Review

Oxidative & nitrosative stress in depression: Why so much stress?

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Abstract

Many studies support a crucial role for oxidative & nitrosative stress (O&NS) in the pathophysiology of unipolar and bipolar depression. These disorders are characterized inter alia by lowered antioxidant defenses, including: lower levels of zinc, coenzyme Q10, vitamin E and glutathione; increased lipid peroxidation; damage to proteins, DNA and mitochondria; secondary autoimmune responses directed against redox modified nitrosylated proteins and oxidative specific epitopes. This review examines and details a model through which a complex series of environmental factors and biological pathways contribute to increased redox signaling and consequently increased O&NS in mood disorders. This multi-step process highlights the potential for future interventions that encompass a diverse range of environmental and molecular targets in the treatment of depression.

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Abbreviations: 5-HT, 5-hydroxytryptophan; 5-HTTLPR, serotonin transporter linked polymorphic region; 8-iso, 8-iso-prostaglandin F2; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; ATP, adenosine triphosphate; BH4, 5,6,7,8-tetrahydrobiopterin; CMI, cell mediated immunity; CRH, corticotropin releasing hormone; DAMP, damage-associated molecular pattern; DNA, deoxyribonucleic acid; GPX, glutathione peroxidase; GSH, glutathione; HDL, high density lipoprotein; HPA, hypothalamic–pituitary–adrenal axis; IDO, indoleamine 2,3-dioxygenase; IFNα, interferon-alpha; IFNβ, interferon-beta; IL-1, interleukin-1; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; KYNA, kynurenic acid; LDL, low-density lipoprotein; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinases; MDA, malondialdehyde; NAC, N-acetylcysteine; NDMA, N,N-dimethyl-2-aminopyridine; NF-kB, nuclear factor (NF)-κB; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOX, nitric oxide synthase; NOS, nitric oxide synthase; ONOO−, peroxynitrite; OSA, obstructive sleep apnoea; OSE, oxidation specific epitope; Ox-LDL, oxidized low density lipoprotein; Ox-PgL, oxidized phospholipids; PAMP, pathogen-associated molecular pattern; PIC, pro-inflammatory cytokine; PON1, paraoxonase 1; PRR, pattern recognition receptor; QUIN, quinolinic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, Superoxide dismutase; SSRI, selective serotonin reuptake inhibitor; TCA, tryptophan anti-depressant; TRK, Toll-like receptor; TNF-α, tumor necrosis factor-α; TRYCAT, tryptophan catabolite.

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1. Introduction

Many studies support dysregulated redox signaling as being crucial in the pathophysiology and neuroprogressive nature of major depression (Maes et al., 2011a). Reactive oxygen and nitrogen species (ROS and RNS), including peroxynitrite, superoxides, peroxides and nitric oxide (NO), are produced during normal physiological processes and, through interacting with proteins, fatty acids and DNA, perform numerous roles in regulation of cellular function. When present in excess however, ROS/RNS can lead to structural and functional changes that produce cellular injury. These potentially toxic effects are offset under normal conditions by intrinsic antioxidant mechanisms that participate in the physiologic and/or pathologic metabolism of ROS/RNS (Maes et al., 2011a). Increased oxidative and nitrosative stress (O&NS), which can arise as a consequence of raised production of ROS and RNS and/or decreased availability of antioxidant defenses, may cause damage to cellular components, induce harmful autoimmune responses, and ultimately facilitate failure of normal cellular processes.

People with unipolar and bipolar depression display dysregulated redox signaling (Lee et al., 2013; Maes et al., 2011a; Moylan et al., 2013c; Scaglioni et al., 2012). Studies using clinical and animal models have demonstrated that depression is associated with increased levels of redox products such as malondialdehyde (MDA, a marker for lipid peroxidation) and 8-iso-prostaglandin F2 (8-iso) (a marker of arachidonic acid peroxidation) (Dimopoulos et al., 2008; Forlenza and Miller, 2006; Galecki et al., 2009; Yager et al., 2010). Additionally, other studies have reported oxidative damage to DNA, as measured by increased levels of 8-hydroxy-2-deoxyguanosine (8-OHdG) in serum (Forlenza and Miller, 2006) oxidative damage to RNA in post-mortem hippocampus in depression (Che et al., 2010) and telomere shortening (Shalev et al., 2014).

Studies conducted in depressed populations demonstrate sustained increases in O&NS. These effects result in depleted levels of n-3 fatty acid concentrations (Peet et al., 1998), a lowered oxidative potential index of serum (Maes et al., 1999), reduced functioning of antioxidant systems represented by lower levels of plasma concentrations of vitamin E (Maes et al., 2000; Owen et al., 2003) and C (Khanzode et al., 2003), decreased albumin levels (Van Hunsel et al., 1996), lowered levels of antioxidants including zinc, glutathione (GSH) and coenzyme Q10 (Maes et al., 2000), and lower levels of amino acids, such as tryptophan and tyrosine (Maes et al., 2000). Similarly, alterations of antioxidant-enzyme levels have been reported. For example, levels of superoxide dismutase (SOD) and glutathione peroxidase (Gpx) are lower in depressed patients (Maes et al., 2011a). Paraoxonase 1 (PON1), an antioxidant enzyme bound to high-density lipoprotein (HDL), was significantly reduced in unipolar, but not bipolar, depression (Vargas et al., submitted for publication). Impairment of these aforementioned antioxidant systems contributes to the pathophysiology of depression via lowered protection to ROS and RNS, which may result in increased risk of sustained O&NS damage (Forlenza and Miller, 2006; Maes et al., 2011a).

NO is an important mediator in many neural processes. Rodents subjected to acute and chronic immobilization stress exhibit increased levels of inducible nitric oxide synthase (iNOS). Although NO levels, iNOS and neuronal NOS (nNOS) expression are increased in depression, recent studies have indicated that NOS participates in the mechanisms underlying antidepressant efficacy (Galecki et al., 2012; Maes et al., 2008b). This suggests that NO may have differential effects at different sites during the course and treatment of depression. Persistently increased levels of NO and O2·− may lead to the formation of peroxynitrite (ONOO−) and subsequent oxidation, nitration and nitrosylation of proteins, thereby contributing to cellular injury (Maes et al., 2008b, 2011d).

Major depression and bipolar depression are also accompanied by increased autoimmune responses against newly formed oxidation specific epitopes (OSEs), following structural damage by O&NS (Maes et al., 2007, 2011d, 2013b). Immunoglobulin (IgG and IgM-mediated immune responses against OSEs of membrane fatty acids, like oxidized low density lipoprotein (LDL), oleic acid, MDA and azelaic acid, and anchorage molecules, such as phosphatidyl inositol, palmitic acid, myristic acid and farnesyl-L-cysteine, can be seen in depression (Maes et al., 2007, 2011d, 2013b). This may have profound functional consequences as oxidative damage to membranes, especially to the major anchorage molecules, may affect the operation of hundreds of functionally "anchored" proteins that regulate basic cellular processes, including cell survival, growth, apoptosis, cell-signaling, neuroplasticity and neurotransmission (Maes et al., 2011a).

Chronically increased NO, following iNOS activation, can nitrosylate (NSO or NO) proteins and amino acids yielding new NO-adducts (NO-neoepitopes) like NO-tyrosine, NO-tryptophan, NO-arginine, NSO-cysteine and NO-albumin. The consequent hyper-nitrosylation may cause dysfunction to intracellular signaling, as well as competitively inhibit the palmitoylation of anchored proteins to the membrane (Maes et al., 2008b, 2011d, 2012a). Moreover, some of these NO adducts can be immunogenic and therefore contribute to further autoimmune responses directed...
against “nitrosative specific epitopes” (NSEs) (Boullére et al., 2002; Maes et al., 2011d, 2012a). Finally, the autoimmune response directed against some of these NSEs (e.g. NSO-cysteine) may result in serious neurotoxic effects (Boullére et al., 2002).

Animal studies have demonstrated that various classes of antidepressants can reduce levels of oxidative stress markers (Eren et al., 2007a,b; Maes et al., 2011a) and increase some endogenous antioxidants (Maes et al., 2011d). Further, some redox modulators appear to have some promise as adjunctive treatments for depression (Maes et al., 2012a; Scapagnini et al., 2012).

The above observations provide greater insight into the pathology of depression, but also raise a pertinent question: what are the underlying pathways and factors that contribute to the onset and maintenance of the increased O&NS state in depression? Greater understanding of the pathways and factors that precipitate a state of subchronic O&NS in depression may inform new therapeutic and preventative strategies. Here, we review numerous pathways and factors that may contribute to increased O&NS in major depression, and discuss the potential implications of these findings.

2. Depression-related pathways causing O&NS

2.1. Activated immune-inflammatory pathways

Considerable evidence supports the role of central and peripheral immune-inflammatory processes in depression pathogenesis. Depression is associated with cell-mediated immune (CMI) activation, increased mononuclear activation and T helper (Th)-1 and Th-17-like cytokine response (Leonard and Maes, 2012). In addition, recent meta-analyses demonstrate that patients with depression have higher serum levels of pro-inflammatory cytokines (PICs) such interleukin (IL)-1, IL-6 and tumor necrosis factor alpha (TNFα) (Dowlati et al., 2010; Howren et al., 2009). Depression is also associated with increased levels of acute phase proteins, including C-reactive protein and haptoglobin, chemokines, adhesion molecules and complement factors (Berk et al., 1997; Maes et al., 1997a; Pasco et al., 2010). An even stronger association between pro-inflammatory cytokines and LPS and depressive-like behaviors has been reported in rodent studies where administration of IL-6, IL-1β, TNFα or LPS resulted in depressive-like and anxiety-like behaviors. Similar manifestations of depressive symptoms are also seen in patients undergoing immunotherapy with IL-2 and INF-α (Dutcher et al., 2000).

The reader is referred to three recent reviews demonstrating that in depression and bipolar disorder peripheral activation of immune-inflammatory pathways coupled with elevated levels of circulating LPS may contribute to neuroinflammation and consequent neuroprogressive changes including decreased neuroplasticity, neurogenesis, and increased neurodegeneration and neuronal apoptosis (Berk et al., 2011b; Leonard and Maes, 2012; Moylan et al., 2013c). In addition, immune-inflammatory pathways affect the expression of key neurotransmitters thought involved in depression pathogenesis (e.g. serotonin, noradrenaline) through multiple pathways. One example is through effects on 5,6,7,8-tetrahydrobiopterin (BH₄), (BH₄) is a critical co-factor of numerous amino acid converting enzymes responsible for the production of neurotransmitters including NO, tryptophan, dopamine and noradrenaline (Sperner-Unterweger et al., 2014). Under acute inflammatory conditions these BH₄ related enzymes are upregulated, leading to increased biosynthesis of neurotransmitters in the short term. However, chronic low-grade inflammation is associated with “oxidative loss of BH₄”, reducing capacity for neurotransmitter biosynthesis (Sperner-Unterweger et al., 2014).

Studies assessing the effect of antidepressants on immune-inflammatory markers in depression provide further corroboration for the role of immune-inflammatory processes in depression. Administration of tricyclic antidepressants (TCAs) and selective serotonin inhibitors (SSRIs) has been shown to suppress CMI, whilst attenuating inflammatory biomarkers and acute phase protein levels in animal models (Leonard and Maes, 2012). Not surprisingly, the relationship between the immune-inflammatory response and depression may be driven, or modulated, by underlying genetic vulnerability. A recent review of genetic variants in neurobiological pathways associated with immune activation and depression demonstrates that allelic variants of IL-1β, TNFα and CRP may increase depression risk. SNPs in the IL-1β, IL-6 and IL-11 genes may also be associated with reduced responsiveness to antidepressants (Bufalino et al., 2013).

Mutual inductions between immune-inflammatory and O&NS pathways may be key in depression pathogenesis (Maes et al., 2011a, 2012a). Activation of immune-inflammatory pathways, O&NS processes and lowered antioxidant defenses are inseparably interrelated (Maes et al., 2012a). Activated phagocytes and M1 macrophages produce large quantities of ROS and RNS. Increased levels of TNFα can upregulate the expression of iNOS via translocation of nuclear factor kappa B (NF-κB), while interferon-gamma (IFNγ) may activate the production of iNOS and thus NO by macrophages. In different cell types, such as macrophages, neutrophils, epithelial cells and microglia, cytokines such as IL-1, TNFα and IFNγ activate ROS production (superoxide) via the NADPH oxidase complex (NOX). Neopterin, a surrogate marker of the Th-1-like response, activates iNOS and NO production and the production of hydrogen peroxide. On the other hand, activated O&NS pathways may increase nuclear factor (NF)-κB, activator protein-1 and mitogen-activated protein kinases (MAPK) thereby increasing the production of inflammatory mediators, such as PICs and chemokines.

Inflammatory and O&NS processes may also affect antioxidant defenses. For example, the inflammatory processes in depression are associated with lowered levels of zinc and vitamin E (Maes et al., 2011e). ROS produced in physiological conditions and during inflammation upregulate antioxidant defense systems. In response to O&NS, cells increase their antioxidant defenses through activation of nuclear factor erythroid 2-related factor (Nrf2) (Maes et al., 2012a). Once activated, Nrf2 increases the expression of multiple endogenous antioxidants. On the other hand, severe inflammation accompanied by increased ROS, as observed in inflammatory bowel disease, causes an increased consumption of tissue antioxidant defenses masking increased antioxidant levels due to the mild O&NS (Blau et al., 2000).

Since antioxidants, such as coenzyme Q10, zinc and glutathione, have anti-inflammatory effects, the lowered levels of those antioxidants in depression increase the inflammatory and O&NS burden (Maes et al.). Moreover, reduced glutathione (GSH) and the regulation of pro-inflammatory cytokines are intimately interlinked. For example, the transcription of IL-1β, IL-6, and TNFα are regulated by the redox state of the cell and depletion of GSH enhances the transcription of these cytokines (Haddad, 2000).

Fig. 1 shows the associations between activated immune-inflammatory pathways, lowered antioxidant defenses and increased damage by O&NS in depression. Factors that are known to activate immune-inflammatory pathways (review: (Berk et al., 2013)) may therefore lead to downstream activation of ROS/RNS production and O&NS. It may be concluded that in depression, lowered levels of antioxidants and activation of immune-inflammatory and O&NS pathways are complex processes that exacerbate each other via multiple feedback loops. Interactions of these seemingly enmeshed pathways further contribute to the complexity of depression pathogenesis.
LPS, because it also detects bacterial LPS when bacteria have not spread into the blood circulation but when the bacteria are translocated into the MLNs (Maes et al., 2013a). The finding that clinical depression is associated with increased IgM/IgA responses to LPS therefore indicates that immune cells are activated by LPS from gram-negative bacteria, which is translocated into the MLNs, the blood stream, or both. Because if their particular role in mucosal defence, Th17 cells, a subset of T helper cells have a particular role against gut infections and are associated with atopic, inflammatory, and autoimmune disorders. Th17 cells may disrupt the blood–brain barrier leading to infiltration of the central nervous system, and drive neuroprogression (Debnath and Berk, 2014).

Through binding with the Toll-like receptor (TLR)2 and TLR4 complexes, LPS activates different intracellular signaling molecules, including NF-κB and MAPK, thereby increasing expression of PIC and O&NS genes (Tsukamoto et al., 2010; Wiest and Garcia-Tsao, 2005). For example, NF-κB induces the production of IL-1, IL-6, TNFα and iNOS (Brazier, 2006). LPS additionally activates NOX, which in turn increases production of iNOS, NO, superoxide and peroxides (Chan and Riches, 2001; Check et al., 2010; Peng et al., 2005). Previously, it has been shown that increased gut permeability is accompanied by elevated plasma LPS and signs of inflammation and O&NS, with these processes being attenuated or reversed upon successful treatment of the leaky gut (Quan et al., 2004; Zhou et al., 2003). This is relevant to depression, as LPS administration increases nitrite, nitrate and MDA levels whilst decreasing brain GSH levels (Tyagi et al., 2010). LPS also reduces the levels of CC16 or uteroglobin, an endogenous anti-inflammatory substance, thereby increasing inflammatory potential (Fransson et al., 2007). CC16 is significantly lowered in depressed subjects; in part explaining the immune-inflammatory responses in that illness (Rief et al., 2001).

In patients with depression there are significant and positive correlations between bacterial translocation (increased IgA and IgM responses to LPS) and signs of increased O&NS (Maes et al., 2012b) including increased plasma oxidized LDL antibodies, IgM responses to NSEs, such as NO-tryptophan and NO-tyrosine, as well as IgM responses directed against OSEs, including azelaic acid, MDA and phosphatidyl inositol (Maes et al., 2012b). These findings indicate that increased bacterial translocation in depression drives chronically activated O&NS pathways (damage to fatty acids and proteins) and autoimmune responses directed against OSEs and NSEs (Maes et al., 2012b). Gut bacteria produce a plethora of compounds that influence redox signaling, with different populations producing different compounds. One example is molecular hydrogen which has wide-ranging biological effects, including anti-oxidative, anti-apoptotic and anti-inflammatory properties (Ghanizadeh and Berk, 2013).

Recently a review of the bidirectional connections between the gut and the brain summarized the evidence that gastrointestinal homeostasis may modulate emotion, affect, neurocognitive functions and motivation (Mayer, 2011). Most importantly, animals exposed to repeated restraint and acoustic stressors demonstrated increased gut permeability, TLR4 activation and neuroinflammation (Garate et al., 2013). Moreover, attenuation of bacterial translocation through antibiotic induced intestinal decontamination reduces stress-induced neuroinflammation, suggesting that stress-induced neuroinflammation is at least partially caused by increased bacterial translocation. For these reasons, increased bacterial translocation may be a promising drug target in stress-related disorders, such as depression (Garate et al., 2013).

2.2. Leaking gut and the microbiome

Clinically depressed patients display higher IgM and IgA responses to lipopolysaccharides (LPS) from gram-negative bacteria, potentially as consequence of bacterial translocation secondary to increased gut permeability (Maes et al., 2008a, 2012b). Gram-negative bacteria including Hafnia alvei, Pseudomonas aeruginosa, Morganella morgani, Proteus mirabilis, Pseudomonas putida, Citrobacter koseri and Klebsiella pneumoniae belong to the normal gut flora and are termed commensal gut bacteria (Yoder, 2006; Wiest, 2005). Under normal conditions the immune system is functionally and geographically separated from these poorly invasive commensal gut bacteria by an intact gut tight junction barrier (Berg and Garlington, 1979; Wiest and Garcia-Tsao, 2005). Due to this, immune cells are not normally primed against commensal gut bacteria. However, when the gut wall is weakened by increased gut permeability, gram-negative bacteria can exploit the loosened gut barrier, thereby translocating from the gut into the mesenteric lymph nodes (MLNs) or the blood stream (Berg and Garlington, 1979; Chavez et al., 1999; Clark et al., 2005; Wiest and Garcia-Tsao, 2005; Yang et al., 2003). Once bacteria are translocated, immunocytes can mount an IgA or IgM-mediated immune response directed against the LPS of gut commensal bacteria. Measuring IgA and IgM responses against LPS of commensal bacteria is a more sensitive method to detect bacterial translocation than the assay of serum

2.3. Activation of the Toll-like receptor radical cycle

Pattern recognition receptors (PRRs), which include TLR2 and TLR4, are an important part of the host defense system (Lucas
and Maes, 2013). PRRs recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which consequently activate MAPK and/or NF-κB leading to activation of immune-inflammatory and O&NS pathways. The TLRs recognize mycoplasma, fungus, viruses and LPS, a typical PAMP derived from gram-negative bacteria. Since depression is accompanied by increased IgM/IgA-mediated immune responses directed against LPS of gut commensals, it may be concluded that the TLR2/TLR4 complexes are activated by PAMP-mediated processes. Typically DAMPs, including β-defensins, high mobility group protein 1 (HMGB1), heat shock proteins (HSPs), extracellular matrix (ECM), cathelicidin (LL37), hyaluronic acid, heparin sulfate, substance P and redox-derived DAMPs, appear following injury and inflammation (Carta et al., 2009; Kaczmarek et al., 2013; Lotze et al., 2007; Rubartelli and Lotze, 2007; Uchida, 2013). Redox-derived DAMPs are produced during lipid peroxidation and consist of oxidatively modified molecules, such as oxidized phospholipids (Ox-PLP), oxidized LDL (Ox-LDL), 4-HNE and MDA modified proteins (Carta et al., 2009; Uchida, 2013). As reviewed in Section 1, depression is accompanied by increased levels of some redox-derived DAMPs, including oxidized LDL, oxidized phospholipids and MDA-derived adducts (Maes et al., 2011a). These molecules can activate the TLR2/TLR4 complex and play a role in the downstream activation of immune-inflammatory and O&NS pathways (Lucas and Maes, 2013). As a consequence, depression may be accompanied by a vicious cycle between TLR2/TLR4 activation and ROS production causing increased levels of redox-derived DAMPs, which further stimulate the TLRs.

Exposure to TLR agonists has been shown to sensitize and prime the TLR response to subsequent stimulation by other agonists. Psychosocial stressors may additionally upregulate TLR4 expression or activation (Lucas and Maes, 2013). Thus, in depression different TLR2/TLR4 agonists, including bacterial LPS and redox-derived DAMPs, and psychosocial stressors may cause hypersensitivity of the TLR complexes, thereby activating downstream immune-inflammatory and O&NS pathways.

2.4. The tryptophan catabolite (TRYCAT) pathway

Interactions between inflammation, O&NS, lowered antioxidant levels and bacterial translocation may occur via changes in the tryptophan catabolite (TRYCAT) pathway. By diverting tryptophan metabolism away from serotonin, N-acetylserotonin and melatonin production, increased activation of indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) have long been identified as being associated with depression and associated conditions (Maes et al., 1993, 2011c). IDO, a heme-centered enzyme, is upregulated in pro-inflammatory states in particular by INFγ, but also IL-1, IL-6, IL-18, TNFα and LPS (Maes et al., 2011a). When IDO is in its ferrous form and in the presence of molecular oxygen, it acts to cleave tryptophan to N-formylkynurenine, initiating induction of further TRYCATs. Alternatively, when IDO is in its ferric form it utilizes O2− as a reducing agent to trigger the TRYCAT pathway. As such, the inflammatory state and redox status regulates how tryptophan is utilized, with significant consequences for processes classically associated with depression (Maes et al., 2011c; Werner and Werner-Felmayer, 2007). In addition, lowered tryptophan and increased levels of most TRYCATs have negative immunoregulatory effects that suppress primary immune-inflammatory responses (Maes et al., 2011c). Thus, induction of the TRYCAT pathway may have a protective function, but the longer-term consequence of activation can be crucial to alterations in neuronal activity and patterning in depression.

IDO is predominantly expressed in microglia within the CNS (Alberati-Giani and Cesura, 1998). Microglia are important regulators and coordinators of central changes in depression and depression-associated neurodegenerative disorders (Maes et al., 2011c). The activation of IDO leads to production of neuroregulatory TRYCATs including kynurenic acid (KYN) and quinolinic acid (QUIN). KYN is inhibitory at the α7 nicotinic receptor, whilst QUIN is excitotoxic at N-methyl d-aspartate (NMDA) receptors by increasing NO-mediated damage to neurons and astrocytes (Braidy et al., 2009).

Moreover, TRYCATs have anti-oxidant and pro-oxidant effects. For example, 3-hydroxykynurenine, 3-hydroxyanthranilic acid and xanthurenic acid perform antioxidant functions including scavenging free radicals, reducing lipid peroxidation, and preventing the spontaneous oxidation of glutathione and damage to 2-deoxy-d-ribose (Christen et al., 1990; Goda et al., 1999; Leipnitz et al., 2007). However, 3-hydroxykynurenine, 3-hydroxyanthranilic quinolinic acid also display pro-oxidant effects by generating ROS (e.g. superoxide and hydrogen peroxide) and causing lipid peroxidation and oxidative cell damage (Dyken et al., 1987; Goldstein et al., 2000; Guidetti and Schwarz, 1999; Murakami et al., 2006; Okuda et al., 1998; Rios and Santamaria, 1991; Santamaria et al., 2001; Smith et al., 2006).

Genetic variants of IDO genes may influence inflammatory status, thereby regulating the etiology, course and outcome of depression (Bufalino et al., 2013). Another important regulator of the TRYCAT pathways is TDO, which in the CNS is predominantly expressed in astrocytes, although also in some neurons (Funakoshi et al., 2011). The activation of TDO is primarily mediated by cortisol (Ren and Correia, 2000). Therefore, increased immune-inflammatory pathway activation and O&NS, through driving increases in hypothalamic parietal adrenal (HPA) axis activity commonly found in depression (Carroll, 1980), will also contribute to increased TDO, further depleting serotonin, N-acetylserotonin and melatonin, whilst changing neuroregulation by the induction of KYN, which is the TRYCAT predominantly produced following TDO induction. Overall, immune-inflammatory processes and O&NS, including via the regulation of IDO and TDO, are intimately linked to processes altered in depression.

2.5. The glutamate–cysteine cycle

Prolonged oxidative stress reduces the capacity of astrocytes to import glutamate facilitating an increase in extracellular glutamate levels (Dallas et al., 2007). Higher extrasynaptic and lower synaptic glutamate may play a role in depression (Sanacora et al., 2003), and depression is associated with glutamate supersensitivity (Berk et al., 2001). A genome-wide association study in depression demonstrated involvement of glutamatergic synaptic neurotransmission genes in depression (Lee et al., 2012). Oxidative-stress increased glutamate levels can inhibit cystine uptake by the xc-antipporter system thereby causing intracellular GSH depletion and consequently oxidative-stress-induced neurotoxicity through excitotoxic effects, a process called “oxidative glutamate toxicity” (Murphy et al., 1989; Schubert and Piasecki, 2001) that is at least in part mediated by increased calcium signaling.

2.6. Mitochondrial dysfunction

The mitochondrial electron transport chain (ETC) is responsible for cellular energy generation via adenosine-5-triphosphate (ATP) production (Adam-Vizi and Starkov, 2010). ATP is generated by transferring electrons through complexes I–V (Green and Kroemer, 2004; Lenaz, 2001). During this process electrons can escape, resulting in the reduction of molecular oxygen, which leads to the generation of the superoxide anion (O2−) (Green and
Kroemer, 2004). Mitochondria are therefore an endogenous physiological source of ROS.

As a consequence of high ROS production, mitochondria are heavily reliant on local antioxidants and antioxidant enzymes, including GSH, coenzyme Q10, zinc, SOD, selenium, vitamin C and vitamin E, to maintain their function. The coordination of mitochondrial oxidant induction with antioxidant response is crucial to normal cellular plasticity, with alterations in this balance contributing to the etiology and course of multiple disorders including depression (Gardner and Boles, 2011; Maes et al., 2011a).

Mitochondrial dysfunction in depression, including reduced activity of the ETC and its enzymes, decreased production of adenosine triphosphate (ATP), changes in mitochondrial structures in the brain (e.g. prefrontal and frontal cortex), mitochondrial DNA deletions and decreased expression of mitochondrial DNA-encoded transcripts, have recently been reviewed (Gardner and Boles, 2011; Maes et al., 2012a). Increased activity of immune-inflammatory pathways in depression, such as increased levels of IL-1β and TNFα, may cause lowered ATP production and concomitant disorders in the ETC and thus impaired oxidative phosphorylation (Maes et al., 2011a, 2012a). The depleted levels of the aforementioned important mitochondrial antioxidants in depression likely contribute to the impact of immune-inflammatory stressors on mitochondrial functions and structures. The consequent lipid peroxidation and increased MDA and 4-HNE production can cause mitochondrial membrane dysfunction, including increased membrane permeability; ultimately leading to mitochondrial dysfunction. Increased NO signaling additionally inhibits mitochondrial respiration and may generate peroxynitrite, which may further reduce ETC functioning, and damage mitochondrial DNA and functional proteins (Morris and Maes, 2013). These mitochondrial dysfunctions, in turn, may lead to an increased production of superoxide, which causes further damage to mitochondria and leads to lowered ATP production.

Some of the key processes altered by O&NS include damage to DNA, which results in an increase in poly(ADP-ribosyl) polymerase (PARP), which, in turn, depletes nicotinamide (NAD+), leading to decreased sirtuins. Both sirtuin-1 and sirtuin-3 are crucial regulators of mitochondrial function. Sirtuin-1 increases peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), the master mitochondria regulator, whilst sirtuin-3 is located at mitochondrial where it is crucial to optimal functioning (D’Aquila et al., 2012). As such increased O&NS, including when produced as a consequence of mitochondrial function, may in fact contribute to mitochondrial dysfunction via the consequences of DNA damage.

Another new putative pathway that plays a key role in mitochondria-related oxidative stress and mitochondria-mediated apoptosis is p66shc (Galimov et al., 2014). p66shc is an adaptor protein that activates the mitochondrial apoptosis pathway and may downregulate cellular antioxidant defenses (Galimov et al., 2014). Importantly, p66 gene deletion reduces emotionality and increases brain plasticity in association with increased brain derived neurotrophic factor (BDNF) levels, suggesting strong links between mitochondrial-generated oxidative stress, emotional behavior and central BDNF (Berry and Cirulli, 2013). Sirtuins and the p66shc gene have been under-investigated in the course of depression; topics requiring further attention given their potential importance in mitochondrial functioning.

These data suggest the potential for development of a new class of antidepressant medications that prevent mitochondrial dysfunction, especially the consequent oxidative damage to DNA, proteins or lipids (Maes et al., 2012a).

2.7. Conclusions

Fig. 2 shows the different pathways in depression that may cause activation of O&NS pathways. The TLR2/TLR4 complexes

![Fig. 2](https://example.com/figure2.png)

**Fig. 2.** Different pathways may play a role in the increased oxidative and nitrosative stress (O&NS) in depression: (a) activated immune-inflammatory pathways; (b) lowered levels of key antioxidants. Increased oxidative stress increases the consumption of antioxidant defenses and activates nuclear factor erythroid 2-related factor (NFE2L2), which increases the expression of endogenous antioxidants; (c) oxidative stress-induced activation of the tryptophan catabolite (TRYCAT pathway) with quinolinic acid (Quin)-induced increases in nitric oxide (NO)-mediated cell damage; (d) oxidative stress-induced glutatione levels depleting intracellular glutathione (GSH) and facilitating consequent “oxidative glutamate toxicity”; (e) oxidative stress-induced mitochondrial dysfunctions leading to increased production of reactive oxygen species (ROS); (f) formation of oxidative (OSEs) and nitrosative (NSEs) specific epitopes which may be immunogenic and mount autoimmunity responses further driving O&NS processes; (g) formation of redox-derived damage associated molecular patterns (DAMPs) activating the Toll-like receptor (TLR) radical cycle thereby inducing immune-inflammatory and O&NS pathways; (h) increased pathogen associated molecular patterns, such as lipopolysaccharide (LPS), and psychosocial stressors may activate or sensitize TLRS.

may be activated or upregulated by LPS and psychosocial stressors leading to downstream production of proinflammatory cytokines and activation of O&NS pathways. Due to this, new redox-derived DAMPs are formed which further activate the TLR radical cycle. Prolonged oxidative stress may cause activation of the TRYCAT pathway leading to NMDA receptor-associated excitotoxicity by increasing NO-mediated cell damage, and increased glutamate levels that deplete intracellular GSH and facilitate oxidative glutamate toxicity.

3. Depression-related factors causing dysregulated O&NS pathways

3.1. Genetic polymorphisms in O&NS genes

Depression is associated with single nucleotide polymorphisms (SNP) in pro-oxidant and antioxidant enzyme genes (Maes et al., 2011a). Polymorphisms in the myeloperoxidase gene, in particular GC homozygote and the G allele, increase the risk of depression (Galecki et al., 2010). This is important, as myeloperoxidase is a pro-oxidant and pro-inflammatory enzyme that is increased in inflammatory disorders. The G/A SNP of the iNOS gene significantly increases susceptibility to recurrent depression, while A/A homozygous carriers demonstrate a lower risk of recurrent depression (Galecki et al., 2011). There is also a significant association between SNPs in MnSOD and depression, which may lead to a slower uptake of MnSOD in the mitochondria and to mRNA instability (Galecki et al., 2010). Variation in the GpX1 gene is associated with increased depression risk (Johnson et al., 2013), and additionally modulates the effects of antioxidants, such as selenium (Johnson et al., 2013). Some, but not all, studies have demonstrated that a functional polymorphism in the PON1 gene (Q→R at the
192 position) increases the odds of unipolar and bipolar depression (Vargas et al., 2013). In addition, gene by environmental effects may be involved. For example, an interaction between PON1 gene SNP and smoking is associated with bipolar depression (Vargas et al., submitted for publication). While polymorphisms of glutamate cysteine ligase, a key synthetic enzyme in the glutathione pathways are associated with disorders such as schizophrenia, this does not appear to be the case in depression (Berk et al., 2011a). SNPs of pro-inflammatory cytokine genes, including IL-1 and IL-6, may also predict responsiveness to treatment with antidepressants (Baune et al., 2010; Uher et al., 2010).

Therefore, underlying genetic vulnerabilities produced by polymorphisms in pro-oxidant, antioxidant and inflammatory genes may contribute to the O&NS processes in depression especially in conditions of increased ROS/RNS production.

3.2. Psychological stressors

A vast literature suggests psychosocial stressors may induce O&NS pathways and reduce antioxidant defenses. Psychological stress causes a pro-oxidant state and oxidative damage to fatty acids (Alekseandrovskii lu et al., 1988; Pertssov et al., 1995; Sosnovskii and Kozlov, 1992). Morimoto et al. (2008) reported that in postmenopausal women, mental stress induces increased lipid peroxidation as measured by plasma 4-HNE. In nurses with high job stress, significantly decreased levels of alpha-tocopherol (vitamin E) and a significant relationship between MDA levels and perceived stress ratings have been detected (Tsuboi et al., 2006).

In workers from a pre-hospital emergency service, Casado et al. (2006) observed a significant association between occupational stress and erythrocyte MDA levels. In females, stress variables, such as perceived stress and workload and less coping with stress, were associated with increased levels of 8-OHdG (Irie et al., 2001). Stressors such as examination stress decrease plasma antioxidant activity and increases oxidative stress-induced damage to DNA (Sivonova et al., 2004). Conversely, lifestyle-modifying programs may significantly improve antioxidant defenses. For example, in patients with coronary artery disease an intensive lifestyle modification program resulted in statistically significant increases in plasma total antioxidant capacity, vitamin E and erythrocyte GSH (Jatuporn et al., 2003). In animal models, many different types of psychophysical stressors, including immobilization stress, restraint stress, chronic unpredictable stress and chronic mild stress, were shown to cause lowered levels of antioxidants, such as GSH, and increased lipid peroxidation, as measured with MDA and 4-HNE (Ahmad et al., 2010; Kubera et al., 2011; Moretti et al., 2012; Wang et al., 2012).

As psychological stressors may cause O&NS, the role of psychological trauma has been examined in animal models and individuals with post-traumatic stress disorder (PTSD). An animal model of PTSD demonstrated that increased expression of oxidative stress and pro-inflammatory cytokine mRNA in the brain and systemic circulation are associated with the onset and exacerbation of PTSD (Wilson et al., 2013). In patients with PTSD, however, no changes in urinary 8-OHdG could be detected, while protein carbonyl levels were lower in the PTSD group (Čepnja et al., 2011). Miller et al. (2013) identified a variant in the gene retinoid-related orphan receptor alpha (RORA) as being protective against the effects of stress on the brain, and subsequent development of PTSD. The authors concluded that this gene plays a crucial role in guarding brain cells from the detrimental effects of oxidative stress (Logue et al., 2013).

3.3. Medical comorbid disorders and conditions

Depression is highly comorbid with many systemic immune and O&NS-related disorders (e.g. Chronic Obstructive Pulmonary Disorder; COPD, atherosclerosis, rheumatoid arthritis, inflammatory bowel disease, psoriasis, diabetes type 1 and type 2, HIV-infection), neuroinflammatory and O&NS-related brain disorders (e.g. Parkinson’s disease, Alzheimer’s disease, stroke, multiple sclerosis) and conditions accompanied by increased inflammatory potential and O&NS (hemodialysis, IFNα-based immunotherapy) (Maes et al., 2011b). Depression may be triggered by these disorders or conditions, or worsen outcomes for those in whom these disorders are present (Maes et al., 2011b).

Increased O&NS and immune-inflammatory pathways may underpin the comorbidity and interaction between depression and these related conditions (Maes et al., 2011a; Wolkowitz et al., 2011). Recently, it has been proposed that the underlying biological processes driving depression intimately overlap with neurodegenerative processes, suggesting that depression may be more than a comorbidity but rather is intertwined with degenerative processes (Anderson and Maes, 2013b). Oxidative stress drives telomere shortening, a key mechanism underlying the aging process (Phillips et al., 2013), and therapies that reduce oxidative stress such as lithium are associated with longer telomeres (Martinsson et al., 2013). There may be additional effects of aging on O&NS pathways and a number of ’age-related’ disorders such as cardiovascular disease (CVD) (Maes et al., 2011e), stroke (El Kossi and Zakharoy, 2000), diabetes (Maritim et al., 2003), metabolic syndrome (Hansel et al., 2004), and sleep apnea (Jelic et al., 2008); all of which are recognized to share common origins of increased O&NS (Forlenza and Miller, 2006).

3.4. Obesity and metabolic syndrome

Accumulating clinical and epidemiological evidence suggests that obesity contributes to the pathogenesis of depression (Atlantis et al., 2009). Cross-sectional studies have linked obesity with depression (Atlantis and Baker, 2008; de Wit et al., 2010) and negative affect (Pasco et al., 2013), and a series of longitudinal studies have demonstrated this association is bi-directional (Luppino et al., 2010; Pan et al., 2012). Traditionally regarded as an energy storage depot, adipose tissue is now recognized as having a role in both physical and mental health.

Excessive accumulation of adipose tissue in obesity perturbs the regulatory network of neural circuits and circulating messengers that has evolved to maintain energy homeostasis. As one of the cell types in adipose tissue, adipocytes (fat cells) serve as depots for energy storage and mobilization. Adipocytes produce biologically active molecules known as adipokines (or adipocytokines) that have pro-inflammatory or anti-inflammatory activities, and these include leptin, TNFα and adiponectin. Leptin is a pro-inflammatory cytokine that plays a key role in regulating energy intake and expenditure and signals the brain when adipocytes become enlarged to modify appetite and behavior (Jequier, 2002). TNFα is a pro-inflammatory cytokine that stimulates the acute-phase reaction and adiponectin is an anti-inflammatory factor. Circulating levels of leptin (Pasco et al., 2008a; Solin et al., 1997) and TNFα (Kern et al., 1995) are elevated in obesity and raised levels of both factors have been reported in depression (Halaris et al., 2012; Pasco et al., 2008a). By contrast, adiponectin levels are reduced in obesity (Ryo et al., 2004) and depression (Leo et al., 2006).

In the obese state, enlarged mature adipocytes become stressed and macrophages accumulate in the expanded adipose tissue, releasing a host of pro-inflammatory cytokines and establishing a low-grade inflammatory state. Such adipose tissue dysregulation also impairs the differentiation of pre-adipocytes and favors the storage of excess lipid in other tissues (ectopic depots) (Gustafson et al., 2009), which is metabolically toxic.

Adipose tissue dysregulation induces oxidative stress and adipose tissue itself is considered an important source of ROS.
hemoglobin oxygen saturation and matrix metalloproteinase 9, C-reactive protein and fibrinogen. The oxygen desaturation index was additionally correlated with advanced glycation end products. Sleep fragmentation and intermittent hypoxia largely determine the molecular signature of OSA, including oxidative stress and inflammation, although comorbid obesity may play a role due to its impact on shared molecular pathways (Arnardottir et al., 2005; 2012). Mitigation of nocturnal symptoms via night-time therapy also appears to neutralize the degree of O&NS damage in OSA patients (Alonso-Fernandez et al., 2009).

Preliminary findings derived from animal studies have highlighted the potential of melatonin administration as an effective therapeutic agent in regard to its O&NS effects (Manda and Bhatia, 2003). Although the possible therapeutic benefits of this hormone in the treatment of a range O&NS specific disorders has been previously described (see review (Reiter et al., 2009)), and independent reports have profiteered the usefulness of melatonin in a range of sleep-disordered populations (Reiter et al., 2007), there is little information integrating this knowledge regarding the possible efficacy of this hormone in targeting sleep-disorder specific O&NS. Moreover, the availability of a unified model describing the impact of O&NS damage in sleep disorders is currently lacking, and thus currently available treatment options are unable to effectively target underlying mechanisms associated with O&NS. Future research will therefore benefit from both further exploring the relationship between insomnia and O&NS, as well as systematically assessing the efficacy of melatonin as a possible therapeutic option.

3.6. Cigarette smoking

The prevalence of cigarette smoking is significantly higher in individuals suffering from depressive and anxiety disorders (Moylan et al., 2012; Pasco et al., 2008b) than those without. This may be linked, at least in part, to the inter-relationship between cigarette smoking and precipitated oxidative stress (Moylan et al., 2013b). Cigarette smoke contains many chemicals that increase levels of O&NS and is a substantial source of exogenous free radicals (Stedman, 1968). Multiple animal models have demonstrated that exposure to cigarette smoke can lead to increases in levels of brain O&NS, as demonstrated by increased levels of reactive oxygen species, including superoxide, thiobarbituric acid reactive substances (TBARS), carboxylated proteins and markers of lipid peroxidation (Anbarasi et al., 2005; Luchese et al., 2009; Stangerlin et al., 2009; Thome et al., 2011; Tuon et al., 2010). In addition to these changes, exposure to cigarette smoke appears to be associated with lowered levels of antioxidant enzymes, such as catalase, vitamins (A, C, E), Gpx, glutathione reductase, PON1, glutathione and SOD (Anbarasi et al., 2005; Luchese et al., 2009).

As with other factors that stimulate production of O&NS, acute exposure to cigarette smoke appears to provoke a protective increase in antioxidant enzymes. However, more chronic exposure overwhelms these defences and leaves the system vulnerable to cellular damage. This is important, as factors which can assist the adaptive protective mechanisms, such as augmentation with vitamin E or active exercise (Thome et al., 2011; Tuon et al., 2010), appear to assist by limiting the increase in O&NS provoked by exposure to cigarette smoke. Investigations also reveal that the major additive component of cigarette smoke, nicotine, may be responsible for the major proportion of increased O&NS attributed to cigarette smoke exposure. For example, studies utilizing exogenous administration of nicotine to isolate cell lines in culture lead to reduced production of antioxidant enzymes and increased markers of lipid peroxidation, lactate dehydrogenase activity and TBARS (Bhagwat et al., 1998; Yildiz et al., 1998). Given the interaction between cigarette smoking and O&NS balance, coupled with the associative findings between O&NS and depressive and anxiety
of nicotine, it is possible that exposure to cigarette smoke, particularly in vulnerable individuals, plays a contributing role in the development of depression through modulation of O&NS. Indeed, it was recently demonstrated that interactions between PON1 genotypes and smoking significantly increased the odds of bipolar depression, while decreased PON1 activity levels, but not smoking, significantly predicted unipolar major depression (Vargas et al., 2012).

However, it should be noted that nicotine has some anti-stress effects, with its activation of nicotinic receptors affording protection in a number of neurodegenerative and psychiatric conditions, including Parkinson’s disease (Anderson and Maes, 2013a), in part via improvements in arousal-associated cognition. Alpha7 nicotinic receptor activation in murine regulatory T cells potentiates their immuno-suppressive capacity (Wang et al., 2010), exacerbating the effects of nicotine via immune system regulation in different CNS disorders (Qui et al., 2012). Given the role of gut permeability in the modulation of depression, it is of note that nicotine ameliorates ulcerative colitis, partly by increasing regulatory T cells, but worsens Crohn’s disease, where it increases Th17 cells (Galietovsky et al., 2011). Cigarette smokers also show a decreased incidence of some inflammatory and allergic disorders, partly mediated by nicotine effects on mast cells (Linneberg et al., 2001). As such, nicotine effects on O&NS in isolated cells require balance with its effects on immune system regulation.

Some of the effects of cigarette smoke are mediated by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which activates the aryl hydrocarbon receptor, which, as well as inducing oxidants and, antioxidants also increases IDO, contributing to TRCP1 induction and serotonin depletion. TCDD-inducible poly (ADP-ribose) polymerase (TIPARP/ARTD14) (Opitz et al., 2011) decreases NAD+, in turn lowering sirtuins and PGC-1α and thereby inhibiting mitochondrial function (Diani-Moore et al., 2010). However, nicotine may have some direct protective effects at mitochondria, suggesting that nicotine effects will interact with those of TCDD in the regulation of mitochondrial function. Other factors in cigarette smoke including 2,3,6-trimethyl-1,4-naphthoquinone (TMN), a MAO-A/B inhibitor, also provide protection, partly via the decreased metabolism of serotonin and dopamine (Castagnoli et al., 2003). Taking these diverse effects together, it is possible that the level of stimulated oxidative stress induced by nicotine and cigarette smoke may alter the balance between protective and damaging effects to cellular structures. Nicotine stimulates acetylcholine receptors in a more sustained fashion than normally occurs in acetylcholine transmission. Depending upon the conditions, this may lead to production of a small, but still regulated amount of oxidative stress that can potentially even augment important aspects of cell signaling that may exert protective effects to cellular function. However, persistent exposure to increased signaling may overwhelm intrinsic protective mechanisms, leading to chronically increased oxidative stress leading to cellular damage (Moynan et al., 2013b; Newman et al., 2002). As such, depending on the individual conditions present, nicotine and cigarette smoke may have diverse effects on processes driving the biological underpinnings of depression, including via the regulation of O&NS, immune-inflammatory processes and their interaction.

3.7. Dietary factors

Levels of ROS/RNS and an individual’s endogenous antioxidant capacity are influenced by dietary factors. Fruits, vegetables, olive oil, nuts and other plant foods are all potent sources of antioxidants, while a range of dietary derived amino acids, found in meats, vegetables, whole grains, eggs and yoghurt, are important precursors for the body’s endogenous antioxidant, Gpx. In contrast, high saturated fat diets (Morrison et al., 2010) and hyperglycaemia (Yu et al., 2006) increase ROS. The effects of dietary factors on the incidence of depression are exemplified in the PREMID randomized trial (Sanchez-Villegas et al., 2013). In patients with comorbid type 2 diabetes, 3-year exposure to a Mediterranean diet (rich in olive oil, fruit, vegetables, legumes, tomato, garlic, onion and fish, but low in meat, cream, butter, fast foods and sugar) supplemented with nuts was significantly and inversely associated with a lower incidence of depression.

The dietary minerals selenium, copper, manganese and zinc are required as cofactors by oxidative enzymes (Parlletta et al., 2013). Selenium is also a co-factor in the synthesis of GSH and its related enzymes. Selenium appears to play a role in modulating mood and has been shown to be inversely associated with an increased likelihood of de novo major depressive disorder (Pasco et al., 2012). In West Texas, residential selenium levels in groundwater have been significantly and negatively associated with depressive symptoms, explaining up 17% of their variance (Johnson et al., 2013).

Reduced dietary intakes of zinc-rich foods have been associated with increased odds for depression (Jacka et al., 2012). Decreased serum zinc is commonly described in individuals with depression (Maes et al., 1994, 1997b; McLoughlin and Hodge, 1990) and is negatively correlated with illness severity (Maes et al., 1994). A meta-analysis showed that zinc supplementation has clinical efficacy in treatment-resistant depression as an adjunct to antidepressants as well as a stand-alone intervention (Lai et al., 2012). Zinc’s antidepressant activity can be explained by its anti-oxidative and anti-inflammatory effects, and also by its neuroprotective effects related to the modulation of neurotransmission, n-3 metabolism, NMDA receptor and glutamate levels (Szewczyk et al., 2011). For example, zinc administration mitigated apoptosis and behavioral changes in rats exposed to malathion, a toxic insecticide known to induce depressive behaviors and oxidative damage to the brain (Brocardo et al., 2007).

Vitamins A, C and E, present in fruits, vegetables and nuts, (Bolling et al., 2011), are antioxidants that scavenge free radicals, protect against cell damage, and upregulate antioxidant capacity (Parlletta et al., 2013). As noted previously, vitamins E and C are significantly lowered in depressed patients. There are few intervention studies examining vitamins in relation to depression, although one randomized, double-blinded, placebo controlled trial did demonstrate improvements in subjective mood in healthy middle-aged men using a high-dose B vitamin complex with vitamin C and minerals (Kennedy et al., 2010). In animal models of depression, administration of vitamin E yields a significant antidepressant-like effect, while long-term treatment also improves the antidepressant defenses in the prefrontal cortex and hippocampus (Lobato et al., 2010).

Another vitamin that appears important in depression pathogenesis is vitamin B6. The active form of vitamin B6, pyridoxal-5-phosphate, can influence synthesis of key neurotransmitters due to its role in tryptophan metabolism. Deficiency in pyridoxal-5-phosphate is associated with depression expression (Hvas et al., 2004) and higher intakes of vitamin B6 appear to be protective against depression expression (Skarpuski et al., 2010).

Reduced folate intake (Tolmunen et al., 2004) and folate status (Nanri et al., 2012) is associated with an increased risk for depression. A Cochrane review supports the use of folate as an adjunctive treatment in major depression, although it is still unclear as to whether supplementation will benefit both those with low and normal levels of folate (Taylor et al., 2004). At this time however there is no evidence that folate is useful as a monotherapy (Luberto et al., 2013). Recent reviews concluded that folic acid levels should be measured and corrected in treatment-resistant depression and in subjects with increased risk for deficiencies in folic acid (Lazarou and Kasparou, 2010).
In elderly (>70 years of age) Japanese individuals, a tomato-rich diet, which contains high levels of lycopene, was inversely associated with depressive symptoms (Niu et al., 2013). In the same study no significant association was detected between depressive symptoms and the intake of other vegetables, suggesting that lycopenes may have the potential to prevent depressive symptoms.

Polyphenols, found in particular abundance in herbs and spices, berries, green tea, nuts, red wine and other plant foods, also have potent antioxidant properties. In elderly subjects, the higher intake of green tea polyphenols is accompanied by a reduced incidence of depressive symptoms, while in animal models green tea polyphenols show antidepressant-like effects, which are in part related to their antioxidant effects (Liu et al., 2013; Zhu et al., 2012). A recent paper reviewed the antidepressant potential of polyphenols, such as curcumin, ferulic acid, hesperidin, rutin, quercetin and resveratrol (Pathak et al., 2013). Resveratrol, one of the phenolic compounds abundant in berries, grapes, red wine, and peanuts, is not only a strong antioxidant and anti-inflammatory compound, but also is neuroprotectant (Joseph et al., 1999). Polyphenols may enhance brain plasticity by modulating signaling pathways to induce the activation of key molecules and proteins, such as BDNF (Williams et al., 2008).

The brain is particularly vulnerable to oxidative damage due to the high content of polyunsaturated fatty acids in erythrocyte membranes. The activated immune-inflammatory and O&NS pathways that commonly accompany depression result in increased lipid peroxidation, which may account for the decreased levels of long chain fatty acids regularly observed in those with depressive disorders (Berk and Jacka, 2012). Such peroxidation decreases cell membrane fluidity and can damage membrane proteins. While long chain n-3 fatty acids help to mitigate the impact of these processes, supplementation with nutritional antioxidants, such as vitamins A and E, polyphenols, lycopenes and zinc might prevent lipid peroxidation. Pre-treatment with antioxidants can prevent cell loss in animal models of acute stress (Lee et al., 2006), while studies in rodents demonstrate that the adverse effects of high fat diets on BDNF expression are ameliorated by antioxidants (Wu et al., 2004b). Similarly, adverse effects of induced traumatic brain injury are ameliorated by n-3 PUFAs (Wu et al., 2004a). Moreover vitamins B6, B12 and folate can reduce levels of homocysteine, increases oxidative stress in endothelial cells (Parletta et al., 2013). These data indicate that nutrient sufficiency is likely to play an important role in reducing the impact of O&NS on the brain via increased antioxidant and anti-inflammatory effects and related neuroprotection.

3.8. Vitamin D status

Vitamin D is a secosteroid that has a primary role in bone and muscle health. Widespread vitamin D deficiency, particularly 25-hydroxyvitamin D, has been identified among western populations at higher latitudes and cultures with restrictive dress codes (Pascual et al., 2001). Many adverse health outcomes including CVD, osteoporosis and cancer are linked to vitamin D insufficiency (Nowson et al., 2012). Additionally, Vitamin D has many less well-appreciated roles in neural physiology and immune regulation that notably overlap with the pathophysiology of depression. Vitamin D also impacts on sleep and circadian rhythms. Receptors for vitamin D are found in brain regions important in mood regulation. Vitamin D influences cell proliferation in the developing brain and embryogenesis as well as influencing neuronal growth. It also plays a role in glucocorticoid physiology (Eyles et al., 2011).

Cross-sectional and prospective data suggest that serum 25-hydroxyvitamin D insufficiency is associated with an increased risk of developing depression (Kjaergaard et al., 2012). There is, however, inconsistent clinical trial data of the antidepressant effects of supplementation with vitamin D, with both positive and null trials reported (Landsdowne and Provest, 1998; Sanders et al., 2011).

Vitamin D also has roles in preventing DNA damage and regulating cell growth. Preclinical data suggest that vitamin D reduces oxidative stress mediated damage, particularly to DNA, evidenced by reduced 8-OHdG, reduced chromosomal aberrations, the prevention of telomere shortening and the inhibition of telomerase activity. It also regulates the cell cycle, preventing propagation of damaged DNA, and regulates cell death pathways and apoptosis (Nair-Shalliker et al., 2012). Vitamin D3 can reverse the induction of diabetes by streptozotocin in animal models; a state which is associated with reduced antioxidant defenses including superoxide dismutase and Gpx (George et al., 2012). In elderly subjects with glucose intolerance, a significant association has been observed between oxidative stress markers, particularly advanced glycation end products, advanced oxidation protein products, LDL susceptibility to oxidation and NO metabolic pathway products with 25(OH)D levels. This effect was more marked in hyperglycemic subjects, a state known to be linked to oxidative stress (Gradinaru et al., 2012).

Early life vitamin D deficiency is associated with increased blood pressure and vascular oxidative stress (Argacha et al., 2011). Calcitriol can reduce expression of inflammation and oxidative stress markers in patients receiving hemodialysis with secondary hyperparathyroidism (Wu et al., 2011). Calcitriol increases brain glutathione levels, and is a catalyst for GSH production, a finding concordant with both the role of GSH as a principal redox defense, and in the modulation of depression (Garcion et al., 2002).

Some of the efficacy of valproate in bipolar disorder is mediated by an increase in bcl-2 associated anthonogen-1 (BAG-1), which prevents the nuclear translocation of cortisols’ glucocorticoid receptor, thereby preventing many of the effects of this stress hormone, including in neuroinflammatory disorders such as multiple sclerosis (Anderson and Rodriguez, 2011). BAG-1 also transports vitamin D3 to the nuclear vitamin D receptor, suggesting that stress and depression associated O&NS may be intimately involved in the regulation of vitamin D3 effects, partly via BAG-1 regulation. Together these findings suggest that oxidative stress may play a modulatory role in the development of depression and other psychiatric disorders.
3.9. Sedentary lifestyle and exercise

Despite the known health benefits of exercise it is estimated that more than 30% of the global population are physically inactive (Organisation, 2002). With increasing sedentary behavior comes the risk of many diseases, including depression. Physical inactivity across the lifespan has been cross-sectionally and prospectively associated with depression (Teychenne et al., 2008). In a study investigating self-reported levels of physical activity in childhood and adult depression, low physical activity levels throughout the early years was associated with a 33% increased risk of self-reported depression in adulthood (Jacka et al., 2010). Furthermore, epidemiological studies of younger, middle aged and older adults, have shown habitual physical activity to reduce the likelihood of de novo depression (Brown et al., 2005; Pasko et al., 2011; Sagatun et al., 2007; Strawbridge et al., 2002). These observational findings are somewhat supported by intervention studies where exercise has been demonstrated to be effective in treating depression (Rimer et al., 2012). For example, older patients with depression randomized to a twice-weekly exercise group for 10 weeks demonstrated a modest reduction in depression scores compared to non-exercise controls (weekly health education talks) (Mather et al., 2002). Larger effect sizes are reported when comparison is made to a waiting list or placebo treatment (Rimer et al., 2012).

Exercise is likely to influence the rate of depression and related disorders through numerous biochemical, physiological and psychological pathways (Eyre and Baune, 2012; Moylan et al., 2013a). However, O&NS is likely to act as a prominent mechanism by which this occurs. O&NS has been shown to be increased in those who are physically inactive as well as in individuals following acute exercise, whereas chronic or habitual exercise has been shown to be associated with a reduction in O&NS via an up regulation of antioxidant defenses (Gomes et al., 2012). For example, in a small group of physical inactive medical students, levels of MDA were shown to be increased when compared with age-matched football players under regular training (Metin et al., 2003). Antioxidant enzyme levels are increased in response to exercise, indicating that physical activity has the ability to diminish lipid peroxidation (Djordjevic et al., 2012; Evelson et al., 2002; Fisher-Wellman and Bloomer, 2009; Metin et al., 2003). Exercise, like antidepressants, is a significant inducer of neurogenesis, with melatonin further potentiating the effects of exercise on rodent neurogenesis (Liu et al., in press). Given the role of O&NS in both depression and exercise, these data highlight the possibility of O&NS modulating exercise-induced mood improvements. However, further research into the optimal type, duration and intensity of the exercise is required.

4. Conclusions

Fig. 3 summarizes the pathways and factors that may contribute to O&NS in depression. A vicious circle of activated immune-inflammatory pathways, lowered antioxidant levels, redox-derived DAMPs and activation of the TLR4 complex with downstream production of immune-inflammatory mediators and ROS/RNS characterizes depression. Psychosocial stressors, metabolic syndrome and obesity, sleep disorders, smoking, lowered vitamin D status, a diet low in antioxidants, such as selenium, folate, zinc, lycopenes and polyphenols, and a sedentary lifestyle may contribute to the interrelationship between (neuro)inflammation, oxidative and nitrosative stress (O&NS), mood disorders and the process of neuroprogression. Multiple medical, environmental and genetic factors predispose to (neuro)inflammation and increased O&NS. (Neuro)inflammation and O&NS products contribute to expression of mood disorder symptoms and to neuroprogressive processes. These products also lead to direct cell damage and dysfunction that contribute to disorder expression, neuroprogression, and to development of autoimmune responses that reinforce a (neuro)inflammatory and O&NS state. This reinforcing cycle contributes to further neuroprogression, and subsequent staging of depression characterized by increasing sensitivity to relapse, treatment resistance and symptom chronicity. LPS – lipopolysaccharide.

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contribute to activated O&NS pathways in depression. Neuroinflammatory brain disorders and systemic immune- and O&NS-related disorders and conditions characterized by O&NS are additionally associated with the onset of depression.

Activated peripheral immune-inflammatory pathways and lowered peripheral antioxidant defenses may have consequences for central immune-inflammatory and O&NS pathways. As previously summarized (Leonard and Maes, 2012), peripherally increased levels of LPS and pro-inflammatory cytokines, driven by activated O&NS pathways and lowered antioxidant defenses, may cause brain neuroinflammation. The latter involves not only inflammation but also O&NS processes fueled by a systemic loss of antioxidant defenses and increased gut permeability. Activated central O&NS pathways may cause lipid peroxidation, and result in new formation of redox-derived DAMPs that in turn may further activate the TLR radical cycle in the brain. Increased levels of peripheral TRYCATs, such as kynurenine, may pass the blood brain barrier to exert depressogenic and neurotoxic activities in the brain. The peripheral autoimmune processes directed against OSEs and NSEs may have grave consequences for CNS functions. In patients and animals with autoimmune conditions, including lupus erythematosus, associations have been detected between serum and brain autoantibodies and neuropsychiatric symptoms (Zameer and Hoffman, 2001). These behavioral changes accompanying autoimmune diseases are centrally mediated through increased blood brain barrier permeability and infiltration of white blood cells through the choroid plexus (Zameer and Hoffman, 2001). Moreover, some of the IgM autoantibodies directed against NSEs that are increased in depressed patients (e.g. S-No-cysteine) are known to be highly neurotoxic and to cause demyelination (Bouillenne et al., 2002).

Fig. 4 depicts the wide-angle lens picture emerging from the reviewed research literature, demonstrating that activation of peripheral and central immune-inflammatory and O&NS pathways are linked to expression of mood disorder symptoms, staging of depression and to neuroprogressive processes. A series of medi- cal, environmental and genetic factors predispose and contribute to development of increased levels of peripheral inflammation that can precipitate development of neuroinflammation. Activated O&NS pathways and lowered antioxidant defenses also drive this process. Increased neuroinflammation and central activation of O&NS pathways have two broad, non-mutually exclusive, effects. First, they can influence development of depressive symptoms through effects on cellular functioning and through influencing key factors underpinning depression effects (e.g. through impairing normal neurotransmitter synthesis and metabolism). Second, neuroinflammatory and O&NS products cause direct cellular damage (e.g. lipid peroxidation) and dysfunction. Cellular damage and dysfunction contributes to expression of depressive symptoms (as above) and to processes underlying neuroprogression, including increased neuronal apoptosis and decreased neurogenesis and neuroplasticity. The cell damage in addition can further stimulate autoimmune pathways, leading to further increases in central neuroinflammation and O&NS and reinforcing further depressogenic and neuroprogressive effects. These effects contribute to the staging of depression, increasing the likelihood of recurrence, treatment resistance and a chronic depressive state. The delineation of these pathways highlights multiple opportunities for therapeutic intervention in preventing and/or reducing levels of neuroinflammation and O&NS in depression. Future research should delineate whether the pathways involved in the immune-inflammatory and O&NS pathophysiology of depression are useful as state, trait or staging biomarkers for depression. Lastly, understanding of the process and its constituents offers both molecular targets for pharmacological intervention and environmental targets for public health and preventive approaches.

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References


Bolling, B.W., Chen, C.Y., McKay, D.L., Blumberg, J.B., 2011. Tree nut phytochemi-


Bursel, N., Roth, T., Rosenthal, L., Andreksi, P., 1996. Sleep disturbance and psychi-


Castagnoli Jr., N., 2003. Inhib-


Christensen, R., Petersen, E., Stocker, R., 1990. Antioxidant activities of some trypto-


iNOS, and sPLA2-IA in patients with recurrent depressive disorder. J. Affect. Disord. 165, 369–376. doi: 10.1016/j.jad.2014.04.007


Murphy, T.H., Miyamoto, M., Sastre, A., Schnaar, R.L., Coye, J.T., 1988. Glutamate toxicity in a neuronal cell line involves inhibition of cystine transport leading to oxidative stress. Neuron 2, 1547–1558.


