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Oxidative/nitrosative stress and antidepressants: Targets for novel antidepressants☆,☆☆

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ABSTRACT

The brain is an organ predisposed to oxidative/nitrosative stress. This is especially true in the case of aging as well as several neurodegenerative diseases. Under such circumstances, a decline in the normal antioxidant defense mechanisms leads to an increase in the vulnerability of the brain to the deleterious effects of oxidative damage. Highly reactive oxygen/nitrogen species damage lipids, proteins, and mitochondrial and neuronal genes. Unless antioxidant defenses react appropriately to damage inflicted by radicals, neurons may experience microalteration, microdysfunction, and degeneration. We reviewed how oxidative and nitrosative stresses contribute to the pathogenesis of depressive disorders and reviewed the clinical implications of various antioxidants as future targets for antidepressant treatment.

1. Introduction

The efficacy of the most widely used antidepressants is limited by their theoretical reliance on the monoamine hypothesis. However, depression is a disease that is too intricate to be explained by the monoamine hypothesis alone. In addition to psychosocial factors, many biological factors apart from those related to monoamines contribute to the development of depression. For instance, factors involved in neurodevelopment, epigenetic modulation, neuroendocrinology, immunology, and exposure to toxins and reactive oxygen species have also been reported to play roles in the pathogenesis of depression (Pae, 2008; Pae et al., 2004).

Indeed, this limitation is underscored by consistent reports of low remission rates associated with the current antidepressants. The famous Sequenced Treatment Alternatives to Relieve Depression (STAR-D) trial achieved initial remission rates of only 28–33%, and these rates declined even further after initial treatment failure (Rush et al., 2006). Therefore, new therapeutic agents, based on theories other than those focused on monoamines, are garnering increasing interest for the treatment of depression (Pae et al., 2011). For example, antioxidants, glutamate, glycogen synthase kinase-3 (GSK3), histone deacetylases, melatonin, neurotrophic factors and etc. are being investigated as candidates for novel antidepressants.

Of the aforementioned candidates, we reviewed agents that may intervene in the damaging process of oxidative/nitrosative stress because the brain is particularly vulnerable to these stressors. Moreover, reactive oxygen species (ROS) and reactive nitrogen species (RNS), working in concert with an inflammatory process, may play a substantial role in the pathogenesis of depression (Leonard and Maes, 2012). Before discussing novel antidepressant target via oxidative/nitrosative stress, we also provide an overview of oxidative/nitrosative stress and the reasons that the brain is especially vulnerable to this phenomenon.

Abbreviations: ARE, antioxidant response element; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; CAT, catalase; COX, cyclooxygenase; CREB, cAMP-response element-binding-protein (CREB); DNA, deoxyribonucleic acid; EFE, ethyl ferulate (ethyl 4-hydroxy-3-methoxycinnamate); ER, endoplasmic reticulum; FA, ferulic acid (4-hydroxy-3-methoxycinnamic acid); FST, forced swimming test; GSK3, glycogen synthase kinase 3; HPA, hypothalamic–pituitary–adrenal axis; IDO, 2,3-dioxegenase; INF-γ, interferon-gamma; NAC, N-acetylcysteine; NAD, nicotinamide adenine dinucleotide; NO, nitric oxide; NOS, NO synthase; Nrf2, nuclear factor E2-related factor 2; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; TST, tail-suspension test; 5-HT, 5-hydroxytryptamine.

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2. Oxidative/nitrosative stress

2.1. Overview of cellular respiration

Cells perform respiration to convert nutrients into readily usable chemical energy such adenosine triphosphate (ATP). During respiration, metabolic reactions occur in the form of redox reactions, which involve the transfer of electrons from a molecule that is oxidized by losing electrons to another molecule whose oxidation is reduced by gaining electrons.

Human cells have two respiration pathways. First, glycolysis, an anaerobic reaction, occurs in the cytosol of cells. Second, a series of aerobic reactions involving the tricarboxylic acid cycle, and then oxidative phosphorylation take place in the mitochondria. Whereas the former gives off two ATPs per 1 mol glucose, the latter yields 34 ATPs per 1 mol glucose. In short, aerobic respiration is much more efficient in producing energy and accounts for 90–95% of the total amount of ATP produced (Acuna-Castroviejo et al., 2001).

Oxidative phosphorylation involves an electron transport chain in which electrons are moved from an electron donor produced in a tricarboxylic acid cycle – nicotinamide adenine dinucleotide H (NADH) or flavin adenine dinucleotide H_2 ($FADH_2$) – to a terminal electron acceptor (oxygen) via a series of redox reactions. In this process, a proton (H^+) gradient is created across the mitochondrial membrane. This, in turn, is utilized in creating ATPs. Normally, the reduced oxygen, which is chemically unstable, then reacts with H^+ to form H_2O. However, oxidative stress occurs when the ROS react with other molecules. As a result, damage to the cellular components and alterations in neuronal functions follow.

2.2. The brain: prone to oxidative stress

The human brain requires considerable energy to function adequately: 4×10^{21} ATP molecules per minute. This high energy demand results from the need for ATPs to maintain and restore the ion gradients that are dissipated in signaling processes such as action potentials (i.e., maintaining the negative membrane gradient of high intracellular K^+ and low Na^+), neurotransmitter releases via exocytosis (i.e., keeping very low intracellular Ca^{2+} to enable sensitive reactions following the Ca^{2+} influx induced by action potentials by sequestering Ca^{2+} in the endoplasmic reticulum and mitochondria; (Simpson and Russell, 1998), and the uptake and recycling of neurotransmitters (Alle et al., 2009; Attwell and Laughlin, 2001).

The brain utilizes aerobic respiration to meet this high demand for energy. Although the brain accounts for only 2% of the total body weight, it consumes about 20% of the oxygen and 25% of the glucose (Belanger et al., 2011). Aerobic respiration allows the brain to produce the needed ATPs in an efficient manner. However, the brain's heavy reliance on oxygen acts as a double-edged sword. Although the oxidative processes meet the brain's high energy needs, they also render the brain vulnerable to oxidative/nitrosative stress.

Both oxidative and nitrosative stresses have been reported to alter lipids, proteins, and genes (Yao and Keshavan, 2011). Lipids account for up to 50% of the brain's dry weight, and 50%–70% of the brain lipids are phospholipids, which are rich in free-radical-prone polyunsaturated fatty acids (Siegel et al., 1981). In addition to the phospholipid-rich composition of the brain, the lack of neuronal regeneration in all but certain stem-cell regions renders the brain susceptible to oxidative/nitrosative stress. This means that the intracellular damage done by oxidative/nitrosative stress may accumulate during the entire life span of neurons (Yao and Keshavan, 2011).

2.3. Oxidative/nitrosative stress

The general concept of how oxidative stress occurs was described above (Section 2.1 Overview of cellular respiration). Although ROS can be generated exogenously from ultraviolet light or ionizing radiation, they are usually generated endogenously. The primary endogenous source is the mitochondria, but ROS can also be generated from the electron transport chains contained in the endoplasmic reticulum and nuclear membranes.

Various enzymatic activities other than those involved in electron transport chains also generate intracellular ROS. These include xanthine oxidase, NADPH oxidase, cytochrome P450 monooxygenase, cyclooxygenase, and monoamine oxidase. It may be noteworthy that H_2O_2 is produced by the metabolism of dopamine or serotonin via monoamine oxidase (Maker et al., 1981). This may, at least in part, underlie the neurotoxicity of dopamine in the exacerbation of psychosis or cocaine/methamphetamine abuse and the neurotoxicity of serotonin in 3,4-methylenedioxy-N-methylamphetamine (MDMA).

Nitric oxide (NO) is synthesized from L-arginine by a family consisting of NO synthase (NOS) isoenzymes: neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). nNOS and eNOS are constitutive enzymes activated by the increase in intracellular Ca^{2+}. iNOS is expressed calcium-independently by inflammatory cells induced by endotoxic or pro-inflammatory cytokines (Zhou and Zhu, 2009). Therefore, inflammation or neuronal excitation leading to increased intracellular Ca^{2+} may enhance the production of NO.

As illustrated by the schematic depiction of the flow characterizing radical generation (Fig. 1), RNS are produced by superoxide anion and NO. Superoxide dismutase (SOD) normally competes with NO for superoxide anion. When insufficient SOD is available or the production of NO is overwhelming, peroxynitrite, a very reactive radical, is formed. Nitrosylation of proteins may inhibit their critical functions or promote apoptosis (Eu et al., 2000) (Fig. 2).

To simplify, oxidative/nitrosative stress occurs when the redox balance is breached, and pro-oxidative processes overwhelm the antioxidant defense system. Factors favoring oxidative processes may also have roots in genetic endowment (Galecki et al., 2011; Shelton et al., 2011), immune activation (Fujii et al., 2006), excitotoxicity, neurogenesis/neuroplasticity, psychosocial stress, energy failure (e.g., stroke) and etc.

Firstly, genetic vulnerability to oxidative/nitrosative stress would be reviewed. A recent study showed that although A/A-homozygous carriers of the gene encoding iNOS showed a decreased risk of developing recurrent depression, the G/A single nucleotide polymorphism (SNP) was associated with an increased risk in this regard. Moreover, the presence of the CC-homozygous genotype for the gene encoding nNOS was associated with decreased risk of recurrent depression, whereas the T allele and T/T-homozygous genotype increased vulnerability in this regard (Galecki et al., 2011). Likewise, a number of genetic studies on the role of enzymes involved in oxidative stress suggested the importance of a SNP in the NOS genes in depression. Indeed, significant associations between depression and different SNPs of these genes have been found previously.

Secondly, the involvement of inflammation on oxidative/nitrosative stress would be discussed. A recent post-mortem study examined the prefrontal cortex samples from psychotropic-naïve persons with a history of major depressive disorder to elucidate the involvement of inflammatory, apoptotic, and oxidative stress (Shelton et al., 2011). The incubation of endothelial progenitor cells with C-reactive protein (CRP) caused a dose-dependent increase in ROS formation and apoptosis. Treatment with either an antioxidant, N-acetylcysteine (NAC), or anti-CRP antibodies reduced toxicity (Fujii et al., 2006). Another antioxidant, superoxide dismutase (SOD), was reported to attenuate tumor necrosis factor-alpha (TNF-α)-induced superoxide anion production and adhesion molecule expression (Lin et al., 2005). Lin et al. suggested that the protective effect of SOD was mediated by decreased c-Jun N-terminal kinases (JNK) and p38 phosphorylation; and activator-protein-1 and nuclear-factor kappaB (NF-κB) inactivation. In summary, inflammatory reactions may escalate pro-oxidative processes, whereas antioxidants may have a protective role.

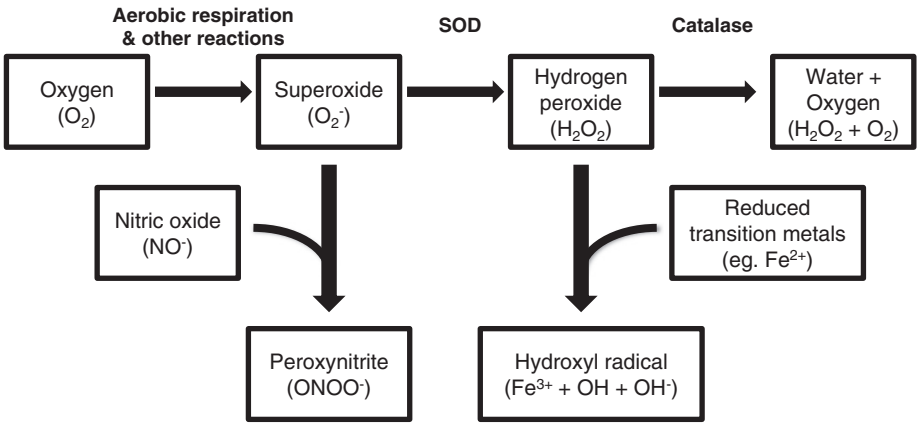

Fig. 1. Productions of radicals. SOD (superoxide dismutase).

Depression is consistently accompanied by increased levels of IL-1, IL-6 and TNF-α (Hannestad et al., 2011). When a macrophage is stimulated by bacterial compounds or INF-γ, it polarizes to a proinflammatory (M1) macrophage. M1 macrophages, in turn, further potentiate inflammatory reaction via production of proinflammatory cytokines such as IL-1, IL-6, IL-12 and TNF-α; and releasing ROS and RNS as killing agents (Wolfs et al., 2011). The fact may point to a possible role of M1 macrophage activation in depression. However, as natural killer cell activities were found to be decreased repeatedly in depression (Caldwell et al., 1991; Evans et al., 1992; Irwin et al., 1990, 1992), the overall role of cell-mediated immunity in depression remains to be elucidated.

Next, involvement of excitotoxicity in oxidative/nitrosative stress would be inspected. Along with immune activation, excitotoxicity may also contribute to oxidative/nitrosative stress. Proinflammatory cytokines such as interleukin (IL)-1b, 2, interferon-gamma (INF-γ), or TNF-α have been reported to enhance indoleamine 2,3-dioxegenase (IDO) activity (Muller and Schwarz, 2007; Zunszain et al., 2012) under stress, promoting the kynurenine pathway instead of the

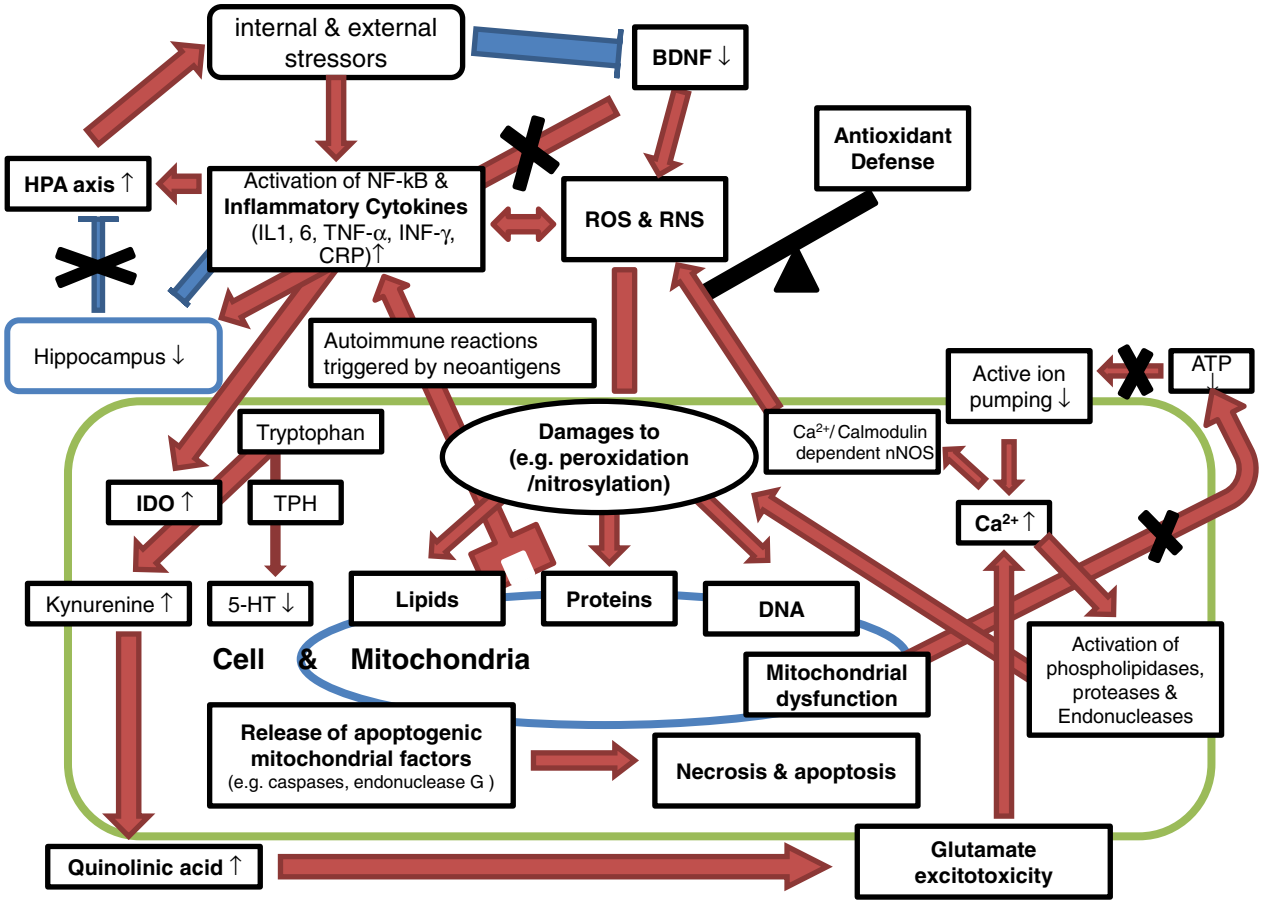

Fig. 2. Mechanisms of oxidative/nitrosative damages. NE (norepinephrine), HPA (hypothalamus–pituitary–adrenal), BDNF (brain-derived neurotrophic factor), ROS (reactive oxygen species), RNS (reactive nitrogen species), nNOS (neuronal nitric oxide synthase), ATP (adenosine triphosphate), IDO (indoleamine 2,3-dioxegenase), TPH (tryptophan hydroxylase), 5-HT (5-hydroxytryptamine, serotonin), NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), TNF (tumor necrosis factor), IL (interleukin), INF (interferon).

5-hydroxytryptamine (5-HT) pathway of tryptophan (Miura et al., 2008). As a result, 5-HT synthesis is reduced and quinolinic acid, known to have a neurotoxicity (Poeggeler et al., 2007), is increased.

Inflammatory cytokines have been reported to exert a negative impact on the hippocampus (Miura et al., 2008). IL-1b induced IDO and also decreased human hippocampal neurogenesis (Zunszain et al., 2012). This finding is in line with the hippocampal atrophy reported in a meta-analysis of brain imaging studies in depression (Videbech and Ravnkilde, 2004). Proinflammatory cytokines are known to activate the hypothalamic–pituitary–adrenal (HPA) axis whereas suppressing sex and growth hormones release as well the inhibiting hypothalamic–pituitary–thyroid axis (Haddad et al., 2002). The stimulating effects of cytokines and the impaired normal hippocampus inhibition on the feedback activity in the HPA axis altogether contribute to the altered HPA axis in depression (Fig. 2).

Finally, the role of neurogenesis/neuroplasticity will be reviewed. In endothelial progenitor cells, treatment with brain-derived neurotrophic factor (BDNF) significantly increased SOD expression and inhibited apoptosis induced by a superoxide anion generator LY83583 (He and Katusic, 2012). However, stress was reported to reduce BDNF levels (Kubera et al., 2011). In addition to BDNF's effect on ROS, decreased BDNF levels may also exert an extra negative impact on the hippocampus, which has a regulatory role in the HPA axis (Razzoli et al., 2011).

Regardless of initial insult, a cascade of events following inflammation or ROS/RNS damage alters the structures and functions of both the mitochondria and the cell. Because of the high reactivity of radicals, covalent modifications of lipids, proteins, and deoxyribonucleic acid (DNA) are likely to occur if radicals are not trapped by scavengers such as glutathione (GSH), ascorbate, or tocopherol. Lipid peroxidation gives rise to cytotoxic aldehydes, like malondialdehyde (MDA), that have to be detoxified by glutathionylation. Unless detoxified, MDA may react with proteins forming protein adducts (Requena et al., 1996) or may react with DNA forming mutagenic DNA adducts (Marnett, 1999).

Oxidized proteins are metabolized by proteases, and radical-mediated DNA-base modifications may be repaired by specific glycosylases. Incomplete repair of DNA and proteins may lead to altered transcriptional responses and protein aggregation. Fig. 2 schematically illustrates the mechanisms of oxidative/nitrosative damages. Together with the dysfunctional proteins expressed by the damaged genes, the accumulated oxidative damage to preexisting structural proteins may also cause neuronal dysfunction, neurotoxicity, and eventually lead to neuronal loss. To summarize, peroxidation or nitrosylation of indigenous cellular components make them reactive/cytotoxic by altered molecular structures and functions.

Moreover, those changes in molecular structures could elicit immunogenicity by acting as neoepitopes. For instance, one may not recognize the deformed protein or lipid adducts as self and initiate autoimmune attacks to these neoantigens. The possible roles of autoimmune responses against the neoepitopes formed by oxidative stress have been well reviewed recently (Maes et al., 2011a). Compared to control, the patients with depression showed higher IgM responses to anchorage molecules, acetylcholine, and nitrated epitopes (Maes et al., in press).

There are numerous evidences suggesting association of depression with autoimmune responses. First of all, high comorbidities of depression exist in various autoimmune disorders such as systemic lupus erythematosus (Meszaros et al., 2012), multiple sclerosis (Vattakatuchery et al., 2011) and etc. Secondly, immune-enhancing interferon therapies to viral hepatitis patients frequently led to depression as a side effect (Dieperink et al., 2003; Gupta et al., 2006). Thirdly, white blood cell counts, as an immunologic marker, were found to be associated with depression (Kobrosly and van Wijngaarden, 2010). Fourth, a recent study demonstrated that 5-HT antibodies were significantly higher in depressed patients and patients with positive 5-HT antibodies displayed higher symptom severity (Maes et al., 2012a). Lastly, loss of immune tolerance, demonstrated by a low ratio of regulatory T cells to effector T cells, by heightened sanitation was suggested to contribute higher depression incidence in the industrialized world (Raison et al., 2010). With increasing evidence of autoimmune reactions involved in depression, further active investigations are suggested to elucidate roles of oxidative/nitrosative stress in the pathophysiology of depression.

3. Current psychotropics as antioxidants

3.1. Antidepressants

Evidence is growing that the current antidepressants may exert their therapeutic effect other than monoamine modulations. In fact, many antidepressants are known to decrease oxidative stress in chronic-stress animal models (Abdel-Wahab and Salama, 2011; Lee et al., 2011) as well as in human studies (Bilici et al., 2001; Herken et al., 2007; Khanzode et al., 2003; Kotan et al., 2011). Although the exact mechanisms have not been fully revealed thus far, they may act by suppressing several proinflammatory cytokines and ROS/RNS production or enhancing antioxidant defense such as SOD or catalase (CAT).

Tricyclic antidepressants (TCAs) demonstrated some beneficial roles in oxidative/nitrosative stress through the aforementioned mechanism of actions. For instance, amitriptyline suppressed proinflammatory cytokines like IL-1β and TNF-α (Vismari et al., 2012). Clomipramine and imipramine significantly reduced the NO production by attenuated iNOS expression. They also decreased proinflammatory cytokines such as IL-1β and TNF-α (Hwang et al., 2008). Acute and chronic imipramine treatments increased SOD and CAT activities while reducing lipid and protein oxidation in rat prefrontal cortex and hippocampus (Reus et al., 2010).

More human clinical data exist for selective serotonin re-uptake inhibitors (SSRIs). Paroxetine was reported to be a potent inhibitor of NOS enzyme activity (Finkel et al., 1996). Khanzode et al. reported that patients with major depression displayed a significant increase in serum SOD, MDA and decrease in plasma ascorbic acid levels, compared to matched control. Fluoxetine and citalopram significantly reversed those differences with citalopram showing greater reduction in oxidative stress than fluoxetine (Khanzode et al., 2003). Treatments with SSRIs (fluoxetine, citalopram, fluvoxamine or sertraline) significantly decreased NO, XO levels (Herken et al., 2007) and lipid peroxidation levels (Bilici et al., 2001). Bilici et al. reported heightened antioxidative enzyme activities and their normalization after SSRI treatment. On the other hand, the other study, carried out by Herken et al., exhibited a significantly lower SOD level, of which was increased after SSRI treatment.

Positive correlation was also found between SOD levels and Hamilton Depression Rating Scale (HDRS) points in depressed patients (Bilici et al., 2001). This provides indirect evidence that oxidative stress may contribute to the symptoms of depression. However, no correlations between the antioxidative enzyme activities, the NO levels and HDRS were found in a later study (Herken et al., 2007). Therefore, future studies should be followed.

Not only the affective symptoms, but also cognitive effects of depression could be ameliorated by SSRI through an antioxidative mechanism. In rodents, sertraline significantly improved cognitive performance tasks and GSH levels under nitrosative stress. Interestingly, the neuroprotective and antioxidant-like effects of sertraline were demonstrated independent of its action on 5-HT receptor (Kumar and Kumar, 2009).

Apart from 5-HT, norepinephrine may also have a role in the antioxidative effect of antidepressants. Venlafaxine, a serotonin–norepinephrine reuptake inhibitor, was shown to protect against stress-induced oxidative cellular and DNA damage. Venlafaxine decreased the hippocampal MDA and NO and increased hippocampal GSH, total antioxidant levels in mice (Abdel-Wahab and Salama,

2011). Bupropion, a norepinephrine–dopamine reuptake inhibitor, dose dependently inhibited the immobility period in mice in both forced swim test and tail suspension test. The antidepressant-like effect was prevented by L-arginine, the precursor of NO, pretreatment. Conversely, co-administration of NOS inhibitors like 7-nitroindazole or methylene blue potentiated the effect of bupropion (Dhir and Kulkarni, 2007). The demonstrated effect, however, may not be exclusive to norepinephrine since similar effects were also shown by escitalopram (Zomkowski et al., 2010).

Still, some controversies remain over the antioxidative effect of antidepressants. A relatively large antidepressant trial, involving sertraline, venlafaxine or reboxtine, failed to display an antioxidative effect (Sarandol et al., 2007). In the patient group, plasma MDA levels and SOD activity were significantly higher and a significant positive correlation existed between the severity of the disease and SOD activity. However, antidepressants did not modify any oxidative/antioxidative parameters. In another study, there was no difference in antioxidative plasma coenzyme Q10 between depressed patients receiving antidepressants and not (Maes et al., 2009). In a recent study, amitriptyline even induced coenzyme Q deficiency and oxidative stress (Moreno-Fernandez et al., 2012). Therefore, to elucidate the antidepressants' antioxidative effect, well-designed prospective studies should follow.

3.2. Mood stabilizers

There are increasing evidences that mood stabilizers may have an antioxidant effect. In a stress induced-depression model of rats, aripiprazole, lamotrigine and escitalopram were compared for their antioxidant effects. Among them, lamotrigine displayed the most protective effects on the oxidative stress (Eren et al., 2007). In addition, lamotrigine significantly decreased oxidative stress induced by pentylenetetrazole (Arora et al., 2010). Valproate also displayed an antioxidant effect in numerous studies (Cui et al., 2007; Fourcade et al., 2010; Frey et al., 2006; Jornada et al., 2011; Kurekci et al., 1995; Nikushkin and Bordiukov, 1993; Zhang et al., 2012). Valproate was associated with higher GSH peroxidase, an antioxidant that reduces H_2O_2 to water (Kurekci et al., 1995). Not only valproate, but other anticonvulsants such as phenobarbital, diphenin and phenazepam also demonstrated an antioxidative property (Nikushkin and Bordiukov, 1993). However, phenobarbital and carbamazepin were also reported to reduce antioxidant enzyme activities (Niketic et al., 1995). Furthermore, prooxidative effects of carbamazepin and valproate have also been reported (Varoglu et al., 2010). Valproate significantly increased ROS levels (Karabiber et al., 2004; Na et al., 2003; Tung and Winn, 2011), lipid peroxidation (Martinez-Ballesteros et al., 2004) and oxidative DNA damage (Schulpis et al., 2006) and depleted antioxidative elements such as zinc and selenium (Hurd et al., 1984). However, studies that investigated for altered oxidative status revealed negative results for carbamazepin (Verrotti et al., 2002) and valproate (Seckin et al., 1999; Verrotti et al., 2002). Toxic effects were only shown in patients with a serious adverse experience associated with valproate, whereas these were not shown in the valproate tolerable patients or healthy controls (Graf et al., 1998). Considering that plasma Cu, Zn, Mn, Se, and Mg concentrations of epileptic children, receiving valproate or carbamazepine, did not show statistical difference from those of control subjects (Kurekci et al., 1995), these findings altogether suggest a possible existence of a susceptible population to oxidative toxicity of valproate. The epileptic patients with a serious adversity displayed lower selenium and zinc concentrations (Graf et al., 1998). This indicates a possible role of antioxidant metals in valproate toxicity in the susceptible ones and may explain, at least in part, the heterogenous effects of valproate on oxidative stress.

Lithium, another widely used mood stabilizer, also showed antioxidative effects by reducing ROS (Cui et al., 2007; Frey et al., 2006; Jornada et al., 2011; Khairova et al., 2012). The antioxidant enzyme activities of SOD and CAT were found to be increased and decreased, respectively, in the brain of ouabain-administered rats (Jornada et al., 2011). Lithium was found to reduce the SOD/CAT ratio significantly in other studies (Khairova et al., 2012; Machado-Vieira et al., 2007). These findings support an antioxidant effect of lithium by modulation of antioxidative enzymes. On the other hand, lithium inhibited caspase activation but was not able to prevent mitochondrial DNA oxidative damage (Ghribi et al., 2003). Further studies should ensue to verify the antioxidant effect of lithium.

3.3. Antipsychotics

Firstly, typical antipsychotics would be reviewed for their effect on oxidative/nitrosative stress. Chlorpromazine diminished the peroxidative damage by ethacrynic acid, a GSH depletor (Babson et al., 1994) and NADPH (Khatua and Bhattacharyya, 2001). However, short-term haloperidol administration significantly increased oxidative stress in the rat brain (Shivakumar and Ravindranath, 1993). Haloperidol was cytotoxic in a dose-dependent manner and cell death by oxidative stress. The activated NF-κB activity by haloperidol was blocked by antioxidants (Post et al., 1998).

While typical antipsychotics showed mixed results, atypical antipsychotics demonstrated more promising outcomes in oxidative stress. In rat brain, chronic haloperidol administration significantly decreased antioxidative enzyme activities like SOD and CAT whereas it markedly increased in hydroxyalkenals, a marker of lipid peroxidation. However, atypical antipsychotic (clozapine, olanzapine, or risperidone) treatments did not alter the levels of antioxidant enzymes and hydroxyalkenals (Parikh et al., 2003). Moreover, olanzapine pretreatment blocked the decrease of SOD-1 mRNA level and increased cell viability against H_2O_2 (Wei et al., 2003). While haloperidol increased lipid peroxidation, olanzapint and quetiapine did not induce oxidative stress. In fact, quetiapine even displayed antioxidant properties (Dietrich-Muszalska et al., 2011). In a recent study, olanzapine, aripiprazole and ziprasidone reversed oxidative stress whereas haloperidol did not (Park et al., 2011). However, another study showed no difference between typical and atypical antipsychotics (Zhang et al., 2006).

There have been growing investigations of antioxidative effect of antipsychotics as evidences suggest that oxidative stress is also involved in the pathophysiology of schizophrenia (Khan et al., 2002; Raffa et al., 2011; Yao et al., 2000). Although the effects of antipsychotics on oxidative/nitrosative stress have not been well demonstrated on depression, their actions were similar to those of antidepressants used in depression. For example, in schizophrenic patients, serum MDA and SOD were significantly increased, while plasma ascorbic acid was decreased. This trend was significantly altered by various atypical antipsychotics treatment (Dakhale et al., 2004). This study result is very similar to the earlier antidepressant study result in depression (Khanzode et al., 2003). In summary, antipsychotics, especially atypical ones, may have potential value as antioxidants. Although the exact mechanism of actions remains elusive, antipsychotics and antidepressants may share common effectors. Further investigations should be followed to reveal the exact antioxidant effect of both types of drugs.

4. Novel antidepressant targets considering oxidative/nitrosative stress

Under the current antidepressant monotherapy, only one-third of patients achieve remission of their depressive symptoms and gain functional recovery. Therefore, exploration of new antidepressant candidates with a different mechanism of action is essential to improve treatment outcome. The major alternatives to monoamine neurotransmission as a proposed pathophysiological basis for depression involve 1) oxidative and nitrosative stress, which damage various cellular components such as lipids, proteins, and DNA; 2) decreased levels of antioxidants and expression of antioxidant enzymes; 3) immune dysfunction

including heightened inflammatory process and altered HPA axis; 4) mitochondrial dysfunction; and 5) neuro-degeneration processes (Kubera et al., 2011; Maes et al., 2011a,b,c).

This review focuses on oxidative and nitrosative stress and related targets. However, instead of targeting one pathway, multi-targeting the aforementioned pathways simultaneously may yield a better therapeutic response in depression (Maes et al., 2012b). Interested readers are suggested to read the article above. Many substances like minocycline, neurotropin-3, omega-3 fatty acid, zinc, and etc. target these pathways and have antidepressant effects. For example, minocycline, a second-generation tetracycline with anti-inflammatory and neuroprotective properties have anecdotal evidence of supporting its usage for augmentation of antidepressants in major depressive disorder (Pae et al., 2008a). Neurotropin-3, which regulates neuronal survival, synaptic plasticity, and neurotransmission, may also have a therapeutic implication in depression (Pae et al., 2008b). Omega-3 fatty acid and zinc would be further discussed on the next section. The following are potential targets for novel antidepressants based on considerations related to oxidative and nitrosative stress.

4.1. Nicotinamide adenine dinucleotide (NAD) and niacin

NAD and NADP are pyridine nucleotides. Nicotinamide is an important precursor of NAD under certain physiological conditions and is synthesized in the liver from tryptophan and then distributed to non-hepatic tissues. Although it is generally accepted that 60 mg tryptophan is equivalent to 1 mg nicotinamide in humans, the conversion ratio for tryptophan to nicotinamide is changeable (Fukuwatari and Shibata, 2007). In fact, tryptophan is a critical nutrient supporting the functions performed by the central nervous and immune systems (Yao et al., 2011).

NAD is best known as an electron carrier and co-substrate of various ROS reactions. However, during the past 20 years, NAD has been shown to be a key signaling molecule that mediates post-translational protein modifications and serves as precursor of ADP-ribose containing messenger molecules (Gossmann et al., 2012). In fact, areas of current interest include the role of ADP-ribose polymerase in the rejoining of DNA strand breaks, including those induced by ROS (Wiseman and Halliwell, 1996). It has been shown that selective depletion of ADP-ribose polymerase from cell extracts improved the repair of DNA exposed to a variety of DNA-damaging agents by removing the NAD+ dependence of the repair reaction (Satoh et al., 1993). NAD+-promoted DNA repair was performed by soluble cell extracts using alkylated DNA as a substrate, and this process was suppressed by 3-aminobenzamide. A similar stimulatory effect by NAD+ was also observed for repair of UV-induced DNA lesions (Satoh et al., 1993).

A number of studies have shown that damage to DNA can stimulate the biosynthesis of NAD, and that the repair of DNA can be increased and accelerated in cells with increased levels of NAD (Wiseman and Halliwell, 1996). Cytotoxic substances cause the intracellular levels of NAD to decrease, and they can also lead to the death of cells. In contrast, NAD also has an important role in the detoxification of cytotoxic biochemicals (Wiseman and Halliwell, 1996). Therefore, NAD may also be a novel candidate for development as an antidepressant, particularly in relation to the altered mitochondrial function related to DNA defects. Additionally, the indirect effect of tryptophan or the direct effect of its metabolites is involved in the development of depression insofar as it is an important precursor of NAD.

4.2. Brain-derived neurotrophic factor (BDNF)

Evidence that BDNF is strongly involved in the development of depression as well as in the modulation of antidepressant effects has been reported (Autry and Monteggia, 2012). This evidence consistently shows a reduction in BDNF secretion in stressful situations, a decreased blood concentration in depression, and a normalization of BDNF following successful antidepressant therapy. BDNF has also been found to be involved in the modulation of ROS reactions under the influence of antidepressants (Shelton, 2007). In fact, SSRIs were found to increase BDNF levels in the ischemic CA1 compared with vehicle-treated ischemic animals. Additionally, SSRIs effectively reduced microglial activation and decreased 4-hydroxy-2-nonenal and Cu/Zn-superoxide dismutase immunoreactivity and levels in the ischemic CA1 compared with vehicle-treated ischemic animals after transient cerebral ischemia. That is, SSRIs may protect against ischemia-induced neuronal death in the CA1 induced by transient cerebral ischemic damage by increasing BDNF as well as by decreasing microglial activation and oxidative stress (Kim do et al., 2007; Lee et al., 2011). Additionally, hippocampal neurogenesis was increased after chronic, peripheral BDNF administration. It was also found that BDNF levels, as well as expression of pCREB and pERK, were elevated in the hippocampi of adult mice receiving peripheral BDNF (Schmidt and Duman, 2010). These findings may also suggest the utility of BDNF for specific symptom domains of depression such as cognitive functions.

4.3. Glycogen synthase kinase 3 (GSK3)

GSK3 plays a key role in synaptic plasticity. Yet, the understanding of how GSK3 is involved in synaptic plasticity remains limited. We will need a more complete picture of how GSK3β contributes to synaptic plasticity as a pathogenesis of depression (Bradley et al., 2012). However, currently available findings suggest that dysregulation of GSK3 prompts mood disorders, including depression, suggesting its role as a potential target in the treatment of mood disorders. Many of the neuromodulators that are widely thought to be deficient in depression, such as serotonin, BDNF, and vascular endothelial growth factor (VEGF), normally stimulate signaling pathways that maintain inhibitory control of GSK3. This is now supported by a huge amount of evidence from animal biochemical, pharmacological, molecular, and behavioral studies and from human post-mortem brain, peripheral-tissue, and genetic studies (Li and Jope, 2010). Thus, deficiencies in these signals in depression leave GSK3 inadequately inhibited, and the restoration of the inhibitory control of GSK3 by therapeutic drugs is an important part of their therapeutic mechanism of action (Jope, 2011). It has been suggested that GSK3 regulates mood by affecting β-catenin, glutamate receptors, circadian rhythms, and serotonergic neurotransmission (Beaulieu et al., 2008).

It is fairly well known that mood disorders are associated with neuronal stress, such as oxidative stress and endoplasmic reticulum (ER) stress. A variety of cell stressors including various insults causing ER stress (Song et al., 2002) or DNA damage (Jope, 2011; Jope et al., 2007) can enhance the activity of GSK3 in specific cellular components. Hyperactivity of GSK3 also prompts detrimental cellular responses to multiple types of insults, including oxidative stress and ER stress (Beurel and Jope, 2006; Jope et al., 2007). Additionally, inhibition of GSK3 effectively reduced the expression of death-inducing transcription factor C/EBP homologous protein and modulated DNA damage; these effects were present in several types of neural-related cells and were evident after application of several structurally diverse GSK3 inhibitors, indicating that inhibitors of GSK3 are capable of shifting cell fate towards survival instead of apoptosis following ER stress (Hu et al., 2009; Meares et al., 2011). However, it is important to consider that such stresses also affect glial cells, and increasing evidence for glial abnormalities in depression has been reported. These cells may be vulnerable to and possibly changeable as a function of the oxidative stress involved in depression (Barakat et al., 2012; Rajkowska and Miguel-Hidalgo, 2007). In fact, GSK3 inhibitors significantly attenuated LPS-induced NO production and iNOS in murine microglial cells and primary microglia-enriched cultures. In this context, GSK3 inhibitors were found to restore the inflammation-induced defects of the Nrf2-inducible antioxidant defense

in astrocytes, possibly via normalized histone acetylation levels (Correa et al., 2011).

4.4. Heme oxygenase (HO)

In the CNS, the heme oxygenase (HO) system has been reported to be active and to operate as a fundamental defensive mechanism for neurons exposed to an oxidant challenge (Scapagnini et al., 2004). There are two isoenzymes HO-1 and HO-2. While HO-2 is a constitutive enzyme, HO-1 could be induced by various stressors like heavy metals, ultraviolet irradiation, and oxidative stress (Dwyer et al., 1995). In rats, neurons with little HO-1 were reported to be sensitive to H_2O_2, whereas astrocytes containing HO-1 were resistant to oxidative damage by H_2O_2 (Dwyer et al., 1995). Dwyer et al. also suggested that the lack of HO-1 induction by neurons may contribute to their vulnerability to oxidative stress.

The expression HO-1 may reverse oxidative stress and may characterize antidepressant mechanisms (Oh et al., 2004). HO-1 significantly reduced IL-1β-induced iNOS expression (Yang et al., 2004). Moreover, antidepressants reduced IFN-α-induced iNOS expression and increased HO-1 expression (Lu et al., 2012). Omega 3 fatty acids also reduced expressions of TNF-α, IL-6, and NOS; whereas it upregulated HO-1. The reduced NO production was abolished when zinc protoporphyrin IX, a HO-1 inhibitor, was applied (Lu et al., 2010). Altogether, HO-1 is a promising target involved in inflammatory and oxidative/nitrosative stress pathways.

4.5. Nuclear factor E2-related factor 2 (Nrf2)

Nrf2 is involved in the major antioxidant transcription for the activation of a redox-sensitive gene regulatory network, reflecting its role in maintaining redox homeostasis in the brain and protecting neurons against cell death (Johnson et al., 2008). Nrf2 induces the expression of antioxidant enzymes that directly regulate GSH, such as GSH cysteine ligase modifier and GSH cysteine ligase catalytic subunits (Maes et al., in press). Nrf2 binds to the antioxidant response element (ARE) in the promoter of target antioxidant genes and tightly regulates its transcription. Nrf2–ARE is a major pathway regulating phase-II antioxidant responses, triggering the simultaneous expression of numerous protective enzymes and scavengers (Johnson et al., 2008; Maes et al., in press). Several compounds may be involved in the activation of the Nrf2/ARE pathway; these range from electrophilic polyphenols to carotenoids and melatonin. Several previous studies investigated the possible antidepressant effects of Nrf2 activators, although few studies have examined the correlation between Nrf2 and depression (Maes et al., 2012b). Curcumin is an activator of Nrf2 and also has anti-inflammatory properties that include the capacity to inhibit 5- and 8-lipoxygenases, cyclooxygenases, and metalloproteinases with regard to induction of GSH *S*-transferase enzymes, to inhibit prostaglandin production, and to suppress oxidative DNA adduct (M(1)G) formation (Scapagnini et al., 2006). The cytoprotective effects of curcumin against oxidative damage in neuronal cells have been consistently reported (Scapagnini et al., 2006, 2011). In fact, higher concentrations of curcumin have caused a substantial cytotoxic effect with no change in HO-1 protein expression, whereas pre-incubation with curcumin resulted in an enhanced cellular resistance to glucose oxidase-mediated oxidative damage. This suggests that Nrf2 restores cellular homeostasis and rebalances redox equilibrium, thereby serving as a dietary agent that prevents oxidative-stress-related diseases including depression (Scapagnini et al., 2006).

4.6. Telomerase

Telomeres are complex structures formed by the end of the DNA molecule at the tip of the chromosomal arms. The telomeric sequence, which results from the repetition of the hexanucleotide TTAGGG, is partly single strand and is associated with more than 10 proteins, including the enzyme telomerase (Teyssier et al., 2010). When telomeres shorten to a critical length, cells become susceptible to senescence and programmed death. Telomere length is determined by the balance between telomere shortening stimuli (e.g., mitotic divisions and exposure to inflammation and oxidative stress) and telomere lengthening or reparative stimuli (Wolkowitz et al., 2011, 2012). Telomere and telomerase alterations have been reported in mood disorders, although the precise role of telomerase in depression remains unclear. Chronic mild stress was found to induce significant decreases in levels of telomerase reverse transcriptase (TERT) and telomerase activity in the hippocampus, indicating that hippocampal telomerase is involved in the modulation of depression-related behaviors, possibly by regulating adult neurogenesis (Zhou et al., 2011). Treatment with the antidepressant fluoxetine reversed the chronic mild stress-induced TERT and telomerase-activity changes. Telomerase activity was also found to be significantly higher in drug-naive depressed subjects compared with non-depressed healthy controls. The elevated telomerase activity was also more profound in depressed patients with worse responses to 8 weeks of antidepressant treatment (Wolkowitz et al., 2012). The possibility that increased telomerase activity reflects a compensatory response to cellular damage is consistent with preclinical and clinical data indicating that telomerase preferentially elongates shorter telomeres and that telomerase reverse transcriptase (the catalytic subunit of telomerase) is induced in response to certain types of cell injury, such as brain insults leading to significant defects in brain cells (Wolkowitz et al., 2012).

5. Antioxidants as candidates for antidepressants

5.1. N-acetylcysteine (NAC)

NAC, an effective GSH precursor that effectively replenishes brain GSH, has also been known to restore the extracellular glutamate concentration in regions of interest in the brain, and glutamatergic dysfunction has been also implicated in the pathogenesis of depression. Additionally, NAC is also a potent antioxidant that upregulates the GSH pathway (Maes et al., 2011a), the efficacy of which has already been reported in accounts of controlled and open clinical trials for depression (Berk et al., 2011; Magalhaes et al., 2011). NAC has also demonstrated its effectiveness for reducing increased oxidative stress. The incubation of endothelial progenitor cells (EPCs) with C-reactive protein (CRP) caused a concentration-dependent increase in ROS production and apoptosis, with an effect quantitatively similar to that of H_2O_2. This effect was also successfully attenuated during coincubation with NAC (Fujii et al., 2006).

5.2. Flavonoid and green tea catechin

Baicalein, a plant-derived flavonoid, has been reported to have an antidepressant effect by reversing the reduction of extracellular ERK phosphorylation and the level of BDNF expression in the hippocampus according to a rat model of chronic unpredictable mild stress (Xiong et al., 2011). Green tea catechin (GTC) was found to be associated with increased levels of cAMP-response element-binding-protein (CREB) phosphorylation in the hippocampus in an animal model. The expressions of BDNF and Bcl-2, two target genes of CREB that can play long-term regulatory roles in synaptic plasticity and synaptic structure and are implicated in the development of depression and antidepressant effects, were also increased. Long-term treatment with GTC prevented age-related decreases in two representative post-synaptic density proteins, PSD95 and Ca(2+)/calmodulin-dependent protein kinase II, through ROS scavenging functions, indicating its role in the synaptic structural changes that are involved in the development of depression (Li et al., 2009). Flavonoids such as liquiritin were also

effective in reversing alterations in immobility times in a forced swimming test (FST) and in sucrose consumption. Additionally, flavonoids were able to increase superoxide dismutase (SOD) activity, inhibit lipid peroxidation, and decrease production of MDA (Zhao et al., 2008).

5.3. Ebselen (2-phenyl-1,2-benzisoselenazol-3[2H]-one)

Ebselen is a seleno-organic compound and demonstrates potent antioxidant activity that mimics that of the endogenous antioxidant GSH peroxidase (Muller et al., 1984). Ebselen inhibits activation of oxidative-stress pathways in relation to the expression of ROS and NADPH oxidase (Lee et al., 2006). The possible antidepressant activity of ebselen in a FST and tail-suspension test (TST) was investigated in an animal model (Posser et al., 2009). Ebselen significantly decreased the immobility time in a FST at a dose of 10 mg/kg, which is consistent with an antidepressant-like action, whereas such a decrease was not observed in changes in locomotor activity assessed in the open-field test, indicating that the effect of ebselen observed in the FST cannot be attributable to a psychostimulant effect (Muller et al., 1984). Intriguingly, the effect of ebselen in a FST was not reversed by pre-treating mice with the neuronal 5-HT store depletor, PCPA, or with the serotonin 5-HT1A and 5-HT2A antagonists, NAN-190 and ketanserin. This clearly shows that the anti-immobility effect of ebselen in the FST is not dependent on an increase in 5-HT levels in the synaptic cleft. However, interactions between ebselen and noradrenergic and dopamine receptors (e.g., α1 and α2-adrenoceptors and D1 and D2 receptors) have been proposed based on findings from challenges with prazosin (α_1-adrenoceptor antagonist), yohimbine (α_2-adrenoceptor antagonist), SCH 23390 (D1 receptor antagonist), and sulpiride (dopamine D2 receptor antagonist) observed in that study.

5.4. Vitamin A

Vitamin-A deprivation may lead to aberrant production of ROS, decreases in ATP and NAD(+) levels, and activation of poly-(ADP-ribose) polymerase (PARP)-1. For example, vitamin-A depletion of exogenous sources or blockade of endogenous vitamin A by anhydroretinol was associated with a rapid increase in mitochondria-derived ROS production, mitochondrial depolarization, significant decreases in cellular levels of ATP and NAD^+, and caspase-independent cell death in Jurkat T cells and MEFs (Chiu et al., 2008). However, vitamin-A supplements efficiently reversed these effects.

5.5. Ascorbic acid (vitamin C) and tocopherol (vitamin E)

The relationship among chronic stress, brain-energy metabolism, and oxidative stress has been implicated in the pathophysiology of depression. This process is known to alter the activities of pyruvate kinase and complex II and IV (cytochrome *c* oxidase) in the hippocampus and prefrontal cortex in the context of chronic variable stress. In a recent animal model, stressed rats demonstrated an inhibition in the activities of complex II and cytochrome *c* oxidase in the prefrontal cortex, whereas only complex IV was inhibited in the hippocampus. Pyruvate-kinase activity was not altered in stressed rats when compared with controls. Vitamins E and C prevented such alterations, suggesting that impairments associated with energy metabolism and oxidative stress may be related to the pathogenic pathways of clinical depression (Tagliari et al., 2010). Additionally, vitamins E and C were also found to have major roles in the cognitive dysfunction observed in depression and other stress-related conditions. In this experiment, chronically stressed rats showed a profound decrease in reference memory in a water-maze task as well as reduced efficiency in finding the platform in a working-memory task, whereas some of these effects were prevented in rats treated with vitamins E and C (Tagliari et al., 2011).

5.6. Zinc

Zinc has strong and proven antioxidative properties that are associated with its effect in the treatment of depression. This effect primarily involves PUFA metabolism and the stimulation of neurogenesis through the increased genetic expression of BDNF (Maes et al., 1997, 2011b, 2012b).

5.7. Ethyl ferulate (ethyl 4-hydroxy-3-methoxycinnamate, EFE)

EFE, the naturally occurring ester derivative of ferulic acid, has been found to promote HO-1 protein expression. It has profound scavenging properties toward both hydroxyl radicals and superoxide anions. The potency of EFE as an inducer of HO-1 expression, at both mRNA and protein levels, and of HO activity in cultured astrocytes and hippocampal neurons was tested in an *in vitro* study (Scapagnini et al., 2004). The results included clear evidence of the cytoprotective effects of EFE against oxidative damage in neuronal cells. Treatment of the cells with low concentrations of EFE resulted in high resistance to GOX/hydrogen-peroxide-induced cell death. ZnPP IX, a specific inhibitor of HO activity, ended the protective effect of EFE, demonstrating the direct involvement of HO-1 induction in the antioxidant mechanisms of this polyphenol (Scapagnini et al., 2004). Although the specific cascade that triggers HO-1 up-regulation has not been fully elucidated in terms of the action mechanism of EFE, the Nrf2 pathway is probably involved in the process in a way similar to the aforementioned role played by curcumin (Scapagnini et al., 2006, 2011). Taken together, these findings suggest that EFE may have therapeutic potential, as a potent inducer of HO-1, related to the protection of brain cells against oxidative stress, which is one of the possible pathogeneses of depression.

5.8. Ferulic acid (4-hydroxy-3-methoxycinnamic acid, FA)

FA, a phenolic compound present in several plants, has strong antioxidant effects and was found to be beneficial in the treatment of disorders linked to oxidative stress and inflammation (Anselmi et al., 2004). A recent study (Pae et al., 2008a) found that FA had a potential antidepressant-like effect in the FST and TST in animal models. Fluoxetine, paroxetine, and sertraline were also administered in the TST to reveal the action mechanisms of FA. The FA produced an antidepressant-like effect in the FST and TST, reflecting an anti-immobility effect and a synergistic antidepressant-like effect when given in combination with SSRIs, without causing hyperlocomotion. That study clearly demonstrated that FA's antidepressant-like effect operated primarily through modulation of the serotonergic system; this contrasts with ebselen, which did not exhibit a modulating effect on serotonin. In a prior study (Pae et al., 2008b), FA also demonstrated its antidepressant effects through simultaneously inhibiting serotonin, norepinephrine, and dopamine reuptake; regulating the HPA axis; and increasing ghrelin. The exact mechanism underpinning these antidepressant effects should be more clearly elucidated in the near future.

5.9. Omega-3 fatty acids

Omega-3 fatty acids are polyunsaturated fatty acids, derived from α-linolenic acids. Docosahexaenoic acid (DHA) and eicosapentaenoic acids (EPA) are omega-3 fatty acids. Both DHA and EPA are important constituents of brain lipid membranes and their early deficiency may decrease serotonin levels at critical periods of neurodevelopment and produce residual developmental deficits (Hibbeln et al., 2006). The major sources of omega-3 fatty acids are walnut and fish oils. Covariation between seafood consumption and rates of mood disorders were found in several epidemiological studies (Parker et al., 2006) whereas inverse relation was with aggression (Hibbeln et al., 2006).

Many *in vivo* studies showed promising results related to omega-3 fatty acids. Omega-3 fatty acids were reported to reduce ROS production

by human monocyte (Fisher et al., 1990). Omega-3 fatty acids were also found to suppress inflammatory cytokines such as TNF-α, IL-6 and induce heme oxygenase-1 expression, suggesting antioxidative property (Lu et al., 2010). Furthermore, omega-3 fatty acids significantly inhibited oxidative DNA damage and decreased neuronal death at induced-ischemia in animals. Omega-3 fatty acids also significantly improved memory function (Okabe et al., 2011).

Since low omega-3 fatty acid levels were associated with depression, numerous trials were conducted. However, equivocal results were produced in randomized placebo-controlled trials present at five positive studies (Gertsik et al., 2012; Nemets et al., 2006; Rondanelli et al., 2010; Su et al., 2003; Tajalizadekhoob et al., 2011) compared with six negative studies (Doornbos et al., 2009; Freeman et al., 2008; Lesperance et al., 2011; Makrides et al., 2010; Marangell et al., 2003; Rogers et al., 2008). One negative study, however, successfully demonstrated antidepressant activity after removing patients with comorbid anxiety disorders (Lesperance et al., 2011). As, depression is highly comorbid with anxiety symptoms, confounding effect by anxiety may have contributed to the mixed results. The antidepressant efficacy of omega-3 fatty acids should be verified in large well designed clinical trials in the future.

6. Conclusion

Hypotheses about the action mechanisms of antidepressants have been based primarily on the notion that they restore dopaminergic, noradrenergic, and serotoninergic neurotransmitter systems. Because the pathophysiology of depression is multifactorial, aberrations in neurotrophic factors, alterations in neurotransmitter receptor–signal pathways, disturbances in the HPA axis, inflammation, immune dysfunctions, imbalance between oxidative stress and antioxidant defenses, neurodegeneration, and mitochondrial dysfunctions including DNA damage have been consistently reported as alternative pathophysiological processes in the development of depression.

As discussed earlier (Section 3), increasing evidence suggests that antidepressants may correct an imbalance between the generation of ROS and the operation of antioxidant defenses, which may be one of the potential action mechanisms of antidepressants and a promising target for novel compounds. Additionally, currently available antidepressants were found to be disappointing in their efficacy in terms of remission rates for depression. Many independent clinical trials, registration clinical trials, and meta-analyses have maintained that the difference in the remission rates associated with approved antidepressants and placebos is approximately 15%. Thus, if we can find novel antidepressant compounds involving oxidative/nitrosative-stress mechanisms along with antioxidant defenses, such new compounds will enhance and extend the options for treating depression in clinical practice (e.g., novel-compound monotherapy or combinations of novel compounds and current antidepressants).

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