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The Role of Oxidative Stress in Depressive Disorders

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Abstract: Studies of the World Health Organization suggest that in the year 2020, depressive disorder will be the illness with the highest burden of disease. Especially unipolar depression is the psychiatric disorder with the highest prevalence and incidence, it is cost-intensive and has a relatively high morbidity. Lately, the biological process involved in the aetiology of depression has been the focus of research. Since its emergence, the monoamine hypothesis has been adjusted and extended considerably. An increasing body of evidence points to alterations not only in brain function, but also in neuronal plasticity. The clinical presentations demonstrate these dysfunctions by accompanying cognitive symptoms such as problems with memory and concentration. Modern imaging techniques show volume reduction of the hippocampus and the frontal cortex. These findings are in line with post-mortem studies of patients with depressive disorder and they point to a significant decrease of neuronal and glial cells in cortico-limbic regions which can be seen as a consequence of alterations in neuronal plasticity in this disorder. This could be triggered by an increase of free radicals which in turn eventually leads to cell death and consequently atrophy of vulnerable neuronal and glial cell population in these regions. Therefore, research on increased oxidative stress in unipolar depressive disorder, mediated by elevated concentrations of free radicals, has been undertaken. This review gives a comprehensive overview over the current literature discussing the involvement of oxidative stress and free radicals in depression.

Methods: We have carried out a medline search "oxidative stress depression", "oxidative stress affective disorders", "free radicals and depression", "free radicals and affective disorders" "antidepressants oxidative stress" "antidepressants and free radicals". We found numerous reports elaborating depressive disorder and oxidative stress. Most of the previous studies concentrated on investigating antioxidants in human blood as well as in animal models. However, few of these reports were able to show correlations of reduced oxidative stress with antidepressant treatment and clinical outcome measures. Fewer studies elaborated the concentrations of antioxidants in the human brain and some pro-oxidative enzymes in depression. However, more studies are needed to elucidate the complex role of oxidative stress in the aetiology of depression.

Keywords: Depression, oxidative stress, affective disorder, psychiatry, free radicals, antioxidants, prooxidants, superoxide, superoxide dismutase, xanthine oxidase, glutathione, gluthatione peroxidase, catalase antidepressants.

INTRODUCTION

Depressive disorders (DD) are extremely common mental disorders, with a life-time prevalence of about 16% [1]. Estimations show that by the year 2020 depressive disorders will be the second most significant contributor to the impairment of global health [2]. To this day, no specific pathophysiological process has been linked to the neuronal morphological changes that go along with this disease. Consistently, volumetric reductions in the prefrontal cortex (PFC) and the hippocampus have been reported from structural brain imaging studies of patients with DD [3]. Striking reductions in glial cell number and density in these brain regions as well as more subtle changes in neuronal density and size have been shown in post-mortem studies [4-9]. One of the most plausible causes for these neuronal alterations is elevated oxidative stress due to increased production of free radicals. Within the last decade, a growing body of literature not only in humans, but also preclinical findings from animal models indeed support this "oxidative stress hypothesis of depressive disorder" [10-12]. The most common definition of oxidative stress is an imbalance of free radical creation and anti-oxidative resistance, which results in an increased release of reactive oxygen species (ROS) [13]. Therefore, oxidative stress is a result of either increased production of ROS or decreased antioxidant defence. ROS are free radicals or reactive anions/molecules containing oxygen atoms such as superoxide, the hydroxyl-radical, and peroxynitrite [14, 15]. These free radicals are extremely reactive due to unpaired electrons (ROS). ROS are a product of processes taking place during the oxygen metabolism.

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ROS play a key role in several cell-signalling mechanisms. Increased oxidative stress results in enzyme inactivation, lipid peroxidation and DNA strand-brakes. Therefore, an increased release of ROS, often in combination with decreased antioxidant defence, can lead to cell disruption and finally apoptosis [14, 15]. Enzymes producing ROS such as xanthine oxidase (XO: EC 1.1.3.32), which is one of the most important, are called pro-oxidants (XO: EC 1.1.3.32) [16, 17]. XO catalyses the oxidation of hypoxanthine to xanthine and catalyses the oxidation of xanthine to uric acid. This leads to the production of a minimum of two reactive oxygen metabolites, superoxide anion and hydrogen peroxide [18, 19]. XO catalyses the reduction of O_2, leading to the formation of superoxide ($O_2^{\cdot}$-) and the downstream product hydrogen peroxide (H_2O_2) [4, 20, 21]. Antioxidant enzymes, namely superoxide dismutase (SOD), catalase (CAT) or glutathione peroxidase (GPX) metabolise ROS into less toxic molecules. SOD catalyses the reaction of superoxide to the less toxic H_2O_2 [22]. SOD is one of the most important antioxidant enzymes and interacts with other neuroprotective substances [23]. However, the role of SOD is somewhat ambiguous, since it is a very potent antioxidant, but can also lead to increased oxidative stress *via* the production of H_2O_2, however, the latter leads to increased oxidative stress if the latter's downstream enzymes are decreased or impaired. SOD can exist in several isoforms containing e.g. copper and zinc (Cu/Zn-SOD) or manganese (Mn-SOD) (see Fig. **1** for overview). The cellular distribution of these enzymes varies. Cu/Zn-SOD is mainly located in glial cells, whilst Mn-SOD is located in neurons and erythrocytes [24].

It has been shown that OS contributes to neuronal and glial cell loss in the central nervous system (CNS) [25-27]. From data of an enormous body of studies, it can be derived that oxidative stress is one of the main contributors to neuronal degeneration, both in the process of aging as well as in neurodegenerative and psychiatric diseases such as amyotrophic lateral sclerosis, Alzheimer's disease,

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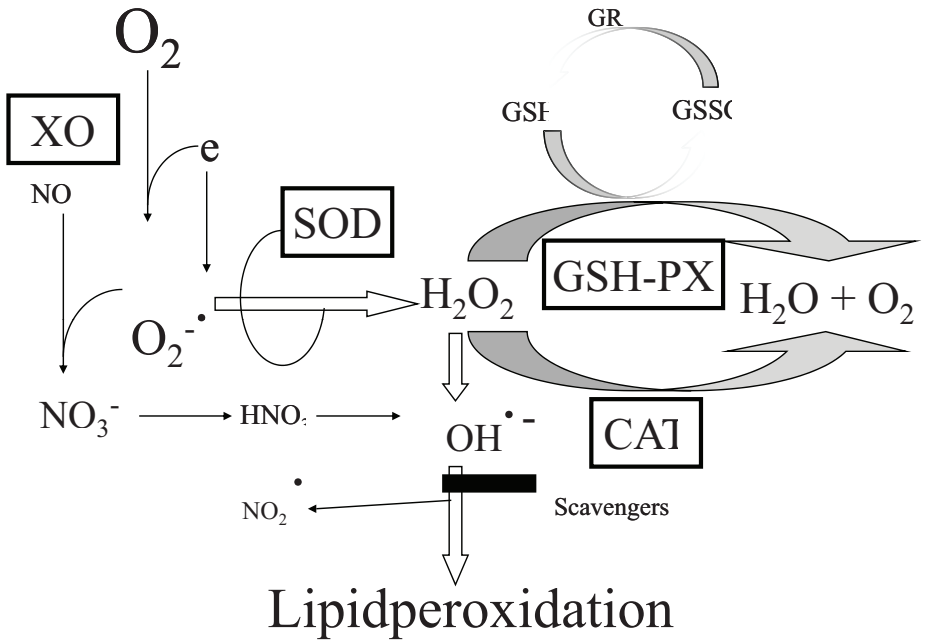

Fig. (1). Abb. 2: Oxidative stress related processes (modified after Youdim *et al*., 2001; Michel, 2011): e=electron, O_2=oxygen, $O_2^{\bullet-}$= superoxide, H_2O_2=hydrogenperoxide, OH=hydroxylradical, NO=nitrogenoxide, NO_2•=nitrodioxide, NO_3=nitrate, HNO_3=hydrogennitrate, GSH=glutathion, GSSG=glutathion-disulfide, GR=gluthatione reductase, GSH-Px=glutathione peroxidase, Cat=catalase, MAO=monoaminoxidase, ALDH=aldehydedehydrogenase, SOD=superoxide dismutase, XO=xanthine oxidase

Parkinson's disease and schizophrenia [10, 11, 24, 26-40]. It has been suggested before that oxidative stress plays a major role in the etiology of depression. Furthermore, it has been discussed that antidepressants influence oxidative stress during a depressive episode. In line with these hypotheses, evidence from post-mortem studies has shown that oxidative stress is responsible for cerebral morphological changes seen in DD [10, 40]. As mentioned earlier on, a growing body of evidence from human and animal studies supports the oxidative stress hypothesis of depression [10, 11, 12, 41, 42] [43]. With this comprehensive review, we intend to give an overview over the different lines of evidence supporting this hypothesis.

METHODS

Medline search using the terms "oxidative stress and depression", "free radicals and depression", "affective disorders and oxidative stress", "affective disorders and free radicals" "mood disorders and oxidative stress" "mood disorders and free radicals" was carried out (as well as the keywords: depression, oxidative stress, free radicals, mood disorder, "OR", "AND").

RESULTS

There is a large body of evidence (over 200 studies up to December 2011) from clinical and preclinical data, which suggests an important role of free radicals in major depressive disorder or recurrent depressive disorder. We will summarize these categories by the abbreviation DD. We have extracted 100 studies concentrating on recurrent or major depressive disorder, oxidative stress and antidepressants (bipolar and schizoaffective disorders were excluded).

The evidence on oxidative stress in major depressive disorder is derived from clinical and preclinical reports in cell and animal models. These either explore disturbed oxidative homeostasis indirectly *via* an increase of neuronal damage induced by increased free radicals, e.g. lipid peroxidation, DNA strand-brakes, in patients with DD or study antioxidants, prooxidants and free radical products directly. In addition to this, there are investigations exploring the antioxidant effect of antidepressants.

1) Evidence for Oxidative Stress in Patients with DD

Oxidative Stress-related Products and Damage in Patients with DD

Oxidative stress-related damage has been described in DD. OS can lead to destruction of neuronal integrity, induced by direct damage to DNA or by lipid peroxidation of the cell membrane. The latter is initiated by free radicals which crack up the polyunsaturated acids (PUFAs) chemical double binds. This process most often leads to a chain reaction. Since the process can be started by only one ROS, membrane lipids are extremely vulnerable. The "double-binds" are responsible for the specific properties of the cell membrane such as integrity and fluidity. These characteristics can be disrupted by ROS leading to the destruction of the cell. Peroxyl radicals further induce destructions of membrane proteins such as receptors and enzymes [44]. These processes, leading to apoptotic cells, have been observed in patients with DD [40].

Membrane damage in blood of patients with depression has been shown by elevated of omega 3- fatty-acids [45] and by increased lipid peroxidation products in patients with DD [42, 45, [46, 47]. Furthermore, DNA-strand brakes have been reported in the blood of these patients [48]. DD has been linked to increased serum levels of malondialdehyde (MDA), a breakdown product of oxidized apolipoprotein B-containing lipoproteins, and thus a marker of the rate of peroxide breakdown [49, 50].

In patients with DD, elevated levels of MDA adversely affect the efficiency of visual-spatial and auditory-verbal working memory, short-term declarative memory and delayed recall declarative memory [51]. Higher concentration of plasma MDA in patients with recurrent depression is associated with the severity of depressive symptoms, both at the beginning of antidepressant pharmacotherapy, and after 8 weeks of treatment. Statistically significant differences were found in the intensity of depressive symptoms, measured on therapy onset versus the examination results after 8 weeks of treatment [51]. Although this is used as a marker of lipid

peroxidation, it is considered to be less stable than 8-iso-PGF2a, and more susceptible to confounding factors such as antioxidants from diet [52]. Therefore, the best way to investigate oxidative disruptions to lipids in humans is via assessing levels of F2-isoprostanes [52-54]. These are stable compounds produced in the process of lipid peroxidation [52, 54]. 8-iso-PGF2a are specific F2-isoprostane molecules produced during the peroxidation of arachnidonic acid. However, the mean serum level of 8-iso-PGF2a was shown to be significantly higher in a group of patients with DD, controlling for lifestyle variables such as body mass index, alcohol consumption, and physical activity [55, 56]. Cerebral membrane abnormalities and altered membrane phospholipids have been suggested by an increased choline-containing compound seen in the putamen of patients with DD [57] which has been interpreted as a result of increased oxidative stress in patients with DD

In addition to that, an association of psychological stress and oxidative stress has been described repeatedly, both in animal models and human. It has been known for some time that DD can be triggered by life events that are accompanied by psychological stress [58].

Furthermore, DD is associated with cardio-vascular problems. Interestingly, oxidative stress is a risk factor linking both disorders on a biochemical level. The levels of 8-iso- PGF2a are increased in healthy individuals with cardiovascular risk profile factors, such as smoking, hypercholesterolemia, chronic infections, obesity, and diabetes [59] as well as in patients with coronary heart disease [60] [61]. Oxidative damage to lipids is one of the early key events in the aetiology of atherosclerosis, the pathologic condition that underlies these diseases. It was possible to show that patients with DD had significantly higher levels of serum 8-iso-PGF2a, while controlling for age, gender, race, years of education, daily smoking, number of alcoholic drinks per week, average amount of physical activity per week, and body mass index. However, no significant association was found between the severity of symptoms and levels of 8-iso-PGF2a, suggesting a threshold rather than a dose- response relationship. In addition to this, it has also been shown that 8-iso-PGF2a acts as a vasoconstrictor, mediates smooth muscle growth, activates platelets and has possible links to immunological parameters [62].

Immunological processes have been discussed in the pathophysiology of DD, since a mild systemic inflammation seems to take place in patients with depressive symptoms [63]. Furthermore, reactive oxygen species, such as superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite are produced by phagocytes as part of the cytotoxic host response [63]. *In vivo* animal models of inflammation and infection show that the systematic oxidation of lipid molecules is part of the host response to infection and inflammation [64]. Therefore, it can be hypothesised that the induction of inflammatory pathways might be responsible for oxidative stress due to elevated levels of oxidized lipids. On the other hand, clinical depression might make the individuals more prone to indulge in behaviours that cause oxidative damage, such as smoking or alcohol use.

Maes *et al*., (2010) found increased plasma peroxides and serum oxidized low density lipoptrotein antibodies in patients with DD. These findings emphazise the role of oxidative stress pathways in DD as well as in coronary heart syndrom, which might partly explain the high comorbidities of these disease entities [65].

Wolkowitz *et al*. (2011) indicated that accelerated aging at the level of leukocyte telomeres is proportional to lifetime exposure to clinical depression [66]. This might be related to cumulative exposure to oxidative stress and inflammation in depression. This suggests that telomere shortening does not antedate depression and is not an intrinsic feature. Rather, telomere shortening may progress in proportion to lifetime exposure to clinical depression.

Antioxidants and Prooxidants in Patients with DD

The expression, activity and concentration of oxidative stress related enzymes in blood, cerebral fluids and different brain regions in patients with depression are impaired. The literature describes the effects of oxidative stress seen in patients with DD by looking at the concentrations and activities of pro- and antioxidants in these patients. These have been examined in the blood of patients during several clinical stages of depression and in brain tissue of these patients post-mortem.

The results of altered antioxidant enzyme levels in the blood of patients with MD have been somewhat conflicting, some showed increased levels of SOD [46, 67], GSH-Px and GR (Bilici *et al*., 2001), others showed decreased SOD [68]. One study failed to find any alterations [69]. Furthermore, elevation of the endogenous inhibitor of endothelial NO synthase asymmetric dimethylarginine (ADMA) [70] was found, as well as diminished NO [69, 70]. Patients with depression seem to have lower albumin levels, which means decreased antioxidant activity [71]. One report of unmedicated patients (for at least 2 months) with depression found a decreased total antioxidant potential and uric acid levels in plasma as well as increased total plasma peroxide and oxidative stress index levels compared to healthy control subjects [72]. Analogously, different studies have also shown associations between the severity of DD and oxidative stress-indices [48, 67, 73]. However, not all studies were able to replicate these findings [69, 74].

In sum, the most replicated finding is an elevation of free radicals and their marker enzymes such as antioxidants during a depressive episode [46, 75]. Furthermore, patients with depression show reduced concentrations of the antioxidants vitamins E and C [76, 77]. These results are independent of nutritional status [77]. Another study in medication-free patients with DD compared to healthy controls showed a lower total antioxidant potential, uric acid concentration, increased lipid peroxidation markers and total oxidative stress index in plasma of these patients [78]. Additionally, the latter showed a positive correlation with depressive symptoms assessed by the Hamilton Depression Rating Scale (HAMD) [78] [79]. Furthermore, albumine, which has antioxidant properties, is compromised in MD [71, 79]. The levels of asymmetric dimethylarginine (ADMA), which obstructs endothelial NO synthase intrinsically, are increased and go hand in hand with reduced NO concentrations. Wang *et al*. (2009) reported increased oxidative stress in the anterior cingulate cortex of patients with bipolar disorder, but not with clinical depression. In this study, oxidative stress was determined by immunohistochemically analyzing 4-hydroxynonenal (4-HNE), a major product of lipid peroxidation [80].

Kodydkova *et al*., (2009) examined the anti-oxidative enzymes and increased oxidative stress in women suffering from DD. The group found that women with depression showed significantly decreased activities of GPX1 (glutathione peroxidase1), decreased concentrations of GSH (glutathione), and increased activities of GR (Gluthatione reductase), CuZnSOD (Cupper-Zinc-superoxide dismutase). Activity of GPX1 was positively correlated with concentration of GSH [81].

In the frontal cortex, Cu/Zn-SOD concentrations are increased in patients with DD compared to matched controls [10]. This finding was of specific interest since Cu/Zn-SOD is located only partly in neurons, but mainly in glial cells, which are more vulnerable to oxidative damage [82, 83]. In contrast to Cu/Zn-SOD, Mn-SOD (Manganese-superoxide dismutase) is a mitochondrial enzyme, which can be found mainly in neurons and only in much smaller amounts in glial cells [84]. In DD, glial cells have repeatedly been described as altered, especially in the frontal cortex [85, 86]. These reports of increased CU/Zn-SOD, but not Mn-SOD in the frontal cortex of patients with DD have been interpreted to be important to explain these histopathological findings of predominant glial cell damage in this brain area [10]. On the other hand, Mn-SOD positive

neurons are mainly located in the forebrain, the thalamus, the nucleus basalis Meynert and the basal ganglia, therefore a difference in the Mn-SOD concentration might be present in these regions which have not been examined so far [10, 37].

Interestingly, there was a significant increase in the classical pro-oxidative enzyme xanthine oxidase activity in the thalamus and the putamen of patients with DD compared to non-affected controls. In addition to this, XO activities were slightly higher in the frontal and parietal cortex, the hippocampus and the caudate nuclei and lower in the temporal and occipital cortex in patients with DD compared to healthy controls. In the entorhinal region, XO activity was increased more than two-fold in patients with DD compared to controls, however, due to technical and statistical reasons, these findings did not reach statistical significance [11, 12]. This report of increased XO activity in the putamen and thalamus of patients with DD was supported by previous reports describing structural and functional neuronal changes in these brain areas in the context of DD [87-92]. In addition to this, specific depressive symptoms, such as cognitive dysfunction, anhedonia and melancholia can be correlated with structural and functional neuronal alterations of both the putamen and the thalamus [88, 93, 94, 95].

Increased oxidation of lipid molecules in depression might be due to activation of the immune response [63] followed by induction of pro-inflammatory mediators like tumor necrosis factor and interleukins [96-99]. Interestingly, patients with DD are also more vulnerable to infections [100]. Oxidation of lipids seems to be part of the host response to infection and inflammation, which has been shown in *in vivo* animal models [101]. The cytotoxic host response against invading pathogens leads to activated phagocytes producing ROS such as superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite [63]. Activated leukocytes then secrete myeloperoxidase, further generating reactive nitricoxide-derived oxidants that induce lipid peroxidation [102]. Therefore, it is possible that depression is linked to lipid oxidation by means of inflammation related to oxidative stress.

Clinical Evidence for the Influence of Antidepressants on Oxidative Stress

Increasing evidence suggests an anti-oxidative role of antidepressants. Via complex interactions with growth factors etc., antidepressants seem to help regaining the so-called „oxidative balance"[40, 68]. In the serum of patients with depression, initial lower concentrations of SOD are normalized through antidepressant treatment [68]. This is accompanied by inverse alterations of the activity of SOD [103]. Furthermore, antidepressants induce a decrease of serum paraoxonase/arylesterase activities and the oxidation of apoliprotein B-containing lipoproteins, a marker of peroxide breakdown correlating with depression severity [42, 50]. Since oxidation of lipoprotein and low paraoxonase activity have been implicated in atherogenesis and coronary artery disease, this is another pathogenetic factor which links DD to cardiovascular disease [50]. Since DD is a devastating disease that afflicts large populations and has also been accepted to be an independent risk factor for cardiovascular disease (CVD), Kotan *et al*., 2011 examined the effects of long-term antidepressant (AD) treatment on the oxidative-anti-oxidative system parameters and CVD risk factors. They examined lipid profiles, oxidation and oxidizability of apolipoprotein B-containing lipoproteins (expressed as apo B-b-MDA and apo B-Δ-MDA, respectively), levels of plasma malondialdehyde (p-MDA), total anti-oxidative capacity (TAOC), antioxidant molecules and antioxidant enzyme activities including paraoxonase/arylesterase, red blood cell superoxide dismutase (RBC-SOD) and glutathione peroxidase during a 24-week of follow-up period in patients with DD under antidepressant treatment compared to healthy controls [104]. They found that p-MDA, apo B-b-MDA and RBC-SOD activity were increased and arylesterase activity was decreased in depressed patients. Body mass index (BMI), vitamin A and total cholesterol levels in patients with DD increased after 24-weeks of AD treatment. RBC-SOD activity, TAOC, p-MDA (peripheral malondialdehyde) and apo B-b-MDA levels were decreased; paraoxonase/arylesterase activities and apo B-Δ-MDA were increased at the end of the 24th week. Kotan *et al*. (2011) concluded that oxidative stress, demonstrated in clinically depressed patients, was partly improved during 24 weeks of AD treatment. Increase in paraoxonase/arylesterase activities and decrease in p-MDA and apo B-b-MDA levels after 24 weeks seem to be beneficial for reduction of CVD risk in MDD patients. However, increased BMI and apo B-Δ-MDA levels are negative cardiovascular effects of long-term AD treatment [104].

SSRI

Galecki *et al*. (2009) examined the influence of fluoxetine on the activities of antioxidant enzymes, lipid peroxidation and total antioxidant status (TAS) in patients suffering from depressive disorder compared to healthy controls in an effort to estimate how fluoxetine influences antioxidant defence and lipid peroxidation. They measured antioxidant enzyme activities and lipid peroxidation levels in erythrocytes as well as TAS in plasma of patients suffering from DD. All measurements were carried out during an acute depressive episode and during depression remission after antidepressive treatment with fluoxetine for three months. In patients with DD, they detected significantly higher levels of activity of antioxidant enzymes, such as copper-zinc superoxide dismutase (Cu/Zn-SOD) and catalase (CAT), as compared to healthy controls. Concentrations of malondialdehyde (MDA) were also significantly higher during depressive episodes. Activity levels of glutathione peroxidase (GPx) did not differ significantly between depressed patients and healthy control subjects. Moreover, the plasma total antioxidant status of patients with DD was decreased in comparison to control subjects. After three months of fluoxetine treatment, the above parameters did not change significantly. Therefore, Galecki and colleagues concluded that DD is accompanied by disturbances in the balance between pro- and anti-oxidative processes; however, these disturbances did not improve in patients in remission after three months of fluoxetine therapy [105].

Galecki *et al*. found that the activity of CuZnSOD in platelets of patients with DD was lower than in healthy controls, but the differences were not significant. Furthermore, they found that the activity of CuZnSOD rises after fluoxetine treatment. In addition to this, the study showed that the concentration of TBARS is higher in patients than in healthy controls. Finally, they found that the intensity of lipid peroxydation is statistically lower after fluoxetine treatment [106].

Since depressive episodes in patients are characterized by the presence of elements of an inflammatory process, which is one of the sources of reactive oxygen species (ROS), Galecki *et al*., studied the influence of fluoxetine mono-therapy versus a combination therapy of fluoxetine and acetylsalicylic acid on oxidative stress in patients suffering from the first depressive episode in their life. The results indicated a significant decrease in the activity of Cu/Zn-SOD, CAT and GSH-Px, as well as in MDA concentration after the combined therapy with fluoxetine and acetylsalicylic acid (ASA) therapy. Considering the results of the study, Galecki *et al*. suggested that combined therapy with fluoxetine and ASA is characterized by the same efficacy and clinical safety as fluoxetine monotherapy, resulting additionally in improvement of oxidative stress parameters in the patients treated for depression [106].

Depressed patients showed significantly higher levels of MDA compared to age- and gender-matched controls. Patients treated with sertraline demonstrated a significant reduction in MDA levels compared to patients refusing this treatment. The patients who were treated with sertraline showed a decrease in BDI score whilst patients who refused the treatment had no changes in BDI scores at follow-up. Furthermore, only the treated patients had a better outcome in psychological testing correlated with the heart condition

[107]. In contrast to that, fluoxetine seems to exert an additive toxic effect on neuronal cells by increasing mitochondrial damage and oxidative stress [108].

TCA

Not all studies report an anti-oxidative effect of antidepressants. Moreno-Fernández and colleagues suggested that oral treatment with the antidepressant amytriptyline induced coenzyme Q10 deficiency and increased lipid peroxidation. Therefore, they suggested to supplement Q10 with this antidepressant to counteract the possible oxidative effect of amytriptiline [109].

Taking all these findings together, oxidative stress as increased production of free radicals and enzymes with pro-oxidant capacities accompanied by a decrease of the antioxidant defence system is present both at the beginning and during the course of a major depressive episode [73-75].

2) Preclinical Evidence for Oxidative Stress in Depression

Preclinical Evidence for the Influence of Antidepressants on Oxidative Stress

Antidepressants in the Animal Models

Various studies so far have examinined antioxidants in several behavioural animal models of depression and in cell culture. These have shown different results such as reduced GSH- and GSH-Px, glutathione and vitamin C [110, 111]. Furthermore, increased lipid peroxidation and NO production have been reported [111].

In addition, glutathione depletion induced by the learned helplessness-experiments in animals could be reversed to a certain degree by antidepressant treatment [110].

Selective Serotonin Reuptake Inhibitors

Fluoxetine

Djordejevic and colleagues suggested that fluoxetine affects the antioxidant system and promotes apoptotic signaling in Wistar rat liver in non-stressed and stressed animals. The stressor was chronic psychosocial isolation. Their results revealed that fluoxetine down-regulates the activity of superoxide dismutases and up-regulates the activity of glutathione peroxidase in both rat groups. However, fluoxetine was shown to elevate glutathione reductase activity and total antioxidant status only in stressed animals. Furthermore, Djordejevic and colleagues hypothesised that fluoxetine interfered with stress-induced pathways of oxidative defence in the liver. In addition to these findings, they were able to detect that in both experimental groups, fluoxetine induced several hallmarks of apoptosis in the liver, including a decrease in Bcl-2 expression and increased DNA fragmentation. However, apoptotic alterations were more pronounced in stressed animals, suggesting that stress-related oxidative damage could have primed the apoptotic effects of fluoxetine [112].

Emotional stress can be viewed as a cause of adverse circumstances that induces a wide range of biochemical and behavioural changes. Oxidative stress is a critical route of damage in various psychological stress-associated disorders such as depression. In an animal study, Novio and colleagues investigated the effect of selective serotonin reuptake inhibitors (SSRIs) on the levels of intracellular reactive oxygen species in peripheral blood leucocytes of „stressed“ mice by using a 2',7'-dichlorofluorescein diacetate probe. The antioxidant response of fluoxetine was evaluated by superoxide dismutase, catalase and reduced glutathione. They found that levels of intracellular reactive oxygen species in leucocytes of peripheral blood in “stressed” mice were significantly increased by an elevated generation of reactive oxygen species in peripheral defence cells. Treatment with fluoxetine seemed to at least partially, reverse the adverse effects of stress. They concluded that the improvement in cellular oxidative status might be an important mechanism underlying the protective pharmacological effects of fluoxetine, which are clinically observed in the treatment of DD [113].

Escitalopram

A further animal study by Eren *et al*. (2007) suggested that escitalopram administration was able to reverse lipiperoxidation as well as GSH-Px-, glutathione- and vitamin C depletion in peripheral tissue [114].

Lee *et al*. (2011) examined the neuroprotective effects of pre- and post-treatments with escitalopram in the gerbil hippocampal CA1 region (CA1) after transient cerebral ischemia (TCI). Pre-treatment with escitalopram protected against ischemia-induced neuronal death in the CA1 after ischemia/reperfusion (I/R) and post-treatment with escitalopram had a neuroprotective effect against ischemic damage. In addition to this, Lee *et al*. found that pre- and post-treatments with escitalopram increased brain-derived neurotrophic factor (BDNF) protein levels in the ischemic CA1 region compared to vehicle-treated ischemia animals. Furthermore, pre- and post-treatments of TCI with escitalopram reduced microglia activation and decreased 4-hydroxy-2-nonenal and Cu/Zn-superoxide dismutase immunoreactivity and their levels in the ischemic CA1 compared to vehicle-treated ischemia animals after TCI. Therefore, Lee *et al*. came to the conclusion that pre- and post-treatment with escitalopram is able to protect against ischemia- and induced neuronal death in the CA1 induced by transient cerebral ischemic damage by increase of BDNF as well as decrease of microglia activation and oxidative stress. These findings emphasize the neuroprotective and anti-oxidative effects of antidepressants [115].

Sertraline

In the forced swimming test, Pedreanez and colleagues examined nitric oxide (NO), MDA, GSH and catalase activity as well as superoxide anion (O2-) by enzymatic and biochemical methods in frozen kidney sections of Sprague Dawley rats. The rats were treated with losartan, sertraline or water for 18 days with further renal O2-analysis. High renal content of NO, MDA and decreased amount of GSH were found. AT1 receptor blocking (losartan) and sertraline reduced both depressive-like behaviour and renal O_2-expression. Pedreanez und colleagues concluded that depression-like behaviour in rats is involved in kidney oxidative stress probably mediated by AT1 receptors and antidepressants [116].

Venlafaxine

Post-mortem experiments investigating the cortical correction of various oxidative stress-related marker enzymes showed a significant correlation of these with venlafaxine treatment [110]. Another animal study found a modulation of antioxidants and anti-apoptotic proteins in the hippocampus after the administration of the antidepressants venlafaxine or fluoxetine [112].

Abdel-Wahab and colleagues (2011) suggested that the antidepressant venlafaxine (VLF) protects against stress-induced oxidative DNA damage in the hippocampus during antidepressant testing in the animal model (forced swim-test and tail suspension test in mice). They examined the effects of VLF on hippocampal lipid peroxidation (MDA), nitric oxide (NO), glutathione (GSH), total antioxidant (TAC) levels and glutathione-S-transferase (GST) activity along with changes in serum and hippocampal 8-hydroxy-2'-deoxyguanosine (8-OHdG). They found that VLF was able to decrease the hippocampal MDA and NO and to increase hippocampal GSH and TAC levels and GST activity in the tested animals. Only GSH and TAC levels were increased by VLF in the non-stressed animals. In addition, both serum and hippocampal 8-OHdG levels were significantly reduced by VLF in animals exposed to antidepressant tests. They concluded that long-term VLF treatment in antidepressant dosages protects against stress-induced oxidative cellular and DNA damage. This action may be mediated through antagonization of oxidative stress and enhancement of antioxidant defence mechanisms [117].

Fluoxetine, Imipramine, TCA and Venlafaxine

A few animal studies have investigated the effect of antidepressants on endogenous antioxidant status in the brain. Zafir *et al.* (2009) employed a 21-day chronic regiment of random exposure to restraint stress in order to induce oxidative stress. Both the behaviour as well as the reversal of the oxidative stress indices indicated the effectiveness of treatment with antidepressants following restraint stress. The antioxidant status was investigated in the brains of these animals. The results showed a significant alteration in the activities of superoxide dismutase (SOD), catalase (CAT), glutathione S-transferase (GST), glutathione reductase (GR) and glutathione (GSH) levels by antidepressant treatments (fluoxetine, imipramine, tricyclic antidepressants and venlafaxine) following a restraint stress-induced depression model in rodents (forced swimming test and sucrose preference test). The lipid peroxidation product MDA and protein carbonyl contents accumulated in stressed animals. These accumulations were normalized by antidepressant treatments [118].

Citalopram and Desipramine

Affective symptoms are often associated with sleep deprivation. A study by Garg and Kumar (2008) explored the neuroprotective effect of citalopram and desipramine in a 72-hour sleep-deprivation test. Normally, 72 hours of sleep-deprivation induce behavioural alterations and oxidative damage in mice. Various behavioural tests (plus maze, zero maze, mirror chamber, actophotometer) as well as body weight followed by oxidative parameters (MDA, GSH, CAT, NO) were assessed in order to investigate oxidative stress-related parameters along with behavioural tests under the influence of antidepressant treatment. Treatment with citalopram for 5 days significantly improved loco-motor activity, anti-anxiety-like behaviour in all tasks („mirror chamber", „plus maze", „zero maze") as compared to controls. Biochemically, citalopram and desipramine treatment significantly restored depleted glutathione- and catalase-activity, attenuated elevated lipid peroxidation and nitrite levels compared to control animals. The results of this study suggest that citalopram and desipramine have neuroprotective effects against sleep deprivation-induced behaviour alterations, which are corrolated with oxidative damage in mice [119].

Antioxidant /Antidepressant-like Effect of Ascorbic acid (Vitamine C) and Fluoxetine

Another study investigated the influence of ascorbic acid (which is an antioxidant with antidepressant-like effects in animals) on both depressive-like behaviour induced by a chronic unpredictable stress (CUS) paradigm and on serum markers of oxidative stress and in cerebral cortex and hippocampus of mice [120]. The CUS-model is an animal model for induced depression-like behaviour in animals. Depressive-like behaviour induced by CUS was accompanied by significantly increased lipid peroxidation (cerebral cortex and hippocampus), decreased catalase (CAT) (cerebral cortex and hippocampus) and glutathione reductase (GR) (hippocampus) activities and reduced levels of glutathione (cerebral cortex). Repeated ascorbic acid as well as fluoxetine administration significantly reversed CUS-induced depressive-like behaviour as well as oxidative damage. No alterations were observed in locomotor activity and glutathione peroxidase (GPx) activity in the same sample. These findings pointed to a rapid and robust effect of ascorbic acid in reversing behavioural and biochemical alterations induced in an animal model [120].

Cellular Model, Antidepressants and Oxidative Stress

Lee and Han (2009) investigated whether antidepressive treatment of depression occuring in the context of Parkinson's disease, might ameliorate the cognitive disability and motor slowness in this disorder. Their study assessed the effect of antidepressants (amitriptyline, tranylcypromine and fluoxetine) against the toxicity of 1-methyl-4-phenylpyridinium (MPP(+)) in relation to mitochondria-mediated cell death process in differentiated PC12 cells. Amitriptyline and tranylcypromine attenuated the MPP(+)-induced cell death that may be associated with mitochondrial membrane permeability change and oxidative stress. Both compounds prevented the loss of the mitochondrial transmembrane potential, over-expression of Bax, reduction in Bcl-2 level, cytochrome C release, caspase-3 activation, formation of reactive oxygen species and depletion of GSH. The inhibitory effect of tranylcypromine was greater than that of amitriptyline. In contrast, fluoxetine revealed a toxic effect and exhibited an additive effect against the toxicity of MPP(+). Results show that amitriptyline and tranylcypromine may attenuate the MPP(+) toxicity by suppressing the mitochondrial membrane permeability change that leads to cytochrome C release and subsequent caspase-3 activation. Han and Lee concluded that the effects of antidepressants in the cell culture seem to be associated with the inhibitory action on the formation of reactive oxygen species and the depletion of GSH. In cell model experiments using neuronal and astroglial cultures derived from cerebrocortical structures of the rat, moclobemide showed a reduction of cell death provoked by processes implicating oxidative stress pathways [121]. The loss of differentiated PC12 cells, which were exposed to chemically induced oxidative stress, was prevented by phenelzine, a monoamine oxidase inhibitor. Furthermore, this drug showed antioxidant effects such as a drop in ROS formation as well as the scavenging of the pro-oxidant hydrogen peroxide [122].

DISCUSSION

The aetiology of depression remains uncertain. However, similar to the "vulnerability stress model" in schizophrenia, it is known that on the basis of a specific vulnerability, e.g. a special genetic make-up combined with environmental factors, certain life events, or an accumulation of these are able to induce clinical depression. Increasing evidence suggests that so called "psycho-social stress" leads to "biological stress". This biological stress is reflected by several different "cascades", one of them being free radicals-induced oxidative stress [10, 12]. These processes can lead to cellular damage and dysfunction, as well as to morphological alterations. All of these processes can be seen in patients with depression. These changes can be held accountable for the clinical symptoms found in patients with DD. (See Fig. **2** for details).

However, pro-oxidative enzymes have been rather neglected in the investigations concerning oxidative stress, although they regulate the free radical balance just like antioxidants. The role of prooxidants is very interesting, especially since inhibitors of prooxidants have been used rather successfully in other areas of medicine. In addition to this, the treatment is cost-effective and well tolerated [123] [124]. Recently, studies have elaborated on the use of these drugs in neuropsychiatric disorders such as Alzheimer's disease [125]. This avenue of research could be very promising since antidepressant treatment in depression have been carried out with ambiguous results [24].

However, all the above findings support the hypothesis that depression especially in later life has certain neurodegenerative aspects [126].

When examining the concentration of Cu/SOD, one of the best known antioxidant enzymes, the literature shows that it is not only altered in the frontal cortex of patients with major depression, but also in patients with schizophrenic psychosis [10, 11]. The overlap of biochemical markers for these distinct diseases goes hand in hand with an overlap of clinical symptoms of schizophrenic and affective psychosis as it is sometomes seen. This might point to a shared neuropathology of these psychiatric disorders. In clinical practice, it often can be observed that on one hand, patients with schizophrenia suffer from accompanying affective symptoms and on the other hand, the so called „negative symptoms" such as flattening of affect and anhedonia in schizophrenia can mimic depressive symptoms [40]. An underlying histopathological basis for these clinical observations could be a decrease of glial cells in the frontal

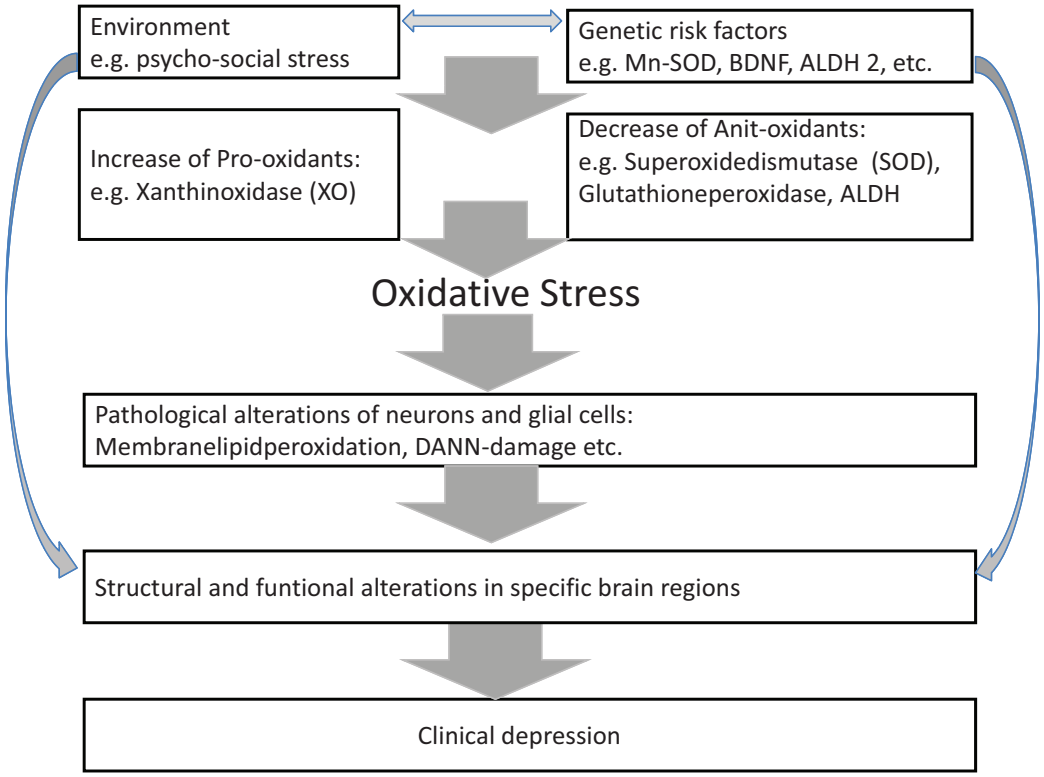

Fig. (2). Model of the aetiology of depression: environmental and genetic factors leading to increased induction of oxidative stress related membrane-lipid-peroxidation and DNA damage. These are responsible for structural and functional neuronal and glial alterations in certain brain regions known to play a role in the development of depression. These lead to some of the clinical presentations of depression modified after Michel *et al.*, 2011.

cortex of both groups of patients. This could lead to the induction of the antioxidant defence system (ADS). Antidepressants could be activated by increased concentration of PUFA from cellular damage. However, the increase of cerebral Cu/Zn-SOD concentration could therefore be interpreted as a compensatory reaction to OS and „the threat" of cell destruction [10, 11, 40]. Furthermore, SOD interacts with other neuroprotecitve substances such as neurotrophic factors [127].

One of the largest sources of oxidative stress, smoking, should be discussed in this context. There is a link between smoking and depression, in so far as depression leads to an increased susceptibility to smoking. Inversely, smoking improves mood and decreases depressive symptoms probably through nicotinergic receptor desensitization. Concomoitantly, nicotine withdrawal can precipitate depression-like symptoms. Several classes of antidepressants, particularly the atypical antidepressant bupropion, can decrease smoking beaviour and help smokers to quit in addition to their ability to improve mood and decrease depressive symptoms [128]. However, when examining the neuronal mechanisms of nicotine, a large inter-individual response heterogeneitey appears [129]. Furthermore, nicotine seems to influence neurotrophic factors, which also play a role in depression and other psychiatric disorders [130, 131, 132, 133] and interact with other neurotransmitters [134]. Therefore, the role of nicotine on the oxidative stress level in depression is difficult to assess in the context of this review.

However, evidence from cell- and animal models as well as clinical data show antioxidant properties of antidepressants. Some studies suggest that the addition of antioxidants or anti-inflammatory drugs enhance the antioxidant properties of antidepressants and produce a better clinical outcome. In this context, the antidepressive and antioxiative effect of herbal medicine has been investigated [135].

Taken together, both clinical as well as preclinical as well as post-mortem studies suggest that oxidative stress is a major contributor to the aetiology of depression. These findings should open new avenues for research not only to elucidate the puzzling enigma of the aetiology of depression, but to find more and possibly better treatment options for this devastating disorder.

CONFLICT OF INTEREST

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