Oxidative Stress and Mitochondrial Dysfunction

Subjects: Clinical Neurology

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Since impaired mitochondria are a major source of reactive oxygen species (ROS), oxidative stress is closely linked to mitochondrial dysfunction and has been assumed to be the principal molecular mechanism for the pathogenesis of various diseases, especially neurodegenerative disorders. Molecular imaging reflecting oxidative stress has improved our insights into the pathological mechanisms of diseases associated with mitochondrial dysfunction, and is a promising tool for monitoring further antioxidant therapies.

Keywords: oxidative stress ; mitochondrial dysfunction ; molecular imaging ; positron emission tomography ; neurodegenerative disorders

1. Oxidative Stress Caused by Reactive Oxygen Species

Oxidative stress is classically defined as an imbalanced redox state in which the oxidation effect caused by increased production of reactive oxygen species (ROS) exceeds the defense capacity of the antioxidant mechanism [1]. Enhanced oxidative stress due to excess ROS generation leads to oxidative damage to the cellular components, such as proteins, lipids, and DNA. Additionally, ROS change the expression of nuclear factor kappa B (NF-κB), a transcription factor responsible for inducing inflammation and apoptosis [2]. These ROS-induced pathological mechanisms provoke tissue and organ dysfunction, especially neuronal degeneration in the brain [3][4]. ROS such as superoxide (O_2^-), hydroxyl radical (OH), and hydrogen peroxide (H_2O_2), are derived from molecular oxygen by the reduction. In particular, superoxide and hydroxyl radical are classified as free radicals, which show high chemical reactivity due to their unpaired electrons [5]. ROS are endogenously produced in the mitochondria, peroxisomes, and endoplasmic reticulum of cells [6]. Among these organelles, mitochondria, which consume more than 90% of intravital oxygen during oxidative phosphorylation (i.e., the aerobic metabolism), are regarded as the principal endogenous source of ROS [7][8]. However, under a healthy condition with normal mitochondrial function, the amount of ROS leakage is so small that it can be eliminated by the endogenous biological antioxidants, such as superoxide dismutase (SOD) and glutathione (GSH) [1][9].

2. Mitochondria as a Major Source of Reactive Oxygen Species

The mitochondrion is an organelle that produces adenosine triphosphate (ATP) as energy essential for life activities using the intrinsic respiratory chains. In the mitochondrial respiratory chains (a.k.a. electron transport chains), which consist of five complexes (i.e., complex I-V), electrons obtained as the reduced form of nicotinamide adenine dinucleotide (NADH) from the metabolism of glucose (i.e., glycolysis), free fatty acids (i.e., β-oxidation), and the tricarboxylic acid cycle are transported to synthesize ATP [5][10][11]. Most of the transferred electrons are ultimately captured by oxygen in the four-electron reduction whereby electrons and oxygen are detoxified to harmless and stable water molecules [12]. However, in respiratory chain impairment due to mitochondrial dysfunction, deteriorated electron transport provokes excessive accumulation of electrons relative to the amount of oxygen, resulting in an over-reductive state [13][14]. Because ROS are produced by the reduction of molecular oxygen, redundant electrons that leak from the impaired respiratory chains in an over-reductive state readily react with oxygen, which generates ROS [15][16]. A total of nine sites have been identified as the sources of mitochondrial ROS; complex I produces superoxide solely in the matrix, while complex III generates superoxide in both the matrix and the intermembrane space [17]. As explained above, mitochondrial respiratory chain impairment provokes an over-reductive state, and this state under the normoxic condition results in oxidative stress, which suggests that the evaluation of an over-reductive state using molecular imaging would be a promising marker for oxidative stress [18][19][20].

3. Oxidative Stress Based on Mitochondrial Dysfunction in Neurodegenerative Disorders

As mentioned above, mitochondrial respiratory chain impairment causes oxidative stress due to an over-reductive state, in addition to an ATP production deficit [15]. Since mitochondria are distributed throughout the body, mitochondrial dysfunction may cause failures of various organs. In particular, the brain consumes 20% of intravital oxygen and has a relatively fragile antioxidant capacity [21][22], which underlies the vulnerability of the neurons and glial cells to oxidative stress due to mitochondrial dysfunction [8][23]. Besides reduced respiratory capacity of mitochondria, there are other possible causes of oxidative stress in the brain, e.g., neuroinflammation, protein aggregation, and decreased antioxidant defenses [4][24]. Aging is also a major factor in promoting these pathological mechanisms, especially decreased mitochondrial function and antioxidant potential, leading to the enhancement of cerebral oxidative stress in elderly people [25]. These factors explain why the prevalence of neurodegenerative disorders increases with advancing age, and many pathological and biochemical studies have demonstrated enhanced oxidative stress in various neurodegenerative disorders [26][27]. Interestingly, basic studies showed that aggregated misfolded proteins induce mitochondrial dysfunction and ROS generation [28][29]. Conversely, ROS may facilitate neurotoxic protein aggregation, such as amyloid-β (in Alzheimer's disease), α-synuclein (in Parkinson’s disease), and SOD1 (in amyotrophic lateral sclerosis (ALS)), as well as mitochondrial impairment, producing a vicious cycle among oxidative stress, mitochondrial dysfunction and protein aggregation [30][31]. These findings may indicate that the increase in ROS production precedes the appearance of plaque deposits and that mitochondrial dysfunction can be an early event that precedes protein aggregation in neurodegenerative disorders. [26][32][33]. Recent studies with positron emission tomography (PET) delineated enhancement of oxidative stress in brain regions of pathologically responsible sites of neurodegeneration in living patients, i.e., the stroke-like lesions of mitochondrial disease (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes: MELAS), the striatum of Parkinson’s disease, and the motor and motor-related cortices of ALS, suggesting that oxidative stress based on mitochondrial dysfunction is closely associated with the neurodegenerative process in these diseases [34][18][19][20]. PET imaging for oxidative stress improves our insight into the pathogenesis of neurodegenerative disorders, and is a promising tool for monitoring further antioxidant and mitochondrial therapies [35].

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