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A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness

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ABSTRACT

This paper reviews the body of evidence that major depression is accompanied by a decreased antioxidant status and by induction of oxidative and nitrosative (IO&NS) pathways. Major depression is characterized by significantly lower plasma concentrations of a number of key antioxidants, such as vitamin E, zinc and coenzyme Q10, and a lowered total antioxidant status. Lowered antioxidant enzyme activity, e.g. glutathione peroxidase (GPX), is another hallmark of depression. The abovementioned lowered antioxidant capacity may impair protection against reactive oxygen species (ROS), causing damage to fatty acids, proteins and DNA by oxidative and nitrosative stress (O&NS). Increased ROS in depression is demonstrated by increased levels of plasma peroxides and xanthine oxidase. Damage caused by O&NS is shown by increased levels of malondialdehyde (MDA), a by-product of polyunsaturated fatty acid peroxidation and arachidonic acid; and increased 8-hydroxy-2-deoxyguanosine, indicating oxidative DNA damage. There is also evidence in major depression, that O&NS may have changed inactive autoepitopes to neoantigens, which have acquired immunogenicity and serve as triggers to bypass immunological tolerance, causing (auto)immune responses. Thus, depression is accompanied by increased levels of plasma IgG antibodies against oxidized LDL; and increased IgM-mediated immune responses against membrane fatty acids, like phosphatidyl inositol (Pi); oleic, palmitic, and myristic acid; and NO modified amino-acids, e.g. NO-tyrosine, NO-tryptophan and NO-arginine; and NO-albumin. There is a significant association between depression and polymorphisms in O&NS genes, like manganese superoxide dismutase, catalase, and myeloperoxidase. Animal models of depression very consistently show lowered antioxidant defences and activated O&NS pathways in the peripheral blood and the brain. In animal models of depression, antidepressants consistently increase lowered antioxidant levels and normalize the damage caused by O&NS processes. Antioxidants, such as N-acetyl-cysteine, compounds that mimic GPX activity, and zinc exhibit antidepressive effects. This paper reviews the pathways by which lowered antioxidants and O&NS may contribute to depression, and the (neuro)degenerative processes that accompany that illness. It is concluded that aberrations in O&NS pathways are - together with the inflammatory processes - key components of depression. All in all, the results suggest that depression belongs to the spectrum of (neuro)degenerative disorders.

Abbreviations: IO&NS, inflammatory and oxidative & nitrosative stress; ROS, radical oxygen species; RNS, radical nitrogen species; SOD, superoxide dismutase; GPX, glutathione peroxidase; NO-tyrosine, nitrotyrosine; Ig, immunoglobuline; GSH, reduced glutathione; CoQ10, coenzyme Q10; NFκB, nuclear factor κB; TNFα, tumor necrosis factor α; TAC, total antioxidant capacity; CMS, chronic mild stress; CuZnSOD, cupper, zinc SOD; XO, xanthine oxidase; NO, nitric oxide; iNOS, inducible NO synthase; cNOS, constitutive NOS; NOx, NO metabolite; IFNα, interferon α; nNOS, neuronal NOS; LC, locus coeruleus; SCN, nucleus suprachiasmaticus; MDA, malondiadehyde; ALE, advanced lipoxidation end (products); 8-OH-dG, 8-hydroxy-deoxyguanosine; BER, base excision repair; LDL, low density lipoprotein; oxLDL, oxidized LDL; Pi, phosphatidyl inositol; MS, multiple sclerosis; SBA, serum bovine albumin; SNP, single nucleotide polymorphism; IL-1, interleukin-1; COX-2, cyclooxygenase 2; MPO, myeloperoxidase; LPS, lipopolysaccharide; MnSOD, manganese SOD; CAT, catalase; UCMS, unpredictable CMS; F&S, fatigue and somatic symptoms; ATP, adenosine triphosphate; IBS, irritable bowel syndrome; CFS, chronic fatigue syndrome; IDO, indoleamine dioxygenase; GSSH, glutathione disulfide; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; I&ND, inflammatory and neurodegenerative.

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1. Introduction

As described in this special issue there is evidence that depression is an inflammatory disorder. Since our first papers showing that activated T cells and monocytes play a role in depression (Maes et al., 1990-1991, 1991, 1993), we have renamed this theory depending on the new findings which emerged from clinical research. Thus, we called this theory the monocyte-T-lymphocyte hypothesis of depression, the cytokine hypothesis of depression, and the inflammatory hypothesis of depression (Maes, 1993, 1995, 1999, 2002; Schiepers et al., 2005). Recently, we formulated a new hypothesis, i.e. that activation of inflammatory and oxidative and nitrosative stress (IO&NS) pathways is a key pathophysiological factor in depression (Maes, 2008).

Inflammatory responses are known to be accompanied by induction of oxidative and nitrosative stress (O&NS) pathways. Inflammation and mitochondrial metabolic processes are accompanied by the generation of free radicals, which are highly reactive molecules. Reactive oxygen (ROS) and reactive nitrogen species (RNS) consist of radicals and other reactive oxygen/nitrogen factors that can react with other substrates. Examples of ROS and RNS are superoxide, nitric oxide, peroxynitrite and hydrogen peroxide. Under physiological conditions, these are counterbalanced by an array of defence pathways, and it needs to be emphasised that ROS and RNS have many physiological roles that include signalling. In excess, or in situations where defences are compromised, ROS and RNS may react with fatty acids, proteins and DNA, thereby causing damage to these substrates.

Under normal conditions, the ROS and RNS produced are tightly regulated by balancing systems consisting of antioxidants, antioxidant enzymes and proteins. Antioxidants regulate oxidative and nitrosative reactions in the body and may remove ROS and RNS through scavenging radicals, decreasing the production of ROS and RNS, thus preventing the damage caused by ROS and RNS. Examples of scavenger antioxidants are coenzyme Q10, vitamin C and E, and glutathione. ROS, like peroxides and superoxide, may also be neutralized by different antioxidant enzymes, e.g. superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase. Some proteins function as antioxidants by binding ROS and RNS, e.g. acute phase proteins such as albumin, transferrin, haptoglobin and ceruloplasmin. These antioxidant systems thus protect the tissues against ROS and RNS. Oxidative and nitrosative stress (O&NS) occur when there is an imbalance between a relative shortage in antioxidant defences with regard to an increased production of ROS and RNS. The former may be caused by lowered antioxidant concentrations in the body and lowered activities of antioxidant enzymes.

Therefore, a lowered antioxidant capacity may impair the protection against ROS/RNS, which eventually may cause oxidative damage to membrane lipids (lipid peroxidation) and DNA, and nitrosative damage to proteins (Maes et al., 2009a,b,c). The latter processes may cause dysfunctions in the cell through damage to the cell wall, mitochondria, DNA and functional proteins, which eventually result in apoptosis and cell death. ROS and RNS are principally generated within the mitochondrion and, as a consequence, oxidative stress has the capacity to damage mitochondrial defence systems, further perpetuating the O&NS. Some organs, like the brain, are more vulnerable to the detrimental effects of O&NS because it has a high metabolic rate and lower antioxidant levels. This may explain why O&NS is involved in neurodegenerative illnesses such as Parkinson's and Alzheimer's disease.

There is also evidence that neurodegeneration is characteristic of depression (Goshen et al., 2008; Campbell and MacQueen, 2006; Stockmeier et al., 2004; Duman, 2002). We have reviewed that activated IO&NS pathways may cause neurodegeneration through different mechanisms, such as neuroinflammation, the neurotoxic effects of by-products of induced IO&NS pathways, such as kynurenine, and damage by O&NS (Maes et al., 2009d). We have called this new theory of depression “the inflammatory and neurodegenerative (I&ND) hypothesis of depression” (Maes et al., 2009d).

Beside tissue damage and its consequences, damage by O&NS may cause an autoimmune response. During inflammation, lipid membranes and thus brain, muscle, and nerve cells may be damaged by oxidative stress. Nitrosative stress, through an increased production of nitric oxide and peroxynitrite by activated neutrophils and monocytes, may cause nitration and nitrosylation of proteins. During these processes, O&NS may change the chemical structures of otherwise ubiquitous molecules to generate a variety of modified new epitopes (neoepitopes), which are highly immunogenic. For example, during nitration of proteins, nitrotyrosine (NO-tyrosine) is formed, a strongly immunogenic neoepitope (Ohmori and Kanayama, 2005). Oxidation of fatty acid autoepitopes, which are normally hidden from the immune system, may cause recognition by immune cells, once the lipid membrane components are damaged by oxidative processes. This explains why O&NS can generate an immunoglobulin (Ig)-mediated (auto)immune response directed against the fatty acid and protein neoepitopes.

Fig. 1 shows the different IO&NS pathways that may generate oxidative and nitrosative damage to fatty acids and proteins. The formation of neoepitopes may mount IgG or IgM-mediated autoimmune responses. These processes together with damage to DNA and mitochondria may cause dysfunctioning of the cells, apoptosis, cell death and eventually (neuro)degeneration. In the next sections we will review the evidence that major depression is accompanied by a) lowered antioxidant and antioxidant enzyme levels; b) increased ROS and RNS; c) increased O&NS; d) increased damage to membrane fatty acids, functional proteins and DNA; e) autoimmune responses against a number of oxidatively modified fatty acid and NO-protein neoepitopes; and f) a significant association between depression and polymorphisms in O&NS genes. Table 1 shows the different O&NS pathways and the assays employed to measure those pathways.

2. Antioxidants and antioxidant enzymes

2.1. Antioxidants

In 2000, Maes et al. (2000) reviewed that depression is characterized by a significantly decreased antioxidant status, as evidenced by lowered tryptophan, tyrosine, albumin, and zinc, which are all antioxidants. The role of zinc in the pathophysiology and treatment of depression is discussed in another review in this special issue (Szewczyk et al., 2010). Maes et al. (2000) investigated plasma vitamin E concentrations in depression and found significantly lower vitamin E levels in patients as compared to normal controls. Owen et al. (2005) were able to confirm these results and found that depressed patients showed significantly lower plasma alpha-tocopherol than was previously reported for healthy Australians. In addition, plasma alpha-tocopherol was significantly and inversely correlated to the severity of depression as measured by the Beck Depression Inventory. Diet analyses showed that the dietary intake of vitamin E was not related to plasma alpha-tocopherol levels, while 89% of the subjects met or exceeded the recommended intake for vitamin E. Tsuboi et al. (2006) reported that nurses who exhibit high job stress had significantly higher depression scores and lower alpha-tocopherol than nurses who exhibit low job stress. In another study, adults older than 60 years were examined (Tiemeier et al., 2002). Vitamin E levels in men with depressive symptoms were lower than in non-depressed men, whereas no such differences were found in women. However, after controlling for biological factors this association was substantially weakened.

Glutathione is another antioxidant that has been examined in depressed patients. Glutathione is formed in the liver from three amino acids, namely glycine, glutamine and cysteine. Cysteine is the rate-limiting step in the synthesis of reduced glutathione (GSH), the active form of glutathione. Glutathione has three major functions: 1) it is a strong antioxidant that protects cells against damage caused by free radicals and it recycles vitamin C and E, so that they again become active

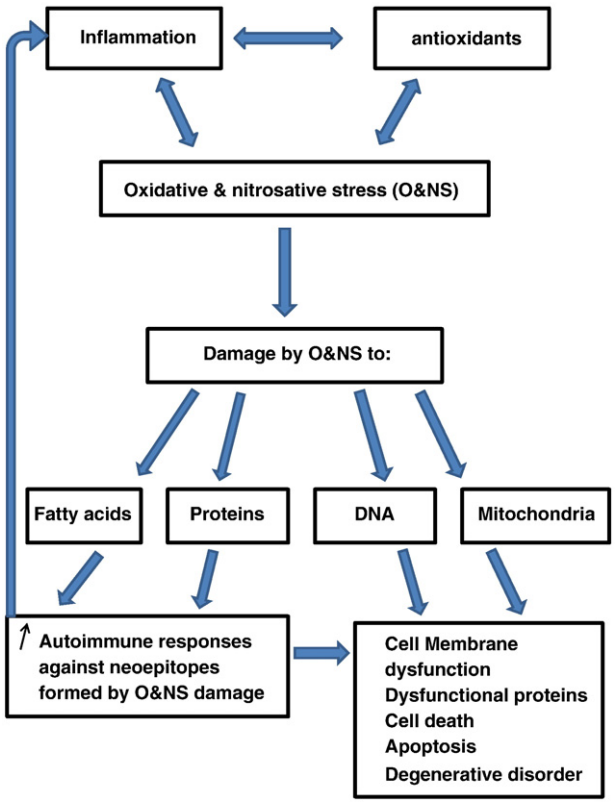

Fig. 1. This Figure shows the inflammatory, oxidative & nitrosative stress (IO&NS) pathways causing degenerative progression. Inflammatory processes and a lowered antioxidant capacity, which is partially induced by IO&NS processes, may cause O&NS. O&NS may augment the inflammatory response. Oxidation of fatty acids and nitration of proteins may render these selfepitopes immunogenic and consequently may mount an (auto)immune response against the neoepitopes formed by the damage caused by O&NS. This process may aggravate the ongoing inflammatory response. All above aberrations may cause cell dysfunctions, e.g. damaged cell membranes and mitochondrial dysfunctions, and loss of proper functioning of proteins. These processes may induce apoptosis, cell death and therefore may cause (neuro)degenerative disorders.

Table 1
This Table shows the different components in the oxidative & nitrosative stress (O&NS) system and the assays employed to measure those components in depression research.

O&NS variables	Measurements
Antioxidants	tryptophan, tyrosine (plasma), albumin, zinc (serum)
	vitamin E and C (plasma)
	glutathione (serum)
	coenzyme Q10 (plasma)
Antioxidant enzymes	glutathione peroxidase (whole blood, plasma, WBC),
	catalase (serum),
	superoxide dismutase (platelets, serum)Total
Antioxidant capacity	antioxidant capacity (TAC) in blood
ROS	peroxides (plasma)
	xanthine oxidase (serum)
RNS	nitric oxide (NO) (plasma)
	inducible NO synthase (WBC)
Damage to:	omega-3 fatty acids (oxidation potential index, serum
fatty acids	fractions, RBC)
	malondialdehyde (TBARS)(plasma, serum)
	8-iso-prostaglandinF2α (plasma)
	4-hydroxynonenal (brain)
proteins	nitrotyrosine (serum)
DNA	8-hydroxy-deoxyguanosine
	(urine, serum, WBC)
Autoimmune reactions	oxidized LDL IgG antibodies (plasma)
against neoepitopes of	IgM against neoepitopes, e.g. phosphatidyl inositol,
fatty acids	and oleic, palmitic and myristic acid (serum)
proteins	IgM against NO-tyrosine, NO-tryptophan and
	NO-albumin (serum bovine albumin) (serum)

as antioxidants after been used in antioxidant processes. b) Glutathione is employed by the white blood cells as a source of energy used for lymphoproliferation. Therefore, glutathione may help increase the resistance to bacterial and viral infections. c) Glutathione is a natural purifier and therefore high concentrations are found in the liver (Maes, in press). As early as 1934, reduction in blood concentration of GSH in major psychiatric disorders has been documented, however attention to this area has lapsed for almost three quarters of a century (Looney and Childs, 1934). More recently, Kodydková et al. (2009) found that depressed women have significantly decreased blood concentrations of GSH. More studies on GSH were performed in animal models of depression showing lowered GSH. These studies will be reviewed in this paper.

Coenzyme Q10 (CoQ10) is a strong anti-oxidant that confers resistance to mitochondrial damage by O&NS and that may suppress the production of proinflammatory substances, like nuclear factor κ B (NFκB)-gene expression and the production of pro-inflammatory cytokines (Schmelzer et al., 2007a; 2007b; 2008; Abd El-Gawad and Khalifa, 2001; Sugino et al., 1987; Chaturvedi and Beal, 2008). Recently, it was found that major depression is characterized by significantly lower serum concentrations of CoQ10 as compared to normal controls. Up to 51.4% of the major depressed patients have plasma CoQ10 values lower than the lowest CoQ10 value established in the normal volunteers, i.e. 490 μg/L. This means that many major depressed patients suffer from a low CoQ10 syndrome. Since CoQ10 has anti-oxidant and anti-inflammatory effects, the low CoQ10 syndrome in depression predisposes towards an impaired antioxidant protection against the damaging effects of O&NS and a greater production of proinflammatory cytokines, such as tumor necrosis factor α (TNFα), which may cause more damage (Maes et al., 2009a).

There is one paper showing that plasma ascorbic acid levels are decreased in patients with major depression as compared to normal controls (Khanzode et al., 2003). It may be suggested that the lowered blood concentrations of zinc, CoQ10, vitamin E and C and GSH may contribute to a lowered total antioxidant capacity (TAC) in the blood that has been described in depression. Thus, Cumurcu et al. (2009) found that TAC was significantly lower in 57 patients with major depression than in 40 healthy volunteers. Moreover, a significant and inverse correlation was established between TAC and the severity of depression using the Montgomery-Asberg Depression Rating Scale. Gałecki et al. (2009a) observed that the lower TAC levels in depression did not normalize after treatment with antidepressants or when the patients were in remission, suggesting that lower TAC is a state marker for depression. One potential explanation for the differences in some of these antioxidants is habitual diet. There is new evidence that a 'traditional' (healthy) dietary pattern is associated with reduced odds for current major depression/dysthymia, whereas a 'western' (unhealthy) dietary pattern is associated with increased risk for mood disorders (Jacka et al., 2010).

2.2. Antioxidant enzymes

GPX is one of the antioxidant enzymes involved in scavenging free radicals (Joseph, 1995). The GPX family comprises different isoforms, two of which are present in high concentrations in blood, i.e. cellular GPX1 expressed in red blood cells and extracellular GPX3 found in plasma and expressed in other organs (Chu et al., 1992). GPXs catalyze the reduction of hydrogen peroxide at the expense of glutathione, which is used as the ultimate electron donor to regenerate the reduced form of selenocysteine (Ceballos-Picot et al., 1992; Forstrom et al., 1978; Ursini and Bindoli, 1987). Therefore, GPXs are important antioxidant enzymes, which scavenge free radicals (Herbette et al., 2007). There are now some data showing that lower GPX plays a role

in the pathophysiology of major depression. Kodydková et al. (2009) reported that depressed women showed significantly lower GPX1 activity. Ozcan et al. (2004) reported that GPX activity was significantly lower in patients with affective disorders than in controls. Maes et al. (2010b) detected that whole blood GPX activity was significantly lowered in major depression as compared to normal controls. In addition, significantly negative correlations were found between GPX activity and the severity of depression. Lower GPX activity may predispose towards an impaired antioxidant protection and consequently O&NS-induced damage to membrane fatty acids and functional proteins and, by inference, to neurotoxic damage, and hence the process of neuroprogression that accompanies severe or persistent illness (Berk, 2009).

Others, however, were unable to find significantly lower GPX activities in the plasma or polymorphonuclear leukocytes of depressed or bipolar patients and controls (Srivastava et al., 2002; Gałecki et al., 2009a; Andreazza et al., 2009). Andreazza et al. (2009), however, did not examine major depressed patients but they assayed GPX activity in bipolar disorder. Srivastava et al. (2002) assayed GPX activity in peripheral blood mononuclear cells and not in whole blood GPX. It should also be added that translational research detected lower GPX activity in experimental models of depression, such as in the bulbectomized rat and in Wistar rats with chronic mild stress (CMS)-induced depression (Song et al., 1994; Eren et al., 2007a,b).

Catalase is a very common enzyme that catalyzes the reduction of hydrogen peroxide to water and oxygen and mediates signalling in cell proliferation, apoptosis, carbohydrate metabolism, and platelet activation (Chelikani et al., 2004; Góth et al., 2004). Humans with low catalase levels (acatalasemia) have an increased risk for diabetes mellitus, while the clinical features of acatalasemia are oral gangrene, altered lipid, carbohydrate, homocysteine metabolism and the increased risk of diabetes mellitus (Góth et al., 2004). Mice with acatalasemia show exacerbated tissue injury to oxidative stress and increased irreversible fibrosis, suggesting that catalase plays a crucial role in the defence against oxidant-mediated peritoneal injury (Fukuoka et al., 2008). A few studies have examined catalase activity in depressed patients. Gałecki et al. (2009a) found increased catalase activity levels during acute episodes of depression as compared to healthy volunteers. Szuster-Ciesielska et al. (2008) also detected increased serum catalase enzyme activities in patients with major depression. Increased catalase activity may reflect a compensatory mechanism that aims to attenuate the induced O&NS pathways, and is congruent with a signalling role of oxidative free radicals.

SODs are a family of enzymes, co-factored with copper and zinc (CuZnSOD), which catalyze the dismutation of superoxide into oxygen and hydrogen peroxide. In humans, three form are present, i.e. SOD1, a dimer located in the cytoplasm; SOD2, a mitochondrial tetramer; and SOD3, an extracellular tetramer. SOD2 is a first line of protection against the superoxide produced during oxidative phosphorylation (Li et al., 1995). Mice lacking SOD2 are exposed to massive amounts of oxidative stress and die soon after birth (Li et al., 1995). Mice lacking SOD1 have persistent and widespread oxidative damage throughout their life span and develop hepatocellular carcinoma (Elchuri et al., 2005). These findings show that SOD is a key antioxidant enzyme. The studies performed in depression, however, show contradictory results. Gałecki et al. (2007) detected lowered platelet SOD1 activities in depressed patients as compared to controls, although these differences did not reach significance. Selek et al. (2008) reported lowered SOD activity in depressed patients. Herken et al. (2007) also found lowered SOD levels in depressed patients. Sarandol et al. (2007), however, detected a significantly increased SOD activity in depression that was significantly correlated to the severity of illness. Andreazza et al. (2007) found increased activity as well an increased SOD / GPX plus catalase ratio, in depressed patients. During the acute phase of illness, depressed patients had significantly higher activity levels of SOD1 as compared to healthy controls (Gałecki et al., 2009a). During treatment with antidepressants the increased SOD1 levels normalized (Gałecki et al., 2009a). Szuster-Ciesielska et al. (2008) found significantly increased serum activity of SOD in depressed patients. Finally, in post-mortem brain tissue of patients with recurrent depressive disorder increased SOD activity has been found in the prefrontal cortex (Michel et al., 2007). Increased SOD activity probably reflects an upregulated SOD system in defence against increased ROS and free radicals in depression. At first sight these results may seem contradictory. A factor that may explain the differences in outcome of these studies is stage or duration of illness (Berk et al., 2007a,b; Maes et al., 2010a). In bipolar disorder, there is evidence that there are stage related alterations in oxidative and inflammatory markers, which may be due to failure of compensatory mechanisms with the process of neuroprogression (Andreazza et al., 2009; Kauer-Sant'Anna et al., 2009). As will be discussed in the next paragraph, there may exist a biphasic response in ROS production, which could account for differences between studies (Maes et al., 2010a).

3. ROS and RNS in depression

There are now many studies showing increased ROS and RNS in depression. The findings entail increases in ROS, such as peroxide levels and increased enzyme activities of prooxidant enzymes, such as xanthine oxidase (XO), changes in nitric oxide (NO) levels, and signs of damage caused by O&NS to fatty acids and DNA. In this section we will focus on peroxide, NO, inducible NO synthetase (iNOS) production and XO levels.

Peroxide is one of the ROS that circulates in the blood. Recently, Maes et al. (2010a) published that major depressed patients have significantly increased plasma peroxide levels as compared to normal controls. However, no significant correlations between the increased plasma peroxide values and the severity of depression could be established. Importantly, it was found that the peroxide levels were significantly higher in patients in a more acute phase of their illness than in patients who suffered from chronic depression (more than two years duration), while the latter did not differ significantly from normal controls (Maes et al., 2010a). Thus, increased peroxide levels are confined to patients who are in a more (sub)acute phase of their illness. Normalization of ROS may occur when the depression tends to become more chronic. Another finding was that the increases in plasma peroxide levels were more pronounced in depressed men than in depressed women. Katalinic et al. (2005) reported greater ROS responses in males than in females and gender-related differences in susceptibility to oxidative stress. This suggests that future research on O&NS pathways in depression should always take into account the duration of illness and the gender-related differences in O&NS responsivity.

NO is synthesized from L-arginine by NOS, a family of enzymes, consisting of a constitutive (cNOS) and an inducible (iNOS) form. The latter is induced by cytokines and generates the inflammatory effects of NO. NO is an important messenger molecule that plays a role in many (patho)physiological processes (Hou et al., 1999). NO has many functions, including smooth muscle relaxation, vasodilatation, neurotransmission, immunomodulating, non-specific defense against microorganisms, and platelet aggregation inhibition. During inflammation, NO production may cause tissue toxicity after reacting with superoxide anions, which generates peroxynitrite anions and peroxynitrous acid. These compounds may nitrate aromatic compounds as tyrosine and phenylalanine, resulting in the generation of NO-tyrosine (Lin et al, 2000). It is believed that the L-arginine-NO pathway plays a role in the pathophysiology of depression and in the mechanisms of action of antidepressants (Pinto et al., 2008).

NO measurements obtained in individuals with depression, however, are mixed. Selek et al. (2008) detected that the NO levels are significantly increased in depressed patients. In 44 bipolar

patients, significantly higher plasma NO levels were detected than in 21 normal controls (Savaşş et al., 2002). NO levels are significantly higher in leukemia or colorectal carcinoma patients with depression than in patients without depression (Zhou et al., 2006; Wei et al., 2009). Kim et al. (2006) measured plasma NO metabolite (NOx) levels in 39 depressive patients who had recently attempted suicide, in 44 non-suicidal depressed patients and 70 normal controls, and found significantly higher plasma NO(x) levels in suicidal depressive patients than in non-suicidal depressive patients or normal controls. In another study, patients with chronic hepatitis C underwent cytokine-based immunotherapy with interferon-α (IFNα) (Suzuki et al., 2003). Of the 146 patients treated, 17 developed depression, some the first 4 weeks after treatment. In those patients plasma nitrate was significantly increased during IFNα treatment. The authors conclude that NO is involved in IFNα-induced depression characterized by an earlier onset. In polymorphonuclear leukocytes from depressed patients, Srivastava et al. (2002) detected a 73% decrease in nitrite content as compared to normal controls. In 30 patients with affective disorders lower NO levels were found than in 21 normal controls (Ozcan et al., 2004). Baseline plasma NO levels are significantly lower in 40 major depressed patients than in 30 age- and sex matched controls (Ikenouchi-Sugita et al., 2009). Chrapko et al. (2004) found that the levels of both plasma NOx and platelet endothelial NOS activity were significantly lower in depressed subjects than in normal controls.

In the locus coeruleus (LC) from 11 to 12 matched pairs of major depressed patients, neuronal NOS (nNOS) immunoreactivity was significantly lower in the LC, but not in the cerebellum, as compared to control subjects (Karolewicz et al., 2004). In a study using stereological analysis, the number of NOS-expressing neurons is greatly reduced in depression (Bernstein et al., 2005). In a immunohistochemical study, it was detected that the cellular expression of NOS in the neurons of the nucleus suprachiasmaticus (SCN) was significantly lower in depressed patients than in matched controls. Patients with major and bipolar depression have greater numbers of nNOS expressing neurons in the CA1 and subiculum regions as compared with controls (Oliveira et al., 2008). In the rodent, Wang et al. (2008) found that suppression of hippocampal iNOS prevents the development of chronic unexpected mild stress-induced depression. Inhibitors of nNOS and iNOS display antidepressant-like effects (Volke et al., 2003; Gigliucci et al., 2010). There is also evidence that NOS activity is involved in the mechanism of action of antidepressants (Finkel et al., 1996).

XO catalyzes the oxidation of xanthine, a process that generates ROS, superoxide and hydrogen peroxide, and RNS (Harrison, 2004). XO-generated O&NS has been implicated in ischemia/reperfusion injury and multisystem organ failure (Meneshian and Bulkley, 2002). Herken et al. (2007) analyzed serum XO concentrations in 36 major depressed patients and 20 normal controls and detected significantly higher XO levels in the patients. In post-mortem brain tissue of patients with recurrent depressive episodes increased XO activity has been detected in cortico-limbic-thalamic-striatal regions (Michel et al., 2008).

4. Damage by O&NS in major depression

4.1. Oxidative damage

The abovementioned results show that there is evidence for lowered antioxidant defences and increased ROS and RNS in patients with major depression. Throughout their lifespan depressed patients may be challenged with several depressive episodes, associated with (sub)chronic inflammatory responses and by inference with significantly increased ROS/RNS production. Increases in ROS/RNS and decreased antioxidant defences may cause oxidative and nitrosative modifications of cellular molecules, such as fatty acids, proteins and DNA. Consequently, O&NS may have detrimental effects on membrane fatty acids, the function and stability of proteins, and DNA damage and its repair mechanisms as well. If unchecked, this may result in apoptois, and in part explain the brain volumetric changes evident in depression. This paragraph aims to discuss findings on O&NS damage to different substrates.

4.2. Oxidative damage to lipids and fatty acids in depression

The first reports showing that depression may be accompanied by an increased oxidative damage to fatty acids came from studies showing lowered omega-3 fatty acid fractions in depression (Edwards et al., 1998; Maes et al., 1999). Polyunsaturated fatty acids (PUFAs) are very vulnerable to lipid peroxidation. Edwards et al. (1989) reported oxidative damage to the red blood cell membranes suggesting increased long-chain degradation via peroxidation. Maes et al. (1999) computed the oxidative potential index (OPI) as an index to estimate the tendency of fatty acids to oxidize (Anttolainen et al., 1996). It was found that depression is associated with a significantly lowered OPI, suggesting that the potential of phospholipids to be oxidized is decreased. This could be the consequence of previously increased long-chain degradation via peroxidation.

Assays of malondialdehyde (MDA), a byproduct of polyunsaturated fatty acid peroxidation and arachidonic acid, is employed as a measure for lipid peroxidation and thus also for oxidative stress. MDA is a reactive aldehyde or reactive carbonyl compound that may modify proteins to generate advanced lipoxidation end (ALE) products. ALEs have detrimental effects as they are pro-inflammatory, weaken the antioxidant defences, and impair DNA repair. ALE additionally play a key role in atherosclerosis and neurodegenerative disorders (Aldini et al., 2007). Khanzode et al. (2003) found that major depression is associated with significantly increased MDA serum levels. Ozcan et al. (2004) detected increased MDA concentrations in 30 patients with affective disorders as compared with 21 healthy controls. Gałecki et al. (2009a) found increased MDA levels in the peripheral blood of major depressed patients as compared to healthy subjects. Moreover, treatment with antidepressants, e.g. fluoxetine, reduced MDA levels (Gałecki et al., 2009a). Serum MDA levels are significantly increased in depressive patients with gastric adenocarcinoma (Wei et al., 2009). Also, Sarandol et al. (2007) found that plasma MDA levels are significantly higher in 96 major depressed patients as compared to 54 controls. MDA concentrations are significantly higher in patients with acute leukemia who are depressed than in those without depression (Zhou et al., 2006). The assay of thiobarbituric acid reactive species (TBARS) is another very commonly used method to quantify MDA. Gałecki et al. (2007) found significantly increased TBARS concentrations in depressed patients when compared to healthy volunteers. In another study, TBARS levels were increased in bipolar patients regardless of the phase of the disorder (Andreazza et al., 2007).

Other findings corroborate the presence of increased lipid peroxidation in major depression. Dimopoulos et al. (2008) measured plasma 8-iso-prostaglandin F2α, a bioactive product of free radical-catalyzed peroxidation of arachidonic acid. These authors found that elderly depressed patients showed significantly higher 8-iso-prostaglandin F2α than normal controls. Moreover, the plasma levels of this lipid peroxidation marker are significantly correlated to the severity of depression. In a post-mortem brain study, Wang et al. (2009) found increased 4-hydroxynonenal (4-HNE) in the anterior cingulate cortex of bipolar patients. 4-HNE is a major aldehyde product generated by lipid peroxidation of omega-6 PUFAs like arachidonic acids and linoleic acid by peroxides and ROS.

4.3. Damage to DNA in depression

In normal conditions, ROS and RNS attack nuclear and mitochondrial DNA causing oxidized nucleosides and, consequently, mutagenic

DNA lesions. One of these lesions is 8-hydroxy-2'-deoxyguanosine (8-OHdG), the end product of the hydroxylation of guanine. The DNA lesions are consequently removed by the base excision repair (BER) pathway, which prevents replication of DNA lesions. Moreover, O&NS, such as the NO-mediated pathways and MDA, inhibit the BER system through direct interactions with cellular repair proteins (Jaiswal et al., 2001; Feng et al., 2006). Since the BER pathway removes the mutagenic 8-OHdG lesions, the inhibitory effects of O&NS pathways on BER activity may potentiate mutagenesis and DNA damage. Once eliminated, the 8-OHdG lesions may be found in the plasma and are excreted in the urine (Wu et al., 2004; Bohr et al., 2002). The assay of 8-OHdG in urine is a biomarker for oxidative DNA damage and more general for O&NS (Wu et al., 2004; Valavanidis et al., 2009).

There are now some reports that major depression is accompanied by increased 8-OHdG, indicating oxidative damage to DNA by ROS. Serum levels of 8-OHdG are significantly increased in depressed patients and are higher in patients with recurrent depressive episodes (Forlenza and Miller, 2006). 8-OHdG is significantly higher in peripheral leukocytes of depressed patients (Irie et al., 2005). Colorectal carcinoma patients with depression have significantly higher serum 8-OHdG levels than those without depression (Wei et al., 2009). Maes et al. (2009b) found a significantly higher 8-OHdG excretion in morning urine in depressed patients with "comorbid" chronic fatigue as compared to normal volunteers. Andreazza et al. (2007) using a single cell gel electrophoresis assay (comet assay) detected an increased frequency of DNA damage in bipolar patients as compared to normal controls. Telomere shortening is additionally reported in mood disorders, thought to be a consequence of this process (Simon et al., 2006).

Mitochondria constantly generate ROS, which are released during oxidative processes that take place in the mitochondria. Antioxidants, such as CoQ10, confer protection against the generation and damaging effects of ROS that are released during the oxidative processes in the mitochondria (Chaturvedi and Beal, 2008; Liu, 2008). Therefore, the low CoQ10 syndrome in depression predisposes towards mitochondrial dysfunctions including O&NS damage to mitochondrial DNA. Mitochondrial disturbances including decreased gene expression and deletions of mitochondrial DNA have frequently been detected in major depression (Shao et al., 2008; Gardner et al., 2003; Suomalainen et al., 1992). The involvement of mitochondrial disturbances in the pathophysiology of depression is reviewed in another paper in this special issue (Gardner and Boles, 2010).

4.4. Nitrosative damage to proteins in depression

As described above, ROS and RNS may cause the formation of NO-tyrosine. The nitration of tyrosine can be employed as a footprint for the in vivo production of ROS/RNS. One study examined NO-tyrosine levels in bipolar patients and found increased NO-tyrosine levels in the patients as compared to controls in the early and late stages of illness (Andreazza et al., 2009). These data suggest that damage due to tyrosine nitration in patients with bipolar disorder may be present from the early phase of illness.

5. Evidence for autoimmune responses against neoepitopes formed by damage to membrane fatty acids and proteins

5.1. Increased oxidized LDL antibodies

IgG autoantibodies against oxidatively modified low density lipoproteins (LDL) reflect O&NS and lipid peroxidation that takes place in vivo. During LDL oxidation, neoepitopes are formed that are strongly immunogenic and may result in the generation of IgG and IgM-mediated autoimmune responses. The latter can be measured in the blood (Mandal et al., 2005). The oxidized LDL (oxLDL) IgG autoantibodies are probably pro-atherogenic (Gounopoulos et al., 2007) and their presence predicts myocardial infarction and progression of carotid atherosclerosis (Vaarala, 2000). Increased oxLDL antibodies can be detected in many disorders, like cardiovascular disorders, e.g. atherosclerosis, and autoimmune disorders, e.g. systemic lupus erythematosus and diabetes (Hulthe, 2004; Steinerová et al., 2001; Kobayashi et al., 2005). Recently, it was published that major depressed patients have significantly increased serum oxLDL antibodies as compared to normal controls (Maes et al., 2010a). These results show that depression is accompanied by increased lipid peroxidation and by autoimmune responses directed against the damaged lipids. These results also show that those depressed patients are at risk for atherosclerosis and may have developed atherosclerotic lesions already (Maes et al., 2010a). The meaning of the oxLDL antibody findings for the comorbidity between depression and cardiovascular disorder will be discussed in another paper in this special issue (Maes et al., 2010c).

5.2. Increased IgM responses to membrane fatty acids in depression

During inflammation, lipid membranes and thus brain, muscle, and nerve cells can be damaged through lipid peroxidation (Maes et al., 2007). As explained above, these processes may be accompanied by chemical modifications of lipids, which may change the structure of ubiquitous epitopes thereby generating a variety of neoepitopes, which may be immunogenic (Shaw, 2004). Consequently, an IgG or IgM mediated autoimmune response can be mounted against these neoepitopes, which may further change the biological activities of the epitopes and damage the fatty acid structures. A number of oxidatively changed self-antigens may be measured, like phosphatidyl inositol (Pi) (Maes et al., 2007). The latter is an important intracellular component of the cell membrane. Inflammatory disorders, such as multiple sclerosis and Guillain Barre syndrome, are frequently accompanied by autoimmune responses directed against Pi (Nakos et al., 2005; Bodet et al., 2004). Lower inositol CSF levels have been detected in depression, while inositol may have some clinical utility in the treatment of depression (Barkai et al., 1978; Levine et al., 1993). It was found that in depression there was a significantly higher IgM-mediated immune response directed against Pi than in volunteers (Maes et al., 2007). Furthermore, the IgM-mediated autoimmune response against Pi was significantly and positively correlated to symptoms such as sadness and fatigue. This autoimmune response is probably related to acute inflammation because a) in multiple sclerosis (MS), the IgM antibody titres appear during relapses and decrease during remissions (Bodet et al., 2004); and b) treatment with gamma globulin intravenously decreases anti-Pi autoantibody levels soon after starting the treatment (Nakos et al., 2005). Pi is not only an important membrane constituent but it is also essential for intracellular processes that may be jeopardized by the autoimmune responses to the Pi neoepitopes generated through damage by oxidative stress. For example, Pi is converted to phosphatidylinositol-4,5-bisphosphate (PIP2), which in turn is the precursor of important second-messenger molecules, like inositol-1,4,5-triphosphate (IP3), diacylglycerol and phosphatidylinositol-3,4,5-triphosphate (PIP3). These molecules modulate intracellular calcium levels, regulate cell survival, growth, polarization and proliferation, activate phosphorylization of cellular proteins, function as lipid messengers at the plasma membrane to the effector in the nucleus, and activate protein kinase C (PKC) (Ananthanarayanan et al., 2005). Pi is also required for proper functioning of the neurotransmitter serotonin (Akin et al., 2004).

Other auto-antigens, which have been shown to be oxidatively modified in depression are oleic, palmitic and myristic acid. Thus, Maes et al. (submitted for publication) found significantly higher IgM antibody levels against anti palmitoyl, myristoyl and oleoyl in depressed patients than in normal controls. As explained above, this indicates that the natural lipid structures of cell membranes made up by those fatty

acids are oxidatively modified to generate neoepitopes that have acquired immunogenicity. Remitting-relapsing MS is also accompanied by increased IgM antibodies directed against those lipids (Geffard et al., 2002; Boullerne et al., 1996). Since these fatty acids are constituents of myelin, it may be hypothesized that these results show that damage to myelin contributes to lesion persistence in MS through peroxidation and consequent autoimmune-induced phagocytosis.

5.3. Increased IgM antibodies against nitrated neoepitopes in sera of depressed patients

Indirect evidence for NO involvement in major depression comes from the characterization of circulating antibodies against NO-epitopes. Strong oxidants, like peroxynitrite anions, are able to nitrate amino acids like tyrosine, tryptophan, arginine, etc., as well as proteins, like albumin or serum bovine albumin (SBA) containing these amino acids. The post-translational modification of the amino acids generates new epitopes to which T and B lymphocytes are not rendered tolerant and thus may serve as a trigger to impair or bypass immunological tolerance (Ohmori and Kanayama, 2005). Phrased differently, nitration reactions result in the formation of highly reactive substances such as NO-tyrosine, NO-tryptophan and NO-arginine (Lin et al, 2000). Maes et al. (2008a; submitted for publication) found significantly increased IgM antibody levels against NO-SBA and NO-tyrosine, NO-tryptophan and NO-arginine in depressed patients as compared to normal controls. Since the nitration of SBA and those amino acids offers a footprint of NO-dependent modification of proteins, the results suggest that increased NO and/or activation of nitration reactions and consequent increases in nitrated containing proteins may be involved in the pathophysiology of depression. These findings suggest that the contradictory results on NO levels in depression indicate that temporarily increases in NO, which are often but not always detected in depression, are sufficient to cause a more persistent nitration of amino-acids and proteins.

6. Polymorphism in O&NS genes in depression

In this section we will discuss the importance of single nucleotide polymorphism (SNP) in O&NS genes in depression. Previously, significant associations of depression with different SNPs of selected cytokine genes were found. Thus, Yu et al. (2003) found depression to be associated with a polymorphism of the interleukin-1 (IL-1) gene, suggesting that T allele carriers have less severe depressive symptoms. Bull et al. (2009) found an association between IL-6 polymorphism and reduced risk of depressive symptoms. SNPs in the TNFα-gene (Jun et al., 2003), monocyte chemoatractant protein -1 (Pae et al., 2004) and genes critical for T-cell functions are associated with susceptibility to depression (Wong et al., 2008).

Significant associations between depression and IO&NS genes, like cyclooxygenase-2 (COX-2), SOD and myeloperoxidase (MPO), have been established. COX-2 is involved in the pathophysiological mechanisms of various inflammatory disorders (Dubois et al., 1998). COX-2 is stimulated by pro-inflammatory cytokines and lipopolysaccharide (LPS) (Dubois et al., 1998; Minghetti, 2004) and participates in the synthesis of prostanoids, like PGE_2 (Smith et al., 2000). Increased activity of COX-2 results in the generation of free radicals and O&NS (Kuehl and Egan, 1980; Madrigal et al., 2003; Vesce et al., 2007). In animal models of depression an increased COX-2 expression was detected in the cortex and hippocampus (Cassano et al., 2006; Guo et al., 2009). Co-therapy with antidepressants and COX-2 inhibitors is effective in the treatment of depression (Müller et al., 2006) and reduces O&NS in depression (Gałecki et al., 2009b). In the promoter of the COX-2 gene, a SNP G-765C has been found (Levy-Lahad et al., 1995). This polymorphism is associated with promoter activity and COX-2 expression: the GG homozygote is associated with an increased expression of COX-2 (Levy-Lahad et al., 1995). Recently, it was reported that the G allele and GG homozygote frequencies are significantly higher in depression (Gałecki et al., in press-b). The GG homozygote not only increases the risk to develop depression but also that of neurodegenerative disorders, such as stroke (Cipollone et al., 2004) and Alzheimer's disease. COX-2 inhibition plays a role in the treatment of depression and in the prevention of these neurodegenerative disorders as well (McGeer and McGeer, 2007).

Shimoda-Matsubayashi et al. (1996) examined the role of the functional SNP Ala-9Val, that results in manganese SOD conformation changes. The functional consequence of this genetic dismorphism incorporating alanine or valine in the mitochondrial targeting sequence of MnSOD modulates a slower mitochondrial import of MnSOD and mRNA instability due to impaired cotranslational import (Sutton et al., 2005). Shimoda-Matsubayashi et al. (1997) found an association between the SNP of Ala-9Val and the mitochondrial expression of MnSOD. In Caucasians, an association study using the Ala-9Val polymorphism showed a significant allelic deviation for the -9Ala allele in depressive females (Gałecki et al., 2010). Pae et al. (2006), on the other hand, found that patients with (bipolar) depression and controls had a similar distribution of the alleles and genotypes in the Ala-9Val polymorphism. These contradictory results may be explained by ethnic differences between the Caucasian and Korean populations. The functional SNP Ile-58Thr in the MnSOD gene affects enzyme stability and activity (Borgstahl et al., 1996, Ho and Crapo, 20008). However, Gałecki et al. (2010) were unable to find an association between Ile-58Thre MnSOD polymorphism and depression in a Caucasian population.

MPO is a myeloid-specific enzyme, that is expressed by neutrophils, monocytes, microglial cells (Yap et al., 2007) and hippocampal neurons (Green et al., 2004). MPO generates potent oxidants, such as hypochloric acid (Spickett et al., 2000), and induces the production of proinflammatory cytokines (Lefkowitz and Lefkowitz, 2008). During chronic inflammatory processes, MPO activation is involved in cell damage (Malle et al., 2007). Piedrafita et al. (1996) found the functional SNP G-463A in the MPO gene, characterized by a G to A transition: the presence of the -463G allele causes increased expression of MPO, whereas the -463A allele decreases the expression of MPO via destruction of the transcriptional factor binding site (Piedrafita et al., 1996). This polymorphism is associated with inflammatory diseases (Hoy et al., 2001, 2002). Recently, polymorphism in the MPO gene was found to be associated with susceptibility to depression (Gałecki et al., in press-a). The GG homozygote and the G allele increase the risk towards depressive disorder (Gałecki et al. (in press-a)). Interestingly, the GG homozygote also increases the risk of neurodegenerative disorders, such as Alzheimer's disease (Crawford et al., 2001).

Catalase (CAT) is - as explained - another antioxidant enzyme participating in the first line defense against free radicals and their derivatives. The -262C>T polymorphism of the CAT gene is associated with an increased CAT expression and activity. No significant association could be detected between this -262C>T polymorphism of the CAT gene and major depression (Gałecki et al., 2009c). Future research should examine the association between functional polymorphisms of other CAT genes and other O&NS genes, like GPX, glutathione-S-reductase, tioredoxin, etc. (Winter et al., 2003; Bohanec Grabar et al., 2009; Mitchell et al., 2009).

7. Conclusions of the clinical studies in depression

Table 2 summarizes that depression is accompanied by a specific O&NS profile characterized by:

a) lowered antioxidants, such as zinc, vitamin E and C, glutathione and CoQ10, lowered levels of antioxidant enzymes, like GPX, and a lowered total antioxidant capacity of the blood;
b) increased ROS as demonstrated by increased peroxide levels and XO activity;

Table 2
Short summary of the key findings in major depressed patients and in animal models of depression.

O&NS variables	Human depression	Animal depression
Antioxidants		
lower tryptophan, tyrosine, albumin	↓↓	↓↓
lower vitamin E	↓	
lower vitamin C	↓	
lower glutathione	↓↓	↓↓
lower coenzyme Q10	↓	
Antioxidant enzymes		
glutathione peroxidase	↓↓↔	↓↓
catalase	↑↑	
superoxide dismutase	↓↑	
total antioxidant capacity in blood	↓	↓
ROS		
peroxides	↑	
xanthine oxidase	↑↑	
RNS		
nitric oxide (NO)	↑↓	
Lipid damage		
malondialdehyde	↑↑	↑↑
8-iso-prostaglandinF2α	↑	
4-hydroxynonenal	↑	
Protein damage		↑
nitrotyrosine	↑	
DNA damage		
8-hydroxy-deoxyguanosine	↑↑	
Autoimmune reactions against lipid neoepitopes		
oxidized LDL IgG antibodies	↑	
IgM against neoepitopes, e.g. phosphatidyl inositol, and oleic, palmitic and myristic acid	↑	
Autoimmune reactions against protein neoepitopes	↑	
IgM against NO-tyrosine, NO-tryptophan and NO-albumin		

↓: lowered levels; ↑: increased levels; ↔: no significant changes.

c) oxidative damage to fatty acids as measured by the oxidative potential of peripheral blood PUFAs; increased MDA and TBARS, increased 8-iso-prostaglandin F2α and 4-HNE; and nitrosative damage to proteins as measured by NO-tyrosine;
d) mounted IgG autoimmune responses against oxidized LDL and IgM responses against lipids and nitrated proteins.

Moreover, there appears to be an increased risk from SNPs in O&NS genes, such as COX-2, SOD and MPO. No consistent changes in SOD and NO could be detected. However, as explained above, differences among studies may be explained by differences in stage or duration of illness (Berk et al., 2007a,b; Maes et al., 2010a). Therefore, the more persistent and severe O&NS aberrations are more reliable markers, e.g. the damage to fatty acids, proteins and DNA, and autoimmune reactions against the neoepitopes formed by damage caused by O&NS. Although the results on NO are mixed, the increased levels of NO-tyrosine and the IgM-mediated immune responses against, for example, NO-tyrosine, NO-tryptophan and NO-albumin, show that patients with depression show an increased nitration of their proteins and, thus, that at some point the nitrosative stress was high enough to cause persistent nitration.

8. O&NS in animal models of depression

In this section, we will summarize the evidence that the above-mentioned results in clinical depression can also be detected in animal models of depression.

8.1. Lowered antioxidants and antioxidant enzymes in animal models of depression

In chronic mild stress (CMS)-induced depression in the rodent, lowered concentrations of brain glutathione are observed (Pal and Dandiya, 1994; Gutteridge and Halliwell, 1994). De Souza et al. (2006) reported that swimming and restraint stress decrease total glutathione (GSH) concentrations. In the olfactory-bulbectomized rat, another depression model, GPX activity was decreased (Song et al., 1994). In male Wistar rats, CMS-induced depression was accompanied by lowered brain cortex GPX activity (Eren et al., 2007a,b). Unpredictable chronic mild stress (UCMS) induces a lowered total antioxidant capacity, glutathione contents, and SOD and CAT activities (Zhang et al., 2009). Rats showing CMS-induced decreases in sweet food intake (a depression model) showed lower SOD activity in the prefrontal cortex, the hippocampus and the striatum (Lucca et al., 2009a; 2009b). In the same rats increased catalase activity was found in the cerebellum, hippocampus, striatum, and the cortex.

8.2. Damage to lipids and proteins caused by O&N stress in animal models of depression

In the rodent, CMS-induced depression, is accompanied by increased lipid peroxidation in the cerebellum and the striatum (Lucca et al., 2009a; 2009b). De Souza et al. (2006) found that restraint and swimming stress increases the levels of TBARS. UCMS results in elevated liver MDA levels (Zhang et al., 2009). In CMS-induced depression in the rodent increased damage to proteins has been detected in the prefrontal cortex, hippocampus, and striatum (Lucca et al., 2009a). Table 2 summarizes the O&NS findings in animal models of depression. The animal experiments show that physical and psychological stress-induced depression are accompanied by lowered antioxidant levels and increased damage to fatty acids and proteins. Thus, these data confirm those of human studies.

9. Symptom formation and pathogenetic significance

Some of the above changes in antioxidants and increased ROS/RNS or damage by O&NS may induce depression and specific symptoms of depression. As explained previously (Maes, 2009), major depression consists of different symptom profiles which show a partial overlap, i.e. melancholic (anhedonia, sadness, anorexia, weight loss, psychomotor retardation); anxiety (tension, behavior at interview - general or physiological- , and respiratory, genito-urinary and autonomic symptoms) and "functional" and "somatic" (F&S) symptoms (Maes, 2009). The latter encompass a flu-like malaise, fatigue, muscular tension, aches and pain, concentration difficulties, failing memory, irritability, irritable bowel, and headache. This symptom profile was labelled the fatigue and somatic (F&S) dimension (Maes, 2009). In this section we describe the symptom profiles of lowered antioxidants and O&NS in major depression.

9.1. Symptom profiles of lowered antioxidant levels

The low COQ10 syndrome in depression is associated with chronic fatigue, one of the F&S symptoms (Maes et al., 2009c). CoQ10 is not only a strong antioxidant that confers resistance to O&NS damage to mitochondria, but it is also a key molecule in the electron transport chain within the mitochondria (Butler et al., 2003; Crane, 2001). On the inner membrane of the mitochondria, CoQ10 transfers electrons, which are needed in the respiratory chain and the synthesis of adenosine triphosphate (ATP) that powers the energy in our cells and our body (Butler et al., 2003; Crane, 2001; Dutton et al., 2000). This alone may explain the fatigue that occurs during the low CoQ10 syndrome. Different reports have shown that lowered plasma CoQ10 concentrations following treatment with statins may induce fatigue (Langsjoen et al., 2005; Passi et al., 2003). This type of statin-induced fatigue is reversible upon supplementation with CoQ10 (Langsjoen et al., 2005; Passi et al., 2003). Treatment with statins induces a 40% reduction in plasma CoQ10 to levels that are detected in the depressed patients (Mabuchi et al., 2005, 2007; Chu et al., 2006; Langsjoen et al.,

2005; Passi et al., 2003). This suggests that the low CoQ10 levels found in major depression are in the range that can cause the fatigue following treatment with statins. Other reports show that low plasma CoQ10 may occur in disorders that are accompanied by fatigue, like autosomal recessive CoQ10 deficiency, mitochondrial disorders, and the Prader-Willi syndrome (Butler et al., 2003; Siciliano et al., 2001; Gempel et al., 2007; Sobreira et al., 1997). The abovementioned findings indicate that the low CoQ10 syndrome in depression is more related to the F&S symptoms rather than to the anxiety or melancholic symptoms.

Another study showed that lowered GPX activity in depression is significantly related to the presence of F&S symptoms, like autonomic symptoms (Maes et al., 2010b). There is now ample evidence that GPX and glutathione are involved in autonomic system activity. Thus, GSH has inhibitory, whereas glutathione disulfide (GSSH) has stimulatory effects on sympathetic nerve activity (Murakami et al., 1987). In patients with hepatitis-C, systemic depletion of GSH is associated with dysfunctions of the cardiac vagal system (Barbaro et al., 1997). In animal models, i.e. stress-exposed rats, reduced glutathione is correlated to increased sympathetic activity (Mercanoglu et al., 2008). Vagal nerve stimulation may have antidepressant effects (Rush and Siefert, 2009).

9.2. Symptom profiles of damage by O&NS

Recently, it was reported that increased urinary 8-OHdG is significantly related to F&S symptoms, such as a flu-like malaise and muscle tension, and also to sadness (Maes et al., 2009b). Thus, the oxidative damage to DNA may be related to key F&S symptoms and to depressive symptoms as well. The increased oxLDL antibodies were significantly correlated to two F&S symptoms, headache and irritable bowel syndrome (IBS). In depression IBS may be a clinical expression of gut-derived inflammation (Maes et al., 2008b; Maes and Leunis, 2008). The same authors hypothesized that this relationship points towards the presence of increased bacterial translocation and consequent induction of the IO&NS pathways in some depressed patients.

The mounted IgM-mediated immune response to Pi was found to be significantly related to fatigue and sadness (Maes et al., 2007). Finally, significant positive correlations were found between serum IgM levels directed against NO-BSA and the F&S symptoms, aches and pain and muscular tension (Maes et al., 2008a). All the abovementioned findings suggest that increased peroxidation and nitration of proteins with subsequent autoimmune responses against the newly formed neoepitopes may induce specific F&S symptoms. Equally, in chronic fatigue syndrome (CFS), significant correlations were detected between F&S symptoms, like aches and pain, muscular tension and fatigue, on the one hand, and decreased antioxidant defences (Vecchiet et al., 2003), and increased serum IgM levels directed against oxidatively modified lipid, on the other (Maes et al., 2006). It has been posited that the damage caused by O&NS may be a causal factor in F&S symptoms, like fatigue, pain and muscle tension. For example, Jammes et al. (2005) reported that in CFS the response to incremental exercise associates an increased O&NS with marked alterations of muscle membrane excitability. Administration of N-acetyl-cysteine, a potent antioxidant that supports glutathione homeostasis, delays muscle fatigue in exercising humans (Matuszczak et al., 2005). In hemodyalisis and cancer patients, supplementation with carnitine reduces chronic inflammation and O&NS thereby reducing fatigue (Laviano et al., 2006).

9.3. O&NS pathways leading to depression

There are many pathways through which O&NS may contribute to the pathogenesis of depression. a) Since antioxidants and antioxidant enzyme levels are decreased, there is a greater inflammatory responsivity, which may be accompanied by higher cytokine levels and, thus, more inflammation-mediated symptoms. b) Indoleamine dioxygenase (IDO), the enzyme that catabolizes tryptophan into the neurotoxic catabolites, like kynurenine, is induced by inflammation and more specifically by IFNγ. It is thought that inflammation-induced IDO may play a role in depression, through decreases in plasma tryptophan and thus brain serotonin, and increased levels of tryptophan catabolites along the IDO pathway, some of which have depressogenic and anxiogenic effects (Maes et al., 1994). Moreover, IDO is an antioxidant enzyme that utilizes the superoxide anion as an oxidizing agent (Sun, 1989). Induction of IDO represents an antioxidant defence against inflammatory reactions (Christen et al., 1990). IDO can be blocked by antioxidants, like Ebselen, etc. (Terentis et al., 2010). Thus, induction of the IDO pathway following O&NS and lowered antioxidant levels may contribute to depression. c) O&NS may cause oxidative damage to membrane polyunsaturated fatty acids (PUFAs), which may lead to an altered membrane viscosity and structure (Peet et al., 1998; Maes et al., 1999). This process may affect the expression of membrane functional proteins and receptors, including serotonergic receptors (Maes et al., 1999). d) As discussed above, intracellular molecules may be damaged by O&NS, like the Pi pathway, interfering with intracellular signalling and serotonergic turnover (Maes et al., 2007). e) Nitration of functional proteins and damage to DNA and mitochondria may cause degenerative processes, with induction of apoptosis pathways, which may occur in depression (Kubera et al., 2010). f) As discussed in Section 12, O&NS may cause neurodegeneration, which is another factor in depression.

10. Trigger factors for depression and O&NS pathways

The IO&NS theory of depression offers an explanation why depression may be caused by multiple etiological trigger factors, such as psychological stressors and the presence of (auto)immune disorders or conditions. The latter is indeed accompanied by inflammatory responses that may induce O&NS whereby NO and peroxynitrite are formed by for example activated neutrophils and monocytes, which in turn may cause oxidation and nitration of fatty acids, proteins and DNA. Examples are MS, inflammatory bowel disorder, atherosclerosis, rheumatoid arthritis, and Alzheimer's disease. Psychological stressors may generate O&NS and even cause damage to fatty acids and DNA. Firstly, emotional stressors induce inflammatory reactions with an increased production of pro-inflammatory cytokines (Maes et al., 1998), which cause ROS and RNS. Secondly, psychological stressors induce a pro-oxidant state and lipid peroxidation (Aleksandrovskii et al., 1988; Pertsov et al., 1995; Sosnovskiĭ and Kozlov, 1992). Even relatively minor stressors, such as examination stress, are accompanied by oxidative damage to DNA, sensitivity to lipid oxidation and a significantly decreased plasma antioxidant activity (Sivonova et al., 2004). In female subjects, the perceived workload, and stress, and the impossibility to cope with stress are significantly related to increased 8-OHdG levels (Irie et al., 2001).

11. Effects of antidepressant treatments on O&NS

11.1. Antidepressants in humans

Ozcan et al. (2004) found that GPX activity normalized during subchronic treatment with antidepressants. In major depressed patients, subchronic treatment with fluoxetine and citalopram partially reverses the depression-related increases in serum SOD and MDA and decreases in plasma ascorbic acid (Khanzode et al., 2003). Bilici et al. (2001) reported that a 3 month treatment with selective serotonin reuptake inhibitors (SSRIs) significantly decreased MDA levels and also the activities of different antioxidant enzymes in the blood. In another study (Gałecki et al., 2009a), the combined treatment of depressed patients with fluoxetine alone and combined

with acetylsalicylic acid during 3 months was examined. The combined treatment significantly reduced SOD, catalase and GSHPx, and the MDA levels, suggesting that this treatment improves lipid peroxidation and may normalize initially disturbed antioxidant levels. Sarandol et al. (2007) investigated 96 patients with major depression and they determined plasma MDA, the susceptibility of red blood cells to oxidation, plasma vitamin E and C, TAC, SOD and whole blood GPX activities. They found that a 6 week treatment with antidepressants did not change the disordered levels in depression. The ex vivo effects of desipramine, imipramine, maprotiline and mirtazapine on the mRNA levels of SOD isoforms, GPX, catalase, gamma-glutamylcysteine synthetase, glutathion-S-transferase and glutathion reductase were examined by Schmidt et al. (2008). These authors detected that short-term treatment with antidepressants (2.5 h) decreased antioxidant mRNA levels, whereas long-term treatment (24 hr) significantly increased the mRNA levels (Schmidt et al., 2008).

Importantly, lowered serum CoQ10 and zinc levels are hallmarks for treatment resistant depression (Maes et al., 1997, 2009c). Treatment resistance is characterized by more severe disorders in different inflammatory pathways, including increased TNFα production (Maes et al., 2009a). Thus, the lower CoQ10 syndrome and lowered serum zinc in major depression may have lowered the protection against the negative effects of IO&NS thereby inducing a refractory state to treatment with antidepressants.

11.2. Antioxidant effects of antidepressants in animal models of depression

Escitalopram, a SSRI, but not venlafaxine, a serotonin and noradrenaline reuptake inhibitor, and lamotrigine, a drug used in the prevention of recurrent depression, significantly increased GPX activity in the brain of rats subjected to CMS (Eren et al., 2007a,b). Kumar and Kumar (2009) established that in rats, subchronic (2 weeks) administration of sertraline, a SSRI, significantly improved the lowered glutathione levels following administration of 3-nitropropionic acid, a mitochondrial toxin. Zafir et al. (2009) employed the forced swimming (FST) and sucrose preference tests to identify depression-like behaviors in response to fluoxetine, imipramine, a tricyclic antidepressant (TCA), and venlafaxine following restraint stress. They found that restraint stress significantly decreased brain levels of glutathione and the activities of SOD, CAT, glutathione S-transferase and glutathione reductase; and that antidepressant treatments normalized the antioxidants and antioxidant enzymes in the brain. In the same study the authors observed that restraint stress significantly causes MDA accumulation and increased protein carbonyl contents in the brain and that antidepressants significantly attenuated this evidence of O&NS damage. In chronically stressed mice, O&NS (lipid peroxidation, nitric activity and reduced glutathione) were attenuated by treatment with imipramine, a TCA, desipramine, another TCA, and citalopram, a SSRI (Kumar and Garg, 2009). In mice, treatments with citalopram and desipramine significantly restored the reduced levels of glutathione and CAT activity, and attenuated the increased lipid peroxidation and nitrite levels following 72 hr sleep-deprivation. This shows that both antidepressants may reduce O&NS and enhance the antioxidant capacity (Garg and Kumar, 2008). Zafir and Banu (2007) examined the antioxidant potential of fluoxetine, a SSRI, versus turmeric, a natural anti-inflammatory and antioxidant substance, which shows significant antidepressive effects. They reported that fluoxetine administration for 21 days prevented the oxidative damage following restraint stress with an efficacy similar to that of turmeric. Thus, fluoxetine was able to restore the depletion of enzymes, like SOD, hydrogen-peroxide:hydrogen-peroxide oxidoreductase (EC 1.11.1.6), glutathion S-transferase (EC 2.5.1.18) and glutathione: NADP(+) oxidoreductase (EC 1.8.1.7); as well as antioxidants, like GSH and uric acid. Fluoxetine treatment also reduced (S)-lactate:NAD(+) oxidoreductase activity (EC 1.1.1.27), MDA levels and protein carbonyl contents. Bilici et al. (2009) reported that the anti-ulcer effects of mirtazapine, a tetracyclic antidepressant, may in part be explained by its interaction with O&NS pathways in the stomach, like reversal of decreased SOD levels and decreases in MDA and myeloperoxiadse. All abovementioned results suggest that antioxidants, antioxidant enzymes and O&NS represent novel targets for antidepressive treatments.

11.3. Some antioxidants have antidepressant effects

Human studies and animal models of depression provide evidence that O&NS pathways are involved in treatment resistance and in the working mechanisms of antidepressant agents. The results also suggest that major depressed patients could benefit from treatments with selected antioxidants. Drug targets are a) increasing the antioxidant levels that have been found to be decreased in depression, e.g. zinc, GSH, GPX, CoQ10 and vitamin E; and b) lowering ROS/RNS and the damage they can provoke. A major contribution was published by Berk et al. (2008a). These authors found that N-acetylcysteine, a potent antioxidant that upregulates the glutathione pathway (Dodd et al., 2008), significantly augments the clinical efficacy of antidepressants in the treatment of depression (Berk et al., 2008a; 2008b). These findings are corroborated by findings that N-acetyl-cysteine administration results in a significant decrease in the immobility time in male Wistar rats (Ferreira et al., 2008).

N-acetyl-cysteine additionally has anti-inflammatory effects and promotes neurogenesis and neuronal survival (Qian and Yang, 2009; Dean et al., 2009; Berk et al., 2008b).

The findings that an upregulation of the glutathion pathway may result in antidepressive effects is further corroborated by studies on the effects of Ebselen (2-phenyl-1,2-benzisoselenazol-3[2H]-one). This substance mimics the activity of GPX (Müller et al., 1984), a strong antioxidant enzyme that displays potent antioxidant and neuroprotective effects in vitro and in vivo (Satoh et al., 2004). In the forced swimming test in the rodent, Ebselen results in an antidepressant effect that is dependent on its interaction with the noradrenergic and dopaminergic systems (Posser et al., 2009). In mouse, Ebselen prevents induction of IO&NS pathways resulting from immobilization stress, like increased interleukin-1, COX-2 and neuronal death in the cerebral cortex (Lee et al., 2006).

Zinc has antidepressive effects and augments the efficacy of antidepressants, in particular, in the treatment of treatment resistant depression (Siwek et al., 2009). The clinical effects of zinc in treating depression are related to its antioxidative properties, effects on PUFA metabolism and stimulation of neurogenesis through an increased gene expression of brain-derived neurotrophic factor (BDNF) (Maes et al., 1997; Siwek et al., 2009). The clinical effects of zinc are explained in detail in the contribution by Szewczyk et al. (2010) to this special issue. Also, other antioxidants, e.g. flavonoids like liquiritin, a substance derived from Glycyrrhiza uralensis, have antidepressant effects. In rats with CMS-induced depression, administration of liquiritin for 3 weeks significantly reversed the increased immobility time and decreased sucrose consumption, while this flavanoid increased SOD activity, and attenuated MDA production (Zhao et al., 2008).

12. Evidence that O&NS causes neurodegeneration and lowered neurogenesis

Recently, it was reviewed that depression is associated with neurodegeneration and a reduced neurogenesis in the brain (Maes et al., 2009d; Campbell and MacQueen, 2006; Stockmeier et al., 2004; Koo and Duman, 2008). The inflammatory and neurodegenerative (I&ND) hypothesis of depression posits that neurodegeneration is caused by inflammatory processes (Maes et al., 2009d). These encompass: the neurotoxic effects of cytokines, such as IL-1beta and

TNFalpha; the neurotoxic effects of glucocorticoids; lowered ω3 polyunsaturated fatty acids (Maes et al., 2009d); and the effects of neurotoxic TRYCATs (tryptophan catabolites along the IDO pathway), which production is induced by proinflammatory cytokines. The same I&ND hypothesis also posits that O&NS may contribute to neurodegenerative processes in depression. There is now ample evidence that ROS produced in the brain by for example activated microglia are deleterious to neurons since they may overwhelm the antioxidant defences in the brain thereby causing oxidative damage to lipids, proteins and DNA, phenomena that play a key role in neuronal cell death and apoptosis. The following section summarizes the evidence that a shortage in some antioxidants and antioxidant enzymes and damage by O&NS may be involved in neurodegeneration.

12.1. Antioxidants and neurodegeneration

There is evidence that vitamin E, which includes eight different molecules, i.e. alpha-, beta-, gamma- and delta-tocopherol; and alpha-, beta-, gamma- and delta-tocotrienol, has neuroprotective activities. These neuroprotective properties may be ascribed to tocotrienols rather than to the tocopherols (Sen et al., 2006). We summarize in this section studies on vitamin E deficiency and vitamin E administration in different models of neurodegeneration. Thus, vitamin E deficiency can result in central nervous pathologies, like abnormal gait and cerebellar degeneration (Cuddihy et al., 2008). In mice expressing human apolipoprotein E4, a vitamin E deficient diet increases phospho-tau, a constituent of the neurofibrilary tangles, which can be reversed by treatment with other antioxidants (Chan et al., 2009). There is now evidence that vitamin E may have efficacy in the prevention of Alzheimer's disorder (Frank and Gupta, 2005). In the experimental cerebral hypoperfusion model, vitamin E shows neuroprotective effects (Annaházi et al., 2007). Vitamin E is beneficial in the prevention of formaldehyde-induced damage in the frontal cortex and hippocampus (Gurel et al., 2005). Vitamin E can attenuate the oxidative stress-induced cell death caused by homocysteinic and linoleic acid (Khanna et al., 2006). The abovementioned neuroprotective effects of vitamin E may be attributed to a number of antioxidative mechanisms: alpha-tocotrienol or vitamin E blocks the stroke-and glutamate-induced cell death through the suppression of C-Src kinase and 12-lipoxygenase activation (Khanna et al., 2005); regulates the genes that play a role in the clearance of amyloid beta, which explains why vitamin E has protective effects in the progression of Alzheimer's disorder (Rota et al., 2005); delays cellular loss in the dopaminergic system in zitter mutant mice, which are characterized by turnover of superoxide inducing cell death (Ueda et al., 2005); and delays, in a Down syndrome mouse model, the onset of cognitive defects and cholinergic neuron degeneration probably through its antioxidative effects (Lockrow et al., 2009).

It is now well established that CoQ10 has significant neuroprotectant properties and may protect neuronal cells against neuronal damages (Chaturvedi and Beal, 2008; Young et al., 2007; Li et al., 2005a,b; Matthews et al., 1998; Kooncumchoo et al., 2006; Ishrat et al., 2006; Somayajulu et al., 2005). This explains why CoQ10 has the potential to be employed as a therapeutic intervention in neurodegenerative disorders (Somayajulu et al., 2005).

GPX has been shown to have neuroprotective effects. This can be deduced from studies that examine the effects of Ebselen. Ebselen has potent antioxidant and neuroprotective effects in vitro and in vivo (Posser et al., 2009). This compound has neuroprotective activities against different injuries, like neuronal damage and cell death caused by ischemic attacks or coronary artery occlusion; oxidatively induced damage to DNA that may cause delayed neuronal death in brain regions; and trimethyltin hydroxide-induced hippocampal injury (Satoh et al., 2004; Jean Harry et al., 2003; Seo et al., 2009; Li and Cao, 2002; He et al., 2007). The neuroprotective effects of Ebselen are based on a number of different mechanisms, like increases in glutathione and ROS-scavenging activity (Satoh et al., 2004; Porciúncula et al., 2004); suppression of iNOS activity (Porciúncula et al., 2003); protecting against oxidative damage of DNA that is involved in the delayed neuronal death in the brain regions following cerebral artery occlusion (Li and Cao, 2002; He et al., 2007); decreases in TNFα production, which induces hippocampal injury by trimethyltin hydroxide injections (Jean Harry et al., 2003); protecting neurons from ischaemic damage via GABA-related mechanisms (Seo et al., 2009); inhibitory effects on neuronal damage during stroke (Yamagata et al., 2008); and preventing impaired neurogenesis within the dentate gyrus of the hippocampus (Herrera et al., 2003).

SOD is expressed in brain neurons and has been shown to be involved in neurodegeneration (Hayashi et al., 2005). Mutations in the SOD1 gene are associated with amyotrophic lateral sclerosis, whereby mutated enzyme products may cause oxidative damage, disorganization of neurofilaments and increased glutamic acid neurotoxicity (Iłlzecka, 2001). When damage occurs to brain neurons SOD undergoes a rapid and profound downregulation, which proceeds a subsequent upregulation in SOD activities in glial cells (Hayashi et al., 2005). SOD and SOD mimetics have a therapeutic efficacy in neurodegenerative models (Pong, 2003). For example, MnTMPgP, a SOD/catalase mimetic, has neuroprotective effects against LPS-induced neurotoxicity (Wang et al., 2004).

12.2. Oxidative damage and neurodegeneration

12.2.1. Lipid peroxidation

The findings of increased ROS and RNS in major depression including lipid peroxidation and damage to proteins and DNA are highly relevant to the I&ND hypothesis of depression (Maes et al., 2009d). There is evidence that oxidative damage to lipids, including lipid peroxidation, and proteins are important factors in the pathophysiology of neurodegenerative disorders (Arlt et al., 2001, 2002; Sultana et al., 2006; Greilberger et al., 2008). Different pathways are involved in neurodegeneration: free radicals and lipid peroxidation products may cause decreased neuronal viability and diminished expression of neurofilaments (Haorah et al., 2008); ROS initiates damage to lipids (proteins and DNA) and consequently results in mitochondrial dysfunction, ion balance deregulation and loss of membrane integrity and destabilization, which are factors causing cell necrosis (Vanlangenakker et al., 2008); oxidative stress and lipoxidation and lipoxidation-derived damage to proteins and membrane fatty acids specifically target cortical astrocytes (Martínez et al., 2008); and peroxides induce the JAK/STAT pathway in glia and astroglia (Gorina et al., 2007). We will now discuss the neurotoxic effects of lipid peroxidation products such as MDA and 4-HNE, which are both increased in major depression and are involved in neurodegenerative processes.

12.2.2. MDA and neurodegeneration

MDA targets the mitochondria causing mitochondrial damage and thus neurodegeneration (Long et al., 2006). The neurodegenerative effects of MDA include: depressing mitochondrial GSH and SOD concentrations; increasing mitochondrial ROS and protein carbonyls; inhibition of the mitochondrial respiratory processes, complexes I, II and V; depressing the mitochondrial membrane potential (Long et al., 2009); causing alterations in the dopaminergic metabolism and inducing the synthesis of protein reactive dopaminergic toxins (Rees et al., 2007). Reduction of mitochondrial complex I activity is documented in bipolar disorder, and lithium upregulates mitochondrial complex I activity (Maurer et al., 2009). Finally, as discussed above, MDA has inhibitory effects on the nucleotide excision repair system through direct interactions with cellular repair proteins. Thus, MDA sensitizes mutagenesis through an inhibitory effect on DNA repair while damaging DNA (Feng et al., 2006).

12.2.3. 4-HNE and neurodegeneration

Modifications of proteins by 4-HNE, a byproduct of lipoperoxidations promoting neuronal excitotoxicity, play a role in the neurotoxicity

causing neurodegenerative disorders (Akude et al., 2010). 4-HNE is, for example, significantly higher in brain tissues and CFS of patients with Alzheimer's disorder and is present in neurofibrilary tangles and senile plaques (Zarkovic, 2003). The different mechanisms whereby 4-HNE may induce neurotoxic effects entail: formation of cytotoxic 4-HNE-histidine adducts in the perikarya of hippocampal cells (Fukuda et al., 2009); formation of conjugated products with glutathione in the cortex, hippocampus and substantia innominata (Völkel et al., 2006); stimulation of fibrogenesis, inflammation and modulation of cell proliferation through interactions with cyclins and protein kinases (Poli and Schaur, 2000); inducing neuronal cell death through apoptosis and interaction with the survival-promoting NFκB signalling pathway (Lovell and Markesbery, 2006; Camandola et al., 2000); suppressing mitochondrial respiration (complexes I, II and III) (Picklo et al., 1999); binding to the glutamate transporter thus impairing glutamate transport (Blanc et al., 1998); causing accumulation of peroxides in astrocytes (Blanc et al., 1998); causing impairments in axon regeneration, aberrant axonal functioning, mitochondrial accumulation and loss of active mitochondria (Akude et al., 2010); and depleting intracellular glutathione and reduction of the mitochondrial membrane potential (Arakawa et al., 2006).

12.3. Oxidatively induced DNA damage and neurodegeneration

There is now evidence that O&NS-induced DNA damage plays a pathophysiological role in neurodegeneration. For example, in subacute sclerosing panencephalitis, not only lipid peroxidation and glutamate transport disturbances, but also oxidative stress to DNA contributes to neuronal damage (Hayashi et al., 2002). As explained in this review, defects in the mitochondrial respiratory chain, increased ROS leakage and accumulation of deleted mitochondrial DNA, which cause secondary mitochondrial DNA mutations in postmitotic cells, are key phenomena underpinning (neuro)degenerative disorders (Tanaka et al., 1996). In Alzheimer's disorder, the accumulation of ROS-induced mitochondrial DNA mutations causes mitochondrial dysfunctions and genomic DNA damage (de la Monte et al., 2000). The increased levels of the 8-OHdG lesions in cortical neurons and increased CSF 8-OHdG levels in Alzheimer patients suggests that DNA damage influences the course of that neurodegenerative disorder (de la Monte et al., 2000; Markesbery and Carney, 1999). Ataxia telangiectasia is accompanied by a progressive neurodegeneration that is characterized by oxidative damage to DNA as measured by 8-OHdG (Reichenbach et al., 2002). In the R6/2 transgenic mouse model of Huntington's disease, increased 8-OHdG was found in striatal microdialysates, while 8-OHdG staining was even higher in the late stages of that illness (Bogdanov et al., 2001).

13. Conclusions

Fig. 2 shows that the IO&NS pathways play a key role in depression and in neuroprogression and degenerative processes that occur in that illness. Major depression is accompanied by lowered plasma concentrations of antioxidants, such as vitamin E, tryptophan, tyrosine, albumin, zinc and CoQ10 and lowered antioxidative enzyme activities, e.g. GPX. This deficit in antioxidant defences may impair the protection against ROS and RNS causing O&NS and damage to fatty acids, proteins, DNA and mitochondria. There is abundant evidence that these phenomena occur in depression and in animal models of depression as evidenced by increased levels of peroxides, XO, MDA, 4-HNE, NO-tyrosine, and 8-OHdG. Increased IgG antibodies against oxidized LDL and IgM antibodies membrane fatty acids and NO-modified proteins not only corroborate the findings of increased O&NS-induced damage but also show that an autoimmune response has been launched against the O&NS modified epitopes. Antidepressants may counteract the above-mentioned disorders, while different antioxidants and antioxidant enzyme mimetics exhibit antidepressant activities. There are significant

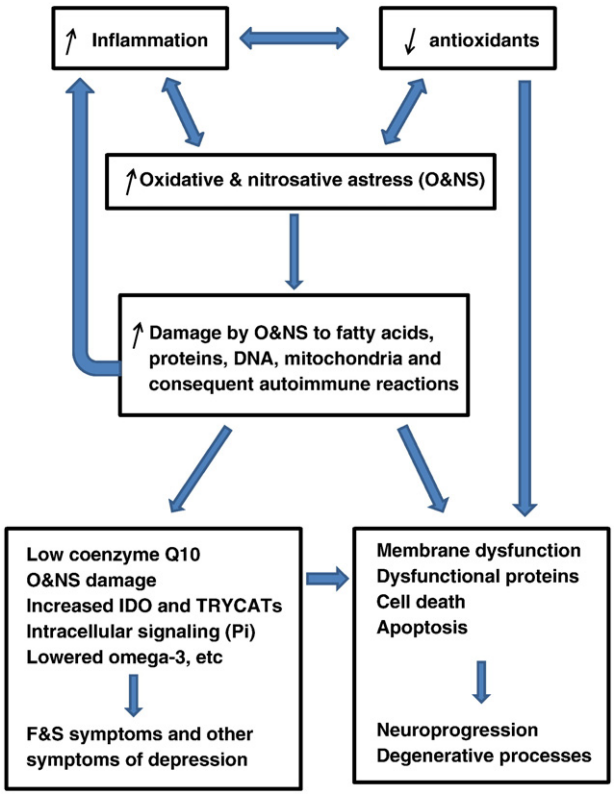

Fig. 2. The IO&NS pathways play a key role in depression, and the neuroprogression and degenerative processes that occur during depression. Major depression is accompanied by lowered plasma concentrations of antioxidants, such as vitamin E, tryptophan, tyrosine, albumin, zinc and CoQ10 and lowered antioxidative enzyme activities. The lowered total antioxidant capacity may impair the protection against ROS and RNS causing O&NS and damage to fatty acids, proteins, DNA and mitochondria. The O&NS modified epitopes may mount an autoimmune response against these neoepitopes, which further may aggravate the initial inflammatory response. These pathways in turn may induce depression and the (neuro)degenerative processes that accompany depression.

associations between depression and functional SNPs in O&NS genes, like the COX-2, MPO and SOD genes. These findings show that O&NS, the consequent damage by O&NS, and functional SNPs in the above-mentioned O&NS genes are involved in the pathogenesis of depression and neuroprogression. Moreover, as we will explain in another review paper in this special issue, O&NS pathways may play a key role in shared degenerative pathways that underpin both depression and cardiovascular disorder (Maes et al., 2010c). These data show that aberrations in IO&NS pathways underpin depression and that these pathways may explain the (neuro)degenerative processes in that illness. There is thus some evidence that depression should be regarded as a (neuro) degenerative disorder and that this illness belongs to the spectrum of (neuro)degenerative disorders.

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