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SHORT OVERVIEW OF OXIDATIVE STRESS IN MENTAL DISORDERS

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Abstract: This short overview explores the relationship between oxidative stress and mental disorders, focusing on the association with psychiatric pathologies such as Alzheimer's disease, schizophrenia, autism, depression, and the impact of sleep deprivation. The mechanisms of mitochondrial disfunction and oxidative stress in these pathologies are described, including the physiological function of limited free radicals in signal transduction, gene transcription, neuronal plasticity and memory. Key free radicals, including hydroxyl and superoxide are highlighted, along with compounds generating free radicals. Moreover, the potential therapeutic implications of dietary supplements (zinc, selenium, magnesium, vitamin C, E, CoQ_{10}) and lifestyle interventions with antioxidant properties are presented, laying the groundwork for future research in the field of mental health.

Keywords: oxidative stress, mental disorder, dietary supplements, antioxidants

1. Introduction

Limited amount of free radicals have beneficial effects for the body, being involved in signal transduction, gene transcription, inflammatory response, neuronal plasticity, and memory (Uttara et al., 2009).

The most important free radicals are hydroxyl (OH·), superoxide ($O2^{-}$·) and nitric monoxide (NO·) as well as substances capable of producing free radicals such as hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^{-}$). Reactive oxygen species (ROS) are formed especially because of metabolic processes that require oxygen. The body's antioxidant defense includes glutathione (GSH), arginine, tocopherol, ascorbic acid, retinol and polyphenols derived from tea, the activity of these compounds being complemented by enzymes with an antioxidant effect e.g. superoxide dismutase (SOD), catalase (CAT), GSH reductase and GSH peroxidase (Sharma et al., 2022). SOD catalyzes the transformation of superoxide to hydrogen peroxide and oxygen, and hydrogen peroxide is converted to water and oxygen by catalase (Rodriguez-Rocha et al., 2013).

Oxidative stress (OS) is induced by a modified equilibrium between the generation of free radicals and the antioxidants effect, and it can lead to impairment of the cellular functions or mitochondrial dysfunction. The brain is highly vulnerable to the impact of free radicals due to the intense oxidative metabolism, the amount low in antioxidants that cross the protective barrier separating the bloodstream from the brain and the increased content of polyunsaturated fatty acids. Although the average weight of the human brain is only 1400 g, it consumes in aerobic energy metabolism more than 20% of the overall oxygen in the organism in order to provide energy to the 86 billion neurons (Cobley et al., 2018). The quantity of oxygen available to the brain is extremely carefully controlled at the level of the *prima fascia* precisely because of the possibility of ROS generation (Fukuto et al., 2012).

OS enhances the process of oxidative degradation of lipids, especially of membrane fats with the formation of compounds such as malondialdehyde (MDA), 4-hydroxy-2-nonenal (HNE), acrolein which can bind to proteins or DNA leading to a change in their function (Reed, 2011). In the case of carbohydrates, due to their reducing character, they react with ROS, the compounds resulting from nonenzymatic combination with proteins are called advanced glycation end-products (AGEs), implicated in the etiology and progression of certain diseases, such as diabetes mellitus, cardiac impairment, and neurodegenerative conditions (Ahmed, 2005). In the case of proteins, the products generated through the influence of ROS and reactive nitrogen species (RNS) are protein carbonyls and nitrated proteins.

This short overview emphasizes the link between OS and cognitive dysfunction, highlighting a few dietary supplements with antioxidant properties. These supplements have the potential to contribute to the prevention and treatment of imbalances associated with OS in the context of mental disorders.

1. General aspects regarding mitochondrial dysfunction in neurological and psychiatric diseases

Mitochondria are cellular organelles with an extremely dynamic structure, continuously subjected to fission and fusion processes in order to sustain a healthy mitochondrial function. The disruption of these repair mechanisms leads to mitochondrial disfunction (Ježek et al., 2018; Ren et al., 2020).

Mitochondria play a crucial role in ensuring proper development of numerous processes at the neuronal level, such as: the main source of energy (ATP) through the process of oxidative phosphorylation, obtaining precursors and initiating the synthesis of heme - glycine and succinyl-CoA, a buffer role in regulating calcium concentration during signal transduction, therefore metabolic changes at the mitochondrial level have profound repercussions on the good functioning of neurons and can be responsible for the occurrence of numerous neurodegenerative diseases (Wang et al., 2020).

Among the mechanisms incriminated in mitochondrial disorders is OS, mitochondria being responsible for the production of ROS. ROS can modify the concentration gradient of Ca^{2+} on either side of the cell membrane through direct damage of Ca^{2+}-regulating proteins, with the mitochondrial increase of [Ca2+]. Intramitochondrial, ROS produce changes in the activity of NADH dehydrogenase, cytochrome c oxidase and ATP synthase, with direct damage to cellular energy metabolism (Sousa et al., 2023).

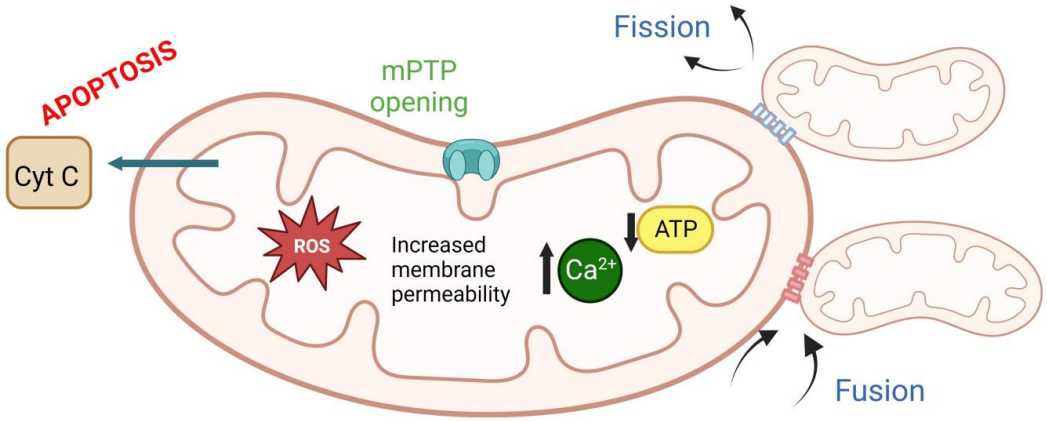

Fig. 1. Mitochondrial dysfunction (MD) pathways (1. Increase in the intramitochondrial concentration of Ca^{2+}, 2. Opening of the mPTP, 3. The liberation of cytochrome c into the cytoplasm, initiating cellular apoptotic processes, 4. Modification of mitochondrial fission and fusion processes, 5. Decrease of ATP concentration by modification of the electron transport chain) (after Norat et al., 2020)

Apart from OS, mitochondrial dysfunction can also arise due to alterations in mitochondrial DNA. Changes in the permeability of the mitochondrial membrane, triggered by the opening of the mitochondrial permeability transition pore (mPTP), result in the release of cytochrome c into the cytoplasm, leading to the initiation of cell apoptosis and mitophagy (see **Fig. 1**) (Liu et al., 2018; Ciocca and Pizzamiglio, 2023). Considering the increased energy requirement and the limited regeneration capacity of neurons, the proper functioning of mitochondria is essential for the survival of neurons (Johri and Beal, 2012). Mitochondrial disfunction is currently the most incriminated pathological process in the ethology of neurological disorders such as: Huntington's disease, Parkinson's disease, schizophrenia, multiple sclerosis and Alzheimer's disease (Wu et al., 2019).

2.1. Oxidative Stress and Alzheimer`s disease

Alzheimer's disease is a gradually advancing neurodegenerative condition identified by cognitive decline. While the precise origin of Alzheimer's disease remains elusive, emerging evidence indicates that OS plays a pivotal role in its development. Multiple mechanisms have been shown to be involved, including mitochondrial dysfunction, accumulation of transition metals, genetic factors, and amyloid beta-mediated processes.

Multiple studies have reported elevated markers of OS in Alzheimer’s disease, especially lipid peroxidation is greatly enhanced in neurons (Misrani et al., 2021). This highlights the complex interplay between OS and the development of hallmark characteristics associated with Alzheimer's disease.

Studies indicate that OS is implicated in the creation of significant pathological characteristics, including the aggregation of amyloid beta into plaques in Alzheimer's disease and hyperphosphorylated tau into neurofibrillary tangles (Ionescu-Tucker and Cotman, 2021). Furthermore, a significant decrease in glucose metabolism was described, which is thought to be at least partially caused by oxidative inactivation of enzymes implicated in glycolysis, the Krebs cycle, and

ATP biosynthesis (Butterfield and Halliwell, 2019). This defect in glucose metabolism further exacerbates the energy deficit in affected brain regions.

Overall, OS is not only a consequence of this pathology but also a contributing factor to its progression.

2.2. Oxidative Stress and depression

OS has been associated with the onset and progression of depression. Research shows a complex interplay between excessive exposure to free radicals and the development of depression. Various factors including smoking, alcohol dependence, obesity, and intense physical activity are associated with depression, all of which contribute to elevated levels of ROS. Chronic stress triggers the release of cortisol, leading to dysfunction in mood regulation, psychomotor drive, and impaired neurogenesis. Additionally, the uncontrolled release of glutamate into synapses, known as glutamatergic hyperactivity, is followed by stressful stimuli. This consequently leads to neurotoxicity, and neuronal death. These OS-induced alterations in the neuronal system, shown by a decreased hippocampal volume, are a dominant factor in the development of depression (Cecerska-Heryć et al., 2022).

The impact of OS extends to DNA damage, suggesting a plausible connection between OS and accelerated aging processes (Cecerska-Heryć et al., 2022). Furthermore, elevated levels of malondialdehyde (MDA) are noted in depressed patients. Supporting these findings, additional studies show reduced levels of crucial antioxidants such as tocopherol, zinc, and coenzyme Q10, contributing to an impaired defence against free radicals. Furthermore, some evidence propose that OS and inflammation may interact in a bidirectional manner, with OS promoting inflammation and vice versa. This bidirectional relationship could further contribute to the onset and advancement of depression (Bhatt et al., 2020). An excess production of inflammatory markers is linked to cognitive alterations and the manifestation of depressive symptoms.

2.3. Oxidative Stress and Autism

OS contributes significantly to the pathophysiology of Autism Spectrum Disorders (ASD). Multiple studies have shown increased markers of OS and decreased levels of antioxidants in individuals with ASD. These markers include abnormal lipid peroxidation, decreased levels of GSH and SOD, and reduced actions of antioxidant enzymes. Neurons, which are unable to produce GSH, are especially vulnerable to the harmful effects of OS. This may contribute to the observed neurological abnormalities in ASD (Pangrazzi et al., 2020).

Research indicates that two factors, mitochondrial dysfunction and the accumulation of transition metals, contribute to the heightened production of ROS in individuals with ASD. This in turn worsens OS, resulting in oxidative deterioration of lipids, proteins, and DNA, inflammation, and other harmful processes that may result in the clinical symptoms of ASD (Liu et al., 2022).

Selenium and selenoproteins play a vital role in individuals with ASD, influencing various processes such as antioxidants, inflammation, and brain cholesterol metabolism. Abnormalities in red blood cell membranes are observed in children with ASD, such as reduced phosphatidylethanolamine levels and elevated phosphatidylserine levels.

It is important to note that both genetic and environmental factors are responsible for increasing OS in individuals with ASD. Genetic factors include polymorphisms in genes associated with GSH metabolism, OS, and detoxification pathways, as well as copy-

number variations, which play a role in ASD pathogenesis (Gonzales et al., 2023). Environmental factors include exposure to heavy metals, infections, drugs, and environmental toxins are also implicated in increasing OS in ASD.

2.4. Oxidative stress and sleep loss/ deprivation

Sleep deprivation refers to the condition of insufficient or inadequate sleep, which can have adverse effects on different facets of health, affecting mainly the brain, liver, kidney, stomach, testes, and heart (Neculicioiu et al., 2023).

One of the potential mechanisms linking sleep deprivation to health problems is OS. Sleep holds significance in maintaining cognitive function and overall well-being. Research has found that chronic sleep deprivation can lead to cellular damage and cognitive impairments because of intense OS. After a period of sleep deprivation, the antioxidant defence mechanisms start to decrease, contributing to impairment of both short- and long-term memory (Atrooz and Salim, 2020).

Furthermore, studies have found a correlation between sleep loss and triggering OS in the gut through ROS accumulation. The reason for the accumulation of ROS during sleep loss is not well known. Levels of ROS may arise due to heightened production, diminished elimination, or a combination of both factors. Some studies have found that NADPH oxidase potentially led to gut dysbiosis induced by the hyperproduction of ROS. The accumulation of intestinal ROS may have systemic effects on gut microbial profiles and immunity, due to their high potential of cellular damage (Vaccaro et al., 2020).

Long periods of wakefulness have additionally shown a more active metabolism, and neuron activity, as well as increased glucose consumption, compared to periods of sleep. These findings correspond to an elevated oxygen-dependent ATP synthesis within the mitochondria, herewith, increasing the production of ROS. Moreover, sleep deprivation can produce a stress response. The activation of the hypothalamic-pituitary-adrenal axis holds a pivotal position in mediating the interaction between stress, sleep deprivation, metabolism, and its potential to induce OS. These results emphasize the crucial significance of prioritizing quality sleep as part of overall health maintenance.

2.5. Oxidative Stress and schizophrenia

OS can potentially contribute to the onset of schizophrenia by disrupting the balance of thiol status. Thiols, including GSH, are essential for maintaining antioxidants and ROS in equilibrium within the body. This disruption in thiol status may have implications for the pathophysiology of schizophrenia. Studies have shown that individuals with schizophrenia often exhibit reduced levels of antioxidants, such as GSH, and elevated levels of markers of oxidative damage compared to healthy individuals (Cuenod et al., 2022).

Moreover, OS can be a consequence of obstetric complications that have been linked to schizophrenia. In addition to its direct impact on the redox control system, OS can also affect DNA metabolism and epigenetic marking, potentially contributing to the vulnerability to schizophrenia (Fraguas et al., 2019).

This growing evidence indicates that OS could represent a shared mechanism by which different genetic and environmental factors impact neurodevelopmental processes underlying schizophrenia. The vulnerability-stress-inflammation model of schizophrenia integrates OS, highlighting the potential for stress to contribute to a persistent pro-inflammatory state. This increased inflammation could be seen within the cerebral

and circulatory systems of these patients (Ermakov et al., 2021).

Additionally, OS in schizophrenia is not only a consequence of genetic factors but can also be influenced by environmental factors such as childhood trauma, initiating the increase of pro-inflammatory cytokines and promote ROS generation. One area of interest represents the impact of OS on PV (parvalbumin) neurons, a specific type of inhibitory interneurons in the brain. Dysfunction or impairment of PV neurons has been associated with several psychiatric disorders, including schizophrenia. In conclusion, OS is considered a potential pathogenic mechanism in schizophrenia and individuals with schizophrenia are believed to be in a state of OS (Cuenod et al., 2022).

3. Diet, dietary supplements and phytochemicals with antioxidant activity

3.1. Diet, macro, and micronutrients

A well-balanced intake of both macro and micronutrients supports mental equilibrium (Quan et al., 2023). Even though glucose is the primary energy substrate for neurons, several studies have shown that the outcome of a high-carbohydrate diet increases the risk of depression by influencing the neuronal metabolism of serotonin leading to the stimulation of inflammatory processes and a reduction in the expression of brain-derived neurotrophic factor (BDNF) (Pinna et al., 2022; Colucci et al., 2020).

Regarding the consumption of fats, both high-fat diets and obesity are major factors that exacerbate depressive states. There are studies suggesting that the expression of the long isoform of the leptin receptor (LepRb) and the cannabinoid receptor type 1 (CNR1) is influenced, selective deletion of these receptors leading to behaviors related to depression (Gallego-Landin et al., 2021; Li et al., 2022). Alternatively, a high-protein diet is linked with a reduced risk of depression, probably attributed to its rich concentration of essential amino acids such as tryptophan, a precursor to serotonin (Reuter et al., 2021).

- *Ketogenic diet*. Ketone bodies become the primary source of energy for cells, including the neurons, during carbohydrate deprivation, and this condition is beneficial for patients with epilepsy as it helps reduce the frequency of epileptic seizures (Dowis and Banga, 2021). Building on this fact, recent studies are focusing on the benefits of the ketogenic diet in other conditions such as Alzheimer's, Parkinson's, migraines. The mechanisms by which this diet offers beneficial effects in neurological disorders are intricate, but there are some evident clues: it modulates the levels of BDNF, enhances mitochondrial function (Dyńka et al., 2022). The neuroprotective impact of the diet is also associated with gut microbiome's composition, as ketone bodies have an impact on the diversity and abundance of the microbiome (Tao et al., 2022). Even though the ketogenic diet holds therapeutic potential in various neurological conditions, its benefits should continue to be assessed through clinical studies in future research.
- *Micronutrients*
  - ✓ **Zinc.** Zinc acts as a cofactor for numerous enzymes participating in carbohydrates, lipid, and protein metabolism, influencing immunity. Several studies highlight the beneficial effect of supplementing zinc when combined with antidepressants at concentrations ranging from 25 to 220 mg for 8 to

12 weeks for the treatment of depression (Quan et al., 2023). The effect is both anti-inflammatory and an elevation of the concentration of BDNF was observed (Wu et al., 2021).

- ✓ **Magnesium.** Among its numerous biological roles, magnesium activates many enzymes involved in metabolism. Numerous studies have shown an inverse relationship between dietary magnesium intake and the risk of experiencing depression, modulating N-methyl-D-aspartate (NMDA) nerve signaling (Del Chierico et al., 2021). Supplementation of 248 to 500 mg/day for 6 to 8 weeks helps maintain mental equilibrium (Quan et al., 2023).
- ✓ **Selenium.** Selenium is involved in several physiological functions, having anti-oxidative and anti-inflammatory effect. However, supplementing with selenium should be preceded by measuring its levels in the blood, as there are controversies surrounding both under and over-dosage. Both scenarios pose a risk factor in promoting depression (Maruki et al., 2022). However, a recent study by *Pereira ME et al*. supports the beneficial antioxidant and anti-inflammatory action of selenium in patients with Alzheimer's disease. Selenium is a trace element that is a crucial component of selenoproteins, such as selenoprotein P, which holds a crucial function in the central nervous system by maintaining an antioxidative status and, as a result, mental health equilibrium. The recommended daily intake of selenium is generally in the range of 55 to 70 micrograms per day for adults (Pereira et al., 2022). Regarding the antioxidant effect, *Cardoso et al.* observed that there was an increase in the activity of GSH peroxidase following selenium supplementation in patients with Alzheimer disease (Cardoso et al., 2019).

3.2. Vitamin C

Vitamin C (ascorbic acid) is a cofactor in a variety of biological processes, being renowned for its antioxidant properties. In recent years, research has revealed that vitamin C plays a role in maintaining mental health by regulating the metabolism of neurotransmitters and, consequently, neuronal activity (Figueroa-Méndez and Rivas-Arancibia, 2015). The recommended dietary allowance (RDA) for vitamin C is established at 75-90 mg on a daily basis. While there are suggestions to intake 3 grams of vitamin C daily, it's important to note that this may lead to side effects such as nausea, vomiting, and diarrhea. (Kaźmierczak-Barańska et al., 2020).

Sim M et al. performed a study emphasizing the importance of vitamin C supplementation in the vitality of healthy young adults (20-39 years), concluding that vitamin C at doses of 500 mg twice daily for one month enhanced motivation for work and improved ability to stay focused positively influencing performance on cognitive tasks that demand prolonged attention (Sim et al., 2022). The presumed mechanism of action appears to involve vitamin C's role in dopaminergic transmission (it acts as a cofactor for dopamine-β-hydroxylase), in the serotoninergic, glutaminergic, cholinergic neurotransmissions by modulating hydroxylation reactions (Moritz et al., 2020).

Even though there are several studies demonstrating the anxiolytic and antidepressant impacts of vitamin C, advanced research is needed for this molecule to become a candidate in psychiatric therapy.

3.3. Vitamin E

Vitamin E (α-tocopherol) is a lipid-soluble vitamin, enhancing immunity and reducing OS (Wang et al., 2023). *Atiq A et al.* published an article regarding the impact of vitamin E using an experimental model of Parkinson's disease, reducing α-synuclein expression, increasing the expression of dopamine transporter in the *substantia nigra* and activating the nuclear factor erythroid-2-related factor 2 (Nrf2) pathways (Atiq et al., 2023).

In the same context, another study conducted on an experimental model of acute and chronic stress demonstrated that the preventive administration of vitamin E reduced OS markers (Al-Sowayan, 2020).

3.4. CoQ_{10}

CoQ_{10} is a part of the electron transport chain. It has anti-inflammatory and antioxidant effects that have been studied in the context of various neurological diseases (Sanoobar et al., 2013; Pandya et al., 2013).

In a randomized, double-blinded study, the impact of supplemental CoQ_{10} on patients with bipolar disorder yielded to changes of total antioxidant capacity and total thiol groups in the serum (Dai et al., 2022).

With these effects, CoQ_{10} is a new potential candidate in addition to those previously described in the prevention and treatment of psychiatric syndromes.

3.5. Phytochemicals (flavonoids, polyphenolic compounds)

Recent studies concluded that flavonoids, especially those derived from berries, have the potential to alleviate depression by exerting antioxidant properties, functioning as neuromodulators, and fostering cognitive well-being (Ali et al., 2021). Also, blackcurrant extracts increased expression of BDNF in the hippocampus of mouse models and reduced OS and inflammation (Currie et al., 2023).

In a recent review emphasizing the significance of nuclear factor erythroid-2-related factor 2 and natural flavonoid activators, it was reported that flavonoids like curcumin, quercetin, and resveratrol were shown to lower OS, increasing GSH concentration *in vitro*, reducing depressive-like behaviors in an experimental model, and decreasing malondialdehyde (MDA) levels (Zuo et al., 2022).

Quercetin is a flavonoid with proven antioxidant and anti-inflammatory properties. Quercetin`s anti-stress effects are achieved through a combination of mechanisms that involve regulating neurotransmitters like serotonin, suppressing the Hypothalamic-Pituitary-Adrenal axis, promoting neurotrophic factors that support brain health and resilience to stress, inhibiting the responses of microglial and astrocyte cells to stress (Colunga Biancatelli et al., 2020; Wang et al., 2020; Zhang et al., 2020).

Resveratrol is another natural compound, having a polyphenolic structure. Resveratrol has shown the potential to protect dopaminergic neurons from methamphetamine-induced neuronal cytotoxicity (Zeng et al., 2021).

The consumption of natural products or extracts containing flavonoids or other natural compounds with antioxidant properties has certain limitations, one of which is the variable content of the active substance in these fruits or extracts.

Conclusions

In conclusion, this short overview highlights the pivotal role of OS in the development and progression of various mental disorders, suggesting a multifaceted relationship between OS and mental disorders, involving disruptions in neurotransmitter balance, Hipothalamic-Pituitary-Axis hyperactivity, DNA damage, and antioxidant deficiencies. Furthermore, it explores the potential therapeutic implications of dietary supplements and lifestyle interventions with antioxidant properties, providing a foundation for future research in the mental health therapeutic field.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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