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Oxidative Stress Involved in the Etiopathogenesis of ADHD

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ABSTRACT:

Background: Attention-Deficit Hyperactive Disorder (ADHD) is a neurodevelopmental disorder that affects people of all ages; however, the etiopathogenesis of this disorder is still unknown. Over the years many theories have been proposed, one recent and prominent theory is oxidative stress.

Description: Through a critical review, the progress that research has made over the past two decades, and evidence that oxidative stress is present in both children and adults diagnosed with ADHD was discussed. Presenting the findings of articles proving the presence of oxidative stress through assessing oxidant and antioxidant biomarkers, enzymatic activity, oxidative metabolism impairment, oxidative DNA damage, and lipid peroxidation in both children and adults with ADHD.

Conclusion: There is sufficient evidence to support that oxidative stress plays a role in the etiopathogenesis of ADHD. Continued research is needed to further the understanding of what causes uncontrollable oxidative stress to occur and why it leads to ADHD. This review discusses the findings and how they highlight the considerable progress made over the years in not only linking oxidative stress and ADHD, but also proposing potential therapies and treatments for those diagnosed.

SYNTHESIS:

There have been many studies done to investigate whether or not oxidative stress is present in patients diagnosed with Attention-Deficit Hyperactive Disorder. Based on the evidence presented in these studies, the argument that oxidative stress plays a role in the etiopathogenesis of ADHD can be and is supported. Several studies were done using children, adults, and using the most widely accepted animal model for ADHD, SHR rats. These studies, done through observation, demonstrate the presence of oxidative stress, an imbalance of antioxidants, or the damage caused by oxidative stress; specifically, lipid peroxidation, impaired oxidative metabolism, or oxidative DNA damage. All studies investigating whether or not there was damage or the presence of oxidative stress have concluded that there is a significant difference in oxidative levels and antioxidant levels between those with and those without ADHD.

Summary Table of Experiments

Parameter	Subject	Compared to Healthy Control Group	Importance/Indication	Reference
Oxidative Damage Biomarker: MDA	Children and Adults	Significantly higher mean levels of MDA	Lipid peroxidation damage and oxidative damage observed	Oztop et al. 2012 Bulut et al. 2013 Verlaet et al. 2018 Ceylan et al. 2010 Bulut et al. 2007
Oxidative Stress Biomarker: 8-OHdG OSI NOS XO	Children and Adults	Significantly increased levels of 8-OHdG, OSI, NOS, and XO	Impaired oxidative metabolism	Oztop et al. 2012 Kurhan & Alp 2021 Selek et al. 2012 Sezen et al. 2016 Guney et al. 2015 Kul et al. 2015 Ceylan et al. 2012
Oxidative Biomarker: TOS ROS Thiols NO	Children, Adults, and Animal Model	Significantly higher levels of TOS, ROS, NO, and Thiols	An imbalance in free radical-antioxidant levels caused by uncontrollable oxidative stress	Selek et al. 2012 Sezen et al. 2016 Guney et al. 2015 Kul et al. 2015 Leffa et al. 2017 Selek et al. 2008
Lipid Oxidation Enzyme: PON-1	Children	Significantly lower levels of PON-1 activity	Presence of oxidative stress observed	Ceylan et al. 2012
Antioxidant Enzyme: PON ARES GSH-Px GST SOD CAT SPON	Children and Adults	Activity levels of PON, ARES, GSH-Px, GST, SOD, CAT, and SPON were significantly lower	Increased antioxidant defense mechanisms but not enough to correct oxidative imbalance leading to low antioxidant activity levels	Bulut et al. 2013 Guney et al. 2015 Ceylan et al. 2010 El-Adham et al. 2011 Ceylan et al. 2012 Namjoo et al. 2020 Selek et al. 2008
Antioxidant Biomarker: TAS	Children and Adults	Significant decrease in TAS level	Impaired oxidative metabolism confirming the presence of oxidative stress	Selek et al. 2012 Sezen et al. 2016 Gueny et al. 2015 Kul et al. 2015
Vitamin D Status Biomarker: 25(OH)D	Children	Significantly lower concentrations of 25(OH)D	Low levels of the body's natural antioxidant production	Goksugur et al. 2014 Sharif et al. 2015
Antioxidant/Oxidant Balance Biomarker: Thiol/Disulfide	Adults	Native thiol levels were significantly lower and disulfide levels were significantly higher	The thiol/disulfide homeostasis has shifted towards disulfide	Kurhan & Alp 2021
Salivatory Biomarkers: Salivary Protein Thiols Pseudocholinesterase Magnesium	Children	Significant increase in salivary protein thiol and pseudocholinesterase levels, significantly lower magnesium levels	Magnesium levels have been shown to be decreased when oxidative stress is present	Archana et al. 2011
Lipid Peroxidation Urinary Biomarker: Acrolein-lysine	Children	Significantly higher levels of urinary acrolein-lysine	Lipid peroxidation damage observed	Kawantani et al. 2013
n-3 FA Oxidative Damage Biomarker: Exhalant Ethane Levels	Children	Significantly higher levels of ethane in exhalant	Higher rate of oxidative breakdown of n-3 polyunsaturated fatty acids	Ross et al. 2013
Inflammation Factors and Cytokine Levels	Children and Animal Model	Decreased cytokine levels in animal model and significantly higher levels of inflammatory factors	Inflammation can be a co-occurring co-factor in ADHD and the decreased cytokine levels indicate basal deficit commonly associated with ADHD	Namjoo et al. 2020 Leffa et al. 2017
Cellular Immunity Biomarker: ADA	Children	Significantly higher levels of ADA activity	Cellular immunity could be a co-factor that co-occurs in ADHD	Ceylan et al. 2012

CONCLUSION:

The causes and reasons for development of the neurodevelopmental disorder Attention-Deficit Hyperactive Disorder are still unknown. It is believed that genetics play a role; however, that alone cannot explain the development. Based on evidence it is theorized that oxidative stress plays a role in the development of ADHD; however, more research is needed. It is still unknown if every person diagnosed with ADHD was born with it or developed it due to other factors involved. So far there have only been observational studies done, which implies correlation; therefore, the next step is to attempt to prove causation by doing manipulation studies. In the future new methods of diagnosis tools need to be studied and implemented to help with earlier diagnosis; methods such as, saliva, urine, and breath testing which are easy, cheap, and non-invasive. Along with new diagnosis methods there need to be more treatment options. One proposed treatment in response to oxidative stress is antioxidant therapy using antioxidant supplements or altering a patient's diet to add antioxidant rich foods. Antioxidants are anti-inflammatory and combat free radical effects, making them a good treatment for ADHD patients. However, more rigorous research and clinical trials are needed before antioxidants can be administered as a co-treatment along with medication (Alvarez-Arellano et al. 2020).

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