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Time to get Personal: A Framework for Personalized Targeting of Oxidative Stress in Neurotoxicity and Neurodegenerative Disease

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Abstract

The annual cost for neurological disorders in the United States was \$789 billion in 2014, and with an aging population these numbers are expected to significantly increase in the next 50 years [1]. Neurodegenerative diseases make up a significant portion of these costs. Neurodegenerative diseases are characterized by the loss of neuronal populations in specific regions of the brain. Although the cause is still unknown for most of these diseases, both genetic and environmental factors are thought to play important roles. There are multiple convergent mechanisms underlying the unique susceptibility of neurons to degeneration, including aging, inflammation, mitochondrial dysfunction, and oxidative stress. Oxidative stress (OS) is of particular importance because evidence indicates that the neuronal populations lost in neurodegenerative diseases are particularly susceptible to OS. OS is a complex neurotoxic mechanism that arises from excessive generation of free radicals such as reactive oxygen species (ROS), reduction in anti-oxidant factors, or a combination of the two. A complex interplay between the endogenous susceptibility of the brain, genetic factors, and environmental exposures leads to the harmful generation of OS in the brain and contributes significantly to the initiation and/or progression of neurodegeneration. Unfortunately, therapeutics for neurodegenerative diseases have consistently failed in clinical trials. Thus, a better understanding of the interplay between genetic susceptibility and common molecular mechanisms of environmental contributors to OS generation could aid in elucidation of novel therapeutic strategies for neurodegenerative diseases. This review will explore the current picture of oxidative stress in the brain as it relates to neurotoxicity, specifically exploring common mechanisms behind the endogenous susceptibility of the brain to OS, genetic susceptibility and environmental exposures leading to neurotoxicity, to identify precision/personalized medicine approaches for improving therapeutic outcome.

The Brain: Unique Susceptibility to Oxidative Stress

Free radicals, such as ROS and nitric oxide (NO), contribute to important functions of the brain. These functions include calcium signaling, synaptic plasticity, memory, and nitric

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oxide even acts as a neurotransmitter inducing the release of other neurotransmitters in the brain [2]. Therefore, free radicals are important factors for normal functioning of the brain. However, excessive levels of free radicals can overwhelm the antioxidant response systems and lead to oxidative stress in the brain. Evidence indicates that OS is a major factor contributing to the initiation and/or progression of the various neurodegenerative diseases, including Parkinson's (PD), Alzheimer's (AD), and Huntington's disease (HD), along with amyotrophic lateral sclerosis (ALS) and cerebral ischemia [3]. Indeed, the brain is thought to be uniquely susceptible to excessive oxidative stress.

Several properties of the brain have been hypothesized to contribute to this unique susceptibility. First, aging represents the primary and shared risk factor among neurodegenerative diseases, and oxidative stress is increased in the brain with age [4]. It is hypothesized that one of the primary contributing factors for increased OS with age is reduced expression of antioxidant factors, including superoxide dismutase (SOD), and catalase [5]. Another reason that neurons are more susceptible to OS is due to high demand for oxygen along with high energy demands and neurotransmitter production [6]. Similarly, mitochondrial dysfunction is a common mechanism in these diseases, and mitochondrial dysfunction leads to increased ROS production and eventually oxidative stress. Indeed, mitochondrial dysfunction has also been linked to aging [7]. These factors, along with others discussed below are intricately involved in the unique susceptibility of the brain to OS.

Glial Contributors to OS in the Brain

In addition to mitochondrial-derived ROS produced from neurons, the primary source of OS that contributes to OS-mediated neurodegeneration is the glial inflammatory response, including contributions from and interactions between microglia and astrocytes. Glial cells are a major component of OS regulation in the brain, with these cells mediating the generation of ROS while also controlling major pathways in the antioxidant defense. Activated microglia and reactive astrocytes are a significant source of ROS in neurodegenerative disease and many of the brain regions affected in these diseases have large glial populations [8]. Extensive evidence indicates that microglial-mediated OS is a prime contributor to neurodegeneration in multiple diseases [9]. Similarly, it has recently been determined that activated microglia results in reactive astrogliosis, and that these reactive astrocytes directly lead to neurotoxicity in models of neurodegenerative diseases [10]. Increased OS also leads to disruption of normal glial function, which is important for normal brain health, such as neurotrophic support. Along with age-related increase in glial cell ROS generation, defects in several genetic factors related to antioxidant support, including DJ-1 and superoxide dismutase (SOD), also play a role in causing both microglia and astrocytes to exacerbate brain OS [15, 16].

In contrast, evidence indicates that the transcription factor Nrf2 is a master regulator in alternative, anti-inflammatory microglial activation and reduction in microglial OS [11]. Therefore, glial cells represent important targets to reduce the generation of OS, along with attenuation of OS-mediated neurotoxicity. Astrocytes are a major source of glutathione, a major antioxidant in the brain, and dysfunction leads to reduced glutathione production from these cells, which leads to increased neurotoxicity [12]. Mitochondrial dysfunction in both

glial populations leads to increased OS and results in increased neurotoxicity. One of the major factors that contributes to glial-mediated OS is the NADPH oxidase (NOX) system [13] and, targeting the NOX system led to a significant reduction in glial-mediated OS in the brain [14].

Genetic Contributors to Brain Sensitivity

Several genes linked to development of neurodegenerative diseases are either involved in generation of OS through mitochondrial dysfunction or serve as antioxidant factors. For instance, mutations in the protein deglycase DJ-1 have been linked to increased PD risk, and more recently AD [17]. DJ-1 has several antioxidant properties that are being elucidated, and increased DJ-1 can protect neurons from OS-mediated toxicity [18]. Additional examples of genes regulating mitochondrial function, and in particular mitophagy, include Parkin and PINK1, which are both PD risk genes [28]. Similarly, altered expression of the mitochondrial fission protein Drp1 has been found in both PD and AD [29].

Additional single nucleotide polymorphisms (SNPs) have been found in antioxidant genes that do not appear to be dominant genetic contributors to neurodegenerative disease, but could be related to the generation of OS in the brain in response to environmental insult and aging. SNPs in the antioxidant enzyme manganese superoxide dismutase (MnSOD) have been associated with increased OS measured in the blood of healthy women [19]. Similar results have been reported for other antioxidant factors, including catalase and glutathione peroxidase-1[20].

Glutathione is one of the major antioxidant factors of the brain that protects cells from OS-induced death, and reduced levels of glutathione have been found in neurodegenerative diseases [21, 22]. Different isoforms of the family of enzymes responsible for glutathione generation, GST, contain various SNPs and these mutations have different effects on OS throughout the body [23]. Similarly, GST isoforms are altered in neurodegenerative diseases, and rescue of particular isoforms have been found to be neuroprotective in animal models of neurodegeneration [24]. One of the most studied antioxidant factors in the brain that directly regulates GSTs is the nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2). Multiple studies have found that increasing Nrf2 activity can protect cells in the brain from oxidative stress [26]. Interestingly, there are multiple SNPs that were found in the promoter of Nrf2, and some of these polymorphisms led to reduced antioxidant response [27]. There has not been an association between any Nrf2 polymorphisms and neurodegenerative diseases, but these SNPs could play a role in individual susceptibility to OS in the brain.

Therefore, there are multiple factors that are involved in mediating OS in the brain and in neurodegenerative diseases. With polymorphisms in multiple regulators of mitochondrial function and antioxidant factors, especially those controlling glutathione generation and Nrf2, it is important to elucidate the specific pathways, factors and genetic mutations that lead to increased free radical production and decreased antioxidant response factors which could substantially impact therapeutic approaches to these diseases and lead to individual differences in responsiveness to treatment.

OS: A Common Mechanism for Neurotoxicant-induced neurodegeneration

Although aging and genetic factors play important roles in the neurodegenerative diseases, environmental components are also significant contributing factors [30]. This is especially evident for OS in the brain, with various environmental factors greatly affecting ROS generation and reduction in antioxidant defense.

Exposure to numerous environmental contaminants has been linked to increased risk of developing neurodegenerative diseases, and OS is the major molecular mechanism mediating the damage from these environmental factors. The selective dopaminergic neurotoxin MPTP, which was first generated from improperly prepared recreational drugs [42], is a well-characterized mitochondrial complex I inhibitor that leads to increased OS and neurotoxicity in the brain. Additionally, multiple pesticides have been found to increase risk of both PD and AD, with increased OS in the brain contributing to neurodegeneration [31]. The list of pesticides that have been found to cause these deleterious effects include organophosphates, paraquat, dieldrin, rotenone and pyrethroids [31]. These pesticides have all been demonstrated to increase ROS generation and reduce antioxidant defense factors in the brain. The pesticide rotenone is has been linked to PD [31] and exerts toxicity through inhibition of mitochondrial complex-I leading to high levels of ROS in neurons and subsequent microglial activation. The herbicide paraquat is also linked with risk for PD and functions as a redox cyler generating OS. It has also been shown to decrease Nrf2 antioxidant function in the mouse brain regions associated with PD [32]. Antioxidant treatments have been successful in attenuating pesticidemediated OS and neurodegeneration in animal models of neurodegenerative diseases [33, 34]. However, generically targeting OS in clinical trials has not yet proven to be a successful strategy.

Two additional environmental factors that have been found to increase OS in the brain are metal exposure [37], and air pollutant particulate matter [38]. The effects of metal exposure on brain OS has been well documented, with heavy metals such as manganese and lead leading to increased brain ROS levels and decreased antioxidant defenses, and subsequently increasing neurodegeneration [39]. Antioxidant therapies have been successful in attenuating OS levels and subsequent neurotoxicity from both heavy metal exposure and particulate matter [40, 41]. Other environmental factors that increase brain OS levels are still under investigation for having roles in neurodegenerative diseases include solvent exposure [43], magnetic fields [44], and cigarette smoke [45].

These environmental exposures, including pesticides, metals, particulate matter, and neurotoxicants, can also induce microglia activation directly or indirectly and lead to an increased inflammatory response and oxidative stress through either direct insult or from signaling factors and ROS produced by damaged neurons [9, 46]. Although these environmental factors work through different mechanisms, increased brain OS is the common deleterious pathway that mediates neurodegeneration. Therefore, targeting OS for different environmental exposures could lead to improved therapeutic outcome.

Personalized medicine for OS in neurodegenerative diseases

Only recently has research into oxidative stress in neurodegenerative diseases shifted from demonstrating OS-mediated damage in neurodegenerative disease models and patients, to now exploring the pathways and factors that drive OS and using this information to develop therapeutics. OS is a common mechanism that is shared with both genetic and environmental components of neurodegenerative diseases. Thus, there is a need to establish viable means to target OS for therapeutic intervention and lead to neuroprotection. However, none of the strategies for targeting OS have developed into a meaningful therapy for neurodegenerative diseases to date. Current research demonstrates that there are several obstacles in reducing OS as a neuroprotective therapy, including inadequate predictive animal models and lack of drug access to the brain. Further, earlier identification of those at risk of neurodegenerative disease is needed, as some of the clinical failure is thought to be related to the fact that by the time a patient reaches the clinic, too much damage exists for a generalized OS-targeted therapeutic approach to succeed. However, these failures might also be attributed to the fact that there are differences in how individuals respond to toxicant exposure and therapy. Indeed, some individuals harbor genetic mutations or particular environmental exposures that may prevent the success of a specific therapy. Therefore, identification of those that may be at particular risk based on a comprehensive analysis of genetic and environmental factors would allow for earlier identification and a more personalized approach to therapy through understanding of the interplay between genetic and environmental factors.

Figure 1 provides a proposed personalized framework for elucidating individual contributors in an attempt to optimize antioxidant therapies and increase therapeutic efficacy. An example of this paradigm is as follows: Genotyping reveals that a patient has a SNP resulting in reduced GST function, suggesting that they may not respond optimally to GST-targeted therapeutics. In this case, treatment options could be focused target another antioxidant system, such as the Nrf2 pathway or glial cell-mediated OS, such as a NOX inhibitor [14]. Activation of Nrf2 signaling has been successful in attenuating OS from environmental toxicant exposure in animal models of disease [48]. Another option could be dietary antioxidants, including vitamin E and natural sources of general antioxidants [49]. Environmental exposures are significant, yet often unappreciated contributors to disease development and progression. Working in concert with genetic susceptibility and through epigenetic mechanisms environmental exposures are rapidly becoming recognized for their contribution to neurodegenerative diseases.

A potential scenario of this strategy is as follows: an individual with a SNP leading to reduced GST function is exposed to the pesticide rotenone, which is a potent complex I inhibitor that leads to mitochondrial dysfunction and OS in the brain. Targeting glutathione production in this individual would not lead to optimal attenuation of OS due to the GST polymorphism, and utilizing mitochondrial-targeting antioxidants could lead to increased therapeutic efficacy. Therefore, exposure history, such as metal or certain pesticide exposures, could indicate that using mitochondrial-targeting antioxidant therapies would have greater success than general antioxidants [50].

Overall, it is clear that oxidative stress is intricately involved in the various neurodegenerative diseases and that understanding the environmental and molecular mechanisms controlling the generation of OS is an attractive therapeutic option. Failure of clinical trials of OS-targeted therapeutics is likely to result from multiple factors. However, personalized approaches incorporating genetic and environmental exposure information may ultimately lead to enhanced efficacy and improved outcomes.

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Highlights

- Although free radicals are necessary for certain brain functions, the brain is uniquely susceptible to oxidative stress due to factors such as aging, neurotransmitter production and high energy demands.
- Oxidative stress is a common mechanism that is involved in neurotoxicity found in various neurodegenerative diseases.
- Glial cells, such as microglia and astrocytes, are major sources of oxidative stress in the brain.
- Genetic polymorphisms in antioxidant enzymes or mitochondrial protective factors can lead to increased OS in the brain and subsequent neurodegeneration.
- Environmental contaminants, such as pesticides and metals, can lead to increased neurotoxicity through the induction of oxidative stress.
- With oxidative stress as a common mechanism mediating neurotoxicity from genetic polymorphisms and environmental exposures, a personalized medicine approach would optimize therapeutic efficiency.

Figure 1. Framework for a personalized medicine approach to improve antioxidant therapies in neurodegenerative diseases

Patients would undergo a battery of tests to determine which antioxidant therapy would likely have optimal therapeutic outcomes. The tests would include genetic testing for polymorphisms in antioxidant factors and mitochondrial proteins, blood tests for oxidative stress and inflammatory biomarkers, exposure history and blood/urine tests for environmental exposures, and potentially PET scans to examine neurotransmitter levels, glial activation and OS levels in the brain. The resulting data would identify individual contributions of genetic and environmental factors that contributed to OS in the brain that could be used to develop a personalized therapeutic approach and monitor therapeutic efficacy.