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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.

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