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Oxidative stress, mitochondrial dysfunction and cellular stress response in Friedreich's ataxia

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Abstract

There is significant evidence that the pathogenesis of several neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, Friedreich's ataxia (FRDA), multiple sclerosis and amyotrophic lateral sclerosis, may involve the generation of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) associated with mitochondrial dysfunction. The mitochondrial genome may play an essential role in the pathogenesis of these diseases, and evidence for mitochondria being a site of damage in neurodegenerative disorders is based in part on observed decreases in the respiratory chain complex activities in Parkinson's, Alzheimer's, and Huntington's disease. Such defects in respiratory complex activities, possibly associated with oxidant/antioxidant imbalance, are thought to underlie defects in energy metabolism and induce cellular degeneration.

The precise sequence of events in FRDA pathogenesis is uncertain. The impaired intramitochondrial metabolism with increased free iron levels and a defective mitochondrial respiratory chain, associated with increased free radical generation and oxidative damage, may be considered possible mechanisms that compromise cell viability. Recent evidence suggests that frataxin might detoxify ROS via activation of glutathione peroxidase and elevation of thiols, and in addition, that decreased expression of frataxin protein is associated with FRDA. Many approaches have been undertaken to understand FRDA, but the heterogeneity of the etiologic factors makes it difficult to define the clinically most important factor determining the onset and progression of the disease. However, increasing evidence indicates that factors such as oxidative stress and disturbed protein metabolism and their interaction in a vicious cycle are central to FRDA pathogenesis. Brains of FRDA patients undergo many changes, such as disruption of protein synthesis and degradation, classically associated with the heat shock response, which is one form of stress response. Heat shock proteins are proteins serving as molecular chaperones involved in the protection of cells from various forms of stress.

In the central nervous system, heat shock protein (HSP) synthesis is induced not only after hyperthermia, but also following alterations in the intracellular redox environment. The major neurodegenerative diseases, Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disease (HD) and FRDA are all associated with the presence of abnormal proteins. Among the various HSPs, HSP32, also known as heme oxygenase I (HO-1), has received considerable attention, as it has been recently demonstrated that HO-1 induction, by generating the vasoactive molecule carbon monoxide and the potent antioxidant

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta-peptide; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease; MS, multiple sclerosis; PD, Parkinson's disease; ARE, antioxidant responsive element; AP-1, activator protein-1; JNK, c-jun N-terminal kinase; CNS, central nervous system; CO, cytochrome oxidase; CAPE, caffeic acid phenylethyl ester; ETC, electron transport chain; GPX, glutathione peroxidase; HSP, heat shock protein; NOS, nitric oxide synthase; NFkB, nuclear factor kappa-B; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; ND, NADH dehydrogenase; 8-OH-dG, 8-hydroxy-deoxyguanosine; GSH, reduced glutathione; GSSG, oxidized glutathione; MPTP, *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MRS, magnetic resonance spectroscopy; ROS, reactive oxygen species; RNS, reactive nitrogen species; SAPK, stress-activated protein kinase; SN, substantia nigra; SOD, superoxide dismutase.

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bilirubin, could represent a protective system potentially active against brain oxidative injury. Given the broad cytoprotective properties of the heat shock response there is now strong interest in discovering and developing pharmacological agents capable of inducing the heat shock response. This may open up new perspectives in medicine, as molecules inducing this defense mechanism appear to be possible candidates for novel cytoprotective strategies. In particular, manipulation of endogenous cellular defense mechanisms, such as the heat shock response, through nutritional antioxidants, pharmacological compounds or gene transduction, may represent an innovative approach to therapeutic intervention in diseases causing tissue damage, such as neurodegeneration.

Keywords: Oxidative stress; FRDA pathogenesis; MR spectroscopy; Cell stress response

1. Introduction

There is increasing evidence for mitochondrial involvement in neurodegenerative diseases including Alzheimer's and Parkinson's diseases, ALS, MS and FRDA. A mutation, whether inherited or acquired, leads to impaired electron transport chain (ETC) functioning [1]. Impaired electron transport, in turn, leads to decreased ATP production, increased formation of toxic free radicals, and altered calcium homeostasis. These toxic consequences of ETC dysfunction may sustain further mitochondrial damage, including oxidation of mitochondrial DNA, proteins, and lipids, and opening of the mitochondrial permeability transition pore, an event associated with cell degeneration and death [2]. There is evidence to support that oxidative stress alters the expression of antioxidant enzymes and enhances expression and/or DNA binding of numerous transcription factors, including AP-1, fos, jun, myc, erg-1, SAPK and NFkB [3]. Moreover, it is well known that brain cells are continually challenged by conditions which may cause acute or chronic stress. To adapt to these environmental changes and survive different types of injuries, a network of different responses have evolved which sense and control diverse forms of cellular stress. One of these responses, the heat shock response, has emerged as a fundamental mechanism necessary for cell survival under a variety of unfavorable conditions [4]. In the central nervous system (CNS), heat shock protein (HSP) synthesis is induced not only after hyperthermia, but also following alterations in the intracellular redox environment, exposure to heavy metals, amino acid analogs or cytotoxic drugs [5,6]. While prolonged exposure to conditions of extreme stress is harmful and can lead to cell death, induction of HSP synthesis can result in stress tolerance and cytoprotection in a variety of metabolic disturbances and injuries, including hypoxia, stroke, epilepsy, cell and tissue trauma, neurodegenerative disease and aging [3,7]. This has opened new perspectives in medicine, as molecules activating this defense mechanism appear to be possible candidates for novel cytoprotective strategies. However, although activation of stress tolerance signaling, leading to protective nuclear responses, (such as increased expression of heat shock proteins, antioxidant enzymes and Bcl-2) may be triggered to withstand all the above mentioned pathogenic changes, a vicious cycle of increasing oxidative damage may insidiously develop over a period of years inducing progressive degenerative cell alterations and death [8].

CNS has a large potential oxidative capacity [2] due to the high level of tissue oxygen consumption. However, the ability of the brain to withstand oxidative stress is limited because of: (a) a high content of easily oxidizable substrates, such as polyunsaturated fatty acids and catecholamines; (b) relatively low levels of antioxidants such as glutathione and vitamin E and antioxidant enzymes (such as glutathione peroxidase, catalase and superoxide dismutase); (c) the endogenous generation of reactive oxygen free radicals via several specific reactions; (d) the elevated content of iron in specific areas of the human brain, such as *globus pallidus* and *substantia nigra* (SN), while cerebrospinal fluid has very little iron-binding capacity owing to its low content of transferrin; (e) CNS contains non-replicating neuronal cells which, once damaged, may be permanently dysfunctional or committed to programmed cell death (apoptosis). Moreover, it is becoming increasingly clear that the mitochondrial genome may play an essential role in neurodegenerative diseases, such as FRDA [9]. It is generally recognized that, in addition to the nuclear genome, each human cell contains multiple copies of a small double-stranded mitochondrial genome. Mitochondrial DNA disorders present tissue specificity, characterized by the fact that even if a mitochondrial DNA mutation is present in all tissues, only some will be affected and express a pathology. Due to the coexistence in cells of both normal and mutated mtDNA, (a situation termed heteroplasmy), the levels of mutation can vary considerably between mitochondria, cells and even tissues. The precise sequence of events in FRDA pathogenesis is uncertain. However, impaired intramitochondrial metabolism associated with increased free iron and the consequent oxidative stress are being considered as a possible pathogenic mechanism. There is now evidence to suggest that frataxin might detoxify ROS via activation of glutathione peroxidase and elevation of thiols [10] and, in addition, that decreased expression of frataxin protein is associated with FRDA [11]. In the present review, we discuss the role of energy thresholds in brain mitochondria and its implications in neurodegeneration. We then review the evidence for the role of oxidative stress in mediating the effects of mitochondrial DNA mutations on brain age-related disorders and, particularly, the oxidative stress