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Mini Review

RECURRENT DEPRESSIVE DISORDER, TYPE 2 DIABETES MELLITUS AND OXIDATIVE STRESS

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ABSTRACT

The imbalance between pro-oxidant and antioxidant factors leads to oxidative stress, which seems to play an important role in the pathogenesis of both depression and type 2 diabetes mellitus. Because ROS is an essential mediator for the activation of pro-inflammatory signalling pathways, obesity and hyperglycaemia-induced ROS production may favour the induction of M1-like pro-inflammatory macrophages during the onset and progression of diabetes. By generating more reactive oxygen species (ROS) and upregulating markers of chronic inflammation, hyperglycaemia can lead to vascular dysfunction. Damage to cellular components brought on by an excess of reactive oxygen species (ROS) generates pro-inflammatory molecules such as 4-hydroxynonenal, neoepitopes, and damage-associated molecular patterns, which in turn trigger the immune system and ultimately result in cell death. In MDD, oxidative stress-induced reductions in NO-dependent dilatation and alterations in vascular smooth muscle function are directly associated with microvascular dysfunction.

Key words: Oxidative stress, depression, diabetes

INTRODUCTION

Reactive oxygen species (ROS) are produced and accumulate in cells and tissues as a result of an imbalance between the biological system's capacity to detoxify reactive products and the occurrence of oxidative stress. But xenobiotics like antiblastic medications, as well as environmental stressors like UV rays, ionizing radiation, pollutants, and heavy metals, significantly increase the production of ROS, which in turn creates an imbalance that damages cells and tissues (oxidative stress). ROS are capable of performing a number of physiological functions, including cell signalling. Typically, ROS are produced as byproducts of the metabolism of oxygen (1).

The functioning of mitochondria and oxidative stress are closely connected. The production of ROS-like superoxide radicals and hydrogen peroxide (H2O2) is associated with the mitochondrial electron transport chain, in addition to the presence of ROS-producing enzymes like monoamine oxidase in the outer membrane of the mitochondria. Nonetheless, the mitochondria's glutathione (GSH) and manganese superoxide dismutase (SOD) molecules serve as an antioxidant system. (2) Superoxide radicals (O2•−), hydrogen peroxide (H2O2), hydroxyl radicals (•OH), and singlet oxygen (1O2) are the most widely recognized definitions of reactive oxygen species (ROS). These ROS are byproducts of metabolism in biological systems. (3, 4) Antioxidant enzymes, not low molecular weight antioxidant compounds, play the primary role in antioxidant defence (5). Reactive oxygen species are mostly produced by mitochondria, both in healthy and diseased conditions (ROS). O2•− can be produced by endothelial cells, inflammatory cells, lipoxygenases (LOX) and cyclooxygenases (COX) during the metabolism of arachidonic acid, and by cellular respiration. (6)

Endogenous and exogenous factors are the two primary sources of free radical generation. Numerous conditions, such as aging, overexertion, mental stress, inflammation, ischemia, infection, cancer, and immune cell activation, can result in the endogenous

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production of free radicals. Exogenous free radicals can be produced by exposure to a variety of substances, including chemicals, solvents, heavy metals, medications (such as cyclosporine, tacrolimus, gentamicin, and bleomycin), smoked meats, used cooking oil and fats, alcohol, cigarettes, and radiation. Free radicals are produced as a byproduct of the breakdown or metabolism that these foreign substances undergo once they enter the body. (1) Under normal physiological conditions, antioxidants found in cells, such as glutathione peroxidases, catalases, and superoxide dismutases balance the effects of free radicals. (7) Reactive oxygen species can trigger proCT expression from the CGRP gene in trigeminal glia via a paracrine regulatory mechanism. This pathway of glial recruitment may follow cortical spreading depression and neurogenic inflammation to augment the nociceptive actions of CGRP in migraine. (8)

Reactive oxygen species (ROS), which include hydrogen peroxide, hypochlorite, superoxide anion, singlet oxygen, lipid peroxides, and hydroxyl radicals, are involved in the processes of cell growth, differentiation, progression, and death. They can react with proteins, enzymes, nucleic acids, membrane lipids, and other small molecules (9). Lipid peroxidation and glycoxidation reactions happen when ROS build up intra- or extra-mitochondrially during oxidative stress. This, in turn, increases the endogenous production of reactive aldehydes and their derivatives, such as glyoxal, methylglyoxal (MG), malondialdehyde (MDA), and 4-hydroxy-2-nonenal (HNE). These reactions impact glycation and lipoxidation pathways, which can be used to further process these end products. Damage to cells and eventual cell death are caused by dysregulated signalling. (10)

At the physiological level, ROS are important for neurogenesis and neuronal activity. Other oxidants that affect important physiological processes like LTP include nitric oxide (NO) and carbon monoxide (CO), which act through glutamate-dependent pathways. Long believed to be mainly linked to neurodegenerative illnesses, such as Parkinson's, Alzheimer's, and Huntington's, oxidative stress is now known to play a role in neuropsychiatric conditions like anxiety and depression. (11) A 2022 study discovered the first indication of increased T-cell mitochondrial reactive oxygen species (T-cell mitoROS) in young, otherwise healthy adults with MDD. Although elevated T-cell mitoROS does not correlate with a proinflammatory profile, these results suggest that it may be an early marker of immune system dysregulation in young adults with MDD. (12) Through the transformation of arginine (Arg) into L-citrulline, the enzyme nitrogen oxide synthase (NOS) is responsible for the production of NO in different cells. (13)

Antioxidants are categorized into five primary groups. A variety of foods are dyed by fat-soluble pigments, called carotenoids. They fall into two primary categories: xanthophylls, which are oxygen-containing molecules like lutein and zeaxanthin, and carotenes, which are non-oxidized molecules like lycopene and alpha-carotene. The flavonoid group includes anthocyanins, flavanols, isoflavones, and flavones. With their anti-inflammatory, anti-cancer, anti-inflammatory, and antioxidant qualities, flavonoids are an important class of natural products that are used in a wide range of pharmacological and nutritional applications. (14) Brain-derived neurotrophic factor (BDNF), which is crucial for the pathophysiology of depression, constitutively regulates the nuclear translocation of the master redox-sensitive transcription factor Nrf2, which activates antioxidant defence. Low levels of BDNF inhibit Nrf2 translocation in susceptible animals, which prevents the activation of antioxidant enzymes and detoxification processes. Chronic oxidative stress develops as a result of this. (15)

Type 2 diabetes mellitus and oxidative stress

By encouraging endothelial activation, elevated NADPH oxidase activity in endothelial microparticles brought on by high glucose levels worsens endothelial inflammation and diminishes endothelial function (16). One of the main risk factors for the emergence of micro- and macrovascular complications in type 2 diabetes is thought to be persistent hyperglycaemia. Proteins, lipids, and DNA have all been shown to be harmed by hyperglycaemia; the degree of this damage is correlated with the quantity of reactive oxygen species generated by the condition and the oxidative stress it causes. (17)

A moderate amount of ROS produced by a healthy kidney can be tolerated because the body naturally possesses antioxidant capacity; however, an excessive amount of ROS will seriously harm the kidney. (18) Since ROS is an

essential mediator for the activation of proinflammatory signalling pathways, obesity and hyperglycaemia-induced ROS production may facilitate the induction of M1-like proinflammatory macrophages during the onset and progression of diabetes. (19) By generating more reactive oxygen species (ROS) and upregulating markers of chronic inflammation, hyperglycaemia can lead to vascular dysfunction. (20) Additional effects of hyperglycaemia include increased flux in the polyol pathway, increased flux in the hexosamine pathway, increased production of advanced glycation end products (AGEs), and activation of the kinase C (PKC) pathway by diacylglycerol (DAG). (21)

DEPRESSION AND OXIDATIVE STRESS

A possible explanation for the neuroprotective effects of antidepressants could be an increase in antioxidant defences, since there seems to be a lot of evidence connecting oxidative stress and depression. (22) Oxidative stress (OS) is more likely to occur in the brain due to its higher lipid content, higher oxygen consumption, and weakened antioxidant defences. It is undeniable that OS is a primary cause of neurodegeneration and plays a significant role in the etiology of major depressive disorder (MDD). (23) In a chronic restraint and stress-induced depressive model, a nanocluster drug (CeO2@BSA) targeting reactive oxygen species (ROS) seems to ameliorate depressive-like behaviour and depression-related pathological changes. (24)

Overabundance of reactive oxygen species (ROS) damages various parts of the cell, resulting in the synthesis of pro-inflammatory compounds like 4-hydroxynonenal, neoepitopes, and damage-associated molecular patterns. These molecules then trigger the immune system and ultimately lead to cell death. The incapacity of cells to adjust to alterations in redox homeostasis and the consequent cell death have been recognized as important factors contributing to neuroprogression and, consequently, MDD, along with the harm inflicted by inflammatory mediators. (25) Polymorphisms in multiple genes linked to reactive oxygen species metabolism, oxidative modifications in nucleotides, and telomerase shortening are also linked to neuropsychiatric disorders, including major depression. Elevated oxidative stress levels are directly linked to mitochondrial dysfunction (26).

Microvascular dysfunction and changes in vascular smooth muscle function in MDD are directly associated with oxidative stress-induced reduction in NO-dependent dilatation. Targeting vascular oxidative stress in MDD patients may be a useful therapeutic approach to enhance NO-mediated endothelial function and reduce cardiovascular risk. (27) The glymphatic system, which was recently discovered in the brain, may be involved in clearing extracellular debris and big molecules from the body. Reactive oxygen species (ROS) can build up in the microenvironment as a result of harm to the lymphatic system. This can trigger cellular damage signalling and activate NLRP3 in microglia, which can result in inflammation and a variety of brain disorders, including psychiatric disorders. Therefore, trauma-induced glymphatic damage may cause inflammation and oxidative stress, which can result in MDD. (28) Myeloid-derived suppressor cells, or MDSCs, are a key immune response suppressor. Myeloid-derived suppressor cells (MDSCs) from depression have substantially higher ROS content than those from healthy controls. Moreover, MDSCs from depressed individuals inhibit T-cell responses in a way that depends on ROS. (29)
Low concentrations of NO are neuroprotective and mediate physiological signalling, whereas higher concentrations are neurotoxic and mediate neuroinflammatory actions. Certain polymorphisms in the neuronal nitric oxide synthase (NOS1) gene are linked to MDD. Reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are linked to an increase in cytokines that promote inflammation, are produced when NO concentrations rise. (30) Studies reveal a connection between mitochondrial dysfunction in several brain regions and depression, due to changes in the way mitochondria function that set off a chain reaction of insults worsening depression's pathophysiology. (31) To maintain the proper operation of the mitochondrial quality control system, several strategies are employed. One such method is mitophagy, which is regulated by mitochondrial biogenesis and uses autophagy to selectively remove damaged mitochondria and their contents. (32, 33)

Mammalian target of rapamycin, or mTOR, regulates mitochondrial biogenesis in two ways: transcriptionally by activating Yin Yang 1 (YY1) via peroxisome proliferator-activated

receptor-gamma coactivator 1-alpha (PGC-1α), and translationally by blocking inhibitory 4E-binding proteins (4E-BPs). (34, 35) Patients with MDD have compromised mTOR signalling pathways in their prefrontal cortex. (36) There is a strong negative correlation between OBS and depression, particularly in women. The findings emphasize the significance of upholding an antioxidant-rich diet and way of life, which seems to help women more than men and prevent depression. (37) Adjuvant antioxidant therapy, when combined with regular psychotropic treatment as advised, was found to be beneficial as evidenced by a statistically significant decrease in depression and anxiety scores after receiving antioxidants in addition to antidepressants or anxiety medications. (38) Lipid hydroperoxides are a biomarker of lipid oxidative damage, and when compared to healthy individuals, those who are depressed (smokers or not) have higher levels of these compounds. (39).

Nitric oxide is a key element in cell signalling (NO). There are three isoforms of NOS. Three types of NOS are constitutively expressed: endothelial NOS (eNOS), neural NOS (nNOS), and inducible NOS (iNOS). Neural-localized nNOS is crucial for neuronal signalling, whereas endothelium-localized eNOS is necessary for vasodilation and blood pressure regulation. (40) The well-known neuronal NOS subtype is found in brain regions linked to stress and depression. The limbic-hypothalamic-pituitary-adrenal axis (LHPA) is the hub of this system. These interrelated pathways share production of glucocorticoids and negative feedback. It is believed that NO works in these domains by regulating the release of other neurotransmitters, interacting with cells during growth and plasticity, and/or controlling blood flow by acting as a vasodilator. (41) In the forced swim test, nNOS-specific inhibitors did not shorten the mice's immobility period, whereas deletion of iNOS (inducible nitric oxide synthase) and selective inhibition of iNOS did. This effect was comparable to that of antidepressant medications. (42) Nitric oxide (NO) is produced from L-arginine by inducible nitric oxide synthase (iNOS), which is an essential mediator of inflammation and immune activation found in a large variety of human diseases. (43).

Numerous pathological conditions, such as neurodegenerative diseases, inflammation, and ischemia, coexist with increased nitrosative/oxidative stress and result in increased nitric oxide (NO) production. It was discovered that plasma nitric oxide metabolites were substantially higher in suicidal patients than in non-suicidal mental patients or in healthy control subjects. (44). Endogenous hippocampus nitric oxide (NOS) can have antidepressant effects when its synthesis is blocked or its levels are lowered, so NOS seems to have a role in the pathophysiology of major depression. (45) It has been discovered that several NOS inhibitors work well as antidepressants. In contrast to these results, some research indicates that nitric oxide levels are lower in patients with major depression, which could explain some of the observed abnormalities in the cardiovascular system. (46) It is common knowledge that individuals with depression show reduced antioxidant capacity, which is dependent on both enzymatic and non-enzymatic antioxidants. For example, glutathione reductase, glutathione peroxidase, vitamin E, and erythrocyte superoxide dismutase are found in lower concentrations in the blood and brains of depressed patients. (47) Depression is linked to lower intake of antioxidants and B vitamins. Elevated intake of particular micronutrients may aid in lowering the incidence and severity of depression. The current state of depression is linked to varying intakes of micronutrients; those who are depressed tend to consume less selenium, vitamin B6, and vitamin B12 on average than those who are not depressed. (48) Major depression is correlated with significantly lower serum concentrations of vitamin E, suggesting a reduction in antioxidant defence against lipid peroxidation. The results could help to explain past research that linked major depressive disorder to higher levels of lipid peroxidation. (49) Higher intake of β-carotene was linked to lower levels of stress, anxiety, and depression. Furthermore, there is an inverse relationship between the risk of stress and vitamin E intake. (50)

In summary, a plethora of evidence indicates that increased levels of ROS and NOS could be crucial in the pathophysiology of type 2 diabetes mellitus and major depressive disorder. These results need to be confirmed by additional research.

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