

The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression

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Abstract Despite extensive research, the current theories on serotonergic dysfunctions and cortisol hypersecretion do not provide sufficient explanations for the nature of depression. Rational treatments aimed at causal factors of depression are not available yet. With the currently available antidepressant drugs, which mainly target serotonin, less than two thirds of depressed patients achieve remission. There is now evidence that inflammatory and neurodegenerative (I&ND) processes play an important role in depression and that enhanced neurodegeneration in depression may—at least partly—be caused by inflammatory processes. Multiple inflammatory-cytokines, oxygen radical damage, tryptophan catabolites—and neurodegenerative biomarkers have been established in patients with depression and these findings are corroborated by animal models of depression. A number of vulnerability factors may

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predispose towards depression by enhancing inflammatory reactions, e.g. lower peptidase activities (dipeptidyl-peptidase IV, DPP IV), lower omega-3 polyunsaturated levels and an increased gut permeability (leaky gut). The cytokine hypothesis considers that external, e.g. psychosocial stressors, and internal stressors, e.g. organic inflammatory disorders or conditions, such as the postpartum period, may trigger depression via inflammatory processes. Most if not all antidepressants have specific anti-inflammatory effects, while restoration of decreased neurogenesis, which may be induced by inflammatory processes, may be related to the therapeutic efficacy of antidepressant treatments. Future research to disentangle the complex etiology of depression calls for a powerful paradigm shift, i.e. by means of a high throughput-high quality screening, including functional genetics and genotyping microarrays; established and novel animal and ex vivo–in vitro models for depression, such as new transgenic mouse models and endophenotype-based animal models, specific cell lines, in vivo and ex vivo electroporation, and organotypic brain slice culture models. This screening will allow to: 1) discover new I&ND biomarkers, both at the level of gene expression and the phenotype; and elucidate the underlying molecular I&ND pathways causing depression; and 2) identify new therapeutic targets in the I&ND pathways; develop new anti-I&ND drugs for these targets; select existing anti-I&ND drugs or substances that could augment the efficacy of antidepressants; and predict therapeutic response by genetic I&ND profiles.

Keywords Depression · Inflammation · Cytokines · Neurodegeneration · Oxidative stress · Nitrosative stress · Tryptophan · Serotonin · IDO.

Introduction

Major depression is a severe psychiatric disorder that has a lifetime prevalence in excess of 15% and is the fourth leading cause of disability worldwide. The total annual cost of depression in Europe is estimated at Euro 118 billion in 2004. The WHO estimates that depression causes 6% of the burden of all diseases in Europe in terms of disability-adjusted life years. This makes depression a major concern to the personal and economic welfare (Sobocki et al. 2006). However, despite extensive biological research, the pathophysiology of depression is still elusive and treatments that target the causal factors of depression are not available yet.

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The findings that depressed patients may exhibit decreased brain serotonin (5-hydroxytryptamine, 5-HT) and alterations in 5-HT receptors, such as a down-regulation in the 5-HT_{1A} and an upregulation of the 5-HT₂ receptors (Maes and Meltzer 1995) as well as elevated cortisol secretion (Dinan 2001) has reached the status of textbook truism. For decades, the serotonin hypothesis of depression fostered research into the etiology of depression, either in clinical studies or in various animal models of depression and in vitro testing paradigms. Accordingly, the development of new antidepressants was targeted at serotonin (with or without noradrenaline) reuptake inhibition. The current view is that serotonin and cortisol in depression may all “be stressed out”, i.e. changes in these systems are the consequence of stress in depression rather than being of major etiological importance (Cowen 2002). In addition, less than 60% of depressed patients achieve remission with the currently available antidepressants. The reported benefit of these drugs over placebo is very modest and not always clinically significant (Kirsch et al. 2008). These findings underscore the urgent need to develop novel conceptual frameworks for understanding the pathophysiology of depression as well as new and more effective treatments for this disorder.

In the current review we describe such recent developments, firstly by focusing on the cytokine hypothesis of depression, which has been pursued in our laboratories and others for almost two decades, and secondly by proposing a novel hypothesis, according to which the inflammatory processes associated with depression are causally related to the enhanced neurodegeneration and reduced neurogenesis that characterize this disorder.

The cytokine hypothesis of depression

Over the last two decades, new developments in psychiatric research have led to the hypothesis that inflammatory processes and neural-immune interactions are involved in the pathogenesis of major depression and may underlie some of the frequently observed serotonergic and adrenocortical correlates. This hypothesis was termed the monocyte-T-lymphocyte or cytokine hypothesis of depression (Maes 1993, 1995, 1999; Maes et al. 1995b; Schiepers et al. 2005). The first paper showing that there is a connection between depression and T cell activation was published in 1990 (Maes et al. 1990). Since then there have been many consistent findings over the years of increased levels of proinflammatory cytokines in patients with depression, e.g. interleukin-1 (IL-1), IL-2, IL-6, IL-8, IL-12, interferon- γ (IFN γ) and tumor necrosis factor- α (TNF α) (review: Schiepers et al. 2005). Many other inflammatory biomarkers have been established in depression, such as increased acute phase proteins and lowered serum zinc (Maes et al. 1993d, 1997d). Figure 1 shows the different inflammatory pathways occurring in depression.

The cytokine hypothesis and depressive symptoms

Systemic exposure to inflammatory challenges, such as lipopolysaccharide (LPS), not only causes a systemic inflammation, but also induces a central neuro-

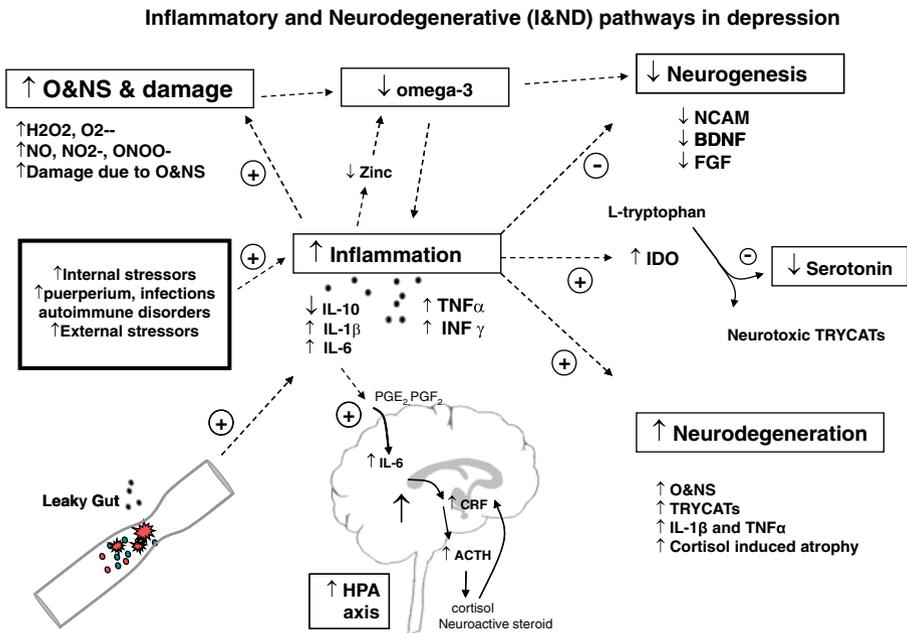


Fig. 1 The inflammatory and neurodegenerative (I&ND) pathways in depression. The key findings in depression are the increased levels of pro-inflammatory cytokines, such as interleukin-1 β (IL-1 β), IL-6, interferon- γ (IFN γ) and tumor necrosis factor α (TNF α), with a relative shortage in the anti-inflammatory cytokine, IL-10. This pro-inflammatory response is induced by external and internal stressors and by an increased translocation of the LPS from gram negative bacteria (*leaky gut*). The inflammatory response in depression is accompanied by lowered levels of zinc and a lowered ω 3 PUFA status; increased oxidative and nitrosative (O&NS) stress; induction of the hypothalamic-pituitary-adrenal (HPA)-axis via stimulated release/production of corticotropin releasing hormone (CRF), adrenocorticotropic hormone (ACTH) and cortisol; the induction of indoleamine-2,3-dioxygenase (IDO) with decreased levels of tryptophan and serotonin and the consequent formation of tryptophan catabolites along the IDO-pathway (TRYCATs). Inflammation induces decreased neurogenesis in depression, which is characterized by decreased brain-derived neurotrophic factor (BDNF); neural cell adhesion molecule (NCAM); and fibroblast growth factor (FGF). Inflammation may also induce neurodegeneration through increased levels of TRYCATs; O&NS; glucocorticoids; and some pro-inflammatory cytokines

inflammation, reflected by activation of brain microglia with a chronically elevated production of pro-inflammatory mediators, such as $\text{TNF}\alpha$, which may remain elevated for 10 months (Qin et al. 2007; Kent et al. 1992). It is well-known that LPS (either peripheral or central), brain neuroinflammation and the increased production of pro-inflammatory cytokines, such as IL-1 β , IL-6 and $\text{TNF}\alpha$, may induce specific symptoms, labeled as the sickness behavior syndrome (Qin et al. 2007). As explained previously (Maes et al. 1993c), symptoms of sickness behavior, such as anorexia, soporific effects, reduction of locomotor activity and exploration, anhedonia and cognitive disturbances, bear a strong similarity with those of depression (Maes et al. 1993c; Yirmiya 1997). In depression, there is a strong correlation between those symptoms and the presence of inflammation. The above suggests that inflammatory reactions may have induced the symptoms of depression (Maes et al. 1993c).

The cytokine hypothesis and oxidative and nitrosative stress (O&NS)

It is known that inflammation is accompanied by increased production of oxygen radicals. Likewise, depression was found to be characterized by increased levels of malondialdehyde (MDA), a byproduct of polyunsaturated fatty acid peroxidation and arachidonic acid, as well as 8-hydroxy-2-deoxyguanosine, indicating damage to DNA by oxygen radicals (Sarandol et al. 2007; Forlenza and Miller 2006). Recently, it was found that depression is accompanied by increased serum IgM levels directed against nitro-bovine serum albumin (BSA) and phosphatidyl inositol (Pi) (Maes et al. 2007d, 2008a). The former indicates that depression is accompanied by increased nitrosative stress, which has induced damage to BSA and which has induced an IgM-mediated immune response directed against the NO-BSA neoepitopes. The latter indicates that oxidative stress has caused an IgM-related immune response directed against Pi.

The cytokine hypothesis, internal and external stressors

The cytokine hypothesis is fueled by the high comorbidity of depression with inflammatory disorders such as coronary-heart disorder (CHD), multiple sclerosis (MS), HIV-infection, inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) (Maes 1995; Yirmiya et al. 1999). For example, in MS inflammatory attacks are often preceded by increased IFN γ production (Mohr et al. 2001), suggesting that, in MS, immune activation induces depression.

Recently, Maes et al. (2008b) detected another mechanism in depression whereby an internal stressor may induce peripheral inflammation, i.e. increased translocation of LPS from gram-negative bacteria, a condition also labeled as leaky gut, increased gut permeability or intestinal mucosal dysfunction (IMD). Indeed, the prevalence and median values for serum IgM and IgA against LPS of six different enterobacteria are significantly greater in patients with depression than in normal volunteers (Maes et al. 2008b). It is well known that the function of the intestinal barrier may be compromised by inflammatory reactions characterized by increased IFN γ and IL-6 levels. The latter may cause a loss of the protective barrier function, which in turn causes enlarged spaces between the cells of the gut wall (Clark et al. 2005; Chavez et al. 1999; Yang et al. 2003). It should be stressed that the important inflammatory mediators which induce “leaky gut“, i.e. IFN γ and IL-6, are both significantly increased in depression (Maes et al. 1993e, 1994). The consequent disruption of the intestinal epithelium allows normally poorly invasive enterobacteria to exploit the enlarged spaces and the lipid raft-mediated transcytotic pathways to cross the gut wall (Clark et al. 2005; Chavez et al. 1999; Yang et al. 2003). This in turn causes a translocation of LPS from the gut into the blood and, thus, an immune response directed against LPS and eventually inflammatory reactions and an increased production of O&NS mediators.

An enhanced responsivity to stress is another characteristic of the early phases of depression. Not only genetic but also early life experiences are thought to modulate the development of appropriate/inappropriate responses to stress and therefore the vulnerability for depressive states. Therefore, the effects of stress on the inflammatory system were examined. Maes et al (1998a, 1998b) were the first to

show that in humans psychological stress induces an inflammatory response with increased production of pro-inflammatory cytokines, such as $\text{IFN}\gamma$ and $\text{TNF}\alpha$. There have been consistent findings over the years of increased levels of proinflammatory cytokines in stress situations (Steptoe et al. 2007; Shapira-Lichter et al. 2008). Also, in experimental animals it was shown that psychological stressors increase cytokine levels, such as $\text{IL-1}\beta$ and IL-6 , in the blood and in various brain regions (Ishikawa et al. 2001; Nguyen et al. 1998).

The cytokine hypothesis and inflammation-related vulnerability factors, such as peptidases and $\omega 3$ fatty acids

It is reported that two vulnerability factors, related to inflammation and the immune system, may facilitate the occurrence of depression. A first vulnerability factor is the decreased plasma concentration of peptidases, such as dipeptidyl-peptidase IV (DPP IV) (Maes et al. 1991). DPP IV is a membrane-bound enzyme which cleaves off dipeptides, catalyses the cleavage of some cytokines and neuro-active peptides, and modulates T cell activation and the production of cytokines, such as IL-2 (Maes et al. 1991). Lowered levels of DPP IV may predict the occurrence of depressive symptoms (Maes et al. 2001a).

A second vulnerability factor is the lowered omega-3 ($\omega 3$) polyunsaturated fatty acid (PUFA) content in depression. In the blood, red blood cell membrane and fat tissues of depressed patients lower levels of two $\omega 3$ PUFAs are detected, i.e. eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In addition, depression is characterized by an increased $\omega 6 / \omega 3$ and arachidonic acid (AA) / EPA ratio (Maes et al. 1996a, 1999a; Peet et al. 1998; Mamalakis et al. 2006). Lower consumption of seafood and, thus, a lower intake of EPA and DHA, is associated with higher rates of depression and postpartum depression (Hibbeln 1998, 2002). Since $\omega 3$ PUFAs have strong anti-inflammatory properties and since $\omega 6$ have strong pro-inflammatory effects, decreases in $\omega 3$ or increases in $\omega 6$ may enhance the propensity towards inflammatory reactions and, thus, to depression and anxiety (Maes and Smith 1998; Maes et al. 2000). Thus, subjects with lower serum $\omega 3$ PUFA or with a higher $\omega 6/\omega 3$ ratio have significantly higher stress-induced $\text{TNF}\alpha$ and $\text{IFN}\gamma$ responses than subjects with higher serum T3 PUFA and a lower $\omega 6/\omega 3$ ratio, respectively (Maes et al. 2000). These greater stress-induced inflammatory responses in subjects with a lowered $\omega 3$ or increased $\omega 6$ status are related to higher anxiety and perceived stress levels (Maes et al. 1998b). Several clinical trials have been performed in which $\omega 3$ PUFAs have been supplemented. A meta analysis of ten double-blind, placebo-controlled studies in patients with mood disorders receiving $\omega 3$ PUFAs, with a treatment period lasting 4 weeks or longer, indicates that $\omega 3$ PUFAs have antidepressant effects. However, the authors also conclude that it is premature to validate the findings due to the heterogeneity of the different studies (Lin and Su 2007). In rat models, $\omega 3$ PUFAs have an antidepressant effect in the forced swim test (Huang et al. 2006). Moreover, supplementation of $\omega 3$ PUFAs also has the potential to counteract many of the effects that are induced by $\text{IL-1}\beta$, e.g. $\text{IL-1}\beta$ induced changes in anxiety and immune responsiveness (Song et al. 2004, 2007).

The lowered $\omega 3$ status in depression cannot be explained by dietary factors (Horrobin 2001) but are probably related to: a) the inflammatory response with a

lowered zinc status and an increased breakdown of PUFAs by O&NS (Maes et al. 1999a); b) genetic factors (Sobczak et al. 2004); and c) a number of enzyme abnormalities, such as phospholipase A(2), and coenzyme A-independent transacylase (Horrobin 2001). The fatty acid abnormalities in depression provide a rational explanation for the association of depression with CHD and other disorders as well, e.g. cancer and diabetic complications (Horrobin 2001). Consistent with the proinflammatory consequences of excessive AA release, Rao et al (2008) have shown that chronic administration of mood stabilizers, such as lithium, valproate and carbamazepine at therapeutically relevant doses, selectively target inhibition of the brain AA cascade.

The cytokine hypothesis and animal and human models of depression

In humans, IL-2- and IFN α -based immunotherapy may induce full blown depression in up to 70% of all patients treated for cancer or hepatitis C (Maes et al. 2001a; Bonaccorso et al. 2001; 2002a, 2002b; Amodio et al. 2005). These studies provide evidence that administration of pro-inflammatory cytokines can induce depression in a considerable number of persons.

Inflammation is also detected in animal models of depression, such as the chronic mild stress (CMS) and the olfactory bulbectomized rat model (Kubera et al. 1996, 2001a; Song and Leonard 1995, Goshen et al. 2008). Animal correlates of depressive and anxious behavior were also detected in novel rat models based on induced inflammation, e.g. the LPS-induced model (Yirmiya 1996; Lacosta et al. 1999) and sustained administration of IL-6 by infecting healthy MRL +/+, C3H.SW and Balb/C mice with adenovirus vector carrying cDNA for murine IL-6 or mice infected with Ad5mIL6 adenovirus (Sakic et al. 1997, 2001). In the rodent, administration of cytokines, such as IL-1 β , TNF α , IL-2 and IFN α , induces depressive-like symptoms, anhedonia and anxiety (Anisman et al. 2002). External and internal stressors may act synergistically to provoke greater responses in cytokines and depressive-like behaviors (Anisman et al. 2005). For example when mice are exposed to psychological stressors the “depressogenic” effects of an intraperitoneal administration of IFN α are significantly augmented (Anisman et al. 2007).

The cytokine hypothesis and antidepressants

Antidepressant treatments were found to have anti-inflammatory effects, by decreasing the production of IFN γ and/or increasing that of IL-10, a major negative immunoregulatory cytokine (Xia et al. 1996, Maes et al. 1999c, 1999d; Lin et al. 2000; Kubera et al. 2001b). Thus, selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and paroxetine; tricyclic antidepressants (TCAs), such as imipramine; reversible inhibitors of monoamino-oxidase (RIMAs), such as moclobemide; “noradrenergic” antidepressants, such as reboxetine; lithium and even atypical antidepressants, such as tianeptine; all have anti-inflammatory effects (Kenis and Maes 2002; unpublished data). The clinical efficacy of antidepressant treatments may be enhanced by concurrent administration of agents with anti-inflammatory effects, such as celecoxib, a cyclooxygenase-2 inhibitor (Muller et al. 2006). These

findings are supported by studies in animal models, demonstrating that antidepressants attenuate inflammation-induced brain cytokine production and actions, as well as depressive-like symptoms (Yirmiya et al. 2001; Castanon et al. 2001). Antidepressants, such as paroxetine, can prevent the development of depression induced by high-dose IFN α (Musselman et al. 2001).

The cytokine hypothesis and the cortisol axis

Although there are now some researchers who think that changes in cortisol and serotonin could be secondary phenomena to the stress in depression, both factors play important roles in the cytokine hypothesis of depression. First, it was found that the cortisol escape from suppression by dexamethasone and the increased baseline hypercortisolemia are significantly related to inflammatory biomarkers, such as increased IL-1 β and IL-6 production by stimulated peripheral blood mononuclear cells (PBMCs) and serum IL-6 levels. This suggests that both cortisol hyperactivity and glucocorticoid resistance—attributable to glucocorticoid receptor (GR) down-regulation—are epiphenomena of the inflammation in depression (Maes et al. 1993a, 1993d). Long-term treatment with some antidepressants has direct effects on the GR leading to enhanced GR function and increased GR expression and normalization of the hypothalamic-pituitary-adrenal (HPA)-axis (Pariante and Miller 2001; Fitzgerald et al. 2006). Furthermore, elevated corticosterone levels were recently found to mediate the critical role of IL-1 β in chronic stress-induced depression and suppressed neurogenesis in mice (Goshen et al. 2008).

The cytokine hypothesis, IDO and serotonin

The lowered availability of plasma L-tryptophan in depression, one of the most robust biomarkers for that illness, is significantly correlated with signs of inflammation (Maes et al. 1993b, 1996b). This phenomenon was explained by increased levels of pro-inflammatory cytokines in depression (Maes et al. 1993b, 1994). Indeed, IFN γ and other cytokines, such as IL-1 β and TNF α , are known to induce IDO (indoleamine 2–3-dioxygenase), an enzyme that induces the catabolism of tryptophan into TRYCATs (tryptophan catabolites along the IDO pathway), such as kynurenine (Babcock and Carlin 2000). Some of those TRYCATs have behavioral effects on their own, e.g. kynurenine has anxiogenic effects (Lapin 2003). During IFN α -based immunotherapy in hepatitis C patients, IDO activation and an increased neurotoxic potential (kynurenine / kynurenic acid ratio) predict the occurrence of depression (Maes et al. 2001a; Bonaccorso et al. 2002a; Wichers et al. 2005). Cytokine-induced depression in IFN α -treated individuals is also strongly related to the development of the neurotoxic and behaviorally active TRYCAT, kynurenine (Wichers et al. 2007). In the early puerperium, IDO activation is significantly related to signs of inflammation and to the severity of depressive and anxiety symptoms (Maes et al. 2001c, 2002). IDO activation is demonstrated in postmortem anterior cingulate cortex (Miller et al. 2006) and in the plasma of individuals with bipolar depression (Myint et al. 2007). In experimental animals immune challenges were found to induce brain IDO (Lestage et al. 2002) and this induction is involved in mediating the depressive-like behavioral alterations following these challenges

(O'Connor et al. 2008). Similar findings were later found in IFN α -treated cancer patients (Capuron et al. 2003).

Based on those results, a shift in the serotonin hypothesis of depression from serotonin depletion to inflammation-induced tryptophan and serotonin depletion with subsequent enhanced neurodegeneration by neurotoxic TRYCATs has been proposed (Wichers and Maes 2004; Wichers et al. 2005, 2007). Indeed, both tryptophan and serotonin depletion are related to neuroinflammation, because due to the IDO activation under this condition more tryptophan is converted to the TRYCATs, including the neurotoxic ones, rather than to serotonin.

The enhanced neurodegeneration & decreased neurogenesis hypothesis of depression

Several lines of evidence indicate that mood disorders are characterized by an enhanced neurodegeneration and decreased neurogenesis. Structural brain changes detected with MRI in unipolar depressed patients have been reported in several brain regions, such as volumetric changes in hippocampus, amygdala, prefrontal cortex, anterior cingulate and basal ganglia (Campbell and MacQueen 2006). Cellular changes in the postmortem hippocampus and neuronal and glial cell modifications have been also observed (Stockmeier et al. 2004).

The selective and persistent loss of hippocampal volume is not only induced by hippocampal neuronal death, but also by decreased neurogenesis (Sapolsky 2004). Neurogenesis occurs in the adult brain and is most prominent in the subventricular zones and in the subgranular zone of dentate gyrus in hippocampus. Early stressors may induce developmental abnormalities in the amygdala, hippocampus, anterior cingulate cortex, and corpus callosum and other structures which play a critical role in mediating response to stress (Bremner and Narayan 1998). In adults, stressful conditions decrease neurogenesis in the subgranular zone of the dentate gyrus (Gould et al. 1997). In contrast, environmental enrichment (Kempermann et al. 1997) including access to running-wheels (van Praag et al. 1999; Bjornebekk et al. 2005; Zhu et al. 2006), as well as virtually all antidepressant treatments (Malberg et al. 2000) have a positive impact on neurogenesis. Significant decreases in neurotrophins, particularly brain-derived neurotrophic factor (BDNF), have been detected in depression and in stress-induced animal models of depression (Angelucci et al. 2005; Smith et al. 1995). However, in the genetic rat model of depression, the Flinder's Sensitive Line Rats (Overstreet et al. 2005), decreased levels of BDNF mRNA were detected in group housed depressed animals but not in single housed animals (Bjornebekk et al. 2005, 2007). The restoration of BDNF levels may underlie the therapeutic efficacy of antidepressant treatments (Duman 2002, 2004; Groves 2007), although there are also situations in which the antidepressant effects of running and antidepressants, such as escitalopram, are independent from BDNF induction (Bjornebekk et al. 2005, 2008). In animal models of depression, rodents were found to display reduced hippocampal neurogenesis (Goshen et al. 2008; Koo and Duman 2008) along with decreases in the levels of BDNF in brain regions associated with depression (Schmidt and Duman 2007; Fuchs et al. 2004). Recent evidence suggests the involvement of another growth hormone, i.e. the fibroblast

growth factor (FGF), in depression (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). Together, these findings suggest that an imbalance between neurodegenerative and neuroprotective factors is involved in the brain dysfunctions in depression.

Hippocampal volume reduction has been related to functional consequences such as the specific neurocognitive deficits in depression (Brown et al. 2004). Reduced hippocampal neurogenesis is now suggested as a final common pathway in many brain disorders associated with mood (Duman 2004) and cognitive dysfunction, e.g. geriatric depression; and the depression–mild cognitive impairment (MCI)-dementia complex. However, this hypothesis has also been questioned (Henn and Vollmayr 2004). Repeated stressful experiences also cause an impaired performance on cognitive tasks in depressed patients (Brown et al. 1999; Ehninger and Kempermann 2006). Some authors propose that problems in information processing within relevant neural networks might underlie depression (Sandi and Bisaz 2007). Evidence implicates alterations in the levels of the neural cell adhesion molecule (NCAM) among the mechanisms contributing to neurocognitive disorders in stress-related mood disorders and the brain changes in response to stress (Sandi, 2004; Sandi and Bisaz 2007). NCAM is expressed on the surface of neurons and glia and has been implicated in cell-cell adhesion, neurite outgrowth, synaptic plasticity, and learning and memory. There is evidence that deletion of the NCAM gene in mice can lead to cognitive impairment and altered emotional behavior and that this is accompanied by changes in serotonergic transmission (Stork et al. 1999; Bukalo et al. 2004). Thus, NCAM may potentially show an antidepressant action by targeting neurogenesis (Sandi and Bisaz 2007).

The inflammatory & neurodegenerative (I&ND) hypothesis of depression

Ample evidence presented in previous sections demonstrates that depression is associated with both inflammatory processes, as well as with neurodegeneration and reduced neurogenesis. Initially, most research in this area focused on the hypersecretion of glucocorticoids by inflammation, which produces a variety of adverse direct and indirect effects in the hippocampus and may contribute to neuronal death (Sapolsky 2004). There is now also evidence that enhanced neurodegeneration and the defects in neurogenesis in depression are caused by inflammatory processes, related to the production of O&NS, TRYCATs, pro-inflammatory cytokines and a lowered ω 3 status. Figure 1 shows these pathways in depression.

The I&ND hypothesis and oxidative and nitrosative stress (O&NS)

As mentioned above, inflammation can increase the production of oxygen radicals, and such an increase was also found in depressed patients (Sarandol et al. 2007; Forlenza and Miller 2006; Maes et al. 2007d). The brain and the nervous system are prone to oxidative stress (OS) since they are inadequately equipped with antioxidant defense systems to prevent oxidative damage (Halliwell 2006). This explains why

OS is a prominent factor in acute and chronic neurodegenerative diseases (Contestabile 2001; Chung et al. 2005). The neurodegenerative effects of OS may be explained by increased generation of reactive oxygen species that overwhelms the antioxidant defenses in the brain causing oxidative damage (Pong 2003). The latter together with subsequent mitochondrial dysfunctions and accumulation of oxidized proteins causes programmed cell death, apoptosis, necrotic cell death, DNA damage, and damage to membrane fatty acids—thereby disrupting lipid signaling and enhancing lipid peroxidation. Moreover, OS can adversely affect gene expression and proteolysis, which all contribute to neurodegeneration (Halliwell 2006; Mancuso et al. 2006; Bazan 2005; Potashkin and Meredith 2006). Interestingly, antioxidant enzymes, such as superoxide dismutase, catalase and glutathione peroxidase have a therapeutic efficacy in neurodegenerative models (Pong 2003). This neuroprotective activity of antioxidants not only relies on free radical trapping in neuronal tissues, but also on the suppression of genes induced by pro-inflammatory cytokines released by glial cells (Wang et al. 2006).

In addition to increased OS, depression is also accompanied by nitrosative stress (NS) (Maes et al. 2008a), which has also been implicated in neurodegeneration. One of the modifications caused by an imbalance in nitric oxide metabolism is the S-nitrosylation of cysteine residues in proteins (Chung et al. 2005). Overproduction of NO may compromise neuronal energy, which may lead to neurodegeneration (Moncada and Bolanos 2006) and may inhibit cell respiration, eventually causing the release of superoxide anions. These anions, in turn, interact with NO superoxide anions, generated by mitochondria, leading to the formation of the powerful oxidant peroxynitrite, which may induce neurotoxicity (Moncada and Bolanos 2006).

The I&ND hypothesis and TRYCATs

IDO activation and the resultant increases in TRYCATs characterize both inflammatory conditions and depression (Maes et al. 2001a; Bonaccorso et al. 2002b; Wichers et al. 2005). Some TRYCATs, e.g. quinolinic acid and kynurenine, are highly neurotoxic (Heyes et al. 1992). In particular, quinolinic acid has neuroexcitatory and neurotoxic effects. Specifically, it causes an acute swelling and destruction of postsynaptic elements, induces a severe degeneration of individual nerve cells, including hippocampal cell death and a selective necrosis of granule cells and intracerebellar nucleus neurons. In addition, quinolinic acid induces a dose-dependent reduction in cerebral cholinergic circuits and it may deplete dopamine, choline, GABA, and enkephalines (Khaspekov et al. 1989; Garthwaite and Garthwaite 1987; Kerr et al. 1998; Levivier and Przedborski 1998; Pemberton et al. 1997; Rios and Santamaria 1991; el-Defrawy et al. 1986). The most susceptible brain areas to the neurotoxic effects of quinolinic acid are the striatum, the pallidum and the hippocampus (Schwarcz and Kohler 1983). The above neurotoxic effects may be caused by several mechanisms, including: 1) agonism at glutamate receptors sensitive to N-methyl-D-aspartate (NMDA) (Stone and Behan 2007); 2) pro-oxidant capacities, for example through formation of ferrous quinolinate chelates with induction of lipid peroxidation; and 3) exacerbation of the neurotoxic effects by corticosterone and cytokines, such as IL-1 (Stone and Behan 2007; Platenik et al. 2001; Stone and Behan 2007; Ngai and Herbert 2005).

Moreover, quinolinic acid has pro-inflammatory effects since it increases the $\text{IFN}\gamma/\text{IL-10}$ production ratio and, therefore, this TRYCAT may further aggravate an initiated inflammatory response (Maes et al. 2007b). It should be noted that differences in enzyme repertoires in various cell types are important. Since astrocytes lack kynurenine hydroxylase, large amounts of kynurenine are produced after stimulation of astrocytes by pro-inflammatory cytokines, whereas only minor amounts of quinolinic acid are formed (Guillemin et al. 2000). Therefore, without microglial activation the induction of local IDO expression can initiate a negative feedback loop, which may underlie the self-limitation of autoimmune inflammation during neurological disorders (Kwidzinski et al. 2005). However, in the presence of microglia, kynurenine—synthesized by astroglia—is metabolized into quinolinic acid (Guillemin et al. 2000) and thus the pro-inflammatory effects of quinolinic acid may prevail, aggravating the initial inflammatory response (Maes et al. 2007b).

The I&ND hypothesis and inflammatory cytokines

Both central and peripheral inflammation induced by immune challenge such as LPS can produce and exacerbate local brain inflammation, neuronal death and reduced neurogenesis, not only through increased brain O&NS, IDO activation and elevated levels of TRYCATs, but also through other effects of the increased production of proinflammatory cytokines. Supporting this notion, microglia were recently suggested to have detrimental effects on neurogenesis (Kempermann and Neumann 2003). Moreover, treatment with inflammatory cytokine inducers, including LPS and radiation, resulted in marked suppression of hippocampal neurogenesis (Ekdahl et al. 2003; Monje et al. 2003). Direct evidence for the influence of IL-1 on neurogenesis was recently provided by showing that both acute and chronic IL-1 exposure results in impaired hippocampal cytogenesis and neurogenesis (Goshen et al. 2008; Koo and Duman 2008).

$\text{TNF}\alpha$ and $\text{IL-1}\beta$, are not only neurotoxic but can also decrease neurogenesis in selected brain areas. $\text{TNF}\alpha$ may cause neurodegeneration through silencing of cell survival signals, caspase-dependent cascades, and potentiation of glutamate neurotoxicity through stimulation of microglial glutamate release by up-regulating glutaminase and blockade of glutamate transporter activity (Zou and Crews 2005). $\text{IL-1}\beta$ may exacerbate cell death through increased seizure activity; and increased NMDA receptor function through activation of tyrosine kinases (Viviani et al. 2006; Patel et al. 2006). Interestingly, IL-10 has a neuroprotective effect which is attributable to inhibition of LPS-stimulated microglial activation; and the inhibition of the microglial production of $\text{TNF}\alpha$, nitric oxide, ROS and superoxide free radicals (Qian et al. 2006). Recently, it became clear that BDNF expression in neurons depends partly on inflammatory cytokines, such as $\text{IL-1}\beta$, IL-6 and $\text{TNF}\alpha$ (Schulte-Herbruggen et al. 2005) and that the expression of neurotrophic factors is differently regulated by TRYCATs (Checa et al. 2000).

The I&ND hypothesis and lowered $\omega 3$ PUFAs

3ω PUFAs influence neurogenesis (Beltz et al. 2007) via their anti-inflammatory and serotonergic effects and their effects on neurotrophins (Maes et al. 1999a). a) $\omega 3$

PUFAs decrease the production of pro-inflammatory cytokines, such as $\text{TNF}\alpha$ and $\text{IL-1}\beta$ (review: Maes et al. 1999a), which have been implicated in mechanisms that regulate neurogenesis and cell fate (Beck et al. 2005). b) $\omega 3$ PUFAs modulate the quaternary structure of membrane proteins and membrane fluidity, which determine the binding of serotonin (Beltz et al. 2007). Serotonin, in turn, stimulates neurogenesis in both vertebrate and invertebrate species (Ueda et al. 2005; Beltz et al. 2003). c) $\omega 3$ PUFAs influence the levels of neurotrophins, such as BDNF (Wu et al. 2004). In the embryonic rat brain, a deficiency in $\omega 3$ PUFAs results in a delay or inhibition of normal neuronal development and thus in decreased neurogenesis (Coti Bertrand et al. 2006). In adult rats, DHA effectively promotes neurogenesis and the differentiation of neural stem cells into neurons by promoting cell cycle exit and suppressing cell death (Kawakita et al. 2006). In the lobster brain (another model for investigating neurogenesis), administration of dietary $\omega 3$ results in significant increases in the numbers of S phase cells (Beltz et al. 2007).

In conclusion, there is growing support for the view the inflammatory processes occurring in depression, i.e. increased cytokine and TRYCAT levels, O&NS and lowered $\omega 3$, play a pivotal role in the long term neurodegenerative and neurogenesis changes that occur in depression. Moreover, it may be hypothesized that anti-inflammatory compounds should be able to counteract the enhanced neurodegeneration and decreased neurogenesis, which are at least partly induced by the abovementioned inflammatory reactions.

Implications of the I&ND hypothesis to the complexity and heterogeneity of depression

The whole picture of depression is very complex and many players are involved (see Fig. 2). In particular, two major pathophysiological pathways may be detected in depression, i.e. inflammation and neurodegeneration. Inflammation with increased production of pro-inflammatory cytokines may induce sickness behavior-like symptoms of depression through central neuroinflammation, a reduction in tryptophan availability resulting in serotonin depletion, and increased production of some TRYCATs, some of which have behavioral effects (anxiogenic). Inflammation may also explain the cortisol-axis overdrive in depression including GR downregulation. Internal stressors, such as the postpartum period and other inflammatory disorders; and external stressors may trigger depression, since these factors can induce inflammatory responses. Vulnerability factors include lower peptidase activity and $\omega 3$ PUFA contents. Increased LPS translocation (leaky gut) may act as a trigger and vulnerability factor. Moreover, pro-inflammatory cytokines, O&NS, and TRYCATs may induce neurodegeneration, whereas the above together with lowered $\omega 3$ status may decrease neurogenesis. Genetic factors in any of the above pathways may be involved in depression.

The I&ND hypothesis, residual symptoms and recurrent depression

Depression is a highly recurrent disorder, with long-term estimates of recurrence ranging as high as 80% (Pettit et al. 2006). The waxing and waning of depressive

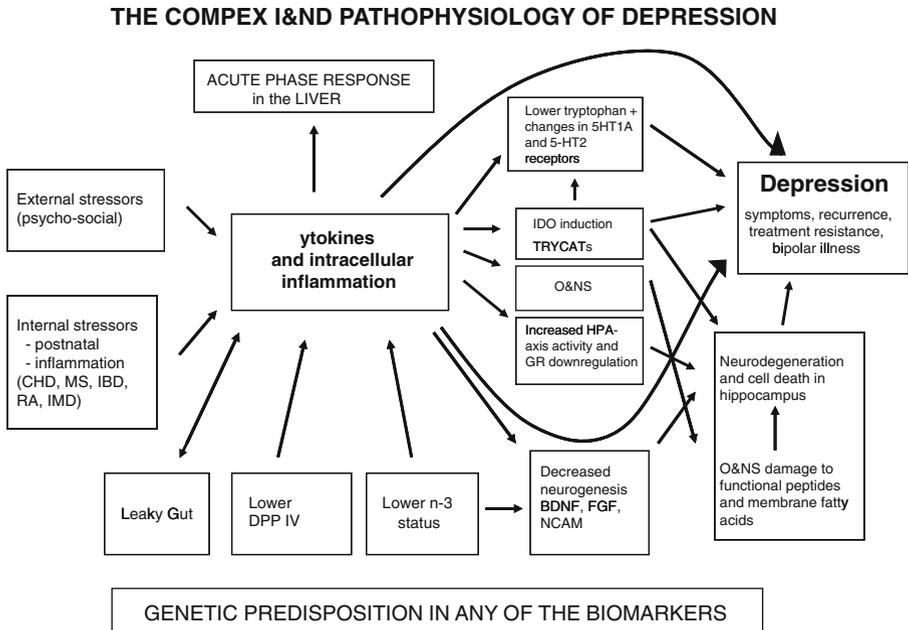


Fig. 2 The complex etiology of depression. Two major pathways determine depression, i.e. inflammation and neurodegeneration (*I&ND*). Internal stressors, such as the postpartum period and other inflammatory disorders and external stressors may trigger depression through an increased inflammatory response. A number of biological vulnerability factors increase the propensity to develop depression, i.e. leaky gut with an increased LPS translocation through the gut wall; lower peptidase activity and a lowered $\omega 3$ PUFA status. Inflammation may induce depression via a decreased availability of tryptophan and thus lowered serotonin contents in the brain; an increased production of some TRYCATs (*tryptophan catabolites along the IDO pathway*); HPA-(hypothalamic-pituitary-adrenal) axis overdrive including GR (*glucocorticoid receptor*) downregulation; increased O&NS (*oxidative & nitrosative stress*); and lowered neurogenesis. Pro-inflammatory cytokines, e.g. IL-1 β and TNF α , have neurotoxic effects and can-through increased TRYCAT, O&NS and cortisol-induce neurodegeneration. Pro-inflammatory cytokines; behaviorally active TRYCATs; and O&NS; and the neurodegenerative pathways may induce multifarious symptoms, such as the vegetative symptoms of depression, anhedonia, anxiety, fatigue, pain and neurocognitive symptoms. The *I&ND* pathways are involved in the recurrent nature of depression, treatment resistance and bipolarity. Genetic factors in any of the above pathways may be involved in depression

episodes has been compared with the typical recurrent attacks in autoimmune disorders (Maes 1995). It was found that depression may induce a sensitization effect with increased inflammatory responses to stressors. For example, women who had suffered from a lifetime history of major depression had amplified inflammatory responses in the early puerperium (Maes et al. 2001b), suggesting that a depressive episode may sensitize the inflammatory system of females to subsequent internal stressors. Moreover, depressive episodes may act as maladaptive responses to stress, thus exerting negative influences on the same brain structures and systems involved in the responses to stress, such as the hippocampal formation and the cortisol axis. These influences leave the individual with an increased probability of relapses after each depressive episode and may cause more permanent changes in the stress-system, predisposing the patient to residual symptomatology and recurrences (Post 1992, 2007).

Impaired neurogenesis with a reduction in the number and survival of mature, functional neurons in the dentate gyrus together with stress-induced remodeling of CA3 pyramidal neurons, dendrites, sprouting and reduced expression of BDNF in hippocampal neurons are neurotoxic markers of repeated episodes of untreated recurrent depression (Vaidya and Duman 2001). Thus, the high recurrence rates of depression are probably at least partly caused by alterations in the I&ND pathways, particularly sensitization in inflammatory pathways and the resultant repetitive neurodegenerative attacks, which may further aggravate the existing I&ND disorders in depression.

The I&ND hypothesis and bipolar disorder

A considerable percentage of depressed patients show recurrent episodes of manic and hypomanic episodes. Bipolar (BP) disorder is a psychiatric condition characterized by episodes of mania, hypomania, depression, and underlying mood instability. Epidemiological studies show that the bipolar spectrum has a lifetime community prevalence of around 5% (Benazzi et al. 2007a, 2007b). Lithium and anticonvulsant drugs have an established place in the treatment of the disorder. It is thought that mood stabilizers, such as lithium and valproate, may exert some of their anti-manic or prophylactic effects by increasing brain serotonergic turnover (Maes et al. 1997b). Previous research has shown that manic episodes are accompanied by increased plasma levels of proinflammatory cytokines, such as IL-6, IL-8, IFN γ and increased acute phase reactants (Maes et al. 1995a, 1997c; Wade et al. 2002; Kim et al. 2004, 2007). Moreover, IFN α -based immunotherapy may induce not only depressive, but also manic episodes (Banerjee et al. 2007). Almost 100 polymorphic genes have been associated with bipolar disorder, such as components of a phosphatidylinositol signaling/AKT1 survival pathway which is activated by growth factors, such as BDNF, and the endoplasmic reticulum stress pathway, which is activated by proinflammatory cytokines, such as IL-1 β , TNF α , and IFNs (Carter 2007). Machado-Vieira et al. (2007a) found decreased plasma brain BDNF in bipolar patients during the manic phase of their illness. Also, oxidative stress parameters have been detected in bipolar subjects (Machado-Vieira et al. 2007b).

Thus, similar disorders in I&ND pathways are observed during depressive and manic episodes. In manic patients, mood stabilizers such as lithium and valproate may normalize the initial acute phase response, but not the increases in proinflammatory cytokines (Maes et al. 1995a, 1997c). It has been demonstrated that lithium and valproate increase BDNF contents in rat hippocampus and frontal cortex and modulate serum and central NT-3 (neurotrophin-3, a neurotrophic factor, in the nerve growth factor-family of neurotrophins) (Walz et al. 2007). These findings further support the notion that the regulation of the I&ND pathways may be related to the mechanisms of action of mood stabilizers (Walz et al. 2007).

The I&ND hypothesis and refractory depression

Up to 15% of depressed patients present with treatment-resistant or refractory depression (TRD). Depression is usually considered resistant or refractory when at least 2 trials with antidepressants from different pharmacologic classes (adequate in terms of dosage, duration, and compliance) fail to produce a significant clinical

improvement (Berlim and Turecki 2007). Pharmacological approaches to TRD include the augmentation of selective serotonin reuptake inhibitors (SSRIs) with pindolol, lithium, tricyclic antidepressants (TCAs), etc, add-on treatments which aim to augment serotonergic neurotransmission (Maes et al. 1999b). It has been shown that patients with TRD exhibit more severe disorders in the I&ND pathways. For example, they show a higher CD4⁺/CD8⁺ T cell ratio and serum IL-6 levels and lower zinc levels than non-TRD patients (Maes et al. 1997a, 1997d; Kubera et al. 1999). Patients with SSRI-resistant depression had significantly higher production of the pro-inflammatory cytokines IL-6 and TNF α compared to normal controls (O'Brien et al. 2007). Also, BDNF appears to play a role in TRD because there is an association between BDNF GA + AA genotypes and an increase in risk of TRD (Anttila et al. 2007). Interestingly, vagal nerve stimulation (NVS), which is approved for use as a TRD treatment both in the EU and the US, attenuates macrophage activation (de Jonge et al. 2005). The abovementioned data support the view that I&ND pathways are involved in treatment resistance and that anti-I&ND drugs could be used as adjunctive treatments in TRD.

The I&ND hypothesis and gender aspects

Epidemiologic research consistently reports gender differences in the rates of major depressive disorder. The gender-specific rate of major depression shows a 1.7:1 prevalence rate in women vs. men (Marcus et al. 2005). Gender-related differences have been observed in serotonin, e.g. a lower plasma tryptophan availability and greater serotonin-agonist-induced cortisol responses (an indication of 5-HT₂ receptor function) (Maes et al. 1987, 1988). There are also marked gender-related differences in the I&ND pathways. For example, women have exaggerated immune responses to psychological stress (Maes et al. 1999e) and show greater reductions in tryptophan and greater increases in kynurenine following IFN α treatment (Bonaccorso et al. 2002).

These results suggest that women have an IDO / TRYCAT pathway that is more sensitive to inflammatory challenge than men. One possible mechanism for a gender difference in the I&ND pathways was recently found in conditional BDNF knockout mice in which the BDNF gene was deleted selectively in the forebrain. It was found that male conditional knock outs (KOs) exhibited hyperactivity but normal depression-related behaviors, whereas female conditional KOs displayed normal locomotor activity but a striking increase in depression-like behavior (Monteggia et al. 2007). These results suggest that gender-differences in I&ND pathways with exaggerated responses in females could play a role in the increased incidence of depression in females.

Future research questions and their investigation by a novel research approach, using a high throughput–high quality screening

The above findings raise many questions which should be examined in future research.

- a) What intracellular inflammatory mechanisms cause the induction of the cytokine network, O&NS and TRYCAT production. The major candidate is nuclear factor

- kappa beta ($\text{NF}\kappa\beta$), which is the major upstream, intracellular mechanism, which regulates inflammatory and oxidative stress mediators, such as the inducible enzymes cyclo-oxygenase-2 (COX-2) and inducible NO synthase (iNOS) (see Maes et al. 2007a, 2007c). But there are many candidates which call for further examination, e.g. mitogen-activated protein kinase (MAPK), MAPK phosphatases, protein kinase A (PKA), PKB, PKC, the extracellular signal-regulated kinases (ERK)1 and ERK2, c-Jun-N-terminal kinase (JNK) and the cAMP response element-binding (CREB) to name a few. Another question is what the cellular sources are of the I&ND mediators in the brain, e.g are microglia involved.
- b) What is the best target for the treatment of depression; is it still serotonin (5-HT_{1A}, 5-HT₂ or 5-HT₄ receptors) and the GR; or is it novel targets as cytokines or cytokine receptors; the novel inflammatory intracellular mechanisms, which still need to be discovered; peptidases; growth and neurotrophic factors (particularly BDNF, NCAM, FGF or other neurotrophins), as well as combinations of all of the above.
 - c) What existing anti-inflammatory drugs, either NSAIDs (non-steroidal anti-inflammatory drugs), or NAIOSs (natural anti-inflammatory and anti-oxidative substances), should be selected in trials aimed to augment the activity of antidepressants? A good example of a NAIOS with a good profile to normalize the I&ND mechanisms in depression is curcumin (curcuma longa, a major constituent of Xiaoyao-san). Curcumin has strong anti-inflammatory and anti-oxidative properties by targeting intracellular $\text{NF}\kappa\beta$, it increases hippocampal neurogenesis and increases BDNF expression, it reverses 5-HT_{1A} receptor downregulation and depressive behavior in rat models of depression, and abolishes the inhibitory effect of cytokines on GR-mediated gene expression (Xu et al. 2007; Periyasamy and Sanchez 2002).

Taking into account the complexity of depression, the approach whereby principal investigators direct relatively small pharmacological or animal studies focusing on only selected I&ND biomarkers or drug targets is not the most efficient one. At this point, the most adequate approach to tackle the above questions is a high throughput–high quality screening which may be obtained by the Experimental Medicine approach. The methods include functional genomics (DNA-chips to examine expression profiling, diagnostics, identification of disease genes and drug discovery); genotyping microarrays (SNP arrays to examine genetic predisposition to a disease); animal models and transgenic (TG) mouse models; novel ex vivo and in vitro models, e.g. dispersed cell cultures, ex vivo electroporation with subsequent brain slice culturing (Polleux and Ghosh 2002; Hand et al 2005) and other organotypic brain slice culture models, including the use of transgenic donor mice (Norberg et al. 2005); knock-down functional screens on neural stem cells; and brain-specific promotor-induction based indicator cell lines with promotor sequences of various inflammatory substances.

The main aims of this high-throughput–high quality screening are to:

- a) discover new I&ND biomarkers and the exact I&ND pathways in depressive patients; identify the I&ND pathophysiology of recurrent, bipolar, TRD and postpartum depression; and delineate the gender-related factors that determine

- the greater I&ND responses and the increased occurrence of depression in females. Most importantly, future research should focus on the I&ND gene signature in depression. Toward this end, genome-wide expression profiles (Affymetrix Exon Arrays) and mutation detection in the I&ND pathways should be examined.
- b) discover the exact I&ND pathways in animal and in vivo/ex vivo models of depression. Here, two internal stress models, i.e. knock-in mouse, characterized by inflammation and inflammatory neurodegeneration, as well as the LPS model of depression in the rat and mice should be examined. The effects of external stressors on the I&ND pathways should be examined using models, such as prenatal stress and maternal deprivation (early-life stresses) and social isolation and chronic mild stress model of depression (late-life stresses). Transgenic (TG) mouse models over-expressing I&ND-related biomarkers, e.g. IDO, or with conditional knock-out of I&ND markers, e.g. IL-10 or NCAM, should be used to characterize depressive behavior in relation to the I&ND pathways. In order to examine the effects of cytokines and LPS, O&NS and TRYCATs on selective neuronal loss and decreased neurogenesis, novel organotypic slice culture models using hippocampal and substantia nigra slice cultures from rats and mice as well as organotypic cultures from TG fluorescent and other TG mice models should be employed (Norberg et al. 2005, 2007). Knock down functional screens of neural stem cells and microglia; and brain-specific, promotor-induction based indicator cell lines will enable to assess the precise inflammatory reactions that occur in depression and that induce neurodegeneration and decreased neurogenesis.
 - c) identify new I&ND targets for new treatments, e.g. cytokines; intracellular inflammatory mediators; neurogenesis; or glia cell activation. Toward this end, existing anti-inflammatory compounds and substances that promote neurogenesis should be examined in order to identify those substances with the greatest anti-I&ND effects which, in turn, could be employed as monotherapy or adjunctive therapy. Examples are; the IL-1 receptor antagonist, selected NSAIDs, selected NAIOSs (e.g. curcumin), IDO inhibitors, tocilizumab (a monoclonal antibody against IL-6), fontolizumab (a humanized anti-IFN γ antibody), minocycline (a tetracycline with anti-inflammatory properties, that prevents microglial activation, and is neuroprotective), and compounds that block TNF α signaling and / or target BDNF, FGF and NCAM.

References

- Amodio P, De Toni EN, Cavalletto L, Mapelli D, Bernardinello E, Del Piccolo F, Bergamelli C, Costanzo R, Bergamaschi F, Poma SZ, Chemello L, Gatta A, Perini G (2005) Mood, cognition and EEG changes during interferon (α IFN) treatment for chronic hepatitis C. *J. Affect. Disord.* 84(1):93–98
- Angelucci F, Brene S, Mathe AA (2005) BDNF in schizophrenia, depression and corresponding animal models. *Mol. Psychiatry* 10(4):345–352
- Anisman H, Kokkinidis L, Merali Z (2002) Further evidence for the depressive effects of cytokines: anhedonia and neurochemical changes. *Brain Beh. Immun.* 16(5):544–556 Review

- Anisman H, Merali Z, Poulter MO, Hayley S (2005) Cytokines as a precipitant of depressive illness: animal and human studies. *Curr. Pharm. Design* 11(8):963–972
- Anisman H, Poulter MO, Gandhi R, Merali Z, Hayley S (2007) Interferon-alpha effects are exaggerated when administered on a psychosocial stressor backdrop: cytokine, corticosterone and brain monoamine variations. *J. Neuroimmunol.* 186(1–2):45–53
- Anttila S, Huuhka K, Huuhka M, Rontu R, Hurme M, Leinonen E, Lehtimäki T (2007) Interaction between 5-HT1A and BDNF genotypes increases the risk of treatment-resistant depression. *J. Neural. Transm.* 114(8):1065–1068
- Babcock TA, Carlin JM (2000) Transcriptional activation of indoleamine dioxygenase by interleukin 1 and tumor necrosis factor alpha in interferon-treated epithelial cells. *Cytokine* 12(6):588–594
- Banerjee A, Jain G, Grover S, Singh J (2007) Mania associated with interferon. *J. Postgraduate Med.* 53(2):150
- Bazan NG, Marcheselli VL, Cole-Edwards K (2005) Brain response to injury and neurodegeneration: endogenous neuroprotective signaling. *Ann. NY Acad. Sci.* 1053:137–147 Review
- Beck RD Jr., Wasserfull C, Ha GK, Cushman JD, Huang Z, Atkinson MA, Petitto JM (2005) Changes in hippocampal IL-15, related cytokines, and neurogenesis in IL-2 deficient mice. *Brain Res.* 1041:223–230
- Beltz BS, Sandeman DC (2003) Regulation of life-long neurogenesis in the decapod crustacean brain. *Arth. Struct. Dev.* 32:39–60
- Beltz BS, Tlustý MF, Benton JL, Sandeman DC (2007) Omega-3 fatty acids upregulate adult neurogenesis. *Neurosci. Lett.* 145(2):154–158
- Benazzi F (2007a) Bipolar II Disorder : Epidemiology, Diagnosis and Management. *CNS Drugs.* 21(9):727–740
- Benazzi F (2007b) Is there a continuity between bipolar and depressive disorders? *Psychoth. Psychosom.* 76(2):70–76
- Berlim MT, Turecki G (2007) Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. *Can. J. Psychiatry* 52(1):46–54
- Bjørnebekk A, Mathé AA, Brené S (2005) The antidepressant effect of running is associated with increased hippocampal cell proliferation. *Int. J. Neuropsychopharmacol.* 8(3):357–368
- Bjørnebekk A, Mathé AA, Gruber SH, Brené S (2007) Social isolation increases number of newly proliferated cells in hippocampus in female flinders sensitive line rats. *Hippocampus.* 17(12):1193–1120
- Bjørnebekk A, Mathé AA, Gruber SH, Brené S (2008) Housing conditions modulate escitalopram effects on antidepressive-like behaviour and brain neurochemistry. *Int. J. Neuropsychopharmacol.* 23:1–13
- Bonaccorso S, Puzella A, Marino V, Pasquini M, Biondi M, Artini M, Almerighi C, Levvero M, Egyed B, Bosmans E, Meltzer HY, Maes M (2001) Immunotherapy with interferon-alpha in patients affected by chronic hepatitis C induces an intercorrelated stimulation of the cytokine network and an increase in depressive and anxiety symptoms. *Psychiatry Res.* 105(1–2):45–55
- Bonaccorso S, Marino V, Biondi M, Grimaldi F, Ippoliti F, Maes M (2002a) Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. *J. Affect. Disord.* 72(3):237–241
- Bonaccorso S, Marino V, Puzella A, Pasquini M, Biondi M, Artini M, Almerighi C, Verkerk R, Meltzer H, Maes M (2002b) Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. *J. Clin. Psychopharmacol.* 22(1):86–90
- Bremner JD, Narayan M (1998) The effects of stress on memory and the hippocampus throughout the life cycle: implications for childhood development and aging. *Developm. Psychopathol.* 10(4):871–885
- Brown ES, Rush AJ, McEwen BS (1999) Hippocampal remodeling and damage by corticosteroids: implications for mood disorders. *Neuropsychopharmacol.* 21(4):474–484
- Brown ES, Woolston D, Frol A, Bobadilla L, Khan DA, Hanczyc M, Rush AJ, Fleckenstein J, Babcock E, Cullum CM (2004) Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. *Biol. Psychiatry* 55(5):538–545
- Bukalo O, Fentrop N, Lee AY, Salmen B, Law JW, Wotjak CT, Schweizer M, Dityatev A, Schachner M (2004) Conditional ablation of the neural cell adhesion molecule reduces precision of spatial learning, long-term potentiation, and depression in the CA1 subfield of mouse hippocampus. *J. Neurosci.* 24:1565–1577
- Campbell S, MacQueen G (2006) An update on regional brain volume differences associated with mood disorders. *Curr. Opin. Psychiatry* 19(1):25–33

- Capuron L, Neurauter G, Musselman DL, Lawson DH, Nemeroff CB, Fuchs D, Miller AH (2003) Interferon-alpha-induced changes in tryptophan metabolism. relationship to depression and paroxetine treatment. *Biol. Psychiatry* 54(9):906–914
- Carter CJ (2007) Multiple genes and factors associated with bipolar disorder converge on growth factor and stress activated kinase pathways controlling translation initiation: implications for oligodendrocyte viability. *Neurochem. Int.* 50(3):461–490
- Castanon N, Bluthé RM, Dantzer R (2001) Chronic treatment with the atypical antidepressant tianeptine attenuates sickness behavior induced by peripheral but not central lipopolysaccharide and interleukin-1beta in the rat. *Psychopharmacol.* 154(1):50–60
- Chavez AM, Menconi MJ, Hodin RA, Fink MP (1999) Cytokine-induced intestinal epithelial hyperpermeability: role of nitric oxide. *Crit. Care Med.* 27(10):2246–2251
- Checa N, Canals JM, Alberch J (2000) Developmental regulation of BDNF and NT-3 expression by quinolinic acid in the striatum and its main connections. *Exp. Neurology* 165(1):118–124
- Chung KK, Dawson TM, Dawson VL (2005) Nitric oxide, S-nitrosylation and neurodegeneration. *Cell Mol. Biol. (Noisy-le-grand)* 51(3):247–254 Review
- Clark E, Hoare C, Tanianis-Hughes J, Carlson GL, Warhurst G (2005) Interferon gamma induces translocation of commensal *Escherichia coli* across gut epithelial cells via a lipid raft-mediated process. *Gastroenterol.* 128(5):1258–1267
- Contestabile A (2001) Oxidative stress in neurodegeneration: mechanisms and therapeutic perspectives. *Curr. Topics Med. Chemistry* 1(6):553–568 Review
- Coti Bertrand P, O'Kusky JR, Innis SM (2006) Maternal dietary (n-3) fatty acid deficiency alters neurogenesis in the embryonic rat brain. *J. Nutr.* 136(6):1570–1575
- Cowen PJ (2002) Cortisol, serotonin and depression: all stressed out? *Brit. J. Psychiatry* 180:99–100
- de Jonge WJ, van der Zanden EP, The FO, Bijlsma MF, van Westerlo DJ, Binnink RJ, Berthoud HR, Uematsu S, Akira S, van den Wijngaard RM, Boeckxstaens GE (2005) Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. *Nature Immunol* 6(8):844–851
- Dinan T (2001) Novel approaches to the treatment of depression by modulating the hypothalamic—pituitary—adrenal axis. *Hum. Psychopharmacol.* 16(1):89–93
- Duman RS (2002) Pathophysiology of depression: the concept of synaptic plasticity. *Eur. Psychiatry* 17 (Suppl 3):306–310
- Duman RS (2004) Depression: a case of neuronal life and death? *Biol. Psychiatry* 56(3):140–145
- Ehninger D, Kempermann G (2006) Paradoxical effects of learning the Morris water maze on adult hippocampal neurogenesis in mice may be explained by a combination of stress and physical activity. *Genes Brain Beh.* 5(1):29–39
- Ekdahl CT, Claassen JH, Bonde S, Kokaia Z, Lindvall O (2003) Inflammation is detrimental for neurogenesis in adult brain. *Proc. Nat. Acad. Sci. USA.* 100(23):13632–13637
- el-Defrawy SR, Boegman RJ, Jhamandas K, Beninger RJ (1986) The neurotoxic actions of quinolinic acid in the central nervous system. *Can. J. Physiol. Pharmacol.* 64(3):369–375
- Fitzgerald P, O'Brien SM, Scully P, Rijkers K, Scott LV, Dinan TG (2006) Cutaneous glucocorticoid receptor sensitivity and pro-inflammatory cytokine levels in antidepressant-resistant depression. *Psychol. Med.* 36(1):37–43
- Forlenza MJ, Miller GE (2006) Increased serum levels of 8-hydroxy-2'-deoxyguanosine in clinical depression. *Psychosomatic Med.* 68(1):1–7
- Fuchs E, Czeh B, Kole MH, Michaelis T, Lucassen PJ (2004) Alterations of neuroplasticity in depression: the hippocampus and beyond. *Eur. Neuropsychopharmacol.* 5(14 Suppl):S481–490
- Garthwaite G, Garthwaite J (1987) Quinolinic acid mimics neurotoxic actions of N-methyl-D-aspartate in rat cerebellar slices. *Neurosci. Lett.* 79(1–2):35–39
- Gould E, McEwen BS, Tanapat P, Galea LA, Fuchs E (1997) Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. *J. Neurosci.* 17 (7):2492–2498
- Guillemin GJ, Smith DG, Kerr SJ, Smythe GA, Kapoor V, Armati PJ, Brew BJ (2000) Characterisation of kynurenine pathway metabolism in human astrocytes and implications in neuropathogenesis. *Redox Report* 5(2–3):108–111
- Goshen I, Kreisel T, Ben-Menachem-Zidon O, Licht T, Weidenfeld J, Ben-Hur T, Yirmiya R (2008) Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. *Mol Psychiatry* 13(7):717–728
- Groves JO (2007) Is it time to reassess the BDNF hypothesis of depression? *Mol. Psychiatry* 12:1079–1088
- Halliwel B (2006) Oxidative stress and neurodegeneration: where are we now? *J. Neurochem.* 97 (6):1634–1658 Review

- Hand R, Bortone D, Mattar P, Nguyen L, Heng JI, Guerrier S, Boutt E, Peters E, Barnes AP, Parras C, Schuurmans C, Guillemot F, Polleux F (2005) Phosphorylation of neurogenin2 specifies the migration properties and the dendritic morphology of pyramidal neurons in the neocortex. *Neuron* 48(1):45–62
- Henn FA, Vollmayr B (2004) Neurogenesis and depression: etiology or epiphenomenon? *Biol. Psychiatry* 56(3):146–150
- Heyes MP, Saito K, Crowley JS, Davis LE, Demitrack MA, Der M, Dilling LA, Elia J, Kruesi MJ, Lackner A et al (1992) Quinolinic acid and kynurenine pathway metabolism in inflammatory and non-inflammatory neurological disease. *Brain* 115(Pt 5):1249–1273
- Hibbeln JR (1998) Fish consumption and major depression. *Lancet* 351(9110):1213
- Hibbeln JR (2002) Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *J. Affect. Disord.* 69(1–3):15–29
- Horrobin DF (2001) Phospholipid metabolism and depression: the possible roles of phospholipase A2 and coenzyme A-independent transacylase. *Hum. Psychopharmacol.* 16(1):45–52
- Huang SY, Yang HT, Chiu CC, Pariante CM, Su KP (2006) Omega-3 fatty acids on the forced-swimming test. *J. Psychiatr. Res.* 42(1):58–63
- Ishikawa I, Kitamura H, Kimura K, Saito M (2001) Brain interleukin-1 is involved in blood interleukin-6 response to immobilization stress in rats. *Jap. J. Veterinary Res.* 49(1):19–25
- Kawakita E, Hashimoto M, Shido O (2006) Docosahexaenoic acid promotes neurogenesis in vitro and in vivo. *Neurosci.* 139(3):991–997
- Kempermann G, Neumann H (2003) Microglia: the enemy within? *Science* 302:1689–1690
- Kempermann G, Kuhn HG, Gage FH (1997) More hippocampal neurons in adult mice living in an enriched environment. *Nature* 386(6624):493–495
- Kenis G, Maes M (2002) Effects of antidepressants on the production of cytokines. *Int. J. Neuropsychopharmacol.* 5(4):401–412 Review
- Kent S, Bluthé RM, Kelley KW, Dantzer R (1992) Sickness behavior as a new target for drug development. *Trends Pharmacol. Sci.* 13(1):24–28
- Kerr SJ, Armati PJ, Guillemin GJ, Brew BJ (1998) Chronic exposure of human neurons to quinolinic acid results in neuronal changes consistent with AIDS dementia complex. *AIDS* 12(4):355–363
- Khaspekov L, Kida E, Victorov I, Mossakowski MJ (1989) Neurotoxic effect induced by quinolinic acid in dissociated cell culture of mouse hippocampus. *J. Neurosci. Res.* 22(2):150–157
- Kim YK, Myint AM, Lee BH, Han CS, Lee SW, Leonard BE, Steinbusch HW (2004) T-helper types 1, 2, and 3 cytokine interactions in symptomatic manic patients. *Psychiatr. Res.* 129(3):267–272
- Kim YK, Jung HG, Myint AM, Kim H, Park SH (2007) Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. *J. Affect. Disord.* 104(1–3):91–95
- Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT (2008) Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS. Medicine* 5(2):e45
- Koo JW, Duman RS (2008) IL-1beta is an essential mediator of the antineurogenic and anhedonic effects of stress. *Proc. Nat. Acad. Sci. USA* 105:751–756
- Kubera M, Symbirtsev A, Basta-Kaim A, Borycz J, Roman A, Papp M, Claesson M (1996) Effect of chronic treatment with imipramine on interleukin 1 and interleukin 2 production by splenocytes obtained from rats subjected to a chronic mild stress model of depression. *Pol. J. Pharmacol.* 48:503–506
- Kubera M, Van Bockstaele D, Maes M (1999) Leukocyte subsets in treatment-resistant major depression. *Pol. J. Pharmacol.* 51(6):547–549
- Kubera M, Lin AH, Kenis G, Bosmans E, van Bockstaele D, Maes M (2001a) Anti-inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio. *J. Clin. Psychopharmacol.* 21(2):199–206
- Kubera M, Maes M, Holan V, Basta-Kaim A, Roman A, Shani J (2001b) Prolonged desipramine treatment increases the production of interleukin-10, an anti-inflammatory cytokine, in C57BL/6 mice subjected to the chronic mild stress model of depression. *J. Affect. Disord.* 63(1–3):171–178
- Kwidzinski E, Bunse J, Aktas O, Richter D, Mutlu L, Zipp F, Nitsch R, Bechmann I (2005) Indolamine 2,3-dioxygenase is expressed in the CNS and down-regulates autoimmune inflammation. *FASEB J.* 19(10):1347–1349
- Lacosta S, Merali Z, Anisman H (1999) Behavioral and neurochemical consequences of lipopolysaccharide in mice: angiogenic-like effects. *Brain Res.* 818(2):291–303
- Lapin IP (2003) Neurokynurenines (NEKY) as common neurochemical links of stress and anxiety. *Adv. Exp. Med. Biol.* 527:121–125

- Lestage J, Verrier D, Palin K, Dantzer R (2002) The enzyme indoleamine 2,3-dioxygenase is induced in the mouse brain in response to peripheral administration of lipopolysaccharide and superantigen. *Brain Behav. Immun.* 16(5):596–601
- Levivier M, Przedborski S (1998) Quinolinic acid-induced lesions of the rat striatum: quantitative autoradiographic binding assessment. *Neurol. Res.* 20(1):46–56
- Lin A, Song C, Kenis G, Bosmans E, De Jongh R, Scharpe S, Maes M (2000) The in vitro immunosuppressive effects of moclobemide in healthy volunteers. *J. Affect. Disord.* 58(1):69–74
- Lin PY, Su KP (2007) A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *J. Clin. Psychiatr.* 68(7):1056–1061
- Machado-Vieira R, Dietrich MO, Leke R, Cereser VH, Zanatto V, Kapczinski F, Souza DO, Portela LV, Gentil V (2007a) Decreased plasma brain derived neurotrophic factor levels in unmedicated bipolar patients during manic episode. *Biol. Psychiatry* 61(2):142–144
- Machado-Vieira R, Andreazza AC, Viale CI, Zanatto V, Cereser V Jr, da Silva Vargas R, Kapczinski F, Portela LV, Souza DO, Salvador M, Gentil V (2007b) Oxidative stress parameters in unmedicated and treated bipolar subjects during initial manic episode: a possible role for lithium antioxidant effects. *Neurosci. Lett.* 421(1):33–36
- Maes M (1993) A review on the acute phase response in major depression. *Rev. Neurosci.* 4(4):407–416 Review
- Maes M (1995) Evidence for an immune response in major depression: a review and hypothesis. *Progr. Neuropsychopharmacol. Biol. Psychiatry* 19(1):11–38 Review
- Maes M (1999) Major depression and activation of the inflammatory response system. *Adv. Exp. Med. Biol.* 461:25–46 Review
- Maes M, Meltzer HY (1995) The Serotonin Hypothesis of major depression. *Psychopharmacology, The Fourth Generation of Progress.* In: Bloom F, Kupfer D (Ed) Raven Press, pp 933–944
- Maes M, Smith RS (1998) Fatty acids, cytokines, and major depression. *Biol. Psychiatr.* 43(5):313–314
- Maes M, De Ruyter M, Claes R, Bosma G, Suy E (1987) The cortisol responses to 5-hydroxytryptophan, orally, in depressive inpatients. *J. Affect. Disord.* 13(1):23–30
- Maes M, De Ruyter M, Claes R, Suy E (1988) Sex-related differences in the relationships between self-rated depression and biological markers. *J. Affect. Disord.* 15(2):119–125
- Maes M, Bosmans E, Suy E, Vandervorst C, De Jonckheere C, Raus J (1990) Immune disturbances during major depression: upregulated expression of interleukin-2 receptors. *Neuropsychobiol.* 24(3):115–120
- Maes M, De Meester I, Vanhoof G, Scharpe S, Bosmans E, Vandervorst C, Verkerk R, Minner B, Suy E, Raus J (1991) Decreased serum dipeptidyl peptidase IV activity in major depression. *Biol. Psychiatry* 30(6):577–586
- Maes M, Bosmans E, Meltzer HY, Scharpe S, Suy E (1993a) Interleukin-1 beta: a putative mediator of HPA axis hyperactivity in major depression? *Am. J. Psychiatry* 150(8):1189–1193
- Maes M, Meltzer HY, Scharpe S, Bosmans E, Suy E, De Meester I, Calabrese J, Cosyns P (1993b) Relationships between lower plasma L-tryptophan levels and immune-inflammatory variables in depression. *Psychiatr. Res.* 49(2):151–165
- Maes M, Meltzer HY, Scharpé S, Cooreman W, Uyttenbroeck W, Suy E, Vandervorst C, Calabrese J, Raus J, Cosyns P (1993c) Psychomotor retardation, anorexia, weight loss, sleep disturbances, and loss of energy: psychopathological correlates of hyperhaptoglobinemia during major depression. *Psychiatr. Res.* 47(3):229–241
- Maes M, Scharpe S, Meltzer HY, Cosyns P (1993d) Relationships between increased haptoglobin plasma levels and activation of cell-mediated immunity in depression. *Biol. Psychiatry* 34(10):690–701
- Maes M, Scharpe S, Meltzer HY, Bosmans E, Suy E, Calabrese J, Cosyns P (1993e) Relationships between interleukin-6 activity, acute phase proteins, and function of the hypothalamic-pituitary-adrenal axis in severe depression. *Psychiatr. Res.* 49(1):11–27
- Maes M, Scharpe S, Meltzer H, Okayli G, D'Hondt P, Cosyns P (1994) Increased neopterin and interferon gamma secretion and lower L-tryptophan levels in major depression: further evidence for immune activation in severe depression. *Psychiatr. Res.* 54:143–160
- Maes M, Bosmans E, Calabrese J, Smith R, Meltzer HY (1995a) Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. *J. Psychiatry Res.* 29(2):141–152
- Maes M, Smith R, Scharpe S (1995b) The monocyte-T-lymphocyte hypothesis of major depression. *Psychoneuroendocrinol.* 20(2):111–116
- Maes M, Smith R, Christophe A, Cosyns P, Desnyder R, Meltzer H (1996a) Fatty acid composition in major depression: decreased omega 3 fractions in cholesteryl esters and increased C20: 4 omega 6/ C20:5 omega 3 ratio in cholesteryl esters and phospholipids. *J. Affect. Disord.* 38(1):35–46

- Maes M, Wauters A, Verkerk R, Demedts P, Neels H, Van Gastel A, Cosyns P, Scharpe S, Desnyder R (1996b) Lower serum L-tryptophan availability in depression as a marker of a more generalized disorder in protein metabolism. *Neuropsychopharmacol.* 15(3):243–251
- Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H (1997a) Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine* 9(11):853–858
- Maes M, Calabrese J, Jayathilake K, Meltzer HY (1997b) Effects of subchronic treatment with valproate on L-5-HTP-induced cortisol responses in mania: evidence for increased central serotonergic neurotransmission. *Psychiatr. Res.* 71(2):67–76
- Maes M, Delange J, Ranjan R, Meltzer HY, Desnyder R, Cooremans W, Scharpe S (1997c) Acute phase proteins in schizophrenia, mania and major depression: modulation by psychotropic drugs. *Psychiatr. Res.* 66(1):1–11
- Maes M, Vandoolaeghe E, Neels H, Demedts P, Wauters A, Meltzer HY, Altamura C, Desnyder R (1997d) Lower serum zinc in major depression is a sensitive marker of treatment resistance and of the immune/inflammatory response in that illness. *Biol. Psychiatry* 42(5):349–358
- Maes M, Song C, Lin A, De Jongh R, Van Gastel A, Kenis G, Bosmans E, De Meester I, Benoy I, Neels H, Demedts P, Janca A, Scharpe S, Smith RS (1998a) The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. *Cytokine* 10(4):313–318
- Maes M, Song C, Lin A, DeJong R, Van Gastel A, Kenis G, Bosmans E, DeMeester I, Neels H, Janca A, Scharpe S, Smith RS (1998b) Immune and clinical correlates of psychological stress-induced production of interferon- γ and IL-10 in humans. In: Plotnikoff NP, Faith RE, Murgu AJ, Good RA (eds) *Cytokines, Stress and Immunity*, pp 39–50
- Maes M, Christophe A, Delange J, Altamura C, Neels H, Meltzer HY (1999a) Lowered omega3 polyunsaturated fatty acids in serum phospholipids and cholesteryl esters of depressed patients. *Psychiatr. Res.* 85(3):275–291
- Maes M, Libbrecht I, van Hunsel F, Campens D, Meltzer HY (1999b) Pindolol and mianserin augment the antidepressant activity of fluoxetine in hospitalized major depressed patients, including those with treatment resistance. *J. Clin. Psychopharmacol.* 19(2):177–182
- Maes M, Song C, Lin AH, Bonaccorso S, Kenis G, De Jongh R, Bosmans E, Scharpe S (1999c) Negative immunoregulatory effects of antidepressants: inhibition of interferon-gamma and stimulation of interleukin-10 secretion. *Neuropsychopharmacol.* 20(4):370–379
- Maes M, Song C, Lin AH, Pioli R, Kenis G, Kubera M, Bosmans E (1999d) In vitro immunoregulatory effects of lithium in healthy volunteers. *Psychopharmacol. (Berl)* 143(4):401–407
- Maes M, Van Bockstaele DR, Gastel A, Song C, Schotte C, Neels H, DeMeester I, Scharpe S, Janca A (1999e) The effects of psychological stress on leukocyte subset distribution in humans: evidence of immune activation. *Neuropsychobiol.* 39(1):1–9
- Maes M, Christophe A, Bosmans E, Lin A, Neels H (2000) In humans, serum polyunsaturated fatty acid levels predict the response of proinflammatory cytokines to psychologic stress. *Biol. Psychiatry.* 47(10):910–920
- Maes M, Capuron L, Ravaut A, Gualde N, Bosmans E, Egedy B, Dantzer R, Neveu PJ (2001a) Lowered serum dipeptidyl peptidase IV activity is associated with depressive symptoms and cytokine production in cancer patients receiving interleukin-2-based immunotherapy. *Neuropsychopharmacol.* 24(2):130–140
- Maes M, Ombelet W, De Jongh R, Kenis G, Bosmans E (2001b) The inflammatory response following delivery is amplified in women who previously suffered from major depression, suggesting that major depression is accompanied by a sensitization of the inflammatory response system. *J. Affect. Disord.* 63(1–3):85–92
- Maes M, Ombelet W, Verkerk R, Bosmans E, Scharpe S (2001c) Effects of pregnancy and delivery on the availability of plasma tryptophan to the brain: relationships to delivery-induced immune activation and early post-partum anxiety and depression. *Psychol. Med.* 31(5):847–858
- Maes M, Verkerk R, Bonaccorso S, Ombelet W, Bosmans E, Scharpe S (2002) Depressive and anxiety symptoms in the early puerperium are related to increased degradation of tryptophan into kynurenine, a phenomenon which is related to immune activation. *Life Sci.* 71(16):1837–1848
- Maes M, Mihaylova I, Bosmans E (2007a) Not in the mind of neurasthenic lazybones but in the cell nucleus: patients with chronic fatigue syndrome have increased production of nuclear factor kappa beta. *Neuro Endocrinol. Lett.* 28(4):456–462
- Maes M, Mihaylova I, DeRuyter MD, Kubera M, Bosmans E (2007b) The immune effects of TRYCATs (tryptophan catabolites along the IDO pathway): relevance for depression—and other conditions

- characterized by tryptophan depletion induced by inflammation. *Neuro Endocrinol. Lett.* 28(6):826–831
- Maes M, Mihaylova I, Kubera M, Bosmans E (2007c) Not in the mind but in the cell: increased production of cyclo-oxygenase-2 and inducible NO synthase in chronic fatigue syndrome. *Neuro Endocrinol. Lett.* 28(4):463–469
- Maes M, Mihaylova I, Leunis JC (2007d) Increased serum IgM antibodies directed against phosphatidyl inositol (Pi) in chronic fatigue syndrome (CFS) and major depression: evidence that an IgM-mediated immune response against Pi is one factor underpinning the comorbidity between both CFS and depression. *Neuro Endocrinol. Lett.* 28(6):861–867
- Maes M, Mihaylova I, Ategis J-C (2008a) Evidence for an IgM-mediated immune response directed against nitro-bovine serum albumin (BSA) in chronic fatigue syndrome (CFS) and major depression (MDD): evidence that the immune response to nitrosative stress-induced damage of BSA is more pronounced in CFS than in MDD. *Neuro Endocrinol. Lett.* 2008, In press
- Maes M, Kubera M, Leunis JC (2008b) The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. *Neuro Endocrinol. Letters.* 29(1):117–124
- Malberg JE, Eisch AJ, Nestler EJ, Duman RS (2000) Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J. Neurosci.* 20(24):9104–9110
- Mamalakis G, Kalogeropoulos N, Andrikopoulos N, Hatzis C, Kromhout D, Moschandreas J, Kafatos A (2006) Depression and long chain n-3 fatty acids in adipose tissue in adults from Crete. *Eur. J. Clin. Nutr.* 60(7):882–888
- Mancuso M, Coppede F, Migliore L, Siciliano G, Murri L (2006) Mitochondrial dysfunction, oxidative stress and neurodegeneration. *J. Alzheimer's Dis.* 10(1):59–73 Review
- Marcus SM, Young EA, Kerber KB, Kornstein S, Farabaugh AH, Mitchell J, Wisniewski SR, Balasubramani GK, Trivedi MH, Rush AJ (2005) Gender differences in depression: findings from the STAR*D study. *J. Affect. Disord.* 87(2–3):141–150
- Miller CL, Llenos IC, Dulay JR, Weis S (2006) Upregulation of the initiating step of the kynurenine pathway in postmortem anterior cingulate cortex from individuals with schizophrenia and bipolar disorder. *Brain Res.* 1073–1074:25–37
- Mohr DC, Goodkin DE, Islar J, Hauser SL, Genain CP (2001) Treatment of depression is associated with suppression of nonspecific and antigen-specific T(H)1 responses in multiple sclerosis. *Arch. Neurol.* 58(7):1081–1086
- Moncada S, Bolanos JP (2006) Nitric oxide, cell bioenergetics and neurodegeneration. *J. Neurochem.* 97(6):1676–1689 Review
- Monje ML, Toda H, Palmer TD (2003) Inflammatory blockade restores adult hippocampal neurogenesis. *Science* 302:1760–1765
- Monteggia LM, Luikart B, Barrot M, Theobald D, Malkovska I, Nef S, Parada LF, Nestler EJ (2007) Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors. *Biol. Psychiatr.* 61(2):187–197
- Muller N, Schwarz MJ, Dehning S, Douhe A, Cerovecky A, Goldstein-Muller B, Spellmann I, Hetzel G, Maino K, Kleindienst N, Moller HJ, Arolt V, Riedel M (2006) The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Mol. Psychiatr.* 11(7):680–684
- Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, Greiner K, Nemeroff CB, Miller AH (2001) Paroxetine for the prevention of depression induced by high-dose interferon alpha. *New Engl. J. Med.* 344(13):961–966
- Myint AM, Kim YK, Verkerk R, Park SH, Scharpe S, Steinbusch HW, Leonard BE (2007) Tryptophan breakdown pathway in bipolar mania. *J. Affect. Disord.* 102(1–3):65–72
- Ngai LY, Herbert J (2005) Glucocorticoid enhances the neurotoxic actions of quinolinic acid in the striatum in a cell-specific manner. *J. Neuroendocrinol.* 17(7):424–434
- Nguyen KT, Deak T, Owens SM, Kohno T, Fleshner M, Watkins LR, Maier SF (1998) Exposure to acute stress induces brain interleukin-1beta protein in the rat. *J. Neurosci.* 18:2239–2246
- Noraberg J, Poulsen FR, Blaabjerg M, Kristensen BW, Bonde C, Montero M, Meyer M, Gramsbergen JB, Zimmer J (2005) Organotypic hippocampal slice cultures for studies of brain damage, neuroprotection and neurorepair. *Curr. Drug Targets. CNS Neurol. Disord.* 4(4):435–452 Review
- Noraberg J, Jensen CV, Bonde C, Montero M, Nielsen JV, Jensen NA, Zimmer J (2007) Developmental expression of fluorescent proteins in organotypic hippocampal slice cultures from transgenic mice with example of excitotoxic neurodegeneration. *ATLA.* 35(1):61–70 Review

- O'Brien SM, Scully P, Fitzgerald P, Scott LV, Dinan TG (2007) Plasma cytokine profiles in depressed patients who fail to respond to selective serotonin reuptake inhibitor therapy. *J. Psychiatr. Res.* 41(3–4):326–331
- O'Connor JC, Lawson MA, André C, Moreau M, Lestage J, Castanon N, Kelley KW, Dantzer R (2008) Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Mol. Psychiatry*. [Epub ahead of print]
- Overstreet DH, Friedman E, Mathé AA, Yadir G (2005) The Flinders Sensitive Line rat: a selectively bred putative animal model of depression. *Neurosci. Biobeh. Rev.* 29(4–5):739–759
- Pariante CM, Miller AH (2001) Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biol. Psychiatr.* 49(5):391–404
- Patel HC, Ross FM, Heenan LE, Davies RE, Rothwell NJ, Allan SM (2006) Neurodegenerative actions of interleukin-1 in the rat brain are mediated through increases in seizure activity. *J. Neurosci. Res.* 83(3):385–391
- Peet M, Murphy B, Shay J, Horrobin D (1998) Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. *Biol. Psychiatr.* 43(5):315–319
- Pemberton LA, Kerr SJ, Smythe G, Brew BJ (1997) Quinolinic acid production by macrophages stimulated with IFN γ , TNF-alpha, and IFN α . *J. Interf. Cytokine Res.* 17(10):589–595
- Periyasamy S, Sanchez ER (2002) Antagonism of glucocorticoid receptor transactivity and cell growth inhibition by transforming growth factor-beta through AP-1-mediated transcriptional repression. *Int. J. Biochem. Cell Biol.* 34(12):1571–1585
- Pettit JW, Lewinsohn PM, Joiner TE Jr (2006) Propagation of major depressive disorder: relationship between first episode symptoms and recurrence. *Psychiatr. Res.* 141(3):271–278
- Pláteník J, Stopka P, Vejrazka M, Stípek S (2001) Quinolinic acid-iron(II) complexes: slow autoxidation, but enhanced hydroxyl radical production in the Fenton reaction. *Free Radical Res.* 34(5):445–459
- Polleux F, Ghosh A (2002) The slice overlay assay: a versatile tool to study the influence of extracellular signals on neuronal development. *Science STKE* 136(19):1–11
- Pong K (2003) Oxidative stress in neurodegenerative diseases: therapeutic implications for superoxide dismutase mimetics. *Exp. Opin. Biol. Therap.* 3(1):127–139 Review
- Post RM (1992) Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am. J. Psychiatry* 149(8):999–1010
- Post RM (2007) Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. *Neurosci. Biobehav. Rev.* 31(6):858–873
- Potashkin JA, Meredith GE (2006) The role of oxidative stress in the dysregulation of gene expression and protein metabolism in neurodegenerative disease. *Antioxidant Redox Sign.* 8(1–2):144–151 Review
- Qian L, Hong JS, Flood PM (2006) Role of microglia in inflammation-mediated degeneration of dopaminergic neurons: neuroprotective effect of interleukin 10. *J. Neural Transm. Suppl.* 70:367–371
- Qin L, Wu X, Block ML, Liu Y, Breese GR, Hong JS, Knapp DJ, Crews FT (2007) Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *Glia* 55(5):453–462
- Rao JS, Lee HJ, Rapoport SI, Bazinet RP (2008) Mode of action of mood stabilizers: is the arachidonic acid cascade a common target? *Mol. Psychiatr.* 13(6):585–596
- Rios C, Santamaria A (1991) Quinolinic acid is a potent lipid peroxidant in rat brain homogenates. *Neurochem. Res.* 16(10):1139–1143
- Sakic B, Szechtman H, Braciak T, Richards C, Gaudie J, Denburg JA (1997) Reduced preference for sucrose in autoimmune mice: a possible role of interleukin-6. *Brain Res. Bull.* 44(2):155–165
- Sakic B, Gaudie J, Denburg JA, Szechtman H (2001) Behavioral effects of infection with IL-6 adenovector. *Brain Beh Immun.* 15(1):25–42
- Sandi C (2004) Stress, cognitive impairment and cell adhesion molecules. *Nature Reviews Neuroscience* 5:917–930
- Sandi C, Bisaz R (2007) A model for the involvement of neural cell adhesion molecules in stress-related mood disorders. *Neuroendocrinol.* 85(3):158–176
- Sapolsky RM (2004) Is impaired neurogenesis relevant to the affective symptoms of depression? *Biol. Psychiatry* 56(3):137–139
- Sarandol A, Sarandol E, Eker SS, Erdinc S, Vatansever E, Kirli S (2007) Major depressive disorder is accompanied with oxidative stress: short-term antidepressant treatment does not alter oxidative-antioxidative systems. *Hum. Psychopharmacol.* 22(2):67–73
- Schiepers OJ, Wichers MC, Maes M (2005) Cytokines and major depression. *Prog Neuropsychopharmacol. Biol. Psychiatr.* 29(2):201–217
- Schmidt HD, Duman RS (2007) The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. *Beh. Pharmacol.* 18(5–6):391–418

- Schulte-Herbruggen O, Nassenstein C, Lommatzsch M, Quarcoo D, Renz H, Braun A (2005) Tumor necrosis factor- α and interleukin-6 regulate secretion of brain-derived neurotrophic factor in human monocytes. *J. Neuroimmunol.* 160(1–2):204–209
- Schwarzc R, Köhler C (1983) Differential vulnerability of central neurons of the rat to quinolinic acid. *Neurosci. Lett.* 38(1):85–90
- Shapira-Lichter I, Beilin B, Ofek K, Bessler H, Gruberger M, Shavit Y, Seror D, Grinevich G, Posner E, Reichenberg A, Soreq H, Yirmiya R (2008) Cytokines and cholinergic signals co-modulate surgical stress-induced changes in mood and memory. *Brain Beh. Immun.* 22:388–398
- Smith MA, Makino S, Kvetnansky R, Post RM (1995) Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. *J. Neurosci.* 15:1768–1777
- Sobocki P, Jonsson B, Angst J, Rehnberg C (2006) Cost of depression in Europe. *J. Ment. Health Policy Econ.* 9(2):87–98
- Sobczak S, Honig A, Christophe A, Maes M, Helsdingen RW, De Vriese SA, Riedel WJ (2004) Lower high-density lipoprotein cholesterol and increased omega-6 polyunsaturated fatty acids in first-degree relatives of bipolar patients. *Psychol. Med* 34(1):103–112
- Song C, Leonard BE (1995) Interleukin-2-induced changes in behavioural, neurotransmitter, and immunological parameters in the olfactory bulbectomized rat. *Neuroimmunomodulation.* 2(5):263–273
- Song C, Leonard BE, Horrobin DF (2004) Dietary ethyl-eicosapentaenoic acid but not soybean oil reverses central interleukin-1-induced changes in behavior, corticosterone and immune response in rats. *Stress* 7(1):43–54
- Song C, Li X, Kang Z, Kadotomi Y (2007) Omega-3 fatty acid ethyl-eicosapentaenoate attenuates IL-1 β -induced changes in dopamine and metabolites in the shell of the nucleus accumbens: involved with PLA2 activity and corticosterone secretion. *Neuropsychopharmacol.* 32(3):736–744
- Stephoe A, Hamer M, Chida Y (2007) The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain Beh. Immun.* 21:901–912
- Stockmeier CA, Mahajan GJ, Konick LC, Overholser JC, Jurjus GJ, Meltzer HY, Uylings HB, Friedman L, Rajkowska G (2004) Cellular changes in the postmortem hippocampus in major depression. *Biol. Psychiatr.* 56(9):640–650
- Stone TW, Behan WM (2007) Interleukin-1 β but not tumor necrosis factor- α potentiates neuronal damage by quinolinic acid: protection by an adenosine A2A receptor antagonist. *J. Neurosci. Res.* 85(5):1077–1085
- Stork O, Welzl H, Wotjak CT, Hoyer D, Dellinger M, Cremer H, Schachner M (1999) Anxiety and increased 5-HT1A receptor response in NCAM null mutant mice. *J. Neurobiol.* 40:343–355
- Turner CA, Akil H, Watson SJ, Evans SJ (2006) The fibroblast growth factor system and mood disorders. *Biol. Psychiatr.* 59(12):1128–1135
- Ueda S, Sakakibara S, Yoshimoto K (2005) Effect of long-lasting serotonin depletion on environmental enrichment-induced neurogenesis in adult rat hippocampus and spatial learning. *Neurosci.* 135:395–402
- Vaidya VA, Duman RS (2001) Depression-emerging insights from neurobiology. *Brit. Med. Bull.* 57:61–79
- van Praag H, Kempermann G, Gage FH (1999) Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nature Neurosci.* 2(3):266–270
- Viviani B, Gardoni F, Bartesaghi S, Corsini E, Facchi A, Galli CL, Di Luca M, Marinovich M (2006) Interleukin-1 β released by gp120 drives neural death through tyrosine phosphorylation and trafficking of NMDA receptors. *J. Biol. Chem.* 281(40):30212–30222
- Wadee AA, Kuschke RH, Wood LA, Berk M, Ichim L, Maes M (2002) Serological observations in patients suffering from acute manic episodes. *Human Psychopharmacol.* 17(4):175–179
- Walz JC, Frey BN, Andreazza AC, Cereser KM, Cacilhas AA, Valvassori SS, Quevedo J, Kapczinski F (2007) Effects of lithium and valproate on serum and hippocampal neurotrophin-3 levels in an animal model of mania. *J. Psychiatr. Res.* 42(5):416–421
- Wang JY, Wen LL, Huang YN, Chen YT, Ku MC (2006) Dual effects of antioxidants in neurodegeneration: direct neuroprotection against oxidative stress and indirect protection via suppression of glia-mediated inflammation. *Curr. Pharm. Design* 12(27):3521–3533 Review
- Wichers MC, Maes M (2004) The role of indoleamine 2, 3-dioxygenase (IDO) in the pathophysiology of interferon- α -induced depression. *J. Psychiatr. Neurosci.* 29(1):11–17

- Wichers MC, Koek GH, Robaey G, Verkerk R, Scharpe S, Maes M (2005) IDO and interferon-alpha-induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity. *Mol. Psychiatr.* 10(6):538–544
- Wichers MC, Kenis G, Koek GH, Robaey G, Nicolson NA, Maes M (2007) Interferon-alpha-induced depressive symptoms are related to changes in the cytokine network but not to cortisol. *J. Psychosom. Res.* 62(2):207–214
- Wu A, Ying Z, Gomez-Pinilla F (2004) Dietary omega-3 fatty acids normalize BDNF levels, reduce oxidative damage, and counteract learning disability after traumatic brain injury in rats. *J. Neurotrauma.* 21:1457–1467
- Xia Z, DePierre JW, Nassberger L (1996) Tricyclic antidepressants inhibit IL-6, IL-1 beta and TNF-alpha release in human blood monocytes and IL-2 and interferon-gamma in T cells. *Immunopharmacol.* 34(1):27–37
- Xu Y, Ku B, Cui L, Li X, Barish PA, Foster TC, Ogle WO (2007) Curcumin reverses impaired hippocampal neurogenesis and increases serotonin receptor 1A mRNA and brain-derived neurotrophic factor expression in chronically stressed rats. *Brain Res.* 1162:9–18
- Yang R, Han X, Uchiyama T, Watkins SK, Yaguchi A, Delude RL, Fink MP (2003) IL-6 is essential for development of gut barrier dysfunction after hemorrhagic shock and resuscitation in mice. *Am. J. Physiol. Gastrointestinal Liver Physiol.* 285(3):G621–629
- Yirmiya R (1996) Endotoxin produces a depressive-like episode in rats. *Brain Res.* 711(1–2):163–74
- Yirmiya R (1997) Behavioral and psychological effects of immune activation: implications for 'depression due to a general medical condition'. *Curr. Opin. Psychiatr.* 10:470–476
- Yirmiya R, Weidenfeld J, Pollak Y, Morag M, Morag A, Avitsur R, Barak O, Reichenberg A, Cohen E, Shavit Y, Ovadia H (1999) Cytokines, "depression due to a general medical condition," and antidepressant drugs. *Adv. Exp. Med. Biol.* 461:283–316
- Yirmiya R, Pollak Y, Barak O, Avitsur R, Ovadia H, Bette M, Weihe E, Weidenfeld J (2001) Effects of antidepressant drugs on the behavioral and physiological responses to lipopolysaccharide (LPS) in rodents. *Neuropsychopharmacol.* 24(5):531–544
- Zhu SW, Pham TM, Aberg E, Brene S, Winblad B, Mohammed AH, Baumans V (2006) Neurotrophin levels and behaviour in BALB/c mice: impact of intermittent exposure to individual housing and wheel running. *Beh. Brain Res.* 167(1):1–8
- Zou JY, Crews FT (2005) TNF alpha potentiates glutamate neurotoxicity by inhibiting glutamate uptake in organotypic brain slice cultures: neuroprotection by NF kappa B inhibition. *Brain Res.* 1034(1–2):11–24