Role of ferroptosis in Parkinson’s disease and intervention mechanism of acupuncture and moxibustion

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Competing interests
The authors declare no conflicts of interest.

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Abbreviations
PD, Parkinson’s disease; TF, transferrin; GPX4, glutathione peroxidase 4; GSH, glutathione; XCT, cysteine-glutamate antiporter; FSP1, ferroptosis suppressor protein 1; CoQ10, coenzyme Q10; TH, tyrosine hydroxylase; SN, substantia nigra; DA, dopamine; GPX, glutathione peroxidase.

Citation

Abstract
Parkinson’s disease (PD) is the second neurodegenerative disease in the world. The pathological characteristics of PD are degeneration, loss and death of dopaminergic neurons in the substantia nigra of the midbrain. At present, most scholars believe that the main pathogenesis of PD is α-synuclein aggregation, oxidative stress, mitochondrial dysfunction and neuroinflammatory reaction. More and more studies have demonstrated that ferroptosis plays an important role in the occurrence and development of PD. Ferroptosis is a new type of cell death that is significantly different from traditional apoptosis, scorching and necrosis. Its main feature is iron-dependent lipid peroxidation. Some studies have found that the efficacy of acupuncture and moxibustion in the treatment of PD may be related to the regulation of ferroptosis. Therefore, this study mainly discusses the occurrence and development mechanism of ferroptosis and its role in PD, and the possible mechanism of acupuncture and moxibustion in the treatment of PD dopaminergic neurons, so as to provide theoretical basis for acupuncture and moxibustion in the treatment of PD.

Keywords: ferroptosis; Parkinson’s disease; acupuncture; moxibustion; intervention mechanism
Introduction

Parkinson’s disease (PD), also known as tremor paralysis, is the second largest neurodegenerative disease after Alzheimer's disease [1]. According to epidemiological research statistics, there are currently over 6 million PD patients worldwide, and the prevalence rate of PD over 65 years old is around 1% [2, 3]. Clinically, most PD patients mainly present four major symptoms, including resting tremor, muscle rigidity, bradykinesia, and disturbance of postural balance [4]. So far, the pathogenesis of PD is still unclear. Previous studies have shown that the main pathogenesis of PD is α-synuclein aggregation, oxidative stress, mitochondrial dysfunction and neuroinflammatory reaction [5-7]. At present, the main therapeutic drugs for PD are dopamine drugs, among which levodopa is the most widely used in clinical practice [8]. Although levodopa can significantly improve the clinical symptoms of PD patients, a series of side effects caused by long-term use of levodopa should not be underestimated. As a chronic progressive disease, PD has a long course of disease, a high disability rate, and a lack of specific drugs for complete cure, which causes great burden to the patients themselves, their families and the society. Therefore, further elucidation of the pathogenesis of PD and search for safer and more efficient drugs are major social problems that need to be solved urgently.

Ferroptosis is a concept proposed by Dixon in 2012. It is an iron-dependent cell death mode, which is significantly different from other known cell death modes in aspects of genetics, morphology and biochemistry [9, 10]. With the elucidation of ferroptosis as a new biological pathway of cell death, more and more studies have proved that it is an important mode of degeneration and death of dopaminergic neurons in the substantia nigra of PD [11]. Some researches have confirmed that features such as increased accumulation of iron ions, increased lipid peroxidation, and glutathione depletion occur in the substantia nigra of PD patients, showing great similarity with the pathological features of ferroptosis [9, 12, 13]. Thus, further illumination of the relationship between ferroptosis and the pathological mechanism of PD is of great importance to explore the new pathogenesis of PD.

Acupuncture and moxibustion therapy is a treasure of Chinese medicine and an important part of traditional Chinese medicine treatment methods. Clinical studies have found that acupuncture and moxibustion has significant advantages in the treatment of PD. Acupuncture and moxibustion is effective in improving the symptoms of PD patients, reducing the use of Western medicine and reducing the side effects of Western medicine. At the same time, acupuncture therapy is safe and reliable, and the degree of acceptance of patients is high. The possible mechanism of acupuncture and moxibustion in treating PD is related to reducing oxidative stress, inhibiting apoptosis and reducing inflammatory reaction. With the gradual deepening of the study, some scholars have found that acupuncture treatment of PD is closely related to ferroptosis, but the specific mechanism is still in further research. This study reviews the possible involvement of ferroptosis in the death of dopaminergic neurons in the midbrain of PD, and lists the preconditions that acupuncture and moxibustion participate in the treatment of PD by inhibiting ferroptosis. As evidence, the study provides scientific evidence for acupuncture and moxibustion targeting iron death therapy for PD.

The mechanism of ferroptosis

Iron metabolism

Normally, the iron in the cell is balanced through the iron transport system. Extracellular Fe\(^{2+}\) binds to transferrin (TF), TF binds to transferrin receptor 1 into the endosome, and Fe\(^{2+}\) in the endosome is reduced to Fe\(^{3+}\), which is transported to the labile iron pool in the cell. Part of iron is stored in ferritin in the form of Fe\(^{3+}\), and a small part is used for the synthesis of hemoglobin, iron-sulfur clusters and DNA. Iron that is not utilized is transported out of the cell by ferroportin [14]. A large amount of free Fe\(^{2+}\) in cells produces a large number of lipid hydroperoxide accumulation through fenton reaction, which promotes the occurrence of ferroptosis [15]. Nuclear receptor coactivator 4 transports macromolecular ferritin into autophagosomes to release free iron, a process known as ferritinophagy. Increased expression of TF and transferrin receptor 1, increased iron autophagy, and decreased ferritin lead to iron overload in cells [16, 17]. Therefore, dysregulation of iron metabolism is an important way to induce ferroptosis. Compared with the rest of the brain, iron deposition was found in the substantia nigra of PD patients [12, 13], which was more likely to cause ferroptosis.

Lipid metabolism

Studies have found that lipid metabolism disorders are closely related to ferroptosis, and lipid peroxidation is a key link in the process of ferroptosis [18]. Under normal physiological conditions, the intracellular redox is in dynamic equilibrium, and when the intracellular redox in the cell is out of balance, the polyunsaturated fatty acids on the cell membrane undergo lipid peroxidation to generate a large amount of reactive oxygen species (ROS), ROS cause the accumulation of lipidhydroperoxide, which leads to the occurrence of ferroptosis [19]. It was found that low expression of Acyl-CoA synthetase long-chain family and lysophosphatidylcholine acyltransferase 3 could effectively prevent ferroptosis, while overexpression could promote ferroptosis [20]. Because Acyl-CoA synthetase long-chain family and long-chain family and lysophosphatidylcholine acyltransferase 3 promote the binding of polyunsaturated fatty acids to phospholipids to generate phosphorus containing polyunsaturated acyl groups, which is an important link in the occurrence of ferroptosis [21].

Metabolism of amino acids and glutathione

Glutathione peroxidase 4 (GPX4) is a key protein regulating ferroptosis. GPX4 is the only enzyme in the glutathione (GSH) peroxidase family that can reduce lipid hydroperoxides. Some studies have shown that GPX4 can effectively eliminate intracellular lipid hydroperoxide, thus inhibiting the occurrence of intracellular ferroptosis. When inhibiting the transcription of GPX4, ferroptosis can be induced [22-24]. It has been found that GSH is essential for the activity of GPX4 and Fe\(^{2+}\) in cells, and the reduction of GSH levels can promote the generation of highly toxic hydroxyl radicals by Fe\(^{2+}\), which leads to ferroptosis [25]. Cysteine, an essential raw material for the synthesis of GSH, requires the use of extracellular cysteine-glutamate antipporter (XCT). XCT is composed of SLC7A11 and SLC3A2 subunits. Ferroptosis inhibitors such as erastin, sulforasazine and sorafenib promote ferroptosis by inhibiting XCT, reducing GSH production and destroying intracellular redox homeostasis.

Other mechanisms

In addition to the above main mechanism, the newly emerging ferroptosis suppressor protein 1 (FSP1) can inhibit ferroptosis during GPX4 deficiency by reducing coenzyme Q10 (CoQ10) to CoQ10-H2 through myristic acylation [26]. Nicotinamide adenine dinucleotide phosphate acts as a molecule that restores lipid hydroperoxides in cells, and changes in nicotinamide adenine dinucleotide phosphate levels will also increase the sensitivity of cells to ferroptosis [27, 28]. In addition, disorders such as mevalonate, polyamine metabolism and selenium also increase the sensitivity of cells to ferroptosis [29, 30].

The role of ferroptosis in PD

Ferroptosis participates in the occurrence and development of PD. Many studies have confirmed that ferroptosis is closely related to the occurrence and development of PD. The lesion of PD is located in the substantia nigra of the midbrain. Studies have found that iron levels in dopaminergic neurons in the compact part of the substantia nigra in patients with PD are increased [12, 13]. In addition, studies have shown that the level of ferroptokin in the substantia nigra of PD patients is decreased, which is consistent with the animal model of PD.
induced by 1-Methyl-4-phenyl-1,2,3,6-tetrahydroypropidine and 6-Hydroxydopamine[31, 32].

At the same time, PD patients also showed characteristics related to ferroptosis, such as depletion of GSH in substantia nigra, increased level of lipid peroxidation and increased level of ROS [33–35]. Bruce and other studies have shown that ferroptosis is the key pathway of Lund human mesencephalic cell, which leads to ferroptosis by activating the ras-independent MEK signal pathway [36]. The interaction between astrocytes and other neurons is mainly manifested in providing GSH and antioxidants for other cells, protecting dopaminergic neurons from iron-mediated neurotoxicity, which is mainly through brain-derived neurotrrophic factor plays a key role in the regulation of astrocyte redox-sensitive transcription factor Nrf2 and the metabolic coordination between astrocytes and neurons [37].

Ferroptosis inhibitors or iron chelating agent improve PD
So far, iron chelating agents such as deferiprone, ferostatin-1, liprostatin-1, CoQ10 and vitamin E have been found to save ferroptosis in PD model. When ferroptosis occurs in cells, the intracellular iron concentration increases, and the balance of intracellular and extracellular iron ion transport is broken. The iron chelator deferiprone is widely used in the research of treating PD. An independent randomized, double-blind, placebo-controlled clinical PD trial found that PD patients receiving deferiprone treatment once a day for 12 months can reduce iron deposition in the substantia nigra and significantly improve motor symptoms in PD patients [38]. In addition, an earlier clinical trial yielded similar results [39]. In experimental studies, antioxidants represented by CoQ10 also played a significant role in anti-PD ferroptosis. The imbalance of lipid peroxidation produces a large number of ROS, including free radicals (such as O2̇ and OH) and non-free radical molecules (such as H2O2). OH is produced by the fenton reaction of free Fe2+ and H2O2, while most of O2̇ is produced by complex I in mitochondria. In practice, the complex is overexpressed in the substantia nigra of PD patients, which leads to the increase of free radicals in the cells. Due to the correlation between complex I and CoQ10, it has been reported that CoQ10 plays an important role in anti-ferroptosis on the FSP1-NAD (P) H-CoQ10 axis [26, 40]. However, the current research on the treatment of PD with ferroptosis inhibitors is still in the experimental stage, and the exact relationship between ferroptosis and PD needs to be further explored.

Acupuncture treats PD by regulating ferroptosis
During the occurrence and development of PD, the total iron concentration in substantia nigra of midbrain increases, which leads to the damage of dopaminergic neurons and the decrease of dopamine production, which further accelerates the progress of PD. Clinically, patients with motor dysfunction and olactory dysfunction in patients with PD were mainly treated with warming acupuncture on governor vessel. The control group was given basic drug treatment, while the observation group was treated with warming acupuncture in governor vessel combined with Jiao’s scalp-acupuncture. It was found that the effective rate was significantly higher than that in the control group [41]. In addition, compared with conventional L-DOPA drugs, acupuncture treatment of “the Seven Acupoints of the Cranial Base” can significantly improve the clinical symptoms of PD patients, such as limb flexibility, ankylosis and prone posture, and its long-term effect is better [42]. On the basis of the control group, electroacupuncture was used to stimulate bilateral parietal-cranial point connection and former SiShencong (EX-HN1)-Xuani (GB6) acupoint connection combined with routine acupuncture at Quihi (LI11), Hegu (LI4), Yanglingquan (GB34), Zubani (ST36), Sanjinyao (SP6), Taixi (KI3) and Taichong (LR3) acupoints, which could improve the tremor and ankylosis symptoms of PD patients [43]. In rotenone-induced rats model, electroacupuncture at Fengfu (DU16) and Taichong (LR3) acupoints can increase the number of tyrosine hydroxylase (TH) positive cells in substantia nigra (SN) area, increase the activity of mitochondrial complex I, reduce the ultrastructural changes of mitochondria, thereby improving the motor dysfunction of PD model rats [44]. In addition, different electroacupuncture (music electroacupuncture, pulse electroacupuncture) to stimulate Baihui (DU20) and Taiyang (EX-HN5) points can increase the dopamine (DA) content in the striatum of PD model rats, inhibit cell apoptosis in the SN area, and reduce the loss of DA neurons [45]. However, electroacupuncture at Tianzhu (ST25) point, Shenting (DU24) point and Shangjuxu (ST37) point can up-regulate the expression of TH, glutathione peroxidase (GPX)-1 and superoxide dismutase 2 in SN area of mice [46]. Studies have shown that electroacupuncture stimulation of bilateral dance tremor area significantly increases the expression of TH in SN region and the level of mitochondrial membrane potential, enhances the activity of mitochondrial complex I, reduces the damage of mitochondrial structure and the loss of DA neurons, and then improves the dyskinesia of PD model mice [47]. In addition, moxibustion at Baihui (DU20) acupoint can increase the expression of TH and GPX4 in SN area of PD model rats, reduce the levels of ROS and malondialdehyde [48]. Some studies have also shown that moxibustion at Baihui (DU20) acupoint can increase the expression of TH and GPX4 in SN area of PD model rats, reduce the content of ROS, improve ferroptosis injury, protect DA neurons, and then improve the dyskinesia of PD rats [49].

Summary
In recent years, with the deepening of research on ferroptosis, a new type of cell death, ferroptosis plays a role that cannot be ignored in the occurrence and development of PD. In addition, a large number of clinical and PD model studies have found that acupuncture plays a good role in the treatment of PD and is closely related to the regulation of ferroptosis-related pathways. Therefore, in future research, we can further explore how ferroptosis is deeply involved in the occurrence and development of PD, and how acupuncture can reduce the degeneration and death of dopaminergic neurons by regulating ferroptosis, thereby improving the clinical symptoms of PD. At the same time, it also provides theoretical and scientific basis for acupuncture treatment of PD, brings good news for PD patients and their families, and lightens the burden on the society.

References


