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# A secret that underlies Parkinson's disease: The damaging cycle

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ABSTRACT

Parkinson's disease (PD) is a movement disorder, and its common characteristics include the loss of dopaminergic neurons and the accumulation of a special type of cytoplasmic inclusions called Lewy bodies in the substantia nigra pars compacta, which are more prevalent in the elderly. However, the pathophysiology of PD is still elusive. In this review, we summarized five common factors involved in PD, namely, (i) oxidative stress, (ii) mitochondrial dysfunction, (iii) inflammation, (iv) abnormal α-synuclein, and (v) endogenous neurotoxins, and proposed a hypothesis involving a damaging cycle. Oxidative stress-triggered aldehydes react with biogenic amines to produce endogenous neurotoxins. They cause mitochondrial dysfunction and the formation of inflammasomes, which induce the activation of neuroglial cells and the infiltration of T lymphocytes. The synergistic effect of these processes fosters chronic inflammation and α-synuclein aggregation and further exacerbates the impact of oxidative stress to establish a damaging cycle that eventually results in the degeneration of dopaminergic neurons. This damaging cycle provides an explanation of progressive neuronal death during the pathogenesis of PD and provides new potential targets beneficial for developing new drugs and approaches for clinical neuroprotection.

## 1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease, and it commonly begins to emerge in people aged 65–70 years and continues to affect people for decades after. From 2009 to 2014, the number of PD patients increased by 1.6 times, and PD affects 1% of the population over 60 years (Ma et al., 2018; Tysnes and Storstein, 2017). PD is characterized by the loss of dopaminergic neurons (DNs) in the substantia nigra (SN) pars compacta (SNpc) and the presence of Lewy bodies (LBs) (Wirdefeldt et al., 2011). Symptoms of PD include motor and non-motor symptoms; the major motor symptoms, including resting tremor, bradykinesia and rigidity, and the non-motor symptoms, including insomnia, hallucinations, and major depressive disorder, have been extensively studied, but the pathophysiology remains unclear (Davie, 2008; Marinus et al., 2018). The pathogenic factors of PD can be divided into genetic and environmental factors. Recently, emerging evidence has reported that genetic factors, such as chromosomal and post-transcriptional regulatory mutations, can cause familial PD (Di Maio et al., 2018; Koros et al., 2017). Several environmental factors, such as oxidative and nitrative stress, ageing, alterations in proteasomal protein degradation, excitotoxicity, and mitochondrial dysfunction, are responsible for neuronal loss and have been proposed to induce sporadic PD (Collier et al., 2011; Lucking et al., 2000). Among the theories about the extent and development of PD, the Braak staging hypothesis is widely accepted and focuses on the pathogenesis of PD (Braak et al., 2003). According to the Braak hypothesis, an unknown stimulus induces the occurrence of PD, and the hypothesis divides the spread of α-synuclein into six stages, which are basically consistent with the progression of the pathological symptoms of PD. PD begins in the olfactory system (stage I) and the raphe nuclei, medulla oblongata and brainstem (stage II); the disease reaches the SN of the midbrain, and LBs begin to form (stage III); the disease then enters the cortex, and damage occurs predominantly in the anterior olfactory nucleus (stage IV); the disease further affects the prefrontal cortex, and DNs begin to die (stage V); the disease eventually damages the neocortex and causes dementia (VI). However, there is still no effective therapeutic approach or PD-specific medications, probably because of one-sided research that has focused on identifying pathogenic factors for the development of potential drugs; consequently, existing drugs are often ineffective due to the complexity of this disease. Some

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**Abbreviations**

| | |
|---|---|
| PD | Parkinson's disease |
| SN | Substantia nigra |
| DNs | Dopaminergic neurons |
| LBs | Lewy bodies |
| DA | Dopamine |
| DAMP | Damage-associated molecular pattern |
| CNS | Central nervous system |
| ANS | Autonomic nervous system |
| ENS | Enteric nervous system |
| MHC | Major histocompatibility complex |
| CTIQs | Catechol tetrahydroisoquinolines |
| TIQs | Tetrahydroisoquinolines |
| 6-OHDA | 6-Hydroxydopamine |
| MPTP | 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine |
| $MPDP^+$ | 1-Methyl-4-phenyl-2,3-dihydropyridinium |
| $MPP^+$ | 1-Methyl-4-phenylpyridinium ion |
| ADTIQ | 1-Acetyl-6,7-dihydroxy-1,2,3,4-tetrahydro-isoquinoline |
| Sal | 1-Methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline |
| NMSal | 1(R) 2(N)-Dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline |
| $DMDHIQ^+$ | 1,2-Dimethyl-6,7-dihydroxyisoquinolinium ion |

drugs are effective but are often used only for a specific period or may lead to various side effects after long-term use, as occurs with levodopa (Walton-Hadlock, 2005). Thus, a new PD-specific drug with an optimized dosage regimen that is effective for preventing the onset of PD is urgently needed for the betterment of the ageing population. Therefore, herein, we discuss the common factors involved in familial and sporadic forms of PD and reveal their possible relationships at the macro-perspective level to alleviate the bottlenecks in PD research and clinical treatment.

## 2. Common factors

### 2.1. Oxidative stress

Oxidative stress is considered a probable pathogenic contributor to PD (Burkhardt and Weber, 1994; Kim et al., 2015) because the brain is the largest aerobic organ in the human body, and the large cell population in the brain contains various easily oxidized substances, such as dopamine (DA) and lipids (Chiurchiu et al., 2016; Crotty et al., 2017; Finkel and Holbrook, 2000). In both familial and sporadic PD, oxidative stress induces α-synuclein misfolding, modification and aggregation, lipid peroxidation, inflammation and mitochondrial dysfunction. Hashimoto M and Owen Scudamore found that oxidative stress induces the formation of amyloid-like α-synuclein aggregates in vitro and exacerbates α-synuclein aggregation in vivo (Hashimoto et al., 1999; Scudamore and Ciossek, 2018). Dexter showed that the production of malondialdehyde from lipid peroxidation is increased in parkinsonian nigra tissue compared to control tissues of the human brain (Dexter et al., 1989). Reactive oxygen species (ROS)/Reactive nitrogen species (RNS) induced by oxidative stress cause the activation of glial cells and inflammation (Stone et al., 2009) and inhibit the normal activity of complex I via oxidative damage, such as S-nitrosylation, during mitochondrial dysfunction (Clementi et al., 1998). Conversely, these conditions also exacerbate the impact of oxidative stress. α-Synuclein interacts with mitochondrial complex I and interferes with its function to promote the production of ROS and RNS (Yasuda et al., 2013). ROS production acts as an inflammatory defence mechanism against pathogens (Winterbourn, 2008), and mitochondrial dysfunction is generally considered to be a major source of oxidants (Hauck and Bernlohr, 2016; Palikaras and Tavernarakis, 2012). These studies strongly suggest that oxidative stress is a contributing factor to the pathogenesis of PD. However, this stage is often triggered by changes in environmental or genetic factors. Oxidative stress is a common phenomenon that routinely occurs in normal ageing; almost all elderly people are exposed to oxidative stress (Violi et al., 2017), but only some people suffer from PD. This fully demonstrates oxidative stress alone is not a convincing pathogenic factors. It is only one of the mechanisms that is triggered by the pathogenic factors of PD. It is worth noting that the subsequent signalling cascade caused by oxidative stress is also very important.

It is worth noting that lipid peroxidation, as a downstream response, may play a more important role in the pathogenesis of PD. Considering that the brain is rich in lipids, lipid peroxidation, which proceeds as a free radical chain reaction of polyunsaturated fatty acids, can easily occur in the brain. The final product of lipid peroxidation is a family of aldehydes of various carbon lengths, such as malondialdehyde and acrolein (Grimsrud et al., 2008). Usually, endogenous aldehydes are maintained at a physiological concentration. However, when antioxidant function is reduced or dysregulated (Venkateshappa et al., 2012), aldehyde molecules can cause damage to the body, especially the nervous system (Garaycoechea et al., 2018; Kalasz, 2003; Kalev-Zylinska and During, 2007). Aldehydes can affect the secretion of the neurotransmitter dopamine, induce protein carbonylation and inhibit the activity of glutathione, which are hidden dangers that indirectly cause PD (Hauck and Bernlohr, 2016; Maruyama et al., 2001; Schmitz et al., 2017; Usanmaz et al., 2002). However, lipid peroxidation (oxidative stress) is a universal injury, and its effects are not specific; thus, oxidative stress alone cannot explain the specific death of DNs in PD. Therefore, there must be some factors that convert the universal damage caused by oxidative stress into specific damage.

### 2.2. Mitochondrial dysfunction

Mitochondrial dysfunction is considered to be the most important factor in both sporadic and familial PD and is mainly caused by abnormalities in mitochondrial electron transport chain complex I, gene mutations and homeostasis changes (Bhat et al., 2015). The impairment of complex I activity due ot oxidative stress has been detected in the substantia nigra and frontal cortex of PD patients (Beal, 2005; Keeney et al., 2006). Mitochondrial dysregulation, in addition to being caused by environmental factors such as exogenous neurotoxins, is more commonly due to gene mutations and the dysregulation of transcription factors. Familial PD, which accounts for 10% of PD, results from mutations in α-synuclein (SNCA), leucine-rich repeat kinase 2 (LRRK2), vacuolar protein sorting 35 (VPS35), Parkin (PRKN), PTEN-induced kinase 1 (PINK1), protein deglycase (DJ-1) and ubiquitin C-terminal hydrolase L1 (UCHL-1) (Cannon and Greenamyre, 2013). These PD-related genes all have direct and indirect relationships with mitochondrial dysregulation (Healy et al., 2004; Krebiehl et al., 2010; Ludtmann et al., 2017; Tang et al., 2015; Verma et al., 2017; Zanellati et al., 2015; Zhi et al., 2019). The majority of PD cases are sporadic and may not involve gene mutations similar to those present in cases of familial PD; however, mitochondrial dysfunction is present in sporadic PD as well, which suggests that sporadic PD patients may exhibit the abnormal expression of mitochondrial DNA (mtDNA) or the abnormal regulation of the transcription of epigenetic genes.

The human mitochondrial genome is mainly composed of 16.6-kb circular double-stranded DNA molecules. In sporadic PD patients, the deletion of and damage to mtDNA induced by oxidative stress is found in individual dopaminergic neurons in the SN, but the relationship between mtDNA mutations and PD has not yet been identified (Bender et al., 2006; Sanders et al., 2014). The regulation of gene transcription is mainly carried out by non-coding RNAs (ncRNAs) in the genome, and

ncRNAs are divided into two categories: small ncRNAs (e.g., miRNAs) and long ncRNAs (lncRNAs). In recent years, the dysregulation of miRNA levels has been reported in PD (Martinez and Peplow, 2017; Sonntag, 2010). Table 1 summarizes the distribution and functional relevance of miRNAs that have been shown to correlate with changes in the brains of PD patients (Hollins and Cairns, 2016; Horst et al., 2018; Li et al., 2018a. b; Martinez and Peplow, 2017; Oh et al., 2018; Shanesazzade et al., 2018). According to Table 1, the majority of miRNAs in PD patients is directly related to mitochondrial function. It is worth noting that the abnormal expression of all miRNAs in the above table can be triggered by long-term environmental stress. Environmental stress includes physiological stress induced by oxidative stress, pathogens or toxins, and psychological stress induced by dilemmas beyond our abilities (Hollins and Cairns, 2016). Long-lived humans face various environmental stresses during their lifespans, and these random environmental stresses may alter the transcriptional regulation of their genes, thereby inducing mitochondrial dysfunction and ultimately causing sporadic PD. In this way, mutations in or the abnormal regulation of PD-related genes make PD appear to be similar to a mitochondrial disease. However, considering that there are mitochondria in almost all cells, with differences only in their quantity and distribution, the abnormal regulation of or mutations in these genes cannot explain the specific damage to dopaminergic neurons. It is difficult to explain why the mitochondria in DNs are specifically impaired and cause the death of DNs in PD. Therefore, there may be some factors that make mitochondrial dysregulation an exclusive feature of DNs.

### 2.3. Inflammation

It was recently reported that the lymphatic system and direct vascular channels connect the skull bone marrow to the brain (Herisson et al., 2018; Louveau et al., 2015), which shows that the brain is not separated from the immune system and that inflammasome microglia, astrocytes and T cells are involved in the immune response (Appel et al., 2010; Yerramothu et al., 2018).

Inflammasomes are large pyrin domain-containing protein complexes and are formed by pattern recognition receptors (PRRs). Damage-associated molecular patterns (DAMPs), which are identified by PRRs, are a series of endogenous damage signals, including extracellular heat shock protein (eHSP) (Asea et al., 2002) and mtDNA (Zhang et al., 2010), released by tissues and cells. DAMPs can activate the formation of inflammasomes, and inflammasomes can activate caspase-1 and caspase-11, cleave the precursors of inflammatory cytokines, such as IL-18 and IL-1β, and release these components to extracellular regions, causing inflammation and pyroptosis (Martinon et al., 2002; Yerramothu et al., 2018). Gordon R showed that NLRP3 inflammasomes can drive progressive dopaminergic neurodegeneration in PD, and the inhibition of inflammasomes can effectively inhibit nigrostriatal dopaminergic degeneration, which suggests that inflammasomes play an important role in the pathological process of PD (Gordon et al., 2018).

The activation of gliocytes and the infiltration of lymphocytes caused by activated inflammasomes has been found in both familial and sporadic PD. PD-related genes, such as Parkin, PINK1, DJ-1 and LRRK2, have been reported to activate reactive astrocytes associated with lesions during stress caused by unfolded proteins and increase the activation of microglia and the expression of monocytes and glial cells in the brains of PD patients (Hakimi et al., 2011; Ledesma et al., 2002; Moehle et al., 2012; Mullett et al., 2009; Wilhelmus et al., 2011). Reactive microgliosis, the infiltration of $CD4^+$ T lymphocytes, a continuous increase in $CD4^{bright+}CD8^{dull+}$ T cells and IgG deposition surrounding degenerating neurons have been detected both in the brains of PD patients and in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice (Hisanaga et al., 2001; Harms et al., 2013).

**Table 1**
The family, alteration, distribution, induction and functional relevance of miRNAs in the brains of PD patients.

| miRNA name | miRNA family | Alteration | Distribution | Induction | Correlation | Reference |
|---|---|---|---|---|---|---|
| miRNA-16–5p | miR-15 | Upregulation | Prefrontal cortex | Stress | Inflammation | Li X et al., 2018a, b |
| miRNA-21 | miR-21 | Upregulation | Midbrain/Substantia nigra | Inflammation | Mitochondria | Liu Y et al., 2018 |
| miRNA-26b | miR-26 | Upregulation | Substantia nigra | Environmental chemicals/Drugs of abuse | Mitochondria | Karbiener M et al., 2014 |
| miRNA-34a | miR-34 | Upregulation | Striatum | Oxidative stress | Mitochondria | Zhong X et al., 2018 |
| miRNA-155 | miR-155 | Upregulation | Substantia nigra | Environmental pathogens/Inflammation | Mitochondria | Yang ZB et al. (2018) |
| miRNA-195 | miR-15 | Upregulation | Frontal cortex | Environmental chemicals | Mitochondria | Wang H et al., 2018 |
| miRNA-204–5p | miR-204 | Upregulation | Putamen/Hippocampus | Environmental chemicals/Maternal stress/ Oxidative stress | Mitochondria | Lin YC et al. (2017) |
| miRNA-221 | miR-221 | Upregulation | Cingulate gyri | Oxidative stress/Inflammation | Mitochondria | Chen L et al., 2012 |
| miRNA-424 | miR-322 | Upregulation | Frontal cortex | Hypoxia/Oxidative stress | Oxidative stress | Li L et al., 2017 |
| miRNA-494 | miR-154 | Upregulation | Substantia nigra | Environmental chemicals | Mitochondria | Lemecha M et al., 2018 |
| miRNA-34b | miR-34 | Downregulation | Putamen/Substantia nigra | Environmental chemicals/Inflammation | Mitochondria | Consales C et al., 2018 |
| miRNA-34c | miR-34 | Downregulation | Substantia nigra | Inflammation/Stress | Mitochondria | Consales C et al., 2018 |
| miRNA-124 | miR-124 | Downregulation | Midbrain/Substantia nigra | Psychological stress/Inflammation/Stress | Mitochondria | Yardeni T et al., 2018 |
| miRNA-133b | miR-133 | Downregulation | Midbrain | Drugs of abuse | Mitochondria | Slagsvold KH et al., 2014 |
| miRNA-135b | miR-135 | Downregulation | Substantia nigra | Oxidative stress | Oxidative stress | Fan JB et al. (2016) |
| miRNA-145 | miR-145 | Downregulation | Cingulate gyri | Cellular stressors/Fetal alcohol syndrome/ Maternal anxiety | Mitochondria | Li R et al., 2012 |
| miRNA-148a | miR-148 | Downregulation | Frontal cortex | Inflammation | Mitochondria | Zhang C et al., 2018 |
| miRNA-155–5p | miR-155 | Downregulation | Putamen | Environmental pathogens/inflammation | Mitochondria | Yang ZB et al. (2018) |
| miRNA-190 | miR-190 | Downregulation | Frontal cortex | Drugs of abuse | Oxidative stress | Avila-Bonilla RG et al. (2017) |
| miRNA-199a-3p | miR-199 | Downregulation | Frontal cortex | Environmental chemicals/Inflammation | Mitochondria | el Azzouzi H et al., 2013 |
| miRNA-208b | miR-208 | Downregulation | Substantia nigra | Stress/Inflammation | Mitochondria | Liu J et al., 2016 |
| miRNA-219-2-3p | miR-219 | Downregulation | Putamen | Maternal anxiety | Inflammation | Fredman G et al., 2012 |
| miRNA-330–5p | miR-330 | Downregulation | Substantia nigra | Oxidative stress/Inflammation | Oxidative stress | Liu J et al., 2019 |
| miRNA-339–5p | miR-339 | Downregulation | Substantia nigra | Fetal alcohol syndrome | Inflammation | Zhang Y et al., 2014 |
| miRNA-382–5p | miR-154 | Downregulation | Putamen | Drugs of abuse | Mitochondria | Dahlmans D et al., 2019 |
| miRNA-429 | miR-8 | Downregulation | Frontal cortex | Cellular stressors/Maternal stress | Oxidative stress | Guo S et al., 2017 |
| miRNA-451 | miR-451 | Downregulation | Frontal cortex | Cellular stressors/Maternal stress | Mitochondria | Yang X et al., 2017 |

Activated microglia and astrocytes are classified as having M1/M2 and A1/A2 phenotypes, of which the M1/A1 phenotypes promote inflammation and accelerate neuronal death, while the M2/A2 phenotypes promote inflammation resolution and protect neurons. (Appel et al., 2010; Hanisch and Kettenmann, 2007; Liddelow and Barres, 2015; Maragakis and Rothstein, 2006; Stone et al., 2009; Sofroniew and Vinters, 2010). However, limitations of these studies is a lack of understanding of how microglia and astrocytes are polarized into M1/A1 or M2/A2 phenotypes and how microglia and astrocytes can be polarized into the M2/A2 phenotype by manual intervention to protect neurons. Fortunately, recent studies see the dawn of breaking this limit. Liddelow SA found that A1 astrocytes are induced by activated microglia via IL-1α, TNF and C1q (Liddelow et al., 2017). ncRNAs have distinct expression patterns in microglia with different polarization states. miR-689, miR-124 and miR-155 mediate the M1-like phenotype, and miR-124, miR-711 and miR-145 regulate the M2-like phenotype in primary murine microglia (Freilich et al., 2013). LncRNA GAS5 is a potent inhibitor of M2 polarization in mouse and human microglia. miRNA-155 directly acts on the response of microglia to α-synuclein, and the deletion of miRNA-155 reduces pro-inflammatory responses to α-synuclein in mice (Sun et al., 2017; Thome et al., 2016).

Although the immune response is considered a negative response, it is a normal response to an abnormal environment in the brain. Clearly, in most cases, hyperactivated immune cells are the chief culprit of toxicity, and they should be regulated to protect neurons from damage. Since in an inflammatory state, immune cells are often accompanied by a massive release of ROS (Blaser et al., 2016; Meier et al., 1989, 2009; Winterbourn, 2008), PD patients face long-term severe chronic inflammation in the brain, which may change the redox equilibrium and induce oxidative stress (Pacher et al., 2007; Roberts et al., 2010). These observations explain why anti-inflammatory drugs and plant flavonoid antioxidants are used for the treatment of PD (Carrera and Cacabelos, 2019). Actually, inflammation and neuronal death occur after neuronal damage, and the occurrence of inflammation is not selective, but its specificity is determined by the damaged area. Therefore, it does not seem to be a key inducing factor.

### 2.4. Abnormal α-synuclein

The main component of LBs is α-synuclein in familial and sporadic PD (Goedert et al., 2013), but the reason that α-synuclein aggregates and forms LBs remains unclear. Some studies have shown that gene mutations are the key to the formation of LBs. The overexpression of SNCA and its mutations (A30P, A53E, A53T, E46K, G51D and H50Q) results in α-synuclein aggregation (Harms et al., 2013; Paleologou and El-Agnaf, 2012). Other gene mutations (in UCHL-1 and LRRK2) that are not directly related to α-synuclein can also cause aggregation (Barrachina et al., 2006; Miklossy et al., 2006). However, when there is no gene mutation, α-synuclein aggregation is also induced by different modifications, such as phosphorylation and nitration (Anderson et al., 2006; Liu et al., 2011), and the zinc-induced impairment of the ubiquitin proteasome system can lead to the aggregation of α-synuclein in DNs (Kumar et al., 2018).

The aggregation of α-synuclein at a toxic level is an important contributor to the pathogenesis of PD. α-Synuclein inclusions that are peripherally administered to mice induce α-synuclein pathology in the CNS, suggesting a prion-like nature of α-synuclein (Ayers et al., 2018). However, the toxicity of α-synuclein can be attributed not only to aggregate formation but also to other forms. Oligomer-prone α-synuclein exacerbates synaptic and neuronal degeneration in the frontal cortex and hippocampus of mice (Rockenstein et al., 2014). The injection of fibrillar α-synuclein into the striatum of rats results in a reduction of DNs and the accumulation of LB-like inclusions after 180 days (Paumier et al., 2015). The overexpression of α-synuclein increases the expression of MHC II, activates the surrounding microglia and renders peripheral blood $CD4^+$ T cells susceptible to apoptosis (Calopa et al., 2010; Harms et al., 2013; Yamada et al., 1992), which suggests that aggregated α-synuclein may act as an antigen to induce an immune response in vivo.

When α-synuclein aggregations appear, the uptake and clearance of these aggregated proteins is often carried out by microglia and astrocytes (Fellner et al., 2013; Kim et al., 2013; Lindstrom et al., 2017), and the incomplete digestion of these aggregated proteins in astrocytes becomes a pathological feature of PD (Fellner and Stefanova, 2013). Interestingly, the uptake and degradation of aggregated proteins in microglia is slowed when primary microglia are activated via lipopolysaccharide (Lee et al., 2008), which suggests that the clearance process may be regulated by inflammation.

LBs occur not only in the CNS but also in the autonomic nervous system (ANS) and enteric nervous system (ENS). α-Synuclein inclusions are found in sympathetic and parasympathetic pre-ganglionic neurons (Braak et al., 2007) and the myenteric and submucosal plexuses of the gastrointestinal tract (Cersosimo, 2015; Lebouvier et al., 2009). LBs have also been shown to first occur in the vagus nerve and spinal cord and to later spread into the CNS (Bloch et al., 2006). These results suggest that the pathogenesis of PD may gradually spread from the peripheral nervous system to the CNS. Considering that neuroimmune interactions are also involved in the peripheral nervous system (Shea-Donohue and Urban, 2017), LBs can also cause immune responses that lead to inflammation in the peripheral nervous system.

Overall, abnormal α-synuclein plays a very complicated role; not only can it be regarded as a result of PD but it can also be considered to contribute to PD or neuronal death. Abnormal α-synuclein may play a role in linking all of the symptoms of PD. However, the role of abnormal α-synuclein in the pathology of PD remains to be further studied.

### 2.5. Endogenous neurotoxins

There are many transgenic and neurotoxin-based animal models of PD that have been developed over many years. Mild PD symptoms are observed in a transgenic α-synuclein animals, but no obvious PD symptoms are observed in transgenic LRRK2, PINK1 and DJ-1 animals (Blesa and Przedborski, 2014), suggesting that a single gene mutation is not sufficient and necessary for PD. 6-Hydroxydopamine (6-OHDA) and MPTP are the most commonly used neurotoxins to develop PD models (Bove et al., 2005; Casarrubea et al., 2019). MPTP can cross the blood-brain barrier and be oxidized into 1-methyl-4-phenyl-2,3-dihydropyridinium ($MPDP^+$) by monoamine oxidase B, and $MPDP^+$ is converted to 1-methyl-4-phenylpyridinium ion ($MPP^+$), which can accumulate in mitochondria, impair oxidative phosphorylation by inhibiting mitochondrial complex I and induce PD-like symptoms in humans (Davis et al., 1979). Unlike MPTP, 6-OHDA cannot cross the blood-brain barrier and enters DNs via the dopamine transporter (DAT), produces ROS via auto-oxidization or oxidization, and induces mitochondrial fragmentation, eventually causing mitochondrial dysregulation that leads to ATP depletion (Solesio et al., 2013; Yamamuro et al., 2006). However, LB-like inclusions cannot be produced in dopaminergic systems damaged by MPTP or 6-OHDA (Blesa and Przedborski, 2014; Deng et al., 2012). Because of the acute toxicity of MPTP and 6-OHDA, dopaminergic neurons are quickly processed for apoptosis or necrosis, and a model can be established in days or weeks. The neurons cannot undergo progressive neurodegenerative processes because α-synuclein cannot aggregate to form inclusions; thus, these models cannot be used to make accurate conclusions about the pathology of PD. Although MPTP and 6-OHDA cannot induce PD very well, it suggests that there may exist other toxic substances similar to MPTP or 6-OHDA in PD brain.

Recently, some naturally occurring MPTP-like neurotoxins have been identified. These neurotoxins can be categorized into two main groups: (i) tetrahydroisoquinolines (TIQs) and (ii) β-carbolines. In 2001, 1-acetyl-6,7-dihydroxy-1,2,3,4-tetrahydro-isoquinoline (ADTIQ), a novel MPTP-like compound, was found in the caudate nucleus,

putamen, SN, frontal cortex and cerebellum of the brains of patients with PD via Z-spray APILC/MS (Deng et al., 2012). ADTIQ is derived from the reaction between dopamine and methylglyoxal. Methylglyoxal is primarily formed by non-enzymatic and/or enzymatic elimination from triose phosphate intermediates during glycolysis. Similar to ADTIQ, catechol tetrahydroisoquinolines (CTIQs), analogues of TIQs, such as 1-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (salsolinol, Sal) and 1(R)- and 2(N)-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (NM-salsolinol and NM-Sal), have been detected in the urine and cerebrospinal fluid (CSF) of parkinsonian patients (Antkiewicz-Michaluk et al., 1997; Sandler et al., 1973). The neurotoxicity of NM-Sal in the rat brain was investigated by Makoto Naoi. NM-Sal induced the deviation of the head and trunk towards the lesioned side and apparent akinesia, and the DA content and the activity of tyrosine hydroxylase (TH) were significantly decreased (Naoi et al., 1996). Makoto Naoi also reported that dopamine endogenously combines with aldehydes to form TIQs because it cannot pass through the blood-brain barrier (Naoi, 2004). Sal synthesis in the human body was

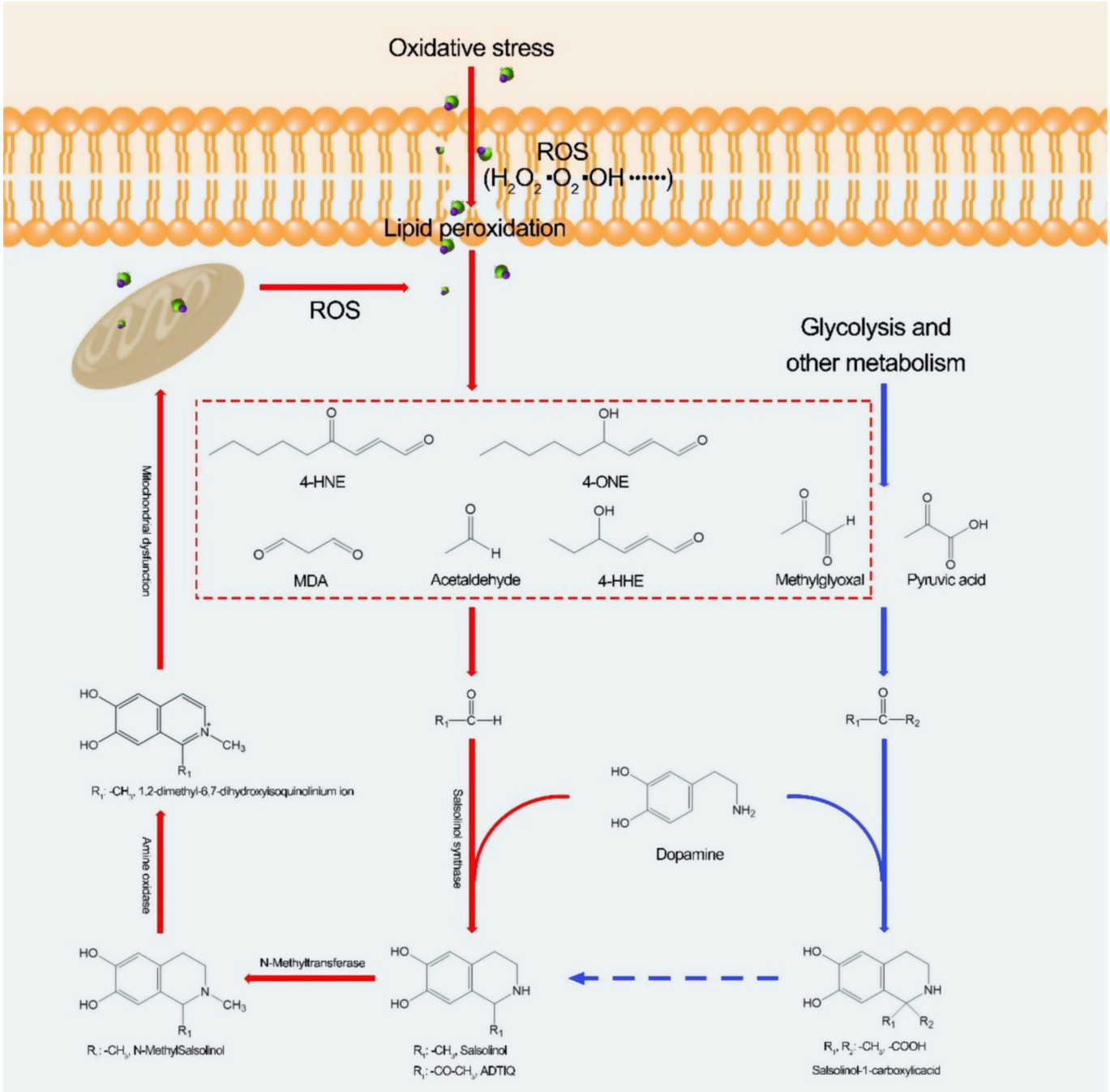


**Fig. 1.** Biosynthesis pathway of endogenous neurotoxins in the brain. Oxidative stress can induce the release of ROS and then lead to lipid peroxidation, which produces a large amount of aldehydes such as acetaldehyde, and metabolism, such as glycolysis, in the body and can also produce methylglyoxal and pyruvic acid. Dopamine can react with acetaldehyde to generate salsolinol via salsolinol synthase and can react with methylglyoxal or pyruvic acid to produce ADTIQ or salsolinol-1-carboxylic acid, which is ultimately converted to salsolinol, but this pathway has not been confirmed. Salsolinol can further be catalysed by N-methyl transferase into N-methylsalsolinol, which can be oxidized into DMDHIQ + by amine oxidase. DMDHIQ + inhibits the mitochondrial electron transport chain and results in mitochondrial dysfunction, which can further exacerbate oxidative stress. The solid arrows indicate a confirmed chemical reaction, and the dotted arrows show pathways that have not been confirmed.

once considered to occur via a nonenzymatic Pictet-Spengler reaction between dopamine and acetaldehyde or pyruvic acid, leading to racemic forms (Zhang et al., 2013). However, more accurate and simpler chromatographic methods for the analysis of Sal enantiomers have confirmed the major occurrence of the (R) enantiomers in mammalian tissues, suggesting that Sal may be synthesized enzymatically (Naoi, 2004). Sal synthase activity was first identified in Sprague Dawley rat brains via high-performance liquid chromatography using an electrochemical detection system (Chen et al., 2011), and the distribution of Sal, NM-Sal and 1,2-dimethyl-6,7-dihydroxyisoquinolinium ion ($DMDHIQ^+$) was examined in the brain. It was found that NM(R)Sal is distributed selectively in the nigrostriatum, that (R)-Sal is distributed uniformly among brain regions and that $DMDHIQ^+$ is distributed only in the SN (Maruyama et al., 1997). These results suggest that the concentration of these factors does not rely on the distribution of dopamine but on the activity of synthesizing enzymes, such as (R)-salsolinol synthase and N-methyltransferase. Recent studies (Mao et al., 2010; Naoi, 2004; Naoi et al., 1996, 2002; Su et al., 2013; Zheng et al., 2018) have suggested that the enzymatic condensation of dopamine with acetaldehyde or pyruvic acid is catalysed by (R)-salsolinol synthase to yield (R)-Sal or (R)-Sal-1-carboxylic acid, respectively. However, the enantioselective synthesis of (R)-Sal from 1,2-dehydrosalsolinol has not been confirmed. (R)-Sal is catalysed by N-methyl transferase into NM (R)-Sal, which enters DNs through the DAT and is further oxidized into $DMDHIQ^+$, which can inhibit the activity of mitochondrial complex I, causing mitochondrial dysfunction. This process is accompanied by the formation of a large number of active oxides that further induce lipid peroxidation and lead to the repeated formation of Sal and the activation of related metabolic processes (Fig. 1). Interestingly, the levels of Sal and NM-Sal are increased in $MPP^+$-treated primary neurons (Deng et al., 2012). This result shows that we may have ignored the involvement of endogenous neurotoxins in the pathogenesis of PD. Considering that the production of endogenous neurotoxins is closely related to oxidative stress, mitochondrial dysfunction and DNs, we speculate that endogenous neurotoxins may play an extremely important role in the pathology of PD and provide the source of specificity we have been searching for.

## 3. The damaging cycle of PD

To date, we have found five common factors involved in the pathogenesis of PD: oxidative stress, mitochondrial dysfunction, inflammation, abnormal α-synuclein aggregation and endogenous neurotoxins. Each of these five factors seems to be able to induce PD alone, but they are related to each other via three cycles.

The first cycle involves oxidative stress, mitochondrial dysfunction and endogenous neurotoxins. The long-term presence of oxidative stress induces aldehyde production by lipid peroxidation, and aldehydes can react with dopamine to form endogenous neurotoxins and potentially avoid oxide-scavenging mechanisms. ncRNAs and endogenous neurotoxins further damage the mitochondria of DNs, as endogenous neurotoxins inhibit the activity of mitochondrial complex I, which is considered to be the site of ROS/RNS formation. Damaged complex I produces a large amount of ROS/RNS, which destroy proteins, DNA and lipids in the mitochondria, and the impairment of mtDNA further leads to defects in the function of complex I and III (Bhat et al., 2015), which in turn further exacerbates oxidative stress and the formation of endogenous neurotoxins and induces mitochondrial dysfunction and energy crisis. Similarly, gene mutations or alterations in ncRNAs can also directly cause mitochondrial dysfunction and induce oxidative stress to further enhance the production of endogenous neurotoxins. Either way, the key is the cycle that ultimately triggers the formation of endogenous neurotoxins.

After the first cycle is triggered, the second cycle between endogenous neurotoxins and inflammation is established. Continuously generated aldehydes, endogenous neurotoxins and/or damaged mtDNA, which are passively released from the intracellular space of damaged cells to the extracellular space (Van Crombruggen et al., 2013), may act as DAMPs and activate the expression of inflammasomes and downstream signalling pathways, thus inducing the activation of microglia and astrocytes. Then cytokines, which further enhance the infiltration of T cells, are released, leading to inflammation that aggravates oxidative stress, thus perpetuating the formation of endogenous neurotoxins.

When these two cycles persist in the brain, their biological effects lead to the emergence of a third cycle of abnormal α-synuclein aggregation. Oxidative stress and/or endogenous neurotoxins may induce the modification of normal α-synuclein; nitrated α-synuclein and ATP depletion impair protein degradation pathways (Bae et al., 2008; Nam et al., 2015), and phosphorylated or carbonylated α-synuclein may lose its function and block subsequent ubiquitination, thereby affecting cellular degradation and enabling protein-protein interactions that promote aggregation (Ferrington and Kapphahn, 2004; Mark et al., 1997; Miyake et al., 2003). Meanwhile, the activation of microglia and astrocytes by inflammation greatly reduces their ability to clear abnormal proteins. α-Synuclein inclusions that fail to be degraded and uptake act as antigens to further induce inflammation and exacerbate the level of oxidative stress (Roberts and Brown, 2015), which again promotes the formation of endogenous neurotoxins.

Considering the amplifying effects of these three cycles, we propose a damaging feedback loop that combines these three cycles in the pathogenesis of PD (Fig. 2). However, the stated order of the aforementioned three cycles needs to be further verified. Endogenous neurotoxin formation may not preferentially occur. As in familial PD, abnormal proteins may be first directly or indirectly formed due to mutations in genes such as SNCA and UCHL-1 and lead to inflammation and endogenous neurotoxin production. In short, each of the three cycles can be an initiation point, but it is necessary to complete the entire damaging cycle to induce the series of biological effects that eventually lead to the death of DNs, the formation of LBs, and the development of PD.

## 4. Discussion and future perspectives

To uncover the causes of Parkinson's disease, many researchers have proposed various pathological mechanisms of PD. Among them, the Brakk staging hypothesis claims that the pathological development of LBs occurs in the CNS via the olfactory bulb and vagus nerve. Our damaging cycle hypothesis is similar to the Braak staging theory. However, in the Braak hypothesis, both the olfactory bulb and enteric neurons in the gut are involved in the initiation of PD (Hawkes et al., 2009). Gastrointestinal problems, such as colitis, constipation, and nausea, and olfactory problems, such as olfactory deficits, have been reported in PD (Devos et al., 2013; Fasano et al., 2015; Soltanzadeh et al., 2011). Intestinal inflammation is related to oxidative stress, and α-synuclein aggregation occurs in the olfactory tract and enteric neurons of PD patients (Braak et al., 2006; Hubbard et al., 2007; Rietdijk et al., 2017; Volpicelli-Daley et al., 2011). The shortcoming of the Braak hypothesis is that it does not address the cause of the disease; it assumes that a foreign pathogen enters the body via the nose or gut and may be responsible for the initiation of PD. Notably, in our hypothesis, endogenous neurotoxins act as a possible unknown trigger. However, our damaging cycle hypothesis does not explain why the intestine and olfactory bulb are the first areas affected by PD or why α-synuclein aggregates form. Because of the distribution of DA and the DAT in the brain (Hall et al., 2003), the basal ganglia possess more dopamine and dopamine receptors than the frontal cortex; thus, according to our hypothesis, the putamen should be the area in which PD is initiated, in contrast to its involvement in stage III in the Braak hypothesis. However, on the one hand, the distribution and enzyme activity of Sal synthase may be different, with the highest enzyme activity occurring in the olfactory bulb. On the other hand, DA is not the only player in the production of endogenous neurotoxin; biogenic amines such as

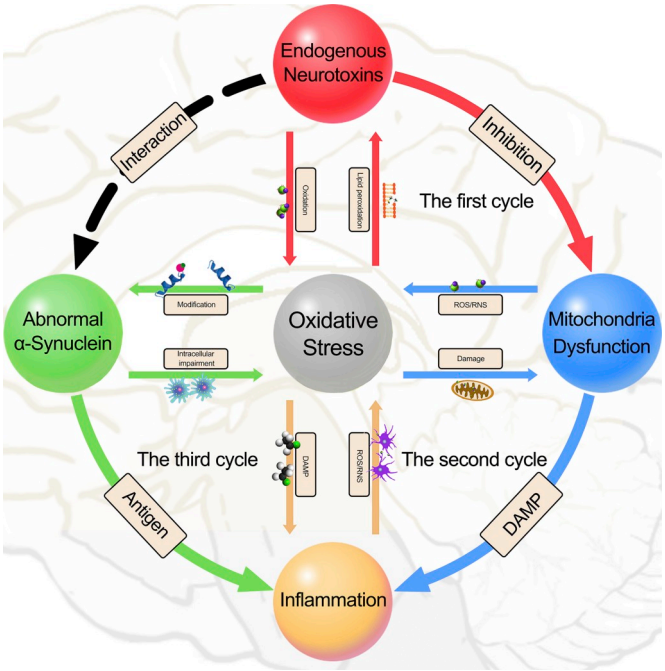


**Fig. 2.** A damaging cycle combining three cycles that consist of oxidative stress, mitochondrial dysfunction, inflammation, abnormal α-synuclein and endogenous neurotoxins in the pathogenesis of PD. When oxidative stress occurs in the body, lipid peroxidation produces large quantities of aldehydes, which react with catecholamine to form endogenous neurotoxins. Endogenous neurotoxins further cause mitochondrial dysfunction by inhibiting the activity of mitochondrial complex I and exacerbating oxidative stress, forming the first cycle. The second cycle, triggered by the first cycle, involves aldehydes, mtDNA and endogenous neurotoxins acting as DAMPs to induce inflammation, which increases oxidative stress levels. These two cycles finally cause the third cycle of protein aggregation; oxidative stress and endogenous neurotoxins may induce α-synuclein modification, and these modified proteins may not be degraded but instead may interact with one another to form aggregates. Aggregated proteins can also act as antigens to induce inflammation and intracellular damage, which in turn further exacerbates oxidative stress. The damaging loop of the three cycles eventually causes the degenerative death of DA neurons, leading to the occurrence of PD. The solid lines indicate confirmed pathways, and the dotted lines indicate pathways that have not been confirmed.

serotonin can also similarly react with aldehydes. The olfactory bulb is dominated by serotonin-containing neurons from the median raphe to the glomerular layer (Brill et al., 2016; Rey et al., 2018), and a recent study showed that monoamine oxidase (MAO)-B, which is also involved in the synthesis of endogenous neurotoxins, is first inhibited by rasagiline and improves odour discrimination in early PD patients (Haehner et al., 2015; Soto-Otero et al., 2006), which suggests that endogenous neurotoxins can be produced in large quantities in the olfactory bulb, making the olfactory bulb the starting point of PD pathogenesis. In addition, catecholamine-containing neurons have been detected in the ENS in humans (Natale et al., 2017), and LBs have been found in ENS, parasympathetic and sympathetic neurons, which indicates that endogenous neurotoxins and/or LBs may also be formed in the ENS and induce intestinal inflammation. This may change the permeability of the intestinal barrier and allow endogenous neurotoxins and/or LBs to invade the peripheral nervous system and eventually damage the CNS, and it may explain why PD is also associated with PD-specific gastrointestinal problems (Devos et al., 2013). The damaging cycle hypothesis supplements the unclear part of the Braak hypothesis and explains why sporadic PD can occur in the alcoholics and the elderly and why gene mutations in familial PD can cause neuron-specific death (Mao et al., 2013; Rodriguez et al., 2015).

At present, there is no cure for PD, and current medical or surgical treatments are unable to control the progression of PD but can often normalize motor symptoms. There are many types of drugs for the treatment of PD, including anticholinergics, levodopa, dopamine agonists, MAO-B inhibitors, catechol-O-methyltransferase (COMT) inhibitors and neuroprotective agents (Kakkar et al., 2018; Leentjens et al., 2009; Muller et al., 2007; Picillo and Munhoz, 2018). Since only symptomatic treatments are currently available, it is necessary to find a treatment that can directly target the mechanism of PD or delay the progression of PD. One of the main obstacles in the development of treatments for PD is that most patients present with 60% degradation of dopaminergic neurons in the presence of typical clinical PD symptoms. Therefore, timely and accurate diagnosis to provide early stage treatment prior to the development of classic symptoms of PD has become a new hope for curing PD. According to our hypothesis, the components of the damaging cycle can be considered targets for the treatment of PD. Some studies have shown that antioxidants can improve clinical symptoms and have a certain therapeutic effect on PD, while some studies have shown that antioxidant intake is not associated with a lower risk of PD (Carrera and Cacabelos, 2019; Hughes et al., 2016). Many drugs targeting α-synuclein have shown certain effects on animal models and in clinical trials, but there have been cases in which the effect was not significant or adverse reactions have occurred (Savitt and Jankovic, 2019). Many therapies related to mitochondrial genes have been identified in the laboratory, but none of them can improve the modifying effect of the disease in PD patients (Choong and Mochizuki, 2017). Moreover, because DA is still the main target of clinical drugs, the intake of a large amount of DA may increase the level of oxidative stress and aggravate the production of endogenous neurotoxins. Although it can temporarily alleviate the symptoms of PD, it actually exacerbates the formation of the damaging cycle, which explains why DA-targeted drugs cannot prevent the development of PD. These studies suggest that the components of the damaging cycle do exhibit the characteristics of potential therapeutic targets, and the current poor treatment results are probably because (i) these components are nonspecific, as drugs that have been developed to target these components do not effectively target symptoms and produce side effects and (ii) they may not break the damaging cycle but instead may cause the cycle to persist and fail to prevent the progression of the disease. Therefore, endogenous neurotoxins, due to their core role in the cycle and their specificity for damaging dopaminergic neurons, are likely to be key therapeutic targets. Given that the damaging cycle may first occur in the intestine, it may be possible to infer the occurrence of PD by detecting the levels of endogenous neurotoxins and their metabolites ($DMDHIQ^+$) in the blood in the future. Endogenous neurotoxins and their metabolites can act as markers for the early diagnosis of PD. If we break the damaging cycle by blocking the production and metabolism of endogenous neurotoxins, it may be possible to prevent the pathogenesis of PD. Additionally, combining treatments that inhibit endogenous neurotoxin production with treatments for other factors in the damaging cycle may represent a new method for the treatment of PD.

In summary, the damaging cycle formed by three cycles can simulate the pathogenesis of PD and explain the symptoms and specific degeneration of DNs in PD. Although there are many different treatments for PD (Mantri et al., 2018; Rabin et al., 2015), there is no treatment to address all of the facets of the disease. Endogenous neurotoxins may represent possible novel targets and promising therapeutic strategies for curing PD. However, further research is needed to verify the accuracy and reliability of this feedback cycle in the context of PD and its role as a therapeutic target.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2019.104484.

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