Neurochemical Research (2019) 44:2273–2279
https://doi.org/10.1007/s11064-018-02711-2

ORIGINAL PAPER

Nrf2/ARE Pathway as a Therapeutic Target for the Treatment of Parkinson Diseases

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Received: 8 November 2018 / Revised: 20 December 2018 / Accepted: 24 December 2018 / Published online: 7 January 2019

Abstract

Instead of the progress in the understanding of etiology of Parkinson's disease (PD), effective methods to prevent the progression of the disease have not been developed and only symptomatic treatment is currently possible. One of possible pathways to slow the progression of the disease is protection of dopaminergic neurons by maintaining mitochondrial quality control in neuron cells. Recent studies showed that the most promising target for pharmacological effects on mitochondria is the Nrf2/ARE signaling cascade. It participates in the maintenance of mitochondrial homeostasis, which is provided by an optimal ratio in the processes of mitochondrial biogenesis and mitophagy, as well as the optimal ratio of ROS production and ROS scavenging. Nrf2 activators are capable of modulating these processes, maintaining mitochondrial homeostasis in neurons. In addition, Nrf2 can synergistically interact with other transcription factors, for example, PGC-1a in the regulation of mitochondrial biogenesis and YY1 with the increase of antioxidant defense. All this makes Nrf2 an optimal target for drugs that could support the mitochondrial quality control, which, in combination with antioxidant protection, can significantly slow down the pathogenesis of PD. Some of these compounds have undergone laboratory studies and are at the stage of clinical trials now.

Keywords Parkinson disease · Nrf2 · Mitochondrial biogenesis · Mitophagy · Mitochondrial quality control

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease, characterized by the loss of dopaminergic neurons in the *substantia nigra pars compacta*. It results in tremors, rigidity, and bradykinesia [1]. The cause of this disease is complex and consists of genetic and environmental factors. The hereditary form of PD is associated with mutations of the genes encoding enzymes that function in mitochondria and are directly or indirectly associated with the functioning of mitochondria [2].

Various toxins, inflammatory processes that affect the mitochondria of dopaminergic neurons, result in increased production of ROS (reactive oxygen species), disturbed calcium homeostasis, damaged mtDNA and disrupted interaction between the nuclear and mitochondrial genomes [3]. It is well established that ROS overproduction and suppression of antioxidant defense is a cause of neuron death [4]. In this regard, the *substantia nigra* of PD patients contains higher levels of oxidized cell component as well as lower levels of antioxidant, in particular reduced glutathione [5]. The strategy of using antioxidants for therapy was repeatedly demonstrated for most ROS-induced diseases such as cancer [6], diabetes [7], infectious diseases [8], but not for neurological diseases. Despite the fact that there are encouraging data on the effectiveness of some plant antioxidants, it is too early to speak about perspectivity of this approach to the therapy of PD [9]. At the moment, treatment is mainly symptomatic. The therapy is based on a dopamine replacement with L-dopa, which often has a number of adverse effects [10].

In recent years, a deeper study of the functioning of mitochondria suggests that the basis of most neurodegenerative processes is a malfunction of the mitochondrial quality control. There is a mismatch of complexly synchronized processes of mitochondrial biogenesis and mitophagy, fission and fusion. In this review, we focused on a discussion of

Special Issue: In honour of Professor Vera Adam-Vizi.

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the regulation mechanism of mitochondrial biogenesis and mitophagy in terms of the pathogenesis of PD, as well as the possibility of pharmacological slowing the progression of the disease by maintaining mitochondrial quality control.

Antioxidant Defense

The Nrf2/ARE (NF-E2-related factor 2/antioxidant responsive element) signaling cascade is a key node that maintains intracellular homeostasis, protects cells from dangerous chemical agents by inducing the expression of phase II detoxifying and oxidative-stress responsive genes. Nrf2 (encoded by *NFE2L2* gene) is a short-lived protein that is subjected to continuous ubiquitination and proteasomal degradation. There are three known ubiquitin ligase systems that contribute to the degradation of Nrf2: Kelch-like ECH-associated protein1 (Keap1); glycogen synthase kinase (GSK3β) and E3 ubiquitin ligase Hrd1 [11] (Fig. 1). All activators have electrophilic properties and abilities to modify SH groups in Keap1 by alkylation, oxidation, or reduction [12]. When the interaction between Nrf2 and ubiquitin ligase systems is disturbed, Nrf2 is transported into the cell nucleus and binds to the ARE region of target genes. These are classically considered to be antioxidant genes, however, in recent years, the number of studies showing a wider involvement of Nrf2 in the regulation of various functions increased. Some of them are directly or indirectly associated with the pathogenesis of PD.

The Nrf2-dependent antioxidant protection of neurons in various PD models was studied in detail. Nrf2 regulates expression of heme oxygenase-1 (*HO-1*) [13], NAD(P)H:quinone oxidoreductase-1 (*NQO1*) [14], sulfiredoxin-1 (*SRXN1*) [15], superoxide dismutase 2 (*SOD2*) [16], peroxiredoxins 3 and 5 (*PRDX3* and *PRDX5*) [17], enzymes involved in GSH metabolism: glutathione S-transferases [18], glutathione-synthesizing enzymes glutamate-cysteine ligase catalytic subunit (*GCLC*) and glutamate-cysteine ligase modifier subunit (*GCLM*) [19] directly. The fact that, Nrf2-dependent signaling cascades play a key role during PD was well illustrated by a microchip analysis of various tissues of patients with PD and Alzheimer's disease. The patients showed a decrease in expression of 31 genes that contain the ARE-sequences in the promoter. At the same time, the expression of Nrf2 was increased in all samples [20].

In addition to direct regulation of antioxidant enzymes, Nrf2 can have an indirect effect on the antioxidant status of neurons in PD. In particular, this refers to the transport of ascorbate. It is known that the level of ascorbate in complex therapy with L-dopa improves the clinical symptoms of PD, by enhancement of drug absorption processes [21]. The transport of ascorbate into neurons depends on the ascorbate

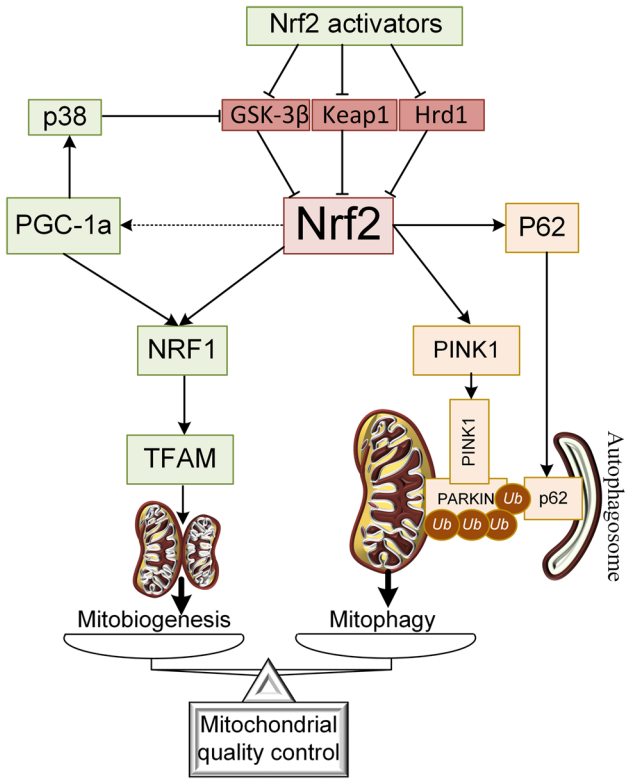

Fig. 1 A scheme that illustrates maintaining of mitochondrial quality control by Nrf2. Nrf2 is negatively regulated by at least three systems: GSK-3β; Keap1 and Hrd1. Nrf2 activators disrupt the interaction with these negative regulators and contribute to the activation of mitochondrial biogenesis and mitophagy. Maintaining the balance between these two processes ensures the maintenance of the mitochondrial quality control required for survival of dopaminergic neurons and slowing down the pathogenesis of Parkinson disease

carrier SVCT2 [22], the expression of which depends on the transcription factor Yin Yang 1 (YY1) [23]. Recent studies indicate a synergistic interaction between Nrf2 and YY1 [24].

Urate is one of the most perspective pharmaceutical activators of Nrf2. It is known that the level of urate is reduced significantly in serum and cerebrospinal fluid during PD [25]. Earlier it was shown that urate itself is a strong antioxidant [26], scavenger of peroxynitrite [27] and stabilizer of ascorbate [25]. Cell treatment with urate leads to Nrf2 activation and demonstrate neuroprotective effects against 6-OHDA toxicity [28]. Currently inosine (the precursor of urate) is on the 3rd stage of clinical trials for the PD treatment [29]. Another classic Nrf2 dimethyl fumarate activator is at the 4th stages of clinical trials for the treatment of another neurodegenerative disease—multiple sclerosis [30]. These studies give us hope that drugs that slow down the pathogenesis of PD may soon appear by maintaining a mitochondrial quality control and maintaining the functional activity of antioxidant defense of dopaminergic neurons.

Mitochondrial Biogenesis

Regulation of a number of mitochondria is controlled by transcription factors encoded by the nuclear genome. The best described and studied regulation factor is PGC-1α, the so-called "master regulation of mitochondrial biogenesis". PGC-1α (encoded by *PPARGC1A* gene) was discovered as the coregulator of PPARγ, a transcription factor expressed in brown adipose tissue during cold exposure and mediating adaptive thermogenesis. It was the reason for the name PGC-1α—PPAR-gamma-coactivator-1α [31]. It was later shown that PGC-1α can interact with nuclear respiratory factors NRF1 and NRF2 [32]. NRF1 binds to specific sites of promoter regions and regulates the expression of the mitochondrial respiratory chain subunits [33] and transcription factor A, mitochondrial (TFAM) [34]. TFAM provides the unwinding and bending of the DNA structure necessary for the binding of POLRMT (RNA Polymerase Mitochondrial) to mtDNA promoters [35].

It was shown that the level of PGC-1α in brain samples from humans with PD compared to the non-diseased individuals decreases, which coincides with a decrease in the downstream factors of mitochondrial biogenesis (TFAM, NRF1) and genes encoded by mtDNA [36]. PGC-1α levels decreased during MPP^+ exposure (PD model), while Δ9-THC, which is a PPARγ agonist, is able to restore mtDNA levels [37].

In recent years, the number of studies showing the key role of the Nrf2/ARE signaling cascade in the regulation of mitochondrial biogenesis has increased significantly. In 2008, the study of Piantadosi et al. showed the role of Nrf2 in the activation of mitochondrial biogenesis and demonstrated that the promoter of the *NRF1* gene contains 4 ARE, with which Nrf2 binds. In addition, authors showed that H_2O_2 stabilizes Keap1 and provides Nrf2 translocation to the nucleus. In parallel, H_2O_2 led to the oxidation of phosphatase and tensin homolog (PTEN). After oxidation of PTEN, Akt/PKB (protein kinase B) phosphorylates and thereby deactivates GSK3β, which leads to the translocation of Nrf2 into the nucleus, where it binds to the ARE regions of the *NRF1* promoter [38].

Over the last 3 years, studies showing the role of Nrf2 in mitochondrial biogenesis in PD have appeared. With MPTP-induced PD dimethyl fumarate and monomethyl fumarate violated the interaction of Keap1-Nrf2 by alkylation of Keap1 cysteine residues, which leads to the translocation of Nrf2 from the cytoplasm to the nucleus, which contributes to the activation of mitochondrial biogenesis. It was confirmed by an increase in the content of mtDNA, protein expression of ETC complexes, genes involved in replication and transcription of mtDNA. It is worth noting that these effects were absent in $Nrf2^{-/-}$ knockouts [39]. Moderate exercise can activate Nrf2 and prevent the development of Parkinsonism due to the activation of mitochondrial biogenesis and the antioxidant system of mitochondria. It was shown on MPP^+ [40] and 6-OHDA [41] PD models.

Interaction between PGC-1α and Nrf2 is poorly investigated. On the one hand, there is evidence that PGC-1α can activate Nrf2 and heterozygous $PPARGC1A^{+/-}$ mice showed a decrease in the expression of antioxidant genes due to the disruption of the interaction of Nrf2 with the ARE region [42]. PGC-1α was shown to positively regulate p38, which inactivates GSK3β and therefore activates Nrf2 [43]. However, there is an assumption that the expression of PGC-1α is dependent on Nrf2, since the PGC-1α promoter contains two ARE regions [44]. Knockout of the $NFE2L2^{-/-}$ gene prevents mitochondrial biogenesis and reduces the expression of *PPARGC1A* in various tissues [45–47].

Mitophagy

Another important process that supports the optimal mitochondrial mass in a cell is mitochondrial autophagy, or mitophagy. During excessive activation of biogenesis and delayed mitophagy, a large number of mitochondria are accumulated in the cell, which can lead to excessive production of ROS. Increased oxidative stress leads to damage and mutations in mtDNA. In the absence of elimination, damaged mitochondria begin to accumulate in the cell, which can lead to activation of apoptotic processes. In addition, accumulation of mutations in mtDNA is possible, which leads to the development of various mitochondrial diseases associated with heteroplasmy [48].

The hereditary form of PD is associated primarily with mutations in the *PARK2* (encoding PARKIN) [49] and PTEN-induced kinase 1 (*PINK1*) genes [50], mediating mitophagy. When mitochondria are damaged, the inner membrane depolarizes, which affects the TIM-mediated protein import. As a result, the PINK1 protein does not penetrate in the mitochondrial matrix, where it is usually degraded. Therefore, the PINK1 protein accumulates on the outer mitochondrial membrane, which leads to the activation of PARKIN. PARKIN is a cytosolic E3-ubiquitin ligase. Ubiquitination of a number of proteins triggers mitophagy [51].

There is a direct crosstalk between Nrf2 and PINK1 due to the fact that Nrf2 can regulate the expression of *PINK1*, since four ARE regions were detected in the promoter of this gene [52]. Thus, activation of Nrf2 can directly regulate mitophagy. It was later shown that the use of MitoQ and melatonin can lead to the coactivation of Nrf2 and PINK1 [53, 54]. There are data showing that PARKIN can directly interact with TFAM and mtDNA, contributing to the

activation of transcription of the mitochondrial genome and maintaining mitochondrial biogenesis [55, 56].

Another key molecule of mitophagy regulation is p62/SQSTM1 (Sequestosome 1). Recently, it was demonstrated that p62/SQSTM1 penetrates mitochondria via PINK1-independent pathways [51]. P62/SQSTM1 acts as an adapter molecule that directly interacts with ubiquitinated molecules with an autophagosome. Knockout p62/SQSTM1 does not participate in the mitochondrial translocation of PARKIN, but completely blocks the final clearance of damaged mitochondria [57].

Recently, regulation of p62/SQSTM1 expression was shown to be partially controlled by the transcription factor Nrf2, due to the presence of ARE in its promoter region [58]. Thus, compounds that induce Nrf2 activity can increase the expression of p62/SQSTM1 [59]. It was later shown that activation of Nrf2 with dimethyl fumarate supports p62/SQSTM1-dependent mitophagy and contributes to PD therapy [60].

Associating PD with SNP

It is classically considered that the hereditary form of PD is associated with mutations in genes of directly mitochondrial enzymes that are involved in mitophagy: PARK2 [61], PINK1 [62]. The relationship of mutations in genes involved in mitochondrial biogenesis and PD is less studied. It was shown that the presence of G/G V380L mutations in the *PARK2* gene and G/G rs2306604 mutation in the *TFAM* gene increased the risk of PD developing significantly [63]. At the same time, a recent study showed that none of the SNPs directly in the *PPARGC1α* gene is associated with the onset of PD, but at the same time, the rs6821591 C allele contributes to the rapid progression of the motor syndrome [64].

However, a number of studies demonstrated the correlation between *NFE2L2* gene and PD. For the Chinese population, individual c.351T>A, D117E and c.423G>T, Q141H mutations were found to be associated with PD, moreover, these mutations lead to a decrease in downstream Nrf2 gene expression [65]. A meta-analysis of several European populations showed that the alleles localized in the introns of the *NFE2L2* gene (rs7557529 G>A and rs2886161 A>G), as well as the allele localized in the promoter of the *NFE2L2* gene (rs35652124 A>G) increases the risk of early onset of PD on average by more than 1 year. The rs1806649 G>A allele, on the contrary, reduces the risk of PD occurrence by more than 1 year [66]. In other studies, no individual SNP associated with the occurrence of PD were identified [67, 68]. van Otter et al. showed a PD protective haplotype of 3 SNPs for the Swedish and Polish population (rs35652124; rs6706649; rs6721961), whereas the haplotype of 5 SNP (rs7557529; rs2886161; rs1806649; rs2001350; rs10183914) is in contrast associated with PD [69].

Conclusion

Symptomatic treatment is currently the only method of PD therapy. The once promising antioxidants have not met expectations, as they can only remove ROS, but not prevent the degeneration of dopaminergic neurons. The basis of neurons destruction is a violation of mitochondrial quality control. The mismatch in the processes of mitochondrial biogenesis and mitophagy leads to the accumulation of damaged mitochondria, leading to ROS overproduction and apoptosis. Studies of the last few years showed that Nrf2 is an optimal target for drugs that could support mitochondrial quality control, which, in combination with antioxidant protection, can significantly slow down the pathogenesis of PD.

Acknowledgements This research was supported by the Ministry of Education and Science of the Russian Federation (State Assessment N 6.4656.2017/8.9); President grant for support of leading scientific school, (Agreement 14.Z57.18.3451-NSh) and Russian Fund for Basic Research (16-04-01014 A).

Compliance with Ethical Standards

Conflict of interest No conflicts of interest, financial or otherwise, are declared by the authors.

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