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The Influence of Oxidative Stress on Ion Homeostasis and Glycolysis Activation, with Implications for Neurological Health and Multiple Sclerosis

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The Influence of Oxidative Stress on Ion Homeostasis and Glycolysis Activation, with Implications for Neurological Health and Multiple Sclerosis

by

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Abstract

Multiple sclerosis (MS) is a neurodegenerative disease in which the body's immune system attacks its own tissues, notably the neural cells, and one of the contributing factors to this is oxidative stress. Oxidative stress is the build-up of reactive oxygen species ROS that causes oxidative damage to the cells. Chronic and environmental stressors are explored as significant factors that exacerbate these conditions by disrupting cellular processes and energy metabolism. The paper reviews current literature on MS, examining the interplay between oxidative stress, environmental factors, and genetic predispositions. Additionally, it discusses how these factors contribute to MS, where the immune system mistakenly attacks the central nervous system (CNS), leading to inflammation and neuronal damage. It also considers potential therapeutic interventions that target these mechanisms, aiming to provide insights into innovative approaches for managing MS. Through a detailed analysis of cellular respiration, the research underlines the complex relationship between metabolism, oxidative stress, and the pathophysiology of MS, offering a comprehensive overview of current scientific understanding and future research directions.

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Dedication

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Multiple Sclerosis (MS)

Oxidative Stress

Environmental Stress

Reactive Oxygen Species (ROS)

Trace Metals

Mutations

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Introduction

The increasing prevalence of neurodegenerative diseases, particularly multiple sclerosis (MS), has highlighted the critical role of oxidative stress and environmental stress in disrupting ion homeostasis and environmental triggers activating glycolysis, with significant implications for nervous system health. Stress is a ubiquitous experience for individuals throughout their lives, ranging from manageable levels to those that pose significant health risks. Two primary types of stress affect people's lives: oxidative and environmental. Both types of stress have detrimental effects on the human body, though they manifest in different contexts and provoke distinct responses. Moreover, these types of stress exert various impacts on the functionality of different systems in the body. Notably, stress adversely affects the nervous system by imposing a heightened workload, potentially leading to neurodegenerative conditions such as MS, where the immune system erroneously targets the body's tissues. This review explores the mechanisms by which oxidative stress impacts MS, focusing on ion homeostasis and glycolysis, and proposes potential therapeutic interventions.

Oxidative Stress

Oxidative stress, characterized by an imbalance between ROS production and antioxidant defenses, plays a central role in the pathogenesis of MS through its damaging effects on cellular and tissue structures. ROS are free radicals characterized by highly reactive atoms or molecules containing one or more unpaired electrons in their outer shell, formed through interactions with electrons that leak from the electron transport chain (ETC), enzymatic reactions, and in the presence of transition metals in the presence of

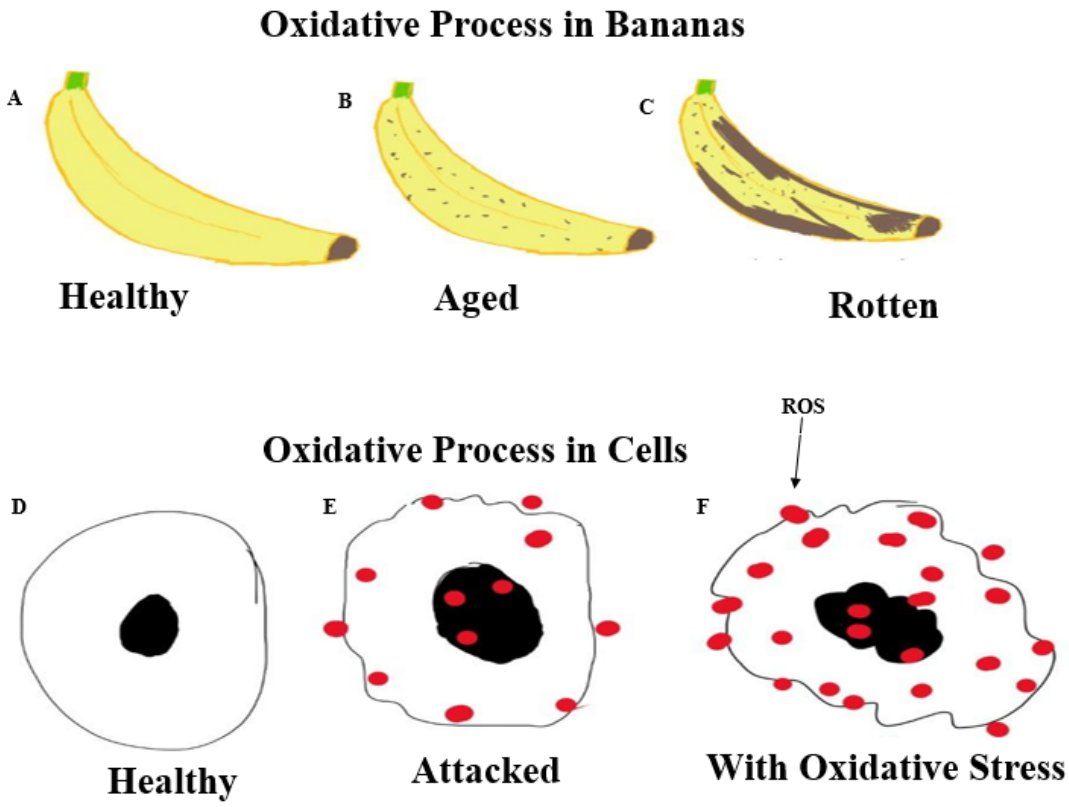
oxygen (Liguori et al., 2018). Thus, oxidative stress results from an imbalance between ROS production and antioxidant defenses and is implicated in the pathogenesis of MS due to ROS, such as hydrogen peroxide and superoxide radicals.

These ROS are commonly found in different forms, such as superoxide radicals, hydrogen peroxide, hydroxyl radicals, and singlet oxygen, produced by-products of different biological systems, such as ETC, NADPH oxidase complex, and Haber-Weiss reactions (Pizzino et al., 2017). However, oxidative stress does not come from the occurrence of ROS in the body. If the ROS is maintained at a relatively low or moderate concentration, an organism obtains many benefits, such as the synthesis of cellular structures and host defense system. Oxidative stress comes from the body's production of ROS exceeding the capacity of the antioxidant defense systems, which are designed to neutralize and eliminate excess ROS (Pizzino et al., 2017). This imbalance leads to an accumulation of ROS, resulting in cellular and tissue damage (see Figure 1). In the same capacity that someone has oxidative stress, the main mechanism to deter someone from having the excess buildup of ROS in the body is the antioxidants that allow for a balance in the body between free radicals to be achieved. The human body has developed several natural defenses to manage ROS accumulation, particularly those resulting from mitochondrial leakage. One of the primary defenses involves antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (Tavassolifar et al., 2020). These antioxidants seek to protect the human body against the damage that occurs from oxidative stress (Sharifi-Rad et al., 2020).

Figure 1

This illustration shows the similarities between the normal aging process with bananas compared to a cell aging with the interaction of oxidative stress. The top half shows three

stages of a banana: healthy (A), aged (B), and rotten (C), demonstrating physical changes. The bottom half illustrates a similar process in cells: healthy (D), attacked (E), and with oxidative stress (F).



Note. Adapted from Antioxidants: The body's natural defense against oxidative stress, by Healthy for Life Meals, n.d., retrieved August 10, 2024, from [*https://www.healthyforlifemeals.com/blog/antioxidants*](https://www.healthyforlifemeals.com/blog/antioxidants)

Environmental Stress

Environmental stress, encompassing chronic and acute stressors, contributes to the disruption of biological systems, exacerbating oxidative stress and impacting nervous system health, particularly in conditions such as MS. Environmental stress is normal in life. However, different stressful states lead to an indecent lifestyle depending on the amount of stress one faces and the length of that stress, such as turning to alcohol or drugs to be used

as a coping mechanism for stress, unhealthy and uncontrolled eating habits that result in obesity, and even pushing individuals to lifestyles that are oriented to illegal activities such as theft and fraud. One of the types of stress that has a long-term effect on the body is chronic stress, which is a longer period of stress that lasts for more than two weeks and can last up to months and affects different organ systems of the body differently (Cleveland Clinic, 2024). For example, chronic cardiovascular stress can increase a person's heart rate and blood pressure, contributing to the wear and tear of blood vessels. In the nervous system, the constant activation of stress causes dysregulation of the autonomic nervous system, causing headaches, anxiety, and depression. The specific effect that will be examined is chronic stress's effect on the activation of glycolysis, as observed through the biochemical pathways, such as the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SN), influenced by prolonged stress. This path is mainly from the hypothalamus, which controls the sympathetic and parasympathetic nervous systems, informally known as the fight-or-flight system, and releases different biochemicals, including adrenalin and noradrenalin (Kooij, 2020). Noradrenalin production increases the metabolism of glucose and lactate production and increases the uptake of glucose in the body (Kooij, 2020). Thus, with chronic stress in the body, various physiological responses are activated to manage stress, such as releasing cortisol and adrenaline and increasing glucose to cope with the accumulation of stress (Kooij, 2020). stress. However, the primary stress response involves the release of glucose into the body to provide sufficient energy for coping with immediate challenges. This response can amplify the body's stress reaction, impacting individuals' overall well-being and daily lives, especially when combined with external environmental pressures. Amore specific type of stress from the current one discussed in this paper is classified as oxidative stress, an environmental stress relevant to a person's interaction with their external environment. Environmental stress comes in

different levels depending on the situation, such as acute, subacute, and chronic stress. Acute and subacute stress is your scale that measures what type of stress an individual faces at that particular moment. Environmental stress is a response that is triggered by potentially threatening stimuli that are found in the environment. Thus, chronic stress is repeated exposure to potentially threatening stimuli over a period of time that is greater than two weeks (Cleveland Clinic, 2024). Chronic stress is the type of stress that is harmful to the body and causes damage to the CNS because of stress's impact on the suppression of cell proliferation and reducing neurogenesis (Juszczyk, 2021). These are inhibitors to the healing mechanisms in the brain, which could exacerbate the effects of any oxidative stress damage to cells of the CNS.

Chronic Stress.

Chronic stress exerts a prolonged influence on the body and increases oxidative stress, which leads to an accumulation of ROS without sufficient antioxidant defenses to counteract the excess, disrupting the balance within the body. The overall course of chronic stress originates in the brain, where its responses regulate many functions in reaction to environmental exposure. This adaptation to different conditions triggers various chemical reactions, primarily regulated by the HPA axis. In chronic stress, this regulation stimulates the secretion of corticotrophin-releasing hormone (CRH) (Juszczyk, 2021). CRHs create the synthesis and secretion of adrenocorticotrophic hormone (ACTH) in the pituitary gland, then go on to stimulate the production of cortisol in the body (Juszczyk, 2021). There are some positives to having an increased or elevated amount of cortisol circulating throughout the body; the positive effects of cortisol reduce a person's fatigue and increase the amount of energy a person has (Hoyt et al., 2016). Chronic stress has a different effect because the outstanding effect of having cortisol in the body lasts longer than the short instances that it

would last. The longer effects of having elevated amounts of cortisol in the body would be the dysfunction of the centers regulating mood, psychomotor drive, mechanism of memory and emotion, disturbances in neurogenesis, and impaired hippocampus function (Juszczyk, 2021). The prolonged elevation of cortisol, often a result of chronic stress, can have detrimental effects on the brain's regulatory centers, including those involved in mood, memory, and neurogenesis. In relation to oxidative stress and MS, elevated cortisol levels can exacerbate the production of ROS, further contributing to oxidative damage within the CNS. This oxidative damage plays a significant role in the pathophysiology of MS by promoting inflammation and neuronal degeneration.

Multiple Sclerosis

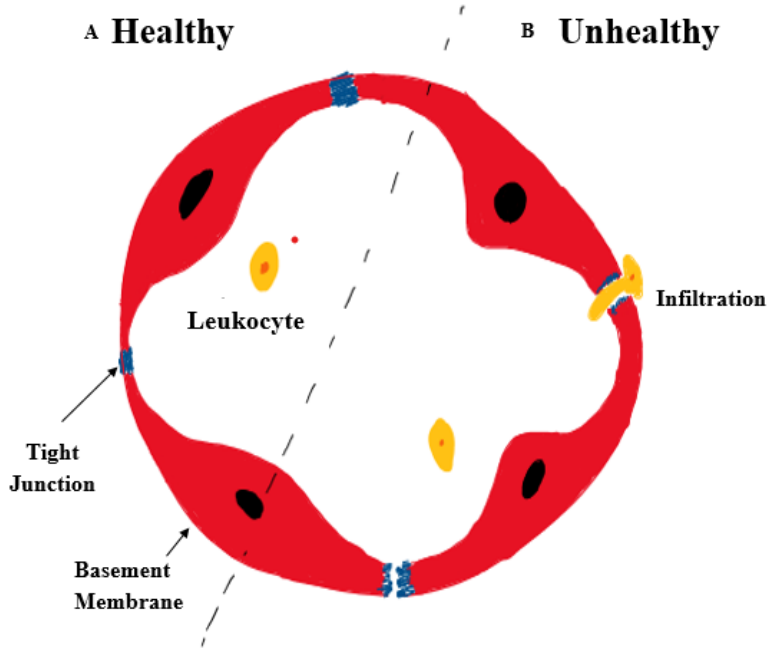
MS is a neurodegenerative disease driven by the immune system's attack on the CNS, where oxidative stress and environmental factors exacerbate the inflammatory and neurodegenerative processes. The inflammation and demyelination of the neurons in the CNS then cause lesions in the central nervous system, explaining the wide array of symptoms in MS. The specified direction in which neurons get damaged in the CNS is through the T-cells immigrating across the blood-brain barrier (BBB), causing the invasion of T-cells into the nervous system that injures the BBB and initiates cytotoxic activities of microglia (Tafti et al., 2022; see Figure 2). This contributes to the pathogenesis of MS by exacerbating the inflammatory and neurodegenerative processes within the CNS. Oxidative stress, primarily through the excessive production of ROS, leads to the damage of neuronal cells, the BBB, and myelin sheaths. Environmental stressors, such as toxins or chronic stress, can further amplify oxidative stress, increasing the likelihood of T-cell infiltration across the BBB. This infiltration triggers an immune response that targets the myelin, leading to demyelination and the formation of lesions within the CNS (see Figure 3). These processes are central to the diverse symptoms of MS, as they disrupt normal neural

signaling and lead to widespread neurological impairments. However, an important aspect of the severity of the disease comes from injury to the BBB, which causes the regulation of the neuronal intracellular environment within a person's body (Zlokovic, 2008). Thus, the dysregulation of oxidative stress management and the immune response within the CNS contributes to the overall deterioration of the nerves within the nervous system, causing an abundance of different symptoms ranging from vision problems to muscular weakness. Overall, the pathophysiology of MS is uncertain; however, some of the key points of MS are that oxidative stress affects the integrity of the BBB, stress affects ROS development, and genetic mutations result from oxidative stress. Together, these factors may contribute to the worsened prognosis of someone with MS. This paper undertakes a comprehensive review of current literature on MS in conjunction with environmental and oxidative stress, aiming to elucidate the underlying mechanisms and identify parallels between these factors. Through this analysis, this literature review seeks to propose potential experimental interventions that capitalize on these shared mechanisms, offering insights into novel therapeutic approaches for MS management.

Figure 2

The diagram shows a comparison between healthy (A) and an unhealthy (B) environment that the BBB has with leukocyte interaction. It shows the changes in cellular structure,

including tight junctions, basement membranes, and infiltration in the unhealthy leukocyte.

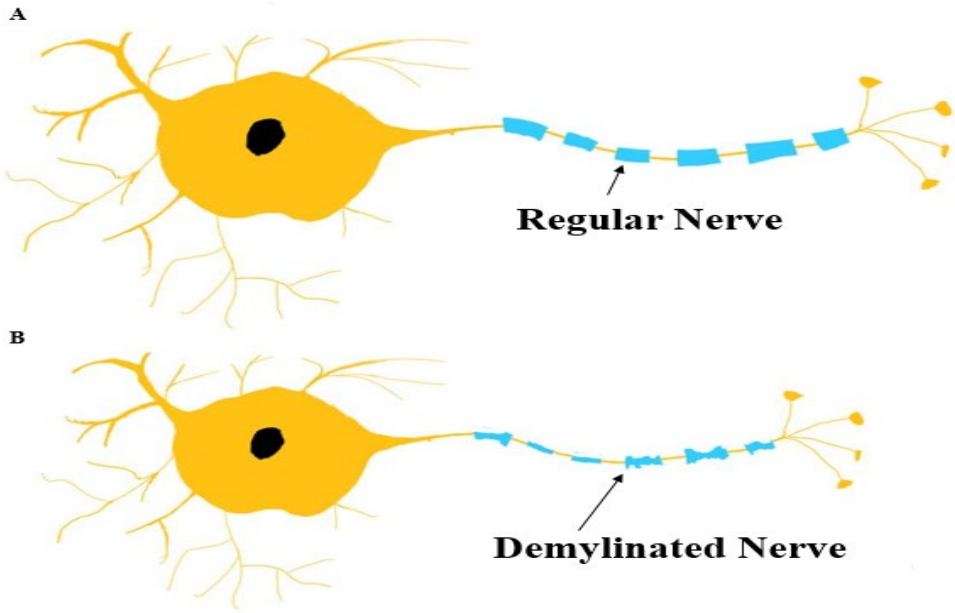


Note. Adapted from Oxidative stress in neuropsychiatric disorders, by Knox., et al., 2022, Molecular Psychiatry. https://www.nature.com/articles/s41380-022-01511-z

Figure 3

This image compares a regular nerve (A) to a demyelinated nerve (B), highlighting the structural differences that are seen in the degradation of the myelin sheath for the

demyelinated nerve.



Note. Adapted from Myelinated and unmyelinated axons, by A Level Biology, n.d., retrieved August 10, 2024, from https://alevelbiology.co.uk/notes/myelinated-and-unmyelinated-axons/

Cellular Respiration Relation to ROS Production

Cellular respiration, involving glycolysis, the tricarboxylic acid cycle (TCA), and the ETC, is critical in maintaining cellular energy balance. However, it also generates ROS that contribute to oxidative stress in MS. Cellular respiration encompasses glycolysis, the TCA cycle, and the ETC, during which ROS is generated as a byproduct. While ROS production is a natural occurrence for the outcome of aerobic metabolism, it plays a dual role in cellular function and pathology, necessitating a delicate balance within cellular respiration.

Glycolysis

The initial stage of glucose catabolism culminates in pyruvate production, which yields two molecules of adenosine triphosphate (ATP) through substrate-level

phosphorylation. The whole process of glycolysis is Glucose + (2NAD+) + 2 ADP + 2 Pi to produce 2 pyruvates + 2NADH + (2H+) +2ATP +2H_2O (Chaudhry & Varacallo, 2023). The relationship between glycolysis and ROS is that it can regulate the pace of cellular glucose uptake through feedback mechanisms from either high or low ROS concentrations that result from glycolysis (Liemburg et al., 2015). This causes an abundance of ROS in the body, leading to further damage and complications because of the nature of ROS. However, the overall course of the ROS that impairs or increases glucose uptake depends on the expression of the GLUT1 gene, which is a facilitative glucose transporter (Nicholas et al., 2020). GLUT1 is a facilitative glucose transporter that helps cells uptake glucose from the bloodstream (Nicholas et al., 2020). Under oxidative stress, the expression of GLUT1 can be modulated, which in turn influences glucose uptake. If ROS levels impair GLUT1 function, it could reduce glucose availability for cellular energy production, exacerbating cell energy deficits, particularly in the nervous system. This is especially relevant in diseases like MS, where energy metabolism is compromised, and further disruptions can worsen the condition.

Tricarboxylic Acid Cycle

The TCA is a series of biochemical reactions all aerobic organisms use that generate energy by oxidizing acetyl-CoA into carbon dioxide (Eapen, 2018). The function of the TCA cycle lies in its role in oxidative processes, where it facilitates the biochemical reactions that lead to acetyl-CoA oxidation, generating energy in the form of ATP. The principal function of the TCA cycle is to provide oxidation and reduction of different coenzymes, including nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) (Haddad & Mohiuddin, 2023). These coenzymes provide, in their reduced forms, a method for transportation for the production of ATP with the use of the ETC (Haddad & Mohiuddin, 2023). Although the TCA cycle does not directly produce

ROS, it indirectly contributes to ROS accumulation by generating reduction equivalents that fuel the ETC (Noster et al., 2019). This allows an increase in the production of ROS if the TCA has an increase in production, which would affect the amount of ROS produced as a byproduct in the ETC.

Electron Transport Chain

The ETC is the final stage of cellular respiration, where ATP is produced through five different complexes. In complexes I and II, an element is donated from the recently reduced NADH and $FADH_2$, where these coenzymes are placed in their oxidized forms of NAD and FAD+ (Tirichen et al., 2021). The electrons donated from complexes I and II are delivered to complex III through ubiquinone and complex IV through cytochrome *c*. As a result, the donated electrons created in complexes I and II create O_2, which interacts with the electrons to form water. Finally, while this is happening, complex I, III, and IV are proton pumps that generate the proton gradient that allows ADP to be synthesized into ATP via complex V. Ultimately, this creates the final product of ATP; however, the overall effect is that while in the mitochondria where energy production is happening, there is ROS production happening at three different complexes: I, II, and III. Complex I and II produce ROS towards the matrix. At complex III, superoxide generation occurs towards the matrix and intermembrane space due to electrons leaking and interacting with molecular oxygen (O_2)(Tirichen et al., 2021). The glutathione (GSH) system also plays a crucial role in scavenging free radicals and reducing oxidative stress. Mitochondrial uncoupling proteins (UCPs) further reduce ROS production by dissipating the proton gradient across the mitochondrial membrane, thereby decreasing electron leakage, a significant source of ROS (Tavassolifar et al., 2020). Other critical proteins, such as peroxiredoxins (Prxs) and thioredoxins (Trxs), help reduce hydrogen peroxide and organic peroxides, maintaining cellular redox balance. The Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway also

regulates the expression of antioxidant proteins and phase II detoxifying enzymes under oxidative stress conditions (Tavassolifar et al., 2020). These mechanism help protect the cells of the body from being damaged by ROS, thus stopping the progression of neurodegenerative diseases such as MS.

Metabolism Relation to Oxidative Stress

The relationship between metabolism and oxidative stress is crucial in understanding MS, as metabolic imbalances can lead to increased ROS production and subsequent oxidative damage. Metabolism encompasses the total sum of reactions occurring within each body cell, providing energy for structural or functional proteins(Nava & Raja, 2022). One associated metabolic mechanism involves ion homeostasis during the mitochondrial process. The mitochondrial process refers to the series of biochemical processes that occur in the mitochondria that relate to the production of ATP. This uses the movement of electrons through a membrane that creates a proton gradient across the inner mitochondrial membrane. It is related to using different compounds in metabolism—specifically, the role of metals such as iron, magnesium, zinc, and copper. Ion homeostasis is the maintenance of optimal ion concentrations within cells to ensure that enzymes can function properly, catalyze necessary reactions, and support healthy metabolism. Thus, ions are crucial for regulating electron transport and cell redox reactions. These ions influence the level of oxidative stress by affecting the balance of oxidants in the body. An increase in oxidants can occur during glycolysis, where anerobic pathways generate ATP, providing the body with necessary energy. The ATP production process involves a lot of reduced and oxidized states of molecules found throughout the processes of TCA and ETC. However, oxidative stress, a key factor in MS, arises from excess oxidized body species without sufficient regulation to reduce them. Oxidative stress is attributed to the process of glucose metabolism that occurs in the body when the body needs energy.

Trace Metals Relation to Oxidative Stress

Trace metals, though essential in small quantities, can become harmful under oxidative conditions, catalyzing the production of ROS and contributing to the pathogenesis of multiple sclerosis MS. Trace metals are inorganic micronutrients present in very low concentrations in bodily fluids and tissues. They are seen as essential to cellular homeostasis because of their roles in other systems' development and signaling processes. The main trace metals that will be looked at are iron, magnesium, zinc, and copper. Although all of the trace metals listed have functionality in the human body, that does not mean that the trace metals do not pose a threat to normal human functionality because of how readily we, as humans, place these metals into food, equipment, and other tools that we interact with daily. Iron primarily functions in oxygen transportation, deoxyribonucleic acid (DNA) synthesis, and electron transport (Abbaspour et al., 2014). Zinc is involved in cellular metabolism, with the catalytic activity of a wide array of enzymes, enhancing immune function, protein and DNA synthesis, wound healing, and cell signaling and division (U.S. Department of Health and Human Services, 2022). Magnesium is important in regulating muscle and nerve function, blood sugar levels, and blood pressure, and making protein, bone, and DNA (U.S Department of Health and Human Services., 2021). Copper plays a role in adequate growth, cardiovascular integrity, lung elasticity, neovascularization, neuroendocrine function, and ion metabolism (National Research Council (US) Committee on Cooper Drinking Water, 2000). The primary problem with all of these trace metals found throughout the body and necessary for function in the body is that, in excess, these trace metals cause an increase in the number of oxidative states that molecules have in the body. The increase in oxidative states will eventually lead to oxidative stress, which damages cells and disrupts their normal function, causing a need to remove ROS through antioxidants. Antioxidants help maintain the balance of oxidants in

the body by acting as a free radical scavenger that interrupts the process of oxidation by donating an electron or hydrogen atom (Tan et al., 2018). Trace metals, while essential in small amounts for various biological processes, become deleterious when present in excess or when their homeostasis is disrupted. These metals, including iron, copper, and zinc, can catalyze the production of ROS through Fenton-like reactions, significantly increasing oxidative stress within cells. This heightened oxidative stress not only damages cellular components like lipids, proteins, and DNA but also contributes to the pathogenesis of various neurodegenerative diseases, including MS.

Nervous System Impact

Oxidative stress significantly impacts the nervous system, particularly in MS, where it contributes to neuronal damage, BBB dysfunction, and a wide array of neurological symptoms.. This allows the disease to cause varying amounts of damage to an individual throughout their life without treatment, and even if there is early treatment, the disease is capable of coming back in different episodic conditions. There are four different types of MS and a general term for the onset of the disease: relapsing-remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), progressive relapsing MS (PRMS), and clinically isolated syndrome (CIS). Additionally, there is a multitude of different symptoms that occur with the disease, as there is a vast amount of dysfunction that occurs in MS because of the wide-scale effects that the disease has. Thus, the disease symptoms are divided into three different categories: primary, secondary, and tertiary symptoms; and the primary symptoms are divided further into common and less common symptoms. The more common symptoms of MS include sensory disturbances; numbness, tingling, itching, and burning; motor disturbances such as walking difficulties due to fatigue, weakness, spasticity, loss of balance and tremors; vision problems such as diplopia, blurred vision, pain in eye movement; intestinal and urinary system dysfunction;

constipation and bladder dysfunction, cognitive and emotional impairment; inability to learn, depression, dizziness, and vertigo sexual problems (Ghasemi et al., 2017). The less common symptoms include dysphagia, dysarthria, respiratory problems, hearing loss, seizures, and headaches (Ghasemi et al., 2017). Secondary symptoms include urinary tract infections, inactivity, and immobility (Ghasemi et al., 2017). The tertiary symptoms include social complications, vocational complications, psychological complications, and depression (Ghasemi et al., 2017). The wide array of symptoms present in MS affects every organ system in the body and causes mild to severe damage depending on the extent of the cellular damage caused by the disease. These form the foundation of treatment options for MS as there is currently no cure; available treatments primarily focus on disease modification to suppress symptoms. The overall course of the disease, however, is believed to be achieved through oxidative stress as there is increased data that depression is related to oxidative stress and other neurodegenerative disorders that are accompanied by the build-up of ROS in the body (Salim, 2016). Depression is linked to oxidative stress and neurodegenerative diseases through multiple biochemical pathways. Chronic oxidative stress leads to cellular damage and inflammation, which are common features in neurodegenerative diseases like MS. The accumulation of oxidative damage can also disrupt neurotransmitter systems and neural plasticity, contributing to the development of depression (Juszczyk et al., 2021). Additionally, oxidative stress can impair the function of the HPA axis, leading to dysregulation of cortisol levels, which is often seen in depression (Juszczyk et al., 2021). The overlap in these pathways suggests that oxidative stress is a critical factor in the comorbidity of depression and neurodegenerative diseases. However, the presence of antioxidants is used to fight against oxidative stress, keeping the oxidative stress to low or moderate amounts to limit the damage that occurs. Thus, these autonomic functions necessary for a person to maintain homeostasis in the body do not require

conscious thought because the regulatory control that the brain has over the body arguably makes it one of the most important organs in the body (Waxenbaum et al., 2024).

Current Research Involving MS

Ongoing research into MS focuses on identifying genetic markers and understanding the role of oxidative stress in disease progression, aiming to develop targeted therapeutic strategies. This leads to genes that are present in individual patients and are related to every person with the MS. Researchers can trace specific genes and follow targeted treatment options to find solutions for that gene. Currently, select genes associated with MS are being studied alongside genes involved with the disease to see if any correlations of interactions occur. The select genes being researched to see if any additional information is linked to MS are CD58, CYP27B1, IL7R, IRF8, and TNFRSF1A. All these genes collectively have been reported in multiple patients with MS; thus, ongoing research accompanies each gene as to what role these genes play in the complexity of MS. A group of genes that are associated with MS is the human leucocyte antigen (HLA) gene, which demonstrates the strongest correlation to genetic linkage with MS. HLA is used by the immune system to help identify foreign invaders, whether they be proteins or pathogens (Nordquist & Jamil, 2023). Keeping the nucleic acids safe inside the cell, preventing the damage and destruction of these biomolecules, and having the foreign objects destroyed by the cell to maintain a state of homeostasis throughout the body ensures the safe regulation of processes within the cell. Therefore, to safeguard beneficial proteins from foreign agents, the body's immune system enacts an attack on the foreign agents to reduce the risk of disease (Nordquist & Jamil, 2023). The function of the HLA gene makes its role in MS evident since the immune system is attacking the CNS inside of the body and causing damage due to misidentification of neurons as foreign invaders. Research mainly involving

the HLA gene is seen as relevant to the cause of MS because understanding why or how the HLA gene group of genes misidentifies the CNS would contribute to developing a cure for the disease itself.

Future Research Involving MS

Future research on MS aims to explore the genetic underpinnings of the disease, focusing on oxidative stress pathways to develop innovative treatment approaches. This research will investigate the individual genes affecting MS, such as CD58, CYP27B1, IL7R, IRF8, and TNFRSF1A (Ottoboni, 2013). The treatment options offered to an MS patient vary, ranging from managing the symptoms and slowing the progression of the disease to restoring functionality that was lost due to the disease. One treatment option would involve a remyelination process that would provide for the myelin sheath to be regenerated on neurons instead of the scar tissue that would have been present on those cells. The remyelination process would bring back those affected neurons' functions and reverse MS's effects on the individual (Institute of Medicine, 2001). Other research concepts include vaccination, suppressor cells, immunodeviation, genetic engineering, neuroprotection, anti-inflammatory strategies, and specific neuroprotective agents (Institute of Medicine, 2001). The vaccination would serve as a protective agent to help the body fight against something similar that may happen, specifically for myelin-specific T cells, T cell receptor peptides, DNA encoding autoantigens, or T-cell receptor (TCR) (Institute of Medicine, 2001).

Genetic Variation in Oxidative Stress

Genetic variations influencing oxidative stress response mechanisms are critical in MS pathogenesis, emphasizing the need for personalized therapeutic strategies. Genetic components associated with uncontrolled ROS in cells are analyzed to understand their role

in MS and their relation to cellular functions. The present research focuses on activating the Nrf2 pathway to activate the antioxidation system used as a defense mechanism against oxidative agents. Dimethyl fumarate is the drug used to activate the Nrf2 pathway (Lastres-Becker, 2016). However, the current research with MS solely focuses on activating pathways to induce some reaction within the body to ultimately lower the amount of oxidative stress in the body. The problems lie with the current state of oxidative stress in the body because there is no place to store ROS; there is only a need to reduce the ROS products to prevent damage. The body's current oxidative stress is an unhealthy amount of oxidants for the body cells to handle, increasing the risk of mutations. Ultimately, this creates different effects that individuals will not see commonly, considering that patients' prognoses tend to differ.

Oxidative Stress Mutational Occurrence

Oxidative stress is associated with increased mutational rates, contributing to genomic instability and the progression of MS that comes cellular dysfunction , such as DNA strand breaks, base modifications, and mitochondrial dysfunction. Since there are increased rates of mutations, the body has adapted, and we as people have developed different mutational signatures found throughout the genome based on the extent of oxidative damage to the cells. The different mutational signatures are derived from the mismatching pair of 8-oxoG-adenine and 8-oxoG. 8-oxoG (8-oxo-2'-deoxyguanosine) is a well-known marker of oxidative stress-induced DNA damage, where guanine is oxidized, leading to mispairing during DNA replication (Chiorcea-Paquim, 2022). In MS, oxidative stress is a significant factor contributing to the disease's pathogenesis, primarily through the generation of ROS that induce such DNA damage. The formation of 8-oxoG-adenine mismatches during DNA replication can lead to mutations, contributing to the neurodegenerative processes observed in MS. These mutations disrupt normal cellular

function and can exacerbate the inflammatory processes and demyelination seen in MS. Thus, oxidative stress-induced mutations like those involving 8-oxoG and 8-oxoG-adenine play a crucial role in the progression of MS by promoting genomic instability and contributing to the neurodegenerative and inflammatory aspects of the disease.

Trace Metals with Genetic Variation

Trace metals, when combined with genetic predispositions, can exacerbate oxidative stress and contribute to the complex pathology of multiple sclerosis MS. Trace metals are another compound that adversely affects the body and causes mutations because of the build-up of ROS produced by these trace metals. Some of the more genetic mutations that occur with the trace metals mentioned above are iron, magnesium, zinc, and copper. Zinc also causes a mutation in the SLC39A8 gene that is present and is associated with neurological phenotypes similar to stress (Ng et al., 2015). Copper is a trace metal, and individuals with a mutation in the ATP7B gene that causes abnormal hepatic copper deposition (Ng et al., 2015). These mutations are associated with MS complexity because of their linkage to stress abnormalities and storage of these trace metals.

Clinical Applications of MS and Oxidative Stress

Understanding the interplay between oxidative stress and MS opens new avenues for clinical applications, including potential therapeutic interventions targeting oxidative pathways. The overarching goal was to evaluate the literature associated with MS, oxidative stress, and environmental stress, as well as concepts surrounding these core ideals, such as trace metals, genetic mutations, and metabolism. Evaluating these concepts and seeing how they potentially play a role in MS leads to developing new strategies and ideas to consider when analyzing MS as a disease regarding what is known and what is

discovered. Thus, considering the application and different research, there could be an advancement of the knowledge we hold as we view MS in terms of stress.

Stress Testing

Stress testing using fluorogenic probes offers a promising approach to diagnosing MS by measuring ROS levels and assessing the body's stress response (Katerji et al., 2019)—specifically looking for hydrogen peroxide, hydroxy, and peroxyl radicals (Katerji et al., 2019). Another test that can be done with fluorogenic probes would be to analyze the amount of cortisol in the body and what is in the body's blood, urine, or saliva portions through a cortisol test. Both of these tests would allow for a physician to get a baseline of where the patient is at in terms of what stage of MS, CIS, or one of the four categories of MS. A cortisol test can indicate how the body is responding to prolonged stress, with elevated cortisol levels potentially leading to reduced fatigue and increased energy. This response is linked to the activation and metabolism of glucose within the body creating an increase in the amount of oxidative stress present in the body. The primary goal of a cortisol test is to determine whether the amount of cortisol are elevated, which would suggest that the individual is experiencing significant stress in their current state. Over a longer period, such as a week or a few weeks, additional tests similar to the cortisol test should be conducted to see if there is chronic stress. Chronic stress is related to the accumulation of oxidative stress in the body.

Trace Metal Testing

Trace metal testing in patients with MS may reveal patterns that link oxidative stress to disease progression, providing insights into potential therapeutic targets. Another path that would lead to an increased deduction of the MS disease and help to identify patterns within the disease would be to test for trace metals in the urinary system and see if

any trace metals are present in their bodies. Trace metals, as previously mentioned, lead to an increase in oxidative stress in the body because of the different signaling techniques that allow the trace metals to act in accord with metabolism. This means that with an increased amount of trace metals, there is an increased amount of metabolism, affecting the amount of oxidative stress throughout the body. The relevance of trace metals is that they are found in the body and usually in small, controlled amounts that help the body function normally. However, at abnormal levels, trace metals cause symptoms similar to those listed in the MS, primary, secondary, and tertiary symptoms (Dales & Desplat-Jégo, 2020). These symptoms are associated with an increase in oxidants in one's body due to harmful substances exacerbating cellular damage, such as lipid peroxidation, mitochondrial dysfunction, and DNA damage.

Genetic Mutations That Occur Through Oxidative Stress

Genetic mutations resulting from oxidative stress play a significant role in the progression of MS, underlining the importance of personalized treatment strategies. This literature review highlights genetic mutations as a key factors, emphasizing the need for a comprehensive approach that considers both internal and external influences. Future research should focus on personalized care strategies for MS patients, accounting for individual variability in responses. Although similar symptoms are viewed in a person with MS, the duration of the symptoms and the episodic features are presented in different ways that would be contrary to another individual. Thus, direct DNA testing should be more widely studied to see if there are differences in the genomic data present with each person. Direct DNA testing is a type of DNA test used for small DNA mutations if the function of a protein is not known and a biochemical test cannot be developed. Specifically, genes that have been associated with the process of the antioxidant system or have a connection to an increased risk factor for oxidative stress should be tested, including heme oxygenase-1

(HMOX1), heme oxygenase-2 (HMOX2), methylenetetrahydrofolate reductase (MTHFR) mutations C677T and A1298C, glutathione peroxidase (GPx) genes, and superoxide dismutase (SOD) genes. Additionally, these tests would require a very small amount of genomic data, thus saving most of the person's health by not requiring many samples to run the direct DNA test (Genetic Alliance, 2010). The purpose of performing such a test is to develop new data regarding the general pathway the MS takes because of the abundance of damage that does occur during the disease due to the accumulation of oxidative stress that is present in the body; there are going to be additional mutations that are found through any given individual. Even if individuals do not have the same sense codons with mutations, mapping the general locations of these mutations provides valuable insights into how MS interacts with the body. This approach helps identify specific biomarkers and genetic loci associated with oxidative stress that contribute to the development and progression of MS. By focusing on these biomarkers, research can better understand the pathways through which oxidative stress exacerbates the disease. This targeted research aims to pinpoint genetic mutations that increase susceptibility to oxidative damage, enabling the development of more personalized treatment options tailored to the unique genetic makeup of each individual with MS. By using genetic testing, researchers can identify common patterns of oxidative damage and inflammation, offering the potential for earlier intervention and customized therapies that address the specific oxidative stress-related mechanisms driving the disease. This strategy not only enhances our understanding of MS but also provides a pathway for more effective and individualized treatment approaches, reducing the impact of oxidative stress on disease progression., therefore combining these genetic tests could significantly enhance our ability to predict an individual's susceptibility to MS, allowing for earlier intervention and more personalized treatment plans based on genetic risk factors.

Future Research Experiments

Future research experiments should focus on the genetic and biochemical aspects of oxidative stress in MS to develop more effective therapeutic interventions. This research aims to demonstrate and correlate various aspects of oxidative stress, environmental stress, metabolism, trace elements, and genetic variation in cell function. Further research recommendations should be proposed to steer the current trajectory of studies toward acquiring supplementary data beneficial for developing alternative treatment modalities for individuals afflicted with MS or diseases exhibiting analogous mechanisms.

Analysis of Mutations with Oxidative Stress

Analyzing genetic mutations induced by oxidative stress in neuronal cells could provide critical insights into the pathogenesis of MS and guide the development of targeted therapies. More effort should be made toward analyzing different or common genetic mutations that occur under oxidative conditions in the more centered aspect of research related to oxidative stress. Thus, a study that mainly analyzes genetic mutations introduced by oxidative stress in neuronal cells focuses on identifying the different mutations associated with MS pathogenesis. After establishing the purpose of the experiment, a stable set of cells would need to be prepared for experimentation. The particularly commonly used cells are SH-SY5Y cells, which help distinguish the difference between neurological-associated problems in these cells. Under normal conditions, these cells would be kept at 37 degrees Celsius with five percent carbon dioxide (CO_2), where there would be two different groups being explored during the experiment: the control and an experimental group with oxidative stress. The oxidative stress agent that would be added to the cells would be an agent commonly found in the body, and a prime example of an oxidant is hydrogen peroxide. The next approach to the experiment would be to use a mutation accumulation (MA) experiment to find the basis of rates, molecular spectra, and fitness of the different

mutations that occur from oxidative stress in the MS experiment (Mahdieh & Rabbani, 2013). However, for the experiment to work, there would need to be a baseline of the right conditions. Researchers would allow cells to survive and still be able to grow and divide normally to see the difference in functionality between cells under the right concentration of ROS in the cells. Establishing a baseline in the MA experiment under oxidative stress conditions will enable researchers to observe and track the various survival pathways cells utilize, such as the antioxidant response pathway that would produce SOD, DNA repair mechanism that would need to activate base excision repair (BER) and nucleotide excision repair (NER), or autophagy. throughout the experiment. Once established, additional testing is performed to note the differences in mutations within the specified line of cells. In the cell lines of the MS, there would need to be a direct sequencing of the cells involved, where each base pair would be identified and compared to the original sequence (Sinclair, 2002). Researchers can analyze the differences in mutations by comparing an original, unmutated DNA sequence with a mutated sequence from someone with MS or from cells exposed to oxidative stress. This comparison helps identify direct correlations between oxidative stress-induced mutations and MS. Furthermore, comparing these results with other human genome data can reveal specific correlations related to MS. The main focus of the direct sequencing would be the genes associated with MS that provide additional insight into the topic, such as HLA genes, myelin formation genes, and neuronal functioning genes. Once mutations are seen, additional testing is done to see the direct consequence of the particular gene mutation and the impact the mutation has on protein structure, function, and regulatory elements. The information these tests provide is interpreted from the experiment used to propose different genetic mechanisms associated with MS, which is used for future applications to find additional therapeutic applications. Overall, the experiment design uses two main tests to determine the mutations that occur in the cells and the sequencing for the

data. The two tests being used, MA and direct sequencing, will try to provide an improved foundation for the association of genetic markers with MS and oxidative stress.

Investigating Mitochondrial Dysfunction with Exposure to Oxidants

Investigating mitochondrial dysfunction under oxidative stress conditions offers potential therapeutic targets for mitigating neurodegeneration in MS. To replicate an oxidative stress environment is similar to that in MS, a cell culture of primary neuronal cells derived from mouse or human embryonic cortical tissue will help simulate a human's CNS. Following the maturation of the primary neuronal cells, there would have to be some stimulus for the oxidative environment that induces oxidative stress symptoms for the cells. Exposing the cells to an oxidative agent such as hydrogen peroxide would be a fair assessment of the overall experiment. However, before using hydrogen peroxide as the oxidative agent, there would need to be a baseline concentration for the concentration of hydrogen peroxide needed for the cells to survive because, at elevated concentrations, most cells will induce apoptosis. After completing that step, fluorescent probes and mitochondrial staining evaluate the cell's mitochondrial membrane potential, ATP, and ROS. Fluorescent probes would allow the researcher to evaluate the mitochondria at different levels of the ATP synthesis process and the introduction of ROS into their environment to see how much of an effect the ROS has on the production process. The measurements then be placed into more of a numerical sense with the 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) assay, which allows for the conversion of MTT to crystals in order to assess mitochondrial activity (Meerloo et al., 2011). In order to keep the core concepts of the experiment in place, there should be additional tests done in terms of ion homeostasis that is seen through the use of fluorescent calcium indicators such as Fluo-4 to monitor any changes that would happen in terms of ion homeostasis. Meanwhile, glycolysis activity is measured through lactate production assay

or glucose consumption assay to help establish the level of glycolytic activity. Finally, immunofluorescence and western blotting will be performed to examine the expression of mitochondrial proteins, oxidative stress markers, and apoptotic markers. While all of these tests happen, four expected outcomes would be due to the oxidants in the cell's environment that would change their natural function. First, oxidative stress leads to mitochondrial dysfunction, an increase in the production of ROS, and damage to ATP production. Second, increasing ROS levels would cause apoptosis due to irreparable cell damage. Although MS cells do not die immediately, the extent of damage to nerve cells determines their survival. At high enough concentrations of oxidative stress, apoptosis occurs. Therefore, it is best to test cells lacking regenerative capabilities and remain as one designated cell type throughout life. Third, oxidative stress would lead to changes in the calcium regulation system, causing calcium dysregulation. Fourth would be the increase in glycolytic activity because of the dysfunction of the mitochondria, which would lead to an increase in glycolytic activity to make up for the lack of energy produced by the mitochondria.

Conclusion

This literature review focused on the mechanism of glycolysis and oxidative stress as these concepts are involved in the progression and beginning of MS. Environmental and oxidative stress are two different types of stress; however, they lead to the same type of outcome which is the production of ROS in the body that causes harm to an individual's cells. Environmental stress in the form of chronic stress induces oxidative stress by producing cortisol throughout the body, increasing the amount of energy used in the body and decreasing the amount of fatigue. Internal stress would be classified as the oxidative agents that accumulate and contribute to oxidative stress. Oxidative stress mainly comes from the metabolic pathway, where glucose is broken down into usable energy for the

body. However, when glucose is broken down, oxidative states are released in cells that need to be controlled through antioxidants. Although the main pathway for controlling oxidative stress is the Nrf2 pathway, if the Nrf2 pathway cannot keep up with the amount of ROS, the oxidative stress will accumulate, destroying the affected cells. Thus, ways to recognize and make an informed decision on a person with MS and collect additional data that surround the disease to develop a more defined treatment option eventually would be to have a multitude of tests that help effectively analyze levels of cortisol and trace metals, while collecting data genomically on if the patient has individual mutations that are occurring in the bodies that are causing different symptoms. Gathering data on the different types of mutations and the drastic differences in mutations could help physicians treat MS patients with more individualized, tailored treatment options that address each symptom of MS in hopes that the goal of patients effectively eliminates the disease or lessen the effects of the disease managing or mitigating the impact of the disease. Also, research is suggested in the hopes that a wider array of experiments can be conducted to provide additional information on the current course of any disease that deals with oxidative stress. Two different research projects that can be implemented include the analysis of mutations with oxidative stress and the investigation of mitochondrial dysfunction. Both of these experiments attempt to look at the implementation of oxidative stress in the environment of the cell and attempt to analyze the surrounding environment of that cell that looks for genetic markers for the cell or the overall pathogenesis that would be followed from an ionic perspective.

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