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Oxidative Stress and Mitochondrial Dysfunction in Neurotoxic Damage

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Abstract

The breakdown of the body's mitochondria and cells is a big cause of a huge range of illnesses. The brain is very sensitive to damages caused by oxygen that's in excess, because of many fatty substances or lipids present, as well as limited antioxidant defense mechanism. Enabling there to be too many toxic molecules called ROS, origin a bodily imbalance and therefore have a lot of bad effects on our cell "origin" and DNA as well. As the major energy producers in a cell, mitochondria are both the roots of oxidative stress as well as being themselves affected by it. Exposure to toxins like lead and mercury really messes with our brain cells, it slows down the brains energy reservoir, from function that manufactures enzyme. These changes increase brain damage by reaching dangerous cellular developments and by messing incidents in the system of mailing signals between the brain's connections. There is proof that imparted damage goes from the muscles to the brain itself through a harmful loop. To find new approaches to treatment and identify symptoms, and quote; oxidative stress simultaneously contributes to mitochondrial dysfunction and quote; is something mankind needs. Doctors feel that certain medicine or methods can help protect the human brain to be safe. New focus on helping treatment to live the outside life with a stronger environment so the essence of what is going on don't die.

Keywords: *Oxidative Stress; Mitochondrial Dysfunction; Neurotoxicity; Reactive Oxygen Species; Neurodegeneration*

Introduction

Neurotoxic damage is the process of neuronal impairment caused by natural or man-made toxic substances [1]. It is associated to various neurological diseases [2].

Oxidative stress (OS) is a key factor in neurotoxicity. It is defined as the biochemical imbalance between oxidants and antioxidants, leading to cellular and molecular deterioration [3]. Reactive oxygen species (ROS) are the main oxidants and are generated through different mechanisms [4]. The primary ROS-producing system is the mitochondrial electron-transport chain, but they may also be

produced by metabolic processes, both enzymatic and non-enzymatic [5]. The central nervous system is particularly sensible to OS due to its high metabolic activity and oxygen consumption coupled with relatively weak antioxidant mechanisms [6]. The consequence is the accumulation of ROS, which alters brain morphology and causes enhanced permeability of the blood-brain barrier [7]. It also triggers neuroinflammatory reactions, which further exacerbate the oxidative injury [8].

Understanding oxidative stress

Oxidative stress is defined as an imbalance between oxidants and antioxidants in favour of the oxidants, leading to a disruption of redox signalling and control and/or molecular damage [1]. The term is used to describe a large group of reactive species, including reactive oxygen species (ROS), free radicals, and reactive nitrogen species [9]. Survival in an aerobic environment requires the presence of oxygen, allowing an efficient supply of energy, with the costs of generating reactive oxygen species as by-products of oxygen metabolism [10]. Major endogenous sources of ROS originate from the mitochondrial electron transport chain during aerobic respiration, while NADPH oxidases, xanthine oxidase, and nitric oxide synthase are also recognised to be potential sources [11]. External factors such as ionising and non-ionising radiations, heavy metals, drugs, cigarette smoke, industrial solvents, and pesticides may also contribute to oxidative stress [12].

Within the cell, mitochondria represent the primary ROS producers and targets of free radicals [13]. Mitochondria generate ATP through oxy-phosphorylation to provide the energy required for biological functions and cellular homeostasis [2]. Their role extends beyond energy production by generating other metabolites indispensable for the functioning of cells, tissues, and the organism. They are necessary to regulate Ca^{2+} homoeostasis, ROS production, apoptosis, steroid synthesis, and cell growth and differentiation [14]. Mitochondrial dysfunction results in an inability to maintain ATP production and cellular homeostasis with a higher release of free radicals [15]. Excessive production of ROS causes oxidative stress with macromolecular damage, such as mitochondrial DNA damage and variations in mitochondrial morphology and dynamics [13].

Definition and mechanisms

Neurotoxic damage results from disruptions to the functional or morphological integrity of the nervous system caused by exogenous or endogenous neurotoxic substances. While this phenomenon is occasionally reversible, irreversible damage can lead to neurodegenerative disease processes [16]. Oxidative stress and mitochondrial dysfunction play key roles in the mechanisms leading to neurotoxicity [2].

Oxidative stress arises when reactive oxygen species (ROS) generation surpasses cellular antioxidant defense capabilities [1]. ROS are generated during physiological processes such as inflammation, apoptosis, and oxidative phosphorylation, as well as from environmental factors like heat exposure and radiation [17]. The imbalance between ROS and antioxidants contributes to cellular impairment and damage to biomolecules including DNA, proteins, and lipids [18]. Existing evidence indicates that oxidative stress is a critical factor in toxic damage to the nervous system; therefore, measuring biomarkers associated with oxidative stress holds promise as a diagnostic tool for neurotoxicity [19].

Mitochondria generate adenosine triphosphate (ATP), which maintains cellular function and homeostasis through oxidative phosphorylation and the citric acid cycle. Additionally, mitochondria regulate cell cycling, growth, and differentiation via signaling molecules [20]. Several neurotoxins damage mitochondria and disrupt their functions, leading to cellular energy depletion and excessive oxidative stress [21]. Dysfunctions in mitochondria significantly influence oxidative stress levels, and excessive ROS accumulation inhibits mitochondrial function, triggering a positive feedback loop that increases ROS production [22].

Sources of oxidative stress

Oxidative stress represents an imbalance between reactive oxygen species (ROS) generation and the cellular antioxidant defense mechanisms [2]. ROS constitute a broad family of molecules formed when oxygen interacts with various intracellular components [23]. Under physiological conditions, cellular antioxidant defenses maintain ROS at low levels to preserve their functional roles, such as in cellular signaling [1]. Imbalances between ROS and antioxidants result in damage to biomolecules [24]. Mitochondria constitute the primary intracellular source of ROS and are particularly vulnerable to oxidative insult [25]. Additional sources include environmental toxicants, such as heavy metals, pesticides, and organic solvents, which induce oxidative stress by affecting specific pro-oxidant and antioxidant proteins [13]. These exogenous agents contribute substantially to oxidative burden and are implicated in neurotoxicity [26].

Mitochondrial function and dysfunction

Observations across neurotoxic agents strongly support the central role of mitochondrial dysfunction in mediating neurotoxic damage [2]. Mitochondria regulate cellular metabolism and are the major source of sub-cellular reactive oxygen species (ROS) [27]. Neurotoxicants handicap mitochondrial function, thereby interfering with ATP synthesis, propelling mitochondrial oxidative stress and both apoptotic and necrotic cell death [28]. Variations in susceptibility among neuron populations underlie the selective nature of mitochondrial impairment in patterns of neurotoxicity [29].

Role of mitochondria in cellular health

Mitochondria are essential for cellular energy and homeostasis, generate ATP via oxidative phosphorylation, produce reactive oxygen species (ROS), and buffer calcium [13]. Neurons, which depend heavily on mitochondrial function, are particularly vulnerable [31]. Mitochondrial dysfunction impairs energy production, elevates oxidative stress, and disrupts calcium dynamics, contributing to tissue damage and disease [30].

Consequences of mitochondrial dysfunction

Mitochondria act as cellular energy hubs, synthesizing adenosine triphosphate through oxidative phosphorylation and maintaining the basis for cellular homeostasis [2]. Mitochondrial impairment, characterized by defective electron transport or ATP production, frequently occurs during ageing and underlies many disease pathologies, including neurodegeneration [32]. The impairment of mitochondrial function predisposes biological systems to major damage in situations of metabolic and neurotoxic stress [3]. Imbalances between antioxidant defence systems and reactive oxygen species (ROS) generated by mitochondrial metabolism, as well as subsequent oxidative damage to mitochondrial DNA, lipids and proteins, feature strongly in many neurodegenerative diseases [13]. Mitochondrial dysfunction is further supported by the observation that neuronal loss in many diseases may be mimicked by neurotoxins that target specific mitochondrial components [33]. Although the origin of such mitochondrial impairments continues to be extensively debated, there is consensus that the mechanisms underpinning the removal of defective mitochondria and their components are unable to fully restore functional mitochondrial capability over time [34]. Furthermore, the inability to remove damaged mitochondria is implicated as the key factor by which increased oxidative stress and mitochondrial impairment potentiate progression of neuropathological and neurodegenerative disease processes [4].

Neurotoxic agents and their impact

A multitude of chemical substances and environmental agents are known to exert neurotoxic effects [2]. The mechanisms behind these neurotoxic effects are varied. They can result from neuronal dynamics alterations interference with electrical signal or chemical neurotransmitter function, as well as disruption of physiological, biochemical, and molecular processes in nervous system cells [13]. Underlying pathways inducing neurotoxicity include oxidative stress, mitochondrial dysfunction, impairment of endogenous antioxidant systems, inflammation, excitotoxicity, glutamate receptor regulation, protein lysis, endoplasmic reticulum stress, specific enzyme activity, and mitogen-activated protein kinase (MAPK) pathways [35].

Common neurotoxins

To examine the impact of common neurotoxic agents on oxidative stress and mitochondrial dysfunction, this section first characterizes prevalent neurotoxins [3]. It then explores their mechanisms at the mitochondrial level, highlighting how their molecular effects lead to increased oxidative burden and functional impairment [36].

Neurotoxic agents-select chemical, biological, or physical substances with adverse central nervous system effects-are introduced [37]. Heavy metals such as lead, mercury, and manganese cross the blood–brain barrier to disrupt fundamental neuronal functions. Industrial chemicals like toluene, n-hexane, and 1,2-dichloroethane impair axonal transport and synaptic transmission and damage the blood–brain barrier [38]. Drugs including methamphetamine and cocaine mediate neurotoxicity through oxidative stress and inflammation pathways [39]. Pharmaceuticals such as haloperidol and penicillamine induce oxidative damage and mitochondrial perturbations [2]. Exposure to any of these agent's risks profound neurological dysfunction [40].

The molecular pathways underpinning neurotoxicity vary widely across agents but frequently converge on compromised mitochondrial function and enhanced cellular oxidative stress [29]. Mitochondrial membrane disruption hinders ATP synthesis, unsettling vital enzymatic processes [13]. Increased reactive oxygen species production promotes lipoperoxidation that damages mitochondria, initiating a self-reinforcing cycle of escalating dysfunction [41]. Membrane depolarization and Ca^{2+} efflux released through the disrupted inner mitochondrial membrane signal release of cytochrome C and other pro-apoptotic factors into the cytosol, triggering cell death [35]. These interlinked processes accelerate neuronal demise in response to acute or chronic neurotoxic exposure [42].

Mechanisms of neurotoxicity

Neurotoxins exert their deleterious effects on the nervous system through various mechanisms, often involving the alteration of neurotransmission and the induction of oxidative stress [2]. A central molecular mechanism associated with several neurotoxicants is the impairment of mitochondrial function, which is critical to neuronal survival given mitochondria's roles in energy production, regulation of calcium homeostasis, and initiation of apoptotic pathways [13]. Many neurotoxins cause neurodegeneration via calcium overload and excessive production of reactive oxygen species (ROS), leading to oxidative stress and mitochondrial dysfunction [43]. Such alterations can precipitate a cascade of events including neurite retraction, mitochondrial calcium accumulation, and glutathione (GSH) depletion, culminating in neuronal cell death [35]. Consequently, neurotoxic substances have been widely employed as experimental tools to model oxidative damage and neurodegeneration [44]. This context underscores the vulnerability of mitochondria to oxidative stress and reinforces the interplay between mitochondrial impairment and neurotoxic damage [45].

The link between oxidative stress and neurotoxicity

Oxidative stress results in the formation of ROS and also induces inflammation; both activities contribute to the neurotoxic effects of a compound [2]. During neurotoxic damage, cells are under continuous attack because of the sustained generation of ROS and persistent activation of inflammatory agents [46]. Oxidative damage leads to inflammation, and inflammation also generates further ROS; in conjunction, these agents act synergistically to cause neurodegeneration [2].

In neurons, according to, oxidative stress impairs mitochondrial function, causing cellular energy failure, damage to mitochondrial DNA, impairment of respiratory chain complexes, and reduction of mitochondrial defense systems [47]. Mitochondrial impairment is detrimental for neurons, which have a limited glycolytic capacity and depend on a continuous supply of ATP derived from oxidative phosphorylation [48]. Free radicals produced within mitochondria further exacerbate the dysfunction, especially when antioxidant defenses are insufficient [49].

Oxidative damage in neurons

Oxidative damage in neuronal cells is one of the most significant processes implicated in neurotoxic damage [2]. The normal function of many neurons is sensitive to oxidative stress derived from free radicals or reactive molecules [45].

Neurotoxicity typically results from the accumulation of metals, insecticides, or organic solvents that increase cellular free radicals or other types of oxidative stress [32]. The brain consumes almost 20% of the body's oxygen supply, yet it contains comparably low levels of antioxidant defenses [50]. Furthermore, brain lipids are rich in polyunsaturated fatty acids [50]. The combined effects of these variables creates an environment highly susceptible to lipid peroxidation, membrane damage, and other oxidative stresses. Reactive-oxygen species generated by mitochondrial activity may lead to DNA damage at the cellular level [13]. Neuronal activity-including axonal growth and synaptic maintenance-requires energy generated by mitochondria to maintain function and to control oxidative damage [51]. Compared to other cell types, neurons have limited capacity to switch to the less efficient pathway of glycolysis when oxidative phosphorylation is impaired; many neurotoxic agents primarily interfere with enzymes involved in oxidative phosphorylation [52].

Oxidative damage is therefore a key factor in neurotoxicity [53]. This aligns with extensive evidence from neurodegenerative diseases, in which several proteins associated with the diseases increase oxidative stress, impair mitochondrial function, induce apoptosis, and promote toxic processes in part through oxidative stress [54]. Additional support for this link appears in the role of inflammation (which is closely associated with oxidative stress) during the initiation and progression of neurodegenerative diseases [8].

Inflammatory responses

During neurotoxic effects, inflammatory pathways are triggered by pro-inflammatory mediators, including interleukins, tumor necrosis factor-alpha (TNF-α), and interferons [55]. These stressors activate specific kinase cascades through altered signaling pathways, leading to the translocation and binding of nuclear factors to target gene promoters [56]. This prompts the expression of genes responsible for producing additional inflammatory mediators [57]. The ensuing neuroinflammatory response attempts to restore central nervous system homeostasis and facilitate tissue repair; however, excessive or prolonged inflammatory processes can exacerbate damage and contribute to cell death [58]. The activation of microglial cells and astrocytes is a pivotal event in neuroinflammation associated with mitochondrial dysfunction, marking an early response to various brain insults [2].

Biomarkers of oxidative stress

The presence and levels of markers indicative of oxidative stress can be evaluated by analyzing biological materials [59]. Commonly assessed products include oxidatively modified lipids, proteins, and nucleic acids [1]. Mitochondria serve as the principal site for cellular energy production via ATP synthesis and participate significantly in the generation of reactive oxygen species (ROS) [60]. Dysfunctional mitochondria, which are enriched with redox-active enzymes, become a major source of intracellular ROS and consequent oxidative damage [13]. Consequently, strategies aimed at modulating mitochondrial function may offer therapeutic potential in mitigating oxidative stress-related neurodegenerative processes [2].

Measurement techniques

The measurement of oxidative stress markers in biological samples can be important in the diagnosis of diseases, such as Alzheimer's disease, as levels of some of these markers, including isoprostanes and 8-OHdG, vary during disease development and progression [61]. They may also be useful in evaluating the nutritional and pharmacological management of diseases associated with oxidative stress [13].

Assays of antioxidant enzyme activities have shown that enzyme markers can decrease during oxidative stress, since excess oxidative stress may lead to the accumulation of inactivated forms of the antioxidant proteins [62]. However, levels of antioxidant enzyme activities may also increase, which could reflect a cellular response to oxidative stress or the induction of antioxidant protein expression by activation

of the Keap1/Nrf2/ARE pathway [62]. Measurement of the levels of reduced glutathione is a widely used approach for identifying both oxidative stress and mitochondrial dysfunction [63]. Reduced glutathione may be depleted following oxidative damage and mitochondrial impairment, so that ratios of reduced glutathione to oxidised glutathione are commonly used as a measurement of overall cellular redox status [64]. However, such measurements cannot discriminate between oxidative stress arising from vicious cycles of mitochondrial damage or that induced by other cellular sources [65].

Clinical implications

An obstacle for the development of efficacious treatments for neurodegenerative diseases is the lack of sensitive and specific clinical biomarkers [66]. The oxidation of biomolecules provides feasible candidates, but interpretations are not always straightforward [67]. Lipids such as malondialdehyde or 4-hydroxynonenal (4-HNE) can be assessed in plasma or urine and changes may relate to alterations to brain lipid status [68]. Similarly, the measurement of DNA oxidation products such as 8-oxo-guanine (8-oxoG) may reflect a global increase in oxidative stress across tissues and mitochondria [69]. Protein oxidation markers such as 3-nitrotyrosine and the activity of enzymes such as superoxide dismutase can also be used to support a diagnosis [70].

Conclusion

The relationship between oxidative stress, mitochondrial dysfunction, and neuronal damage has been demonstrated in vitro and in vivo following intentional neurotoxic exposure [71]. The brain's natural susceptibility to oxidative injury arises from its high oxygen consumption, low antioxidant defenses, and vulnerability of neural lipids to oxidation [2]. Accumulated reactive oxygen species (ROS) damage mitochondria, activate neuroinflammatory cascades, and increase the permeability of the blood-brain barrier, thereby intensifying neuronal injury [31]. Neurons are particularly sensitive to ROS-induced damage because their energy metabolism depends heavily on mitochondrial function [72]. When this function is disrupted, neuronal homeostasis, energy supply, and synaptic plasticity all suffer, ultimately driving the neurodegeneration process [73].

Under oxidative pressure, ROS can induce mitochondrial DNA mutations and damage components of the respiratory chain, altering membrane permeability, calcium homeostasis, and defense systems in ways that culminate in neuronal dysfunction [13]. Given the centrality of oxidative stress to neurotoxicity, many studies focus on identifying biomarkers for its quantification [25]. Measuring levels of compounds such as peroxides, aldehydes, ketones, protein carbonyls, and 8-hydroxy-2-deoxyGuanosine (8-OHdG) in biological fluids has attracted considerable interest because these analytes have the potential to track the initiation and evolution of neurotoxic impairment [74].

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