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Review

Modulation of mitochondrial dysfunction in neurodegenerative diseases *via* activation of nuclear factor erythroid-2-related factor 2 by food-derived compounds

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ABSTRACT

Oxidative stress and mitochondrial dysfunction are early events in the pathogenesis of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS). Mitochondria are important key players in cellular function based on mitochondrial energy production and their major role in cell physiology. Since neurons are highly depending on mitochondrial energy production due to their high energy demand and their reduced glycolytic capacity mitochondrial dysfunction has fatal consequences for neuronal function and survival. The transcription factor nuclear factor erythroid-2-related factor 2 (Nrf2) is the major regulator of cellular response to oxidative stress. Activation of Nrf2 induces the transcriptional regulation of antioxidant response element (ARE)-dependent expression of a battery of cytoprotective and antioxidant enzymes and proteins. Moreover, activation of Nrf2 protects mitochondria from dysfunction and promotes mitochondrial biogenesis. Therefore, the Nrf2/ARE pathway has become an attractive target for the prevention and treatment of oxidative stress-related neurodegenerative diseases. Small food-derived inducers of the Nrf2/ARE pathway including L-sulforaphane from broccoli and isoliquiritigenin from licorice displayed promising protection of mitochondrial function in models of oxidative stress and neurodegenerative diseases and represent a novel approach to prevent and treat aging-associated neurodegenerative diseases.

Contents

Abbreviations: 3-NPA, 3-nitropropionic acid; 6-OHDA, 6-hydroxy dopamine; AD, Alzheimer's disease; AIF, apoptosis inducing factor; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; Aß, β-amyloid peptide; CA, *trans*-cinnamaldehyde; Cat, catalase; CBP, cAMP-response-element binding protein (CREB) binding protein; CEppt, aqueous cinnamon extract; CGA, chlorogenic acid (5-*O*-caffeoylquinic acid); CoQ, coenzyme Q; CREB, cAMP-response-element binding protein; C-SLNs, curcumin encapsulated solid lipid nanoparticles; Cytc, cytochrome c; DGC, dehydroglyasperin C; Drp1, dynamin related protein 1; FAD, familial Alzheimer's disease; FIS1, fission protein 1; Gcl, glutamate cysteine ligase; Gen, genistein; Gpx, glutathione peroxidase; Gr, glutathione reductase; GSH, glutathione; GSSG, glutathione dimer; Gst, glutathione-*S*-transferase; HD, Huntington's disease; HO-1, heme-oxygenase 1; IDC, instant decaffeinated coffee; IMM, inner mitochondrial membrane; ISL, isoliquiritigenin; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH associated protein 1; Mfn1/2, mitofusin 1/2; MMP, mitochondrial membrane potential; MnSOD, manganese superoxide dismutase; MPP^+, 1-methyl-4-phenyl-pyridinium ion; mPTP, mitochondrial permeability transition pore; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Neh, Nrf2-ECH homologues; NO, nitric oxide; Nqo1, NAD(P)H:quinone oxidoreductase-1; Nrf2, nuclear factor erythroid-2-related factor 2; OMM, outer mitochondrial membrane; Opa1, optic atrophy 1; PC12, rat pheochromocytoma; PD, Parkinson's disease; PGC-1α, proliferator-activated receptor γ coactivator alpha; PINK1, phosphatase and tensin homolog–induced putative kinase 1; ROS, reactive oxygen species; RNS, reactive nitrogen species; SAC, *S*-allyl-L-cysteine; SFN, L-sulforaphane; shNrf2, shRNA targeting the Nrf2 gene; shNT, not targeting shRNA; SNP, sodium nitroprusside; SOD, superoxide dismutase; tBHP, tert-butyl hydroperoxide; XN, xanthohumol.

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1. Introduction: mitochondrial dysfunction and oxidative stress as common features in neurodegenerative diseases

Most prominent neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) share several dysfunctions including oxidative stress and mitochondrial dysfunction [1–3]. Mitochondria are very specialized organelles that are of great importance not only for energy production but also for cell physiology. Impairment of mitochondrial function is observed in several disorders, including cancer, chronic inflammation, metabolic disorders and neurodegenerative diseases among others AD, PD, HD and ALS [4–8]. The accumulation of reactive oxygen species (ROS), byproducts of the mitochondrial energy production primarily derived from complexes I and III of the respiratory chain (Fig. 1) leads to oxidation of important macromolecules such as lipids, proteins and nucleic acids [9–12]. A notable decrease of complex I activity during normal brain aging has been reported, whereas the activity of complex III remains almost unchanged [11–13]. This suggests the major part of complex I in brain aging progress and the pathogenesis of neurodegenerative diseases. As important key players of cellular function mitochondria are responsible for the generation of energy *via* the respiratory chain which is located in the inner mitochondrial membrane and consists of four membrane spanning complexes which are functionally connected by two mobile electron carriers and the ATP-Synthase (Fig. 1) [14]. As electrons are transferred along these complexes a fixed number of protons are pumped from the matrix into the inner membrane space setting up an electrochemical gradient (Ψm) referred to as mitochondrial membrane potential (MMP) (Fig. 1). This redox energy drives the oxidative phosphorylation of adenosine diphosphate (Fig. 1). Especially neurons are highly depending on the mitochondrial ATP production due to their high energy demand and reduced glycolytic capacity [15–17]. Deficiency and reduced activity of respiratory chain complexes resulting in decreased MMP and ATP production are strongly associated with neurodegenerative diseases including AD, PD, HD and ALS [2].

Impaired function of the mitochondrial permeability transition pore (mPTP) (Fig. 1) represents a common feature in neurodegenerative diseases including AD, PD, HD and ALS [18–21]. Opening of the mPTP can be triggered by several effectors, including calcium ions, free fatty acids, ROS and reactive nitrogen species (RNS) resulting in the release of proapoptotic proteins like cytochrome c (Cytc) and apoptosis inducing factor (AIF) which active caspases 3 and 9 finally leading to apoptosis [22–25]. Therefore, impairment and consequently dysfunction of mitochondria have a major impact on neuronal function and are suggested to play a crucial role in the pathophysiology of neurodegenerative diseases [26–32].

Mitochondria are dynamic organelles capable of migrating, fusion and fission. Mitochondrial dynamics are important for mitochondrial quality control including energy metabolism, content of mitochondrial DNA and the number and shape of mitochondria inside the cell. The intact regulation of these mechanisms is critical for ordinary cell function [33]. Moreover, it has been reported, that these dynamics are important for the control of cell death, organelle distribution and mitophagy (Fig. 1) [34]. An impaired balance between fission and fusion processes is associated with common neurodegenerative diseases including PD and AD [35,36]. Mitochondrial fission is controlled by the cytosolic protein dynamin-related protein 1 (Drp1) and by the mitochondrial protein fission protein 1 (FIS1) [37–39] (Fig. 1). In contrast, mitochondrial fusion requires the recruitment of the proteins mitofusin (Mfn) 1 and 2 for fusion of the outer mitochondrial membrane (OOM) whereas optic atrophy 1 (Opa1) is required for fusion of the inner mitochondrial membrane (IMM) [40,41] (Fig. 1). Amyloid beta (Aβ) overproduction induces an imbalance in mitochondrial fission and fusion processes by affecting the levels of Drp1, Opa1, Mfn1/2 in postmortem brains of AD patients resulting in mitochondrial fragmentation and impaired mitochondrial distribution inside neurons [42,43]. Excessive mitochondrial fragmentation induced by alterations in Drp1 can also be seen in cell models of PD [36]. Furthermore, interaction of mutant huntingtin with Drp1 causes excessive fragmentation of mitochondria in HD [6]. A tipped balance of mitochondrial dynamics towards increased fission processes an also be seen in models of ALS [44]. Moreover, besides impaired mitochondrial dynamics mitophagy (Fig. 1) the process of removing damaged and dysfunctional mitochondria is also disturbed in neurodegenerative diseases including AD, PD, HD and ALS [45].

Enhanced antioxidant activity has been reported to lower the risk of neurodegenerative diseases [46–48]. Therefore, in recent years the idea of utilizing compounds with mitochondrial protective properties for the treatment of neurodegenerative diseases has emerged [14,49–51]. Several constituents of vegetables such as L-sulforaphane (SFN) from broccoli or ingredients of spices