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REVIEW

Succinate dehydrogenase in Parkinson's disease

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BACKGROUND: The prevalence of neurodegenerative disorders such as Parkinson's disease (PD) is increased by age. Alleviation of their symptoms and protection of normal neurons against degeneration are the main aspects of the researches to establish novel therapeutic strategies. Many studies have shown that mitochondria as the most important organelles in the brain which show impairment in PD models. Succinate dehydrogenase (SDH) as a component of the oxidative phosphorylation system in mitochondria connects Krebs cycle to the electron transport chain. Dysfunction or inhibition of the SDH can trigger mitochondrial impairment and disruption in ATP generation. Excessive in lipid synthesis and induction of the excitotoxicity as inducers in PD are controlled by SDH activity directly and indirectly. On the other hand, mutation in subunits of the SDH correlates with the onset of neurodegenerative disorders. Therefore, SDH could behave as one of the main regulators in neuroprotection.

OBJECTIVE: In this review we will consider contribution of the SDH and its related mechanisms in PD.

METHODS: Pubmed search engine was used to find published studies from 1977 to 2016. "Succinate dehydrogenase", "lipid and brain", "mitochondria and Parkinson's disease" were the main keywords for searching in the engine.

RESULTS: Wide ranges of studies (59 articles) in neurodegenerative disorders especially Parkinson's disease like genetics of the Parkinson's disease, effects of the mutant SDH on cell activity and physiology and lipid alteration in neurodegenerative disorders have been used in this review.

CONCLUSION: Mitochondria as key organelles in the energy generation plays crucial roles in PD. ETC complex in this organelle consists four complexes which alteration in their activities cause ROS generation and ATP depletion. Most of complexes are encoded by mtDNA while complex II is the only part of the ETC which is encoded by nuclear genome. So, focusing on the SDH and related pathways which have important role in neuronal survival and SDH has a potential to further studies as a novel neuroprotective agent.

Keywords Parkinson's disease, mitochondria, succinate dehydrogenase, neuroprotection

Introduction

Parkinsons disease (PD) is a neurodegenerative disorder with the second highest prevalence in the world which affects 1% of over 60 adults (de Rijk et al., 1995). Loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) is the main character of PD caused motor symptoms including resting tremor, rigidity, bradykinesia, and postural instability (de Lau and Breteler, 2006). Progression of PD depends on environmental toxins, oxidative stress, mitochondrial dysfunction, protein aggregation, neuroinflammation and disturbance in fatty acid metabolism (Chen et al., 2003; Jenner 2003; Yasuda et al., 2013; Jodeiri Farshbaf et al., 2016). Mitochondria play crucial role in the high energy demand cells such as neurons and muscle. Any disruption in the activity or function of it triggers other factors which accelerate the neuronal death (Exner et al., 2012). Moreover, mitochondria can control intracellular Ca^{2+} homeostasis and reactive oxygen species (ROS) level. Any dysfunction in mitochondrial activity leads to ROS generation, ATP depletion, caspase releasing and electron transport chain (ETC) defection (Martin, 2010). During neurodegeneration mitochondrial dysfunction and lipid accumulation prompt each other. Oxidative stress, neuroinflammation, mitochondrial dysfunction and ROS generation have potential roles in lipid droplet (LD)biogenesis and formation which is hallmark in some neurodegenartive diseases like PD (Khatchadourian et al., 2012; Schwall et al., 2012; Younce and Kolattukudy, 2012; Liu et al., 2015).

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Here, we seek to understand the role of succinate dehydrogenase (SDH) as a member of ETC complex in PD onset and progression. SDH as a main element in the connection of the oxidative phosphorylation (OXPHOS) and tricarboxylic acid cycle (TCA) is altered in neurodegenration. So, focusing on the activity and function of it could open new therapeutic avenues in front of PD treatment.

Mitochondria and PD

metabolism of fatty acids, steroids, and the generation of energy as adenosine triphosphate (ATP). Components of the mitochondria include outer membrane, inner membrane, intermembrane space and matrix. Inner membrane contains ETC structures that are responsible for OXPHOS process and ATP production. Mitochondrion has distinct DNA (mtDNA) with the size of 16.6 kb which encodes proteins for OXPHOS system and consistent functions of it (Legros et al., 2004). In the OXPHOS system, five multimere protein complexes are located in inner membrane: Complex I (NADH CoQ dehydrogenase) that contains 45 subunits which 7 subunit of them are encoded by mtDNA (Davis and Williams 2012), complex II (succinate dehydrogenase (SDH) or succinate: ubiquinone oxidoreductase (SQR) includes 4 subunits which are encoded by nuclear DNA (Hattori et al., 1999), Complex III (Ubiquinol: cytochrome c oxidoreductase) with 11 subunits that one of them is encoded by mtDNA, complex IV (cytochrome c oxidase) comprises 12 subunits which 3 of them are derived from mtDNA encoding genes (Kühlbrandt, 2015) and complex V (ATP synthase) with 16 subunits that two of them come from mtDNA (Perier and Vila, 2012). Defection in the activity of complex I correlate with the pathogenesis of the PD. 1-methyl-4- phenyl-1,2,3,4-tetrahydropyridine (MPTP) which was used as pesticide showed irreversible parkinsonian syndrome by inhibiting complex I (Langston et al., 1983). MPTP using in the *in vivo* models shows degeneration of dopaminergic neurons in the SNpc. Active metabolite of the MPTP, 1-methyl-4-phenylpyridiniumion (MPP +), induces neuronal death in *in vitro* models (Schulz and Falkenburger, 2004; Dauer and Przedborski, 2003). Close correlation with complex I activity and sporadic PD onset is supported by some evidences that confirm reduced activity of complex I in the platelet and skeletal muscles of PD patients (Schapira et al., 1990). MPTP and its active metabolite increase oxidative stress, ROS level and decrease ATP level by inhibiting complex I (Ali et al., 1994). Beside sporadic PD, familial form of this disease is detectable and this type of onset depends on wide various genes e.g. PINK, Parkin, DJ-1 and LRRK2 (Fig. 1) (Bonifati, 2007). But recent evidences showed changing in the activities of the mitochondrial complexes in PD patients (Hanagasi et al., 2005). But here we focus on complex II and its charge in the PD onset or progression.

Succinate dehydrogenase as the smallest member of mitochondrial respiratory chain contains four subunits (SDHA, SDHB, SDHC and SDHD). All subunits are encoded by nuclear DNA and it bonds Krebs cycle and the respiratory chain (Cecchini, 2003). SDHC and SDHD as transmembrane proteins of complex, anchor the complex to inner mitochondrial membrane (Sun et al., 2005). All subunits together can make hydrophilic head in matrix side of mitochondria. SDHA and SDHB as the catalytic cores of complex II can oxidize succinate to fumarate in the Krebs cycle. Eight enzyme control TCA cycle and their activities can be influenced by metabolite concentrations and activities of mitochondrial ETC. Succinate dehydrogenase activity is influenced by the concentrations of malate, fumarate, citrate and specifically oxaloacetate (Fig. 2) (Gutman et al., 1971). Mutation or succinate dehydrogenase inhibition leads to accumulation of malate, fumarate in the mitochondria (Van Vranken et al., 2014). For ATP generation low concentration of fumarate is so important (Rottenberg and Gutman 1977), so high level of fumarate in matrix can decrease ATP production. SDH not only influences Krebs cycle but also has a role in ROS generation (Ralph et al., 2011). Mutation in SDHC subunit in transgenic mice causes mitochondrial dysfunction and ROS production (Ishii et al., 2011). Based on previous studies, SDH can be a source for ROS generation, mitochondrial dysfunction and controlling mitochondrial hemostasis. Krebs cycle by controlling the concentration of some metabolites such as fatty acids alters cell signaling, this function of the Krebs cycle links mitochondrial matrix to cellular physiology (Owen et al., 2002). In cancer cell lines using complex II inhibitors induces lipid synthesis (Guo et al., 2016). Activity of N-methyl-D-aspartate (NMDA) receptors is increased by using 3-Nitropropionic acid (3-NP), an irreversible inhibitor of complex II (Liot et al., 2009). Enhancement of the NMDA receptors in the neurons increase Ca^{2+} entrances into the cell which excess amount of that cause neuronal death and injuries of central nervous system (Zhou and Sheng, 2013).

Brain is so active in lipid synthesis (Fahy et al., 2005) and excess lipids in the brain are stored in the forms of LDs which are cytoplasmic lipid storage organelles (Fujimoto and Parton 2011). Densities of the LDs are low in normal condition (Etschmaier et al., 2011) but during neurological disorders like PD they are extended (Cole et al., 2002). Therefore, LD accumulation in the brain could be early hallmark of the PD onset. In the muscle SDH activity shows capacity of the cell for TCA cycle. Using specimen from patients with hereditary myopathy showed that LD accumulation is high in their myofibrils. That features of the patients correlated with SDH low activity which could cause low ATP, high malate and low citrate levels (Linderholm et al., 1990). Malate moves into the cytoplasm through malate-aspartate shuttle which is located in the mitochondria membrane. Malate presents in the cytoplasm in the form of aspartate and α-ketoglutarate. By increasing the aspartate in the cytoplasm the mammalian target of rapamycin (mTOR) is converted into active form. mTOR works through activation of various targets in the cell (Meijer, 2003) (Fig. 3).

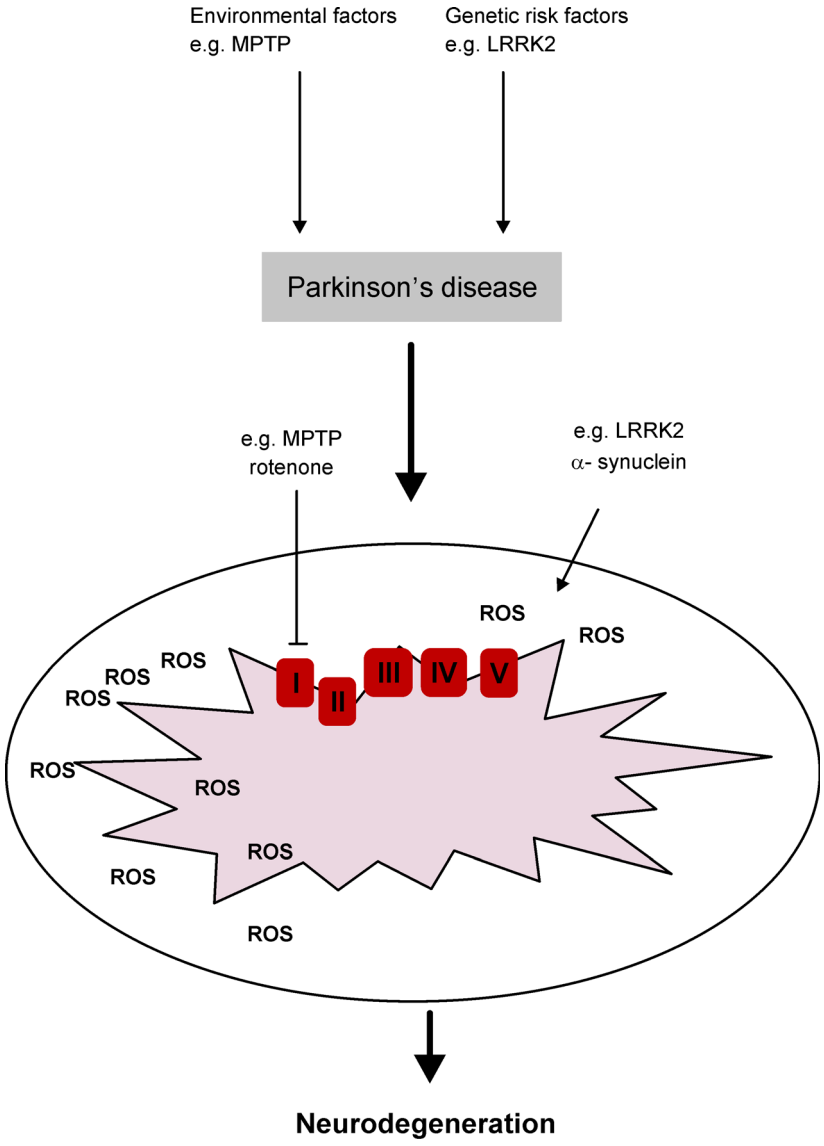

Figure 1 Environmental factors such as MPTP and genetic factors like mutant LRRK2 damage mitochondria directly and indirectly. MPTP increases ROS level by inhibiting mitochondrial complex I. But LRRK2 and α synuclein indirectly could influence mitochondrial ROS level. Both factors finally induce neurodegenration.

LD biogenesis is controlled by sterol regulatory element binding protein (SREBP) in the CNS (Liu et al., 2015). SREBP is a helix–loop–helix leucine zipper transcription factor that can translocate into nucleus after activation (Horton et al., 2002). SREBP is synthesized in inactive form and bind to endoplasmic reticulum (ER). Upon activation SREBP in precursor form is cleaved and NH2-terminal as active domain translocate into the nucleus (Eberlé et al., 2004). SREBP can control the expression of lipogenic genes, and the production of various classes of lipids such as unsaturated and saturated fatty acids, phosphatidylcholine, and phosphatidylglycerol (Porstmann et al., 2008). In PD modulation of SREBP-1 and downstream pathway can be a as neuroprotective strategy (Schmitt et al., 2016). SREBP overexpression in mice, showed high mitochondrial cholesterol levels in cortical neurons (Fernández et al., 2009). Moreover, SREBP transcription level is changed in hypothalamus or cerebrum by aging (Okamoto et al., 2006). SREBP is a spot of the mTOR which is a PI3K-like serine/threonine protein kinase and acts as a sensor for nutrients in cell. mTOR has role in the proliferation of neural stem cells, the assembly and maintenance of neuronal circuits, experience-dependent plasticity, and regulation of complex behaviors like feeding, sleep, and circadian rhythms (Lipton and Sahin, 2014). Inhibition of the mTOR in various species show enhancement in lifespan and longevity (Selman et al., 2009). In the PD models misfloding of protein, α-synuclein, triggers other signaling pathways which lead to apoptosis and neurodegeneration. Accumulation of the α-synuclein is detectable in the cytoplasm of postmortem brain tissues (Recchia et al., 2004).

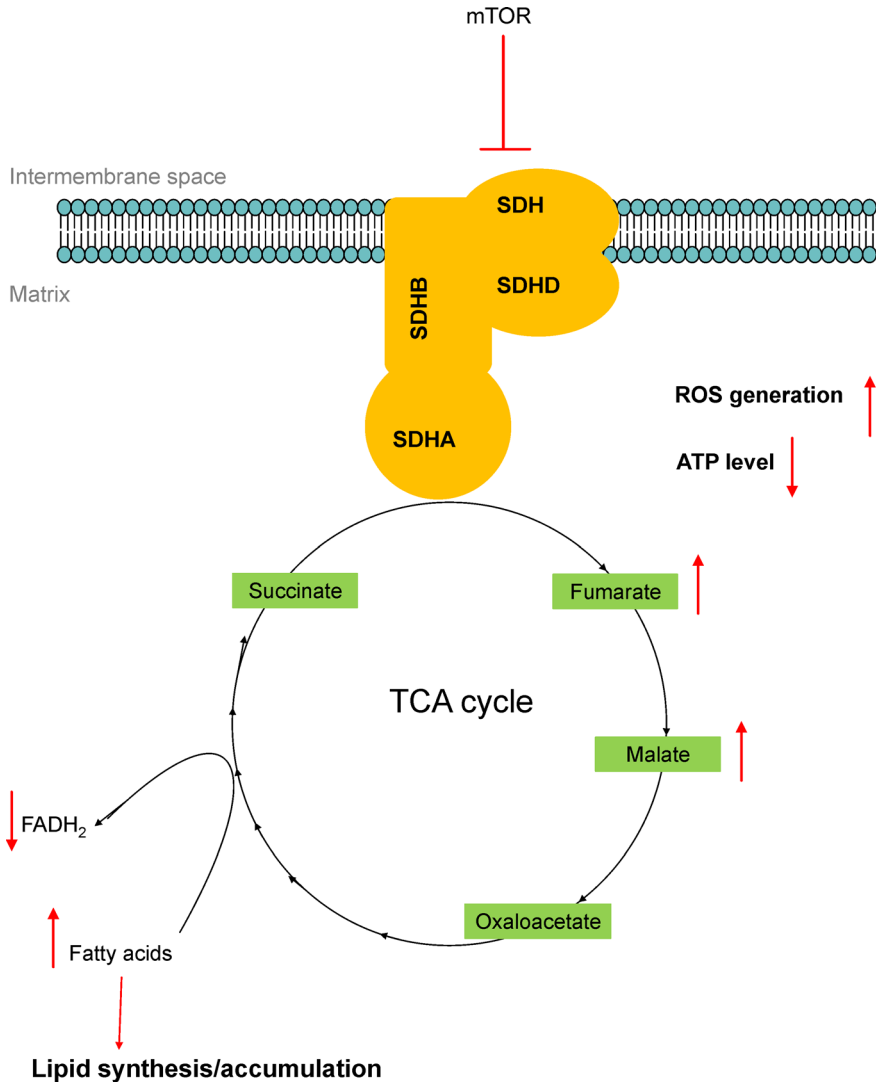

Figure 2 Mitochondria ETC directly involved in the TCA cycle through SDH complex. By inhibiting that complex malate and fumarate and lipid contents of the mitochondria.

By activation of the mTOR sutophagy mechanism which helps to clear the msifolded proteins is inhibited. So, beside the activation of the SREBP and LD accumulation, the autophagy system is inhibited in PD models (Ivatt and Whitworth, 2014). In addition, α-synuclein is the powerful inducer of the lipid synthesis and LD accumulation in PD (Gitler et al., 2008). Recent studies showed that mTOR deficiency in muscle can decrease SDH and oxidative metabolism in cell (Risson et al., 2009). Rapamycin as a specific inhibitor for mTOR signaling pathway can increase the activity of SDH in *Drosophila*. Fatty acid oxidation generates FADH2 which is the main stimulator of the SDH activity and rapamycin is another inducer for SDH too (Villa-Cuesta et al., 2014). Malonate is another inhibitor of the SDH can cause neuronal injuries and degeneration (Beal et al., 1993). Mechanism of neurodegeneration in the presence of malonate is happened not only by secondary excitotoxicity but also by mitochondrial membrane potential collapse and cyt C releasing (Fernandez-Gomez et al., 2005). Excitotoxicity is a process that leads to neuronal death because of excitatory amino acids such as glutamate. Previous studies showed excessive exposure to glutamate causes neuronal death and injury (Berliocchi et al., 2005). Glutamatergic neurons are the main excitatory system in the CNS and play important role in learning and memory. Glutamate acts through three major types of ionotropic receptors such as NMDA, α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) and kainic acid (KA receptors) (Lodge, 2009). NMDA receptors are expressed in most parts of the CNS and their favorite cation is Ca^{2+} . Their activation in continuous pattern cause high concentration of intracellular Ca^{2+} which is trigger for mitochondrial membrane depolarization, caspase activation, production of ROS and nitrogen free radicals, and cellular toxicity (Rothstein 1996; Jung et al.,

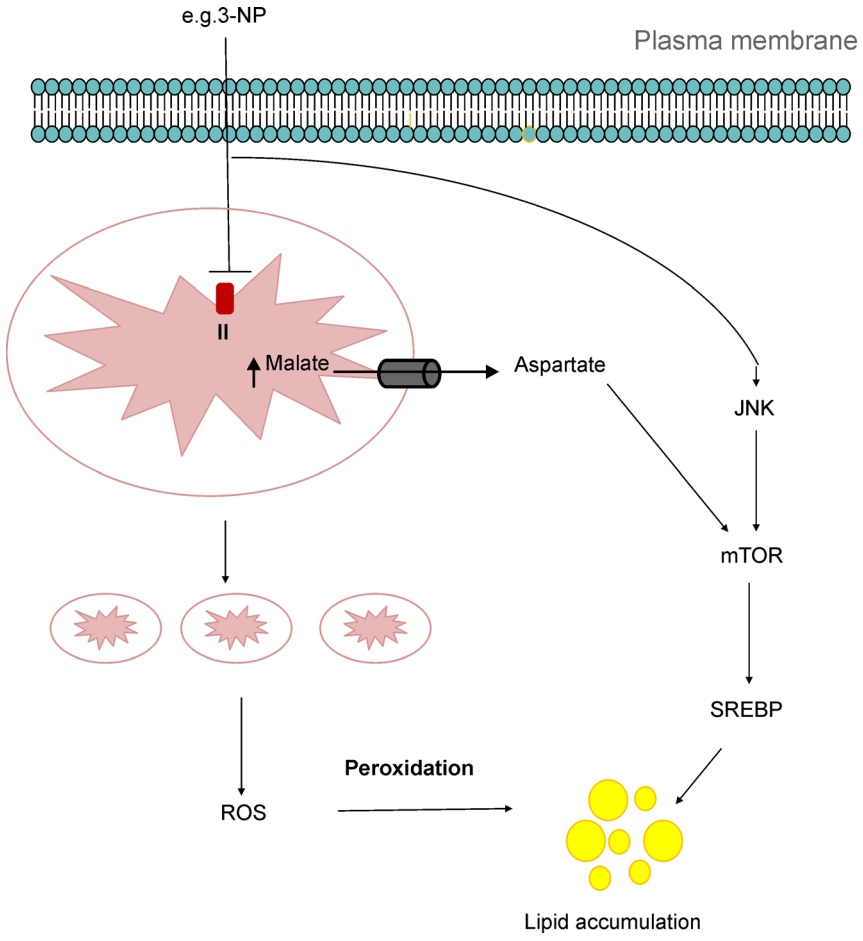

Figure 3 Inhibition of the SDH leads to enhancement in malate level in the mitochondria. Through malate-aspartate shuttle mitochondrial malate comes into the cytoplasm in the form of aspartate. Aspartate works as an activator for mTOR complex which causes SREBP activation and lipid biosynthesis.

2009). In PD models using of the NMDA receptors antagonists showed alleviation of parkinsonian motor symptoms (Hallett ang Standaert, 2004). So, we can hypothesize that inhibition of the mitochondrial complex II can accelerate neurodegeneration through various mechanisms such as LD accumulation, ROS generation, ATP depletion and excitotoxicity process. With these recent reports raising questions about the roles of SDH, it is imperative to further validate and reach a consensus regarding this potentially important mitochondrial subunit.

Prospective studies

Mitochondria as key organelles in the energy generation plays crucial roles in PD. ETC complex in this organelle consists four complexes which alteration in their activities cause ROS generation and ATP depletion. Most of complexes are encoded by mtDNA while complex II is the only part of the ETC which is encoded by nuclear genome. Defects in complex II lead to neuronal injuries and in many neurodegenerative disorders abnormalities of SDH activity have been reported. Lipid accumulation and excitotoxicity are the main hallmarks of the neurodegenerative disorders like PD. Mitochondrial complex II can regulate both lipid metabolism and excitotoxicity directly and indirectly: mTOR as one of the main signaling proteins is active in PD and its activation can inhibit the activity of the SDH which is linker between OXPHOS process and Krebs cycle. Moreover, fatty acid oxidation is involved in Krebs cycle through SDH complex. Therefore, inhibition of the SDH by active mTOR decreases fatty acid oxidation that leads to lipid accumulation. On the other hand, mTOR can induce SREBP activity which is responsible for lipid biosynthesis. Studies showed that lipid accumulation is the early hallmark of the neurodegeneration. Most of evidences from previous studies could candidate SDH as an effective target for therapeutic interventions in neurological diseases like PD and aging. SDH overexpression or manipulation of its activity could control lipid overloading in neurodegenerative disorders. Moreover, by increasing protein level of SDH, it can be possible to control excitotoxicity and NMDA dependent signaling. The identification and characterization of the SDH protein provides

important new insights into the mechanisms which SDH protects neurons from lipid overloading and ROS generating, and it can be therapeutic candidate to ameliorate PD progression.

Abbreviations

3-NP, Nitropropionic acid; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionate; ATP, adenosine triphosphate; ER, endoplasmic reticulum; ETC, electron transport chain; MPP +, 1-methyl-4-phenylpyridiniumion; MPTP, 1-methyl-4-phenyl-1,2,3,4 tetrahydropyridine; mtDNA, mitochondrial DNA; mTOR, mammalian target of rapamycin; NMDA, N-methyl-D-aspartate; OXPHOS, oxidative phosphorylation; PD, Parkinson's disease; ROS, Reactive oxygen species; SDH, succinate dehydrogenase; SNpc, substantia nigra pars compacta; SQR, succinate: ubiquinone oxidoreductase; SREBP, sterol regulatory element binding protein; TCA, tricarboxylic acid cycle.

Compliance with ethics guidelines

Mohammad Jodeiri Farshbaf declares that he has no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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