plays a role in the pathophysiology of depression (Sapolsky, 2004; Henn and Vollmayr, 2004; Maes et al., 2009c, 2011d; Berk et al., 2011). Volumetric changes in hippocampus, amygdala, prefrontal cortex, anterior cingulate and basal ganglia have been detected in patients suffering from long-term recurrent depression (Campbell and MacQueen, 2006). Hippocampal volume reduction is associated with the neurocognitive deficits found in mood disorders, such as geriatric depression; and the depression – MCI – dementia complex (Brown et al., 2004; Duman, 2004; Maes et al., 2009c). Neuronal and glial cell modifications are found in the post-mortem hippocampus (Stockmeier et al., 2004). In many brain disorders, mood alterations are associated with reduced hippocampal neurogenesis (Duman, 2004). The lowered neurogenesis in depression is associated with lower levels of neurotrophins, e.g. brain-derived neurotrophic factor (BDNF) (Angelucci et al., 2005; Smith et al., 1995). A recent meta-analysis showed that BDNF levels may be lower in depression although this is challenged by recent findings that lowered plasma BDNF may be a marker for neuroticism (Brunoni et al., 2008; Terracciano et al., 2011). In a recent large-scaled study, Molendijk et al. (2011) detected that low serum BDNF levels are a state abnormality that normalizes during remission. On the other hand, serum BDNF was significantly lower in bipolar depression than in unipolar depression, suggesting that it is a staging marker in bipolar mood disorder only (de Oliveira et al., 2009; Fernandes et al., 2009). Some data suggest that the high recurrence rates of depression and treatment resistance may be associated with neuroprogressive processes. Thus, impaired neurogenesis and reduced expression of BDNF in hippocampal neurons are markers of repeated episodes of untreated recurrent depression (Vaidya and Duman, 2001). An association between BDNF genotypes and an increases risk of treatment resistant depression has been observed (Anttila et al., 2007). Recent evidence suggests the involvement of another neurotrophic factor in depression, i.e., the fibroblast growth factor (FGF) (Turner et al., 2006). A reduced activity in the FGF system might alter brain development and result in a predisposition or vulnerability to depression (Turner et al., 2006). Depletion of cell adhesion molecule (NCAM) is another mechanisms that causes neurocognitive disorders in mood disorders (Sandi, 2004; Sandi and Bisaz, 2007). NCAM is expressed on the surface of neurons and glia and is implicated in learning, memory and neurogenesis.

Neuroprogression, including neurodegeneration and reduced neurogenesis and lower BDNF levels, are observed in animal models of depression. For example, the olfactory bulbectomized (OB) rat model of depression is associated with neurodegeneration, including decreased cortical, hippocampal, caudate and amygdaloid volumes, and ventricular enlargement (Wrynn et al., 2000); and degenerated neurons in the piriform cortex (Wang et al., 2007). Lowered BDNF levels are found in brain regions associated with depression (Schmidt and Duman, 2007; Fuchs et al., 2004). Exposure to acute and chronic stressors, e.g. immobilization and chronic inescapable foot shock, reduces hippocampal neurogenesis (Duman and Monteggia, 2006; Koo and Duman, 2008; Gould et al., 1998; Ben Menachem-Zidon et al., 2008; Vollmayr et al., 2003). In mice, deletion of the NCAM gene is associated with cognitive impairment and emotional behavior (Stork et al., 1999; Bukalo et al., 2004).

Chronic administration of antidepressants increases cell regeneration (Czeh et al., 2001; Dranovsky and Hen, 2006; Jayatissa et al., 2006) and neurogenesis (Malberg et al., 2000). Treatment with antidepressants may normalize the lowered BDNF levels in blood and brain of depressed patients (Shimizu et al., 2003; Castrén et al., 2007; Brunoni et al., 2008). It was even hypothesized that the clinical efficacy of antidepressants depends on BDNF levels in the hippocampus (Adachi et al., 2008). Molendijk et al. (2011) reported that the normalization of serum BDNF levels in depressed patients who were treated with antidepressants is confined to treatments with SSRIs and St John's wort. In animal models, the rapid antidepressant effect of ketamine is associated with increased hippocampal BDNF protein levels (Garcia et al., 2008). In depressed patients, on the other hand, ketamine treatment did not change serum BDNF levels, suggesting that the rapid antidepressive effects of ketamine are not mediated by BDNF (Machado-Vieira et al., 2009). Administration of BDNF in the midbrain reverses learned helplessness, suggesting that learned helplessness-induced decreases in BDNF are involved in depressive-like behaviors (Siuciak et al., 1997). In other studies, however, chronic BDNF administration did not have antidepressant activities. Thus, while a small, acute dose of BDNF administered to the hippocampus resulted in antidepressant effects, chronic administration did not result in any antidepressant effects (Sirianni et al., 2010). All in all, these data suggest that imbalances between neurodegenerative and neuroprotective factors are involved in depression and that neurotrophic and neurogenic effects contribute to the therapeutic effects of antidepressants.

### *10.2. Inflammation and CMI activation and their concomitants/sequels may cause neuroprogression*

Initially, research focused on the neuroprogressive effects of glucocorticoids, which are known to evoke adverse effects in the hippocampus (Sapolsky, 2004). Glucocorticoids are increased in some patients with depression and this could be a consequence of inflammatory processes through increased levels of IL-1, TNFα and IL-6, which are known to activate the hypothalamic-pituitary-adrenal (HPA) axis (Maes, 1995). Based on novel knowledge that inflammatory and CMI activation and their sequels/concomitants may cause neuroprogression, the inflammatory and neuroprogressive (IN-PRO) hypothesis of depression was formulated (Maes et al., 2009c, 2011d; Song and Wang, 2011; Berk et al., 2011). The IN-PRO theory considers that CMI activation and inflammatory pathways and their sequels/concomitants are causes for the neuroprogressive processes (Maes et al., 2009c).

- PICs and CMI-cytokines cause neuroprogression.
- Injections of IL-2 (ip) in Sprague-Dawley rats show that IL-2 is associated with neuroprogression in association with neurocognitive impairments, such as reduced spatial memory (Robinson et al., 1997). Chronically elevated IL-2 levels in the brain cause (a) changes in receptors, including decreased cholinergic M1 and M2 and/or dopaminergic D1 and D2 receptor binding in selected frontoparietal cortex, hippocampal CA1 region and nucleus accumbens; and (b) microglial activation, reactive astrogliosis, myelin damage and neuronal loss in the brain regions invaded by immune cells (Hanisch et al., 1997). There is also evidence that loss of the IL-2 gene in congenic C57BL/6scid-IL-2(−/−) knockout mice is characterized by reduced CD11b(+) microglial phagocytic clusters and a more appropriate neuronal regeneration (Petitto et al., 2003). IL-2, when co-applied with NMDA, significantly potentiates the effects of NMDA (Ye et al., 2001).
- Increased IFNγ production activates IDO, a major route leading to neuroprogression through the effects of TRYCATs (see further). IFNγ plays also a role in demyelinating diseases, such as multiple sclerosis (Lees and Cross, 2007). IFNγ may sensitize cortical and cerebellar neurons to the toxic effects of neurotoxic peptides found in prion diseases and increased neuronal death in response to for example amyloid-beta1-42 (Bate et al., 2006). IFNγ may be involved in the neuronal loss that characterizes neurodegenerative disorders, such as Alzheimer's disease (Bate et al., 2006). IFNγ also exacerbates ischemia-induced neurotoxicity and brain damage (Lambertsen et al., 2004).
- IL-6 appears to have neuroprotective as well as neurodegenerative effects. Mice with chronic overexpression of IL-6 show marked neurodegeneration in association with increased IL-6 plasma and/or brain concentrations (Allan and Rothwell, 2003). On the other hand, IL-6 may have neuroprotective effects since administration of IL-6 (icv) to the rodent inhibits neuron death induced by ischemic and excitotoxic insults (Lucas et al., 2006).
- There is direct evidence for the influence of IL-1β on neurodegeneration and decreased neurogenesis. The neurotoxic effects of IL-1β are related to: (a) exacerbation of cell death via mechanisms related to increase seizure activity; and NMDA receptor function through activation of tyrosine kinases (Viviani et al., 2006; Patel et al., 2006); and (b) neurotoxic effects on astrocytes and endothelial cells causing the production of glial free radicals and metaloproteinases which cause neuronal death (Pinteaux et al., 2009; Thornton et al., 2006, 2008). Chronic IL-1 exposure causes impairments in hippocampal cytogenesis and neurogenesis (Goshen et al., 2008; Koo and Duman, 2008). Song and Wang (2011) reported that subchronic elevations of IL-1 reduce BDNF and NGF expressions at both the mRNA and protein level; reduce neurotrophin TrK receptor expression in the hippocampus, which is related to neuronal survival; and increase expression of the p75 receptor, which may promote apoptosis. Since these effects are abrogated by minocycline and RU486, a glucocorticoid receptor antagonist, it is concluded that inflammation causes neurodegeneration and decreased neurogenesis through microglial activation and HPA axis activity.
- TNFα is involved in the persistence of brain cellular damage 2 weeks after repeated stressors (Munhoz et al., 2004). TNFα induces neuroprogression through different pathways, including caspase-dependent cascades; potentiation of glutamate neurotoxicity; stimulation of microglial glutamate release by up-regulating glutaminase and blockade of glutamate transporter activity; and silencing of cell survival signals (Zou and Crews, 2005). The neuroprotective effects of IL-10 are in part attributable to inhibition of the microglial production of TNFα (Qian et al., 2006).
- Lower 5-HT and increased TRYCATs cause neuroprogression. 5-HT plays an important role as a neurotrophic factor in the adult brain (Djavadian, 2004). 5-HT promotes neurogenesis and BDNF expression, while BDNF promotes the survival of 5-HT neurons. Thus, the lowered 5-HT metabolism in depression may contribute to reduce neurogenesis. There are many different mechanisms trough which TRYCATs may exert neuroprogressive effects (Maes et al., 2011b). These effects, which are most often associated with quinolinic acid, comprise: increased production of ROS; mitochondrial dysfunctions; agonistic effects by quinolinic acid at the NMDA receptor leading to excitotoxicity; inhibition of glutamate uptake; destruction of postsynaptic elements; degeneration of nerve cells; hippocampal cell death; and reduction in central cholinergic system (Schwarcz et al., 1983; Garthwaite and Garthwaite, 1987; Khaspekov et al., 1989; Levivier and Przedborski, 1998; Tavares et al., 2002).
- LPS causes neuroprogression. Administration of LPS directly activates microglia and is a driving force that causes neurodegeneration (Hauss-Wegrzyniak et al., 1998; Hunter et al., 2007; Hirsch, 2007). LPS can cause cell death in PC12 cells, a model

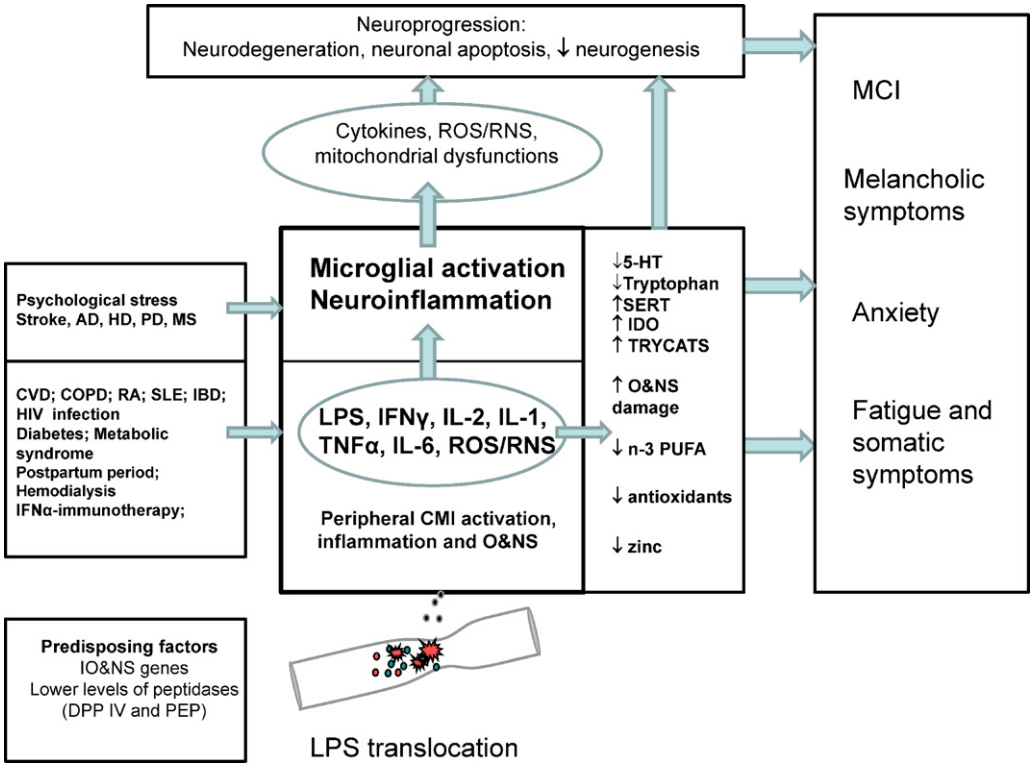


**Fig. 3.** Causal pathways from (neuro)inflammation and its sequels and concomitants to depressive symptoms.
Interconnections between peripheral cell-mediated immune (CMI) activation, characterized by increased interferon-γ (IFN) and interleukin-2 (IL-2); inflammation, characterized by increased interleukin-1β (IL-1β), tumor necrosis factor-α (TNFα) and IL-6; and oxidative and nitrosative stress (O&NS) pathways, including the production of increased reactive oxygen and nitrogen species (ROS/RNS). Increased levels of lipopolysaccharide (LPS) caused by bacterial translocation may aggravate existing aberrations in inflammatory and O&NS (IO&NS) pathways or function as a primary inflammatory trigger. The above pathways may cause neuroinflammation and microglial activation. Long-term sequels/concomitants of both peripheral and central IO&NS activation are increased damage by O&NS to DNA, proteins and fatty acids, lowered antioxidant, zinc and omega-3 polyunsaturated fatty acids (ω3 PUFAs) levels, and mitochondrial dysfunctions that occur both in the periphery and brain. Other peripheral and central sequels of IO&NS activation are: upregulation of the 5-HT transporter and induction of indoleamine 2,3-dioxygenase (IDO), which causes depletion of tryptophan and serotonin (5-HT) and increased production of tryptophan catabolites (TRYCATs). The abovementioned pathways all contribute to (a) depressive phenomenology, including melancholic symptoms; anxiety; fatigue and somatic symptoms; and mild cognitive impairment (MCI); and (b) neuroprogressive processes that are associated with mild cognitive impairment (MCI).
Trigger factors of depression are known to cause inflammation and CMI activation and/or neuroinflammation (Maes et al., 2011c): (a) systemic disorders, such as cardiovascular disorder (CVD), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), HIV infection, diabetes and the metabolic syndrome; (b) neurodegenerative and neuroinflammatory disorders, e.g. Alzheimer (AD), Huntington (HD) and Parkinson's disorder (PD), multiple sclerosis (MS) and stroke; and (c) conditions that are known to cause peripheral inflammation and CMI activation, e.g. the postnatal period, hemodialysis, IFNα-induced depression; and psychological stressors. Single nucleotide polymorphisms in inflammatory and T cell genes and lowered activity of peptidases, including dipeptidyl peptidase IV (DPP IV) and prolyl endopeptidase (PEP) increase the vulnerability to develop depression (Maes, 2011; Maes and Bonaccorso, 2004).

for neuronal differentiation, through apoptosis and increased expression of caspase 3 and Bax (Sharifi et al., 2010; Franchi et al., 2003). LPS induces ROS and RNS that are strongly involved in ensuing neuron apoptosis or death (Pang et al., 2010). For example, in wild-type mice, LPS provokes increased ROS in the striatum, a phenomenon related to the gp91phox-containing NADPH oxidase complex (Clement et al., 2010). LPS is also known to suppress neurogenesis in dentate gyrus of mature rats by inhibiting proliferation of neural precursor cells (Fujioka and Akema, 2010). Prenatal inflammation induced by LPS has been shown to reduce adult neurogenesis and recognition memory through hippocampal TGFβ1 downregulation, while TGFβ1 overexpression was able to restore neurogenesis and memory functions (Graciarena et al., 2010). Since TGFβ1 can inhibit T cell function and activity of PICs these results underscore the dependence of neurogenesis on inflammatory processes.

- Oxidative and nitrosative stress cause neuroprogression. Damage by O&NS is one of the major pathways causing neuroprogression (Maes et al., 2011a). In the latter paper it is reviewed that neuroprogression is caused by lipid peroxidation; oxidatively induced DNA damage; and byproducts of lipid peroxidation, such as MDA and 4-HNE.
- Lowered antioxidant levels cause neuroprogression. The reduced levels of various antioxidants and antioxidant enzymes may predispose depressed individuals towards neuroprogressive processes (Maes et al., 2011a). For example, vitamin E deficiency predisposes towards neurodegenerative processes, whereas vitamin E supplementation has neuroprotective effects. Coenzyme Q10 is a neuroprotectant and therefore may be employed as a therapeutic intervention in neurodegenerative disorders (Somayajulu et al., 2005). GPX displays neuroprotective effects against cell death, and neuronal and DNA damage and neurotoxin-induced hippocampal damage. These effects are deduced from studies on Ebselen showing that it increases glutathione and ROS-scavenging activity; suppresses iNOS activity; decreases TNFα production; and prevents impaired neurogenesis in the hippocampus (review: Maes et al., 2011a).
- Lower zinc causes neuroprogression. Lowered dietary zinc reduces hippocampal vesicular zinc which in turn decreases the number of progenitor cells and immature neurons (Corniola et al., 2008; Suh et al., 2009); increases glucocorticoid production (Takeda and Tamano, 2009); reduces the inhibitory effects of zinc on excitatory glutamatergic neurons (Takeda and Tamano, 2009), glutamate dehydrogenase and glutamate decarboxylase,

enzymes that are involved in glutamate metabolism (Ebadi et al., 1990); and increases cytosolic $Ca^{2+}$ concentrations (Takeda and Tamano, 2009). Zinc is, as many antidepressants an inhibitor of glycogen synthase kinase-3 (GSK-3) (Ilouz et al., 2002), which may cause neurodegeneration and impairs hippocampal memory formation (Giese, 2009). Moreover, chronic treatment with zinc increases BDNF in the rat's hippocampus after 1 week of treatment, whereas higher doses may increase BDNF mRNA in the cerebral cortex (Nowak et al., 2004; Sowa-Kucma et al., 2008; Szewczyk et al., 2011).

- Mitochondrial dysfunctions cause neuroprogression. Mitochondria plays a key role in neurodegenerative disorders because the high metabolic rate of the brain strongly depends on mitochondrial ATP production (Petrozzi et al., 2007). Hyperproduction of ROS derived from mitochondria is a critical event in the onset of neurodegenerative disorders. For example, in Parkinson's disorder increased mitochondrial ROS may cause loss of dopaminergic neurons in the substantia nigra (Hunter et al., 2007). The intrinsic mitochondrial apoptotic pathway that controls caspase 9 and the release of cytochrome c is another key pathway that leads to cell death in neurodegeneration (DiMauro and Schon, 2008). There is now evidence that dysfunctional mitochondria, inflammation and O&NS play synergistic roles in Parkinson's, Alzheimer and Huntington's disorder and amyotrophic lateral sclerosis as well (Mancuso et al., 2007; Lin and Beal, 2006).
- Lower ω3 PUFAs cause neuroprogression. Lowered ω3 PUFAs are associated with decreased neurogenesis, while treatment with ω3 PUFAs results in beneficial effects on neurogenesis. ω3 PUFA deficiency in the embryonic rat brain delays and inhibits normal neuronal development and results in deceased neurogenesis (Coti Bertrand et al., 2006). In rats, DHA promotes neurogenesis and the differentiation of neural stem cells into neurons by suppressing cell death (Kawakita et al., 2006). In the lobster brain, which is used as a model for investigating neurogenesis, dietary ω3 PUFAs enhance cells in the S phase of the cell cycle (Beltz and Sandeman, 2003). Treatment with DHA significantly increases 5-bromo-2′-deoxyuridine (an thymidine analogue), indicating enhanced neurogenesis (Kawakita et al., 2006). The beneficial effects of ω3 PUFAs on neurogenesis (Beltz and Sandeman, 2003) may be explained by a number of factors, such as anti-inflammatory effects; effects on 5-HT metabolism stimulating neurogenesis (Ueda et al., 2005); and effects on neurotrophins. For example, ω3 PUFAs upregulate BDNF expression and the BDNF receptor; and up-regulates NGF (Wu et al., 2004a; Song et al., 2009b; Kou et al., 2008).

## 11. Conclusions and directions for future research

Fig. 3 depicts an overview of the main interconnections in the IO&NS pathways and their sequels that are involved in the pathophysiology of depression. Many of these pathways are actually still under investigation and are strongly debated. Our review shows that many different peripheral and central pathways related to CMI activation, inflammation and O&NS are related to the onset of depressive symptoms and through modulation of other functions, such as the TRYCAT pathway and ω3 PUFAs or serum zinc, may further cause depressive symptoms. Each of those pathways consists of many different molecules that influence each other and act together to modulate other networks. For example, inflammation induces IDO, gut permeability, O&NS pathways, neuroprogression, etc. Activation of O&NS pathways activates the inflammatory network and the TRYCAT pathway, and causes lowered antioxidant levels and neuroprogression. Needless to say that these pathways and the actors in the different pathways, as well as the dynamic non-linear interactions between these pathways have remained incompletely characterized in depression.

Moreover, there is evidence that cell signaling networks, such as MAPK (mitogen-activated protein kinase), JAK-STAT (Janus kinase/signal transducers and activators of transcription), and nuclear factor κB (NFκB) regulate some of the abovementioned pathways, such as the cytokine, the O&NS and apoptotic pathways (Maes et al., 2011d). Considering the broad spectrum inflammatory state observed in depression it is likely that these cell signaling networks are hyperactive in depression. Future research should delineate the complex dynamic interactions between the peripheral and central cell signaling networks and the different pathways described in this review. However, the regulation of these networks and pathways and the dynamic interactions between them are overwhelmingly complex. This complexity necessitates a systems biology approach to delineate mathematical models that best fit the complex dynamics of these networks and pathways (Chen et al., 2008; Aderem and Smith, 2004). Thus, high throughput technologies should be employed to collect genetic and/or gene expression and protein data from the blood of patients with depression; brain tissues from people with depression prior to death; and blood/brains of well-validated animal models of depression and those data should be analyzed by means of systems biology methods. This new methodology will enable to unravel the highly non-linear and complex networks and pathways that are involved; pinpoint the relevant pathways in these networks that lead to depression; develop mathematical models that identify the molecular and genetic signature of depression; and identify new drug targets in these networks and pathways.

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