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Oxidative Stress in Autism Spectrum Disorder: Therapeutic Interventions Targeting Parvalbumin (PV) Interneurons

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1. Editorial

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterised by social communication deficits and repetitive behaviours. Increasingly, research has identified oxidative stress as a critical factor in the pathophysiology of ASD, particularly its impact on Parvalbumin (PV) interneurons, a class of GABAergic neurons essential for maintaining the balance between excitatory and inhibitory signalling in the brain. PV interneurons play a crucial role in network synchronisation and information processing, and their dysfunction has been linked to the core symptoms of ASD. Oxidative stress, defined as an imbalance between reactive oxygen species (ROS) and the body's ability to detoxify or repair the damage they cause, has been shown to disrupt PV interneuron function, leading to neuronal damage and synaptic dysfunction. This correspondence explores the mechanistic link between oxidative stress and PV interneuron dysfunction in ASD and reviews therapeutic interventions targeting oxidative stress, aiming to protect or restore PV interneuron functionality. We discuss pharmacological, genetic, and environmental strategies that have been proposed to mitigate oxidative stress and improve outcomes in individuals with ASD.

2. Oxidative Stress Mechanisms in ASD

Oxidative stress has become a crucial factor in the development of Autism Spectrum Disorder (ASD). It refers to an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these harmful intermediates or repair the damage they cause. When ROS accumulate excessively, they lead to oxidative damage to cellular components, significantly contributing to the neurological dysfunctions seen in ASD. Understanding the specific mechanisms by which oxidative stress impacts ASD can help identify therapeutic strategies aimed at reducing this damage. Below, we provide detailed explanations of the key mechanisms of oxidative stress related to ASD.

3. Mitochondrial Dysfunction

Mitochondria is a crucial cell organelle with an array of functions like maintaining cellular ATP levels, apoptosis and maintaining calcium homeostasis, but an inevitable consequence of all of these functions is the generation of ROS as by-products. The link between mitochondrial dysfunction and increased oxidative stress. This excess oxidative load often overpowers the body's antioxidant defence mechanisms and causes substantial damage to critical cellular components like proteins, lipids, and DNA. This further leads to neuronal dysfunction and impaired synaptic plasticity, contributing to the neurological deficits observed in ASD [1]. Several studies have shown the source of ROS to be mitochondrial dysfunctionalities like mitochondrial enzyme activity, membrane potential, and energy production, all of which eventually lead to the leakage of electrons and the formation of superoxide radicals, which subsequently give rise to other ROS. This substantial increase in ROS can potentially overwhelm the body's antioxidant

defence mechanisms, leading to an overall increase in oxidative stress and damage to critical cellular components, which further causes neuronal dysfunction and impaired synaptic plasticity, contributing to the neurological deficits observed in ASD [2,3]. Dysfunction has been consistently implicated as a key source of oxidative stress in ASD. Mitochondria generate cellular energy through oxidative phosphorylation, which produces ROS as by-products. In individuals with ASD, mitochondrial dysfunction leads to increased production of ROS, which overwhelms the body's antioxidant defences, causing oxidative damage to cellular components, including lipids, proteins, and DNA. This oxidative damage has been linked to neuronal dysfunction and

4. Reactive Oxygen Species (ROS) in ASD

Elevated levels of ROS have been observed in both preclinical models and individuals with ASD. ROS, including superoxide anions, hydrogen peroxide, and hydroxyl radicals, can directly damage neuronal cells by inducing lipid peroxidation, protein oxidation, and DNA damage. These oxidative modifications not only compromise cellular integrity but also trigger neuroinflammation, further exacerbating oxidative stress. Chronic oxidative stress leads to neuronal cell death and disruption of neural circuits, particularly in regions of the brain responsible for cognitive function and behaviour, such as the prefrontal cortex and hippocampus [2,4].

5. Neuronal Network Disruptions

PV interneurons are highly susceptible to oxidative stress due to their high metabolic activity and reliance on proper mitochondrial function for maintaining ion gradients and synaptic activity. Oxidative stress impairs synaptic plasticity, disrupts GABAergic signalling, and contributes to excitatory-inhibitory (E/I) imbalance in the brain, which is a hallmark of ASD. In particular, oxidative stress has been shown to impair the function of PV interneurons, leading to dysregulated neuronal synchronisation and abnormal gamma oscillations, both of which are essential for cognitive processes such as attention, learning, and memory [5].

Impact on PV Interneurons

6. Reduction in PV+ Neurons

Several studies have reported a reduction in the number of PV+ neurons in the brains of individuals with ASD and animal models of the disorder. This reduction is correlated with increased levels of oxidative stress and altered neurotransmitter levels. PV interneurons are particularly vulnerable to oxidative damage due to their high energy demands and their role in maintaining inhibitory control over excitatory neurons. The loss of PV+ neurons contributes to E/I imbalance, which is believed to underlie many of the behavioural and cognitive symptoms of ASD (Qi, 2024).

6. Disruption of GABAergic Signaling

GABAergic signalling, mediated by PV interneurons, plays a crucial role in controlling neuronal excitability and synchronising neural networks. Oxidative stress impairs the ability of PV interneurons to release GABA, leading to a decrease in inhibitory signalling and an increase in excitatory activity. This imbalance between excitation and inhibition is a defining feature of ASD and has been linked to hyperactivity, seizures, and impaired cognitive function [6].

7. Biomarkers and Pathways

Biomarkers of oxidative stress, such as oxidised low-density lipoprotein (ox-LDL), malondialdehyde (MDA), and 8-hydroxy-2'-deoxyguanosine (8-OHdG), have been identified in individuals with ASD. These biomarkers are associated with PV interneuron dysfunction and are used to assess the extent of oxidative damage in the brain. Additionally, pathways involved in redox homeostasis, such as the nuclear factor erythroid 2-related factor 2 (Nrf2) signalling pathway, have been implicated in regulating oxidative stress and protecting neurons from damage.

8. Therapeutic Interventions

8.1. Pharmacological Approaches

Several pharmacological interventions aimed at reducing oxidative stress have been investigated in ASD. Antioxidants such as N-acetylcysteine (NAC), Vitamin E, and melatonin have been studied for their potential to scavenge ROS and protect PV interneurons from oxidative damage. NAC, in particular, has been shown to improve behavioural symptoms in individuals with ASD by reducing oxidative stress and modulating glutathione levels, a key antioxidant in the brain. Vitamin E, a lipid-soluble antioxidant, protects cell membranes from lipid peroxidation, while melatonin acts as a potent free radical scavenger and modulates mitochondrial function.

8.2. Genetic Interventions

Emerging gene therapy approaches targeting oxidative stress pathways offer promising avenues for restoring PV interneuron function in ASD. Gene therapy can be used to enhance the expression of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, which neutralise ROS and reduce oxidative damage. Additionally, genetic interventions targeting Nrf2 signalling have been proposed as a strategy to boost the brain's endogenous antioxidant defences. Recent studies have explored the use of biomimetic nanoparticles to deliver therapeutic genes to specific brain regions, improving the efficiency of gene therapy and reducing off-target effects [6].

8.3. Environmental Strategies

In addition to pharmacological and genetic interventions, environmental strategies such as dietary modifications and lifestyle changes have been shown to reduce oxidative stress and improve ASD symptoms. Diets rich in antioxidants, such as fruits, vegetables,

and omega-3 fatty acids, can enhance the body's natural antioxidant defences and reduce the burden of oxidative stress. Additionally, environmental enrichment, which provides sensory, cognitive, and social stimulation, has been shown to improve neuronal plasticity and reduce oxidative damage in animal models of ASD.

8.4. Current Challenges and Future Directions

While significant progress has been made in understanding the role of oxidative stress in ASD and developing therapeutic interventions, several challenges remain. One major challenge is the heterogeneity of ASD, which complicates the identification of universal biomarkers and treatment strategies. The multifactorial nature of ASD, involving genetic, environmental, and immune factors, requires a multifaceted therapeutic approach that addresses the diverse underlying mechanisms of the disorder. Another challenge is the need for more targeted therapies that can specifically protect or restore PV interneurons without affecting other neuronal populations. Future research should focus on developing precision medicine approaches that tailor interventions to the individual's specific oxidative stress profile and neuronal dysfunction. Moreover, clinical trials are needed to evaluate the long-term efficacy and safety of antioxidant therapies, gene therapies, and environmental interventions in individuals with ASD. Such studies will provide critical insights into the therapeutic potential of targeting oxidative stress in ASD and pave the way for new treatment options [7].

9. Conclusion

Oxidative stress plays a critical role in the pathophysiology of ASD, particularly in PV interneuron dysfunction. Therapeutic interventions targeting oxidative stress, including pharmacological agents, gene therapies, and environmental strategies, hold promise for improving ASD outcomes. However, the complexity of ASD requires a comprehensive approach that addresses multiple aspects of the disorder. Continued research is needed to refine these interventions and develop personalised treatment strategies that can effectively mitigate oxidative stress and protect PV interneurons in individuals with ASD.

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