Review

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Can kynurenine pathway be considered as a next-generation therapeutic target for Parkinson's disease? An update information

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SUMMARY By far, no revolutionary breakthrough in the treatment of Parkinson's disease (PD) was found. It is indeed a knotty problem to select a satisfactory strategy for treating some patients with advanced stage PD. Development of novel therapeutic targets against PD has been an urgent task faced by global PD researchers. Targets in the tryptophan–kynurenine pathway (KP) were then considered. Metabolites in the KP are liposoluble. Some neurotoxic metabolites, including 3-hydroxykynurenine and its downstream 3-hydroxyanthranilic acid and quinolinic acid, are mainly produced peripherally. They can easily cross the blood–brain barrier (BBB) and exert their neurotoxic effects in the central neuron system (CNS), which is considered as a potential pathophysiological mechanism of neurodegenerative diseases. Hence, agents against the targets in the KP have two characteristics: (1) being independent from the dopaminergic system and (2) being seldom affected by the BBB. Inspiringly, one agent, namely, the inhibitor of indoleamine 2,3-dioxygenase 1, has been currently reported to present satisfactory efficacy comparable to levodopa, implying that the KP might be a potential novel target for PD. This review collected and summarized the updated information regarding the association of the KP with PD, which is helpful for understanding the clinical value of the KP in the PD scenario.

Keywords Tryptophan-kynurenine pathway, Parkinson's disease, Indoleamine 2,3-dioxygenase 1 (IDO1), Dopaminergic medication, Blood-brain barrier

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease (NDD) (*1,2*). Approximately 10 million people are suffering from PD, and the number of cases is expected to be more than doubled in the next 20 years (*3*). PD remarkably affects the patients' activity of daily living (ADL), particularly for those who are in the advanced stage, whose daily living has to depend on the caregiver. This situation reduces the patients' quality of life (QOL). Moreover, it significantly enhanced the financial burden not only for the government but also for each involved family. With the aging of population, PD has gradually become an important global public health concern. Hence, development of novel treatments against PD has been an urgent task faced by global PD clinicians and scientists. Understanding PD pathogenesis, particularly elucidating the involved molecular mechanisms, is the key to explore the potential new therapeutic targets in treating PD.

Unfortunately, by far, all treatments against PD are far from satisfactory (*4*). Dopaminergic medication is the mainstream therapy, where levodopa (L-dopa) is the mainstay agent for PD. Dopaminergic agents combined with non-dopaminergic agents are commonly prescribed clinically. Nevertheless, only few kinds of non-dopaminergic drugs are available for clinical use, such as amantadine (promoting the release of dopamine and neuroprotective effects), anticholinergic drugs (such as benzhexol), whose efficacy along with indications have noticeable limitations. Finding new agents whose mechanisms are independent from the dopaminergic system is challenging. Additionally, by far, all the mainstream agents recommended by the PD guidelines worldwide are remarkably affected by the blood–brain barrier (BBB) along with their peripheral metabolism. In case of an agent, which is seldom affected by the BBB, it can influence the central neuron system (CNS) peripherally and will be convenient for clinical use. In this regard, the keywords "non-dopaminergic" as well as "seldom affected by the BBB" should be a novel direction in exploring new agents for PD.

Our previous study reported that electrical stimulation of the peripheral tissue may improve the striatal dopamine levels, indicating that intervention in the peripheral tissue (other than in the CNS) may affect the dopamine content in the CNS (*5*). Meanwhile, our preliminary experiments found that the plasma tryptophan levels in PD animal models significantly reduced, whereas the plasma kynurenine levels increased (Figure 1). These preliminary data suggest that the tryptophan–kynurenine pathway (KP) might be involved in the regulation of PD pathogenesis. Moreover, it is known that indoleamine 2,3-dioxygenase 1 (IDO1), the key enzyme of the KP, is very lowly expressed in the CNS. However, it is highly expressed in the peripheral organs such as the lung, kidney, and liver. IDO1 regulation is mainly in the periphery, rather than in the CNS. Therefore, the KP regulated by IDO1 has two major characteristics, namely, independent of neural dopaminergic systems and seldom affected by the BBB, thereby are considered as a novel therapeutic target for PD. The elements of the KP, particularly IDO1, are reported to be closely associated with neurological diseases, including depression (*6-8*), Alzheimer's disease (AD) (*9*), multiple sclerosis (*10*), stroke (*11*), and PD (*12-14*).

Several reviews have discussed the role of the KP in the CNS disorders. Mazarei *et al.* reviewed the special role of the KP in Huntington's disease. They pointed out that although most of the previous the KP studies focused on depression, CNS tumors, and multiple sclerosis, the role of IDO in the NDDs cannot be ignored (*15*). Later, Lovelace reviewed the role of the KP and IDO1 in multiple sclerosis (*10*). Kennedy *et al.* reported

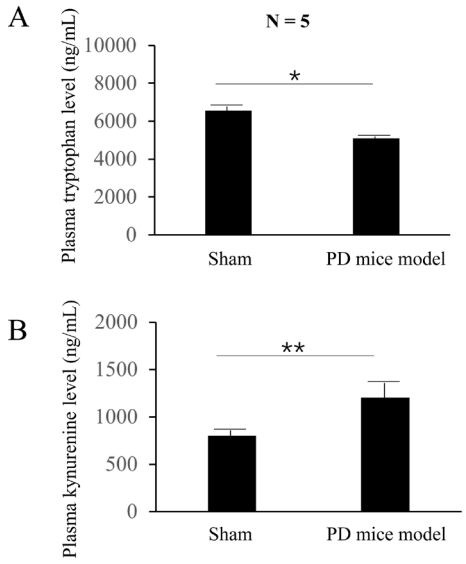

Figure 1. Preliminary data of the changes of plasma tryptophan and kynurenine in PD mice model. (A). Plasma tryptophan levels in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced PD mouse models significantly reduced (*vs*. sham group). **(B)**. Plasma kynurenine levels in MPTP-induced PD mouse models significantly increased (*vs*. sham group). $n = 5$ in each group; *represents $p < 0.05$; **represents $p < 0.01$.

that the KP metabolism may affect the CNS function and relate to the CNS disorders *via* the microbiota–gut–brain axis (*16*). A recent review study discussed the relationship between PD and the KP from the angles of microbiota–gut–brain, genetic link, and enzyme. They believe that the KP might be considered as a promising biomarker as well as therapeutic target for PD (*17*). Based on the abovementioned information and the current progress in the experimental studies of IDO1 on PD, we were motivated to conduct this review, focusing on the potential therapeutic role of the KP, particularly IDO1, in treating PD. We believe that this review will be beneficial in deepening insights regarding the effects of the KP on PD and helpful for developing novel therapeutic targets against PD, which are independent from the dopaminergic system and less affected by the BBB.

2. Status quo of PD treatment

The etiology and pathogenesis of PD are very complex and, presently, remain unclear, particularly the underlying causes of dopaminergic neuron apoptosis in the nigrostriatal pathway. Indeed, this may delay the development of efficacious treatments against PD since therapies focused on PD etiology cannot be created. Since the emergence of L-dopa in 1967 and the development of deep brain stimulation (DBS) in 1993, no revolutionary breakthrough regarding the treatment of PD has been reported (*4*). Dopaminergic medication and DBS still remain the mainstay treatments against PD. However, these treatments cannot stop dopaminergic neuron apoptosis, and hence, cannot halt PD progression either. Due to this, the PD treatments that are available nowadays are symptomatic. Our previous studies confirmed that both L-dopa and DBS can significantly improve PD symptoms in patients (*18-20*) and rodent PD (*21-23*) and primate PD (*24,25*) models. However, these treatments cannot halt the progression of PD and depletion of dopaminergic neurons. Currently, the first-line therapies for PD, including L-dopa, dopamine receptor agonists, monoamine oxidase inhibitors, or catechol-O-methyltransferase inhibitors, all act on the dopaminergic system and are collectively associated with the principle of dopamine replacement. However, the efficacy of these dopaminergic medications is far from satisfactory. For example, with PD progression, the decline of L-dopa efficacy (well known as the "wearing-off phenomenon") and side effects caused by the drug itself (such as dyskinesia; "on-off phenomenon") are becoming predominant problems following the long-term prescription of L-dopa. Surgical treatment, including DBS, also exhibits several limitations. For example, DBS is effective only for those patients who respond suitably to L-dopa. Additionally, DBS is a symptomatic treatment, which cannot stop PD progression. As an invasive surgery, the long-term efficacy of DBS remains

controversial and its mechanisms have never been clarified (*4,18-20,24,25*). Hence, selecting a satisfactory strategy for treating patients with advanced stage PD, particularly the selection of appropriate drugs, is indeed a difficult quandary. For some patients in the end stage, clinicians might be in a dilemma since no suitable drugs are available. In other words, the development of effective therapies against PD is urgently required, particularly the development of new agents with novel mechanisms (such as a mechanism of action independent of the dopaminergic system). This is where the KP system comes into the picture.

3. Roles of the KP in the CNS

Tryptophan, one of the eight essential amino acids in humans, plays indispensable roles in maintaining human growth, metabolism, and positive nitrogen balance. Approximately, over 95% of tryptophan is metabolized *via* the KP, while less than 5% of tryptophan generates 5-hydroxytryptamine (5-HT) (Figure 2). Under normal physiological conditions, tryptophan is found in almost all mammalian tissues, but mainly in the liver. The KP involves a series of steps by which tryptophan is finally converted to nicotinamide adenine dinucleotide + (NAD +) in the liver (Figure 2). The process of the KP is as follows: first, tryptophan is converted into n-formyl-kynurenine by two groups of rate-limiting enzymes, namely, IDO and tryptophan 2,3-dioxygenase (TDO). IDO is divided into two subtypes: IDO1 and IDO2. N-formyl-kynurenine is unstable and quickly converts into kynurenine. Kynurenine is nontoxic and forms the core of the KP. Kynurenine is then catalyzed by kynurenine-3-monooxidase (KMO) and converted into toxic 3-hydroxykynurenine (3-HK). Subsequently, 3-HK is converted into toxic 3-hydroxyanthranilic acid (3-HAA) catalyzed by kynureninase. Simultaneously, kynurenine can also be converted into anthranilic acid under the action of kynureninase. Anthranilic acid is also further converted into 3-HAA by monohydroxylase. Then, 3-HAA is converted into toxic quinolinic acid (QUIN), which is catalyzed by the kynurenine aminotransferase family. QUIN forms nicotine, which is converted into the end products (NAD +/NADP +) under the action of transamination. Additionally, there is another pathway where kynurenine is converted into a neuroprotective kynurenic acid (KA) catalyzed by kynurenic aminotransferase (*26-28*) (Figure 2).

In this review, the term "kynurenine-ergic substances (KESs)" was used for the metabolites generated in the KP, which exhibit multifold biological activities and are liposoluble. Of these KESs, only KA is neuroprotective. The remaining substances, including 3-HK, downstream 3-HAA, and further downstream QUIN, are neurotoxic (Figure 2). The KP mainly activates in the liver and most of the KESs are derived from the peripheral tissues. Nevertheless, under certain physiological (aging) or some pathological (BBB damage) conditions, these liposoluble substances may cross the BBB and affect the CNS. The KESs might be important "neurotoxins" that contribute to neuronal apoptosis in NDDs. Early in 1981, Stone and Perkins reported the agonistic effects of QUIN on central N-methyl-D-aspartic acid (NMDA) (*29*). Subsequently, Kessler *et al*. discovered the antagonistic effects of KA on the NMDA receptor (*30*). Till date, numerous studies have elucidated the physiological and pathological effects of these KESs from multiple dimensions: (1) IDO1, IDO2, and TDO act as the first rate-limiting enzymes in the KP. TDO is mainly expressed in the liver, whereas IDO is widely expressed in several organs, including the brain, liver, and kidney, and several cells, including monocytes and dendritic immune cells. IDO is

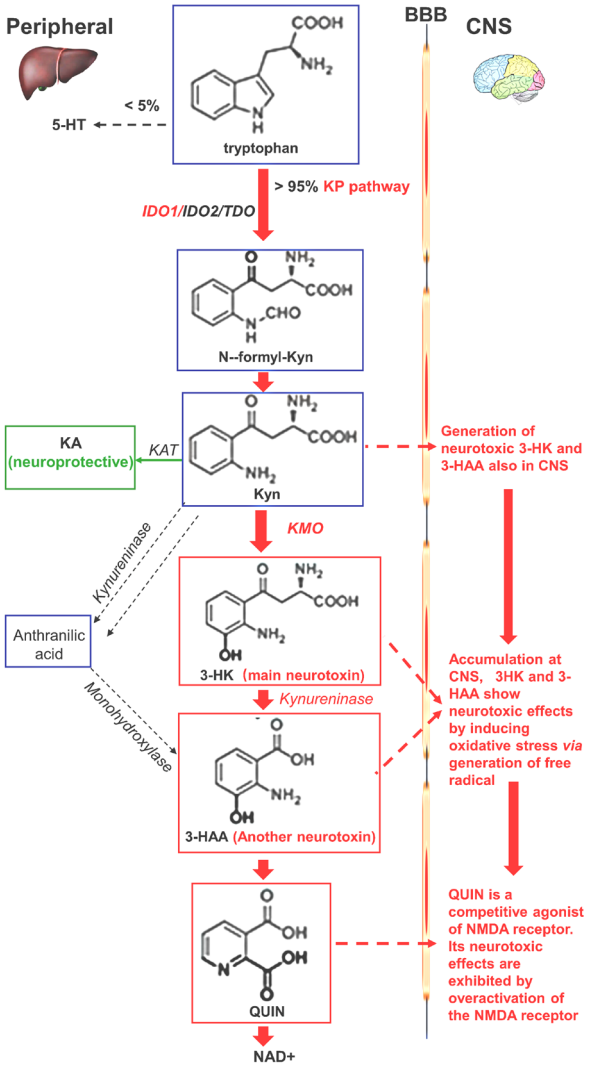

Figure 2. Metabolic processes of the tryptophan–kynurenine pathway and its pathophysiological roles in the CNS. 3-HAA: 3-hydroxyanthranilic acid; 3-HK: 3-hydroxykynurenine; 5-HT: 5-hydroxytryptamine; BBB: blood–brain barrier; CNS: central neuron system; KA: kynurenic acid; KAT: kynurenic aminotransferase; KMO: kynurenine-3-monooxidase; KP: tryptophan–kynurenine pathway; Kyn: kynurenine; IDO: indoleamine 2,3-dioxygenase; NAD: nicotinamide adenine dinucleotide; TDO: tryptophan 2,3-dioxygenase; QUIN: quinolinic acid.

commonly considered the predominant catalytic enzyme produced under inflammatory and/or stressful conditions (*31*). IDO1 can activate both anti-inflammatory and proinflammatory cytokines. Moreover, the activated T-cells, along with numerous inflammatory signaling pathways (such as NF-κB and TLR4), play a role in IDO1 activation (*31*). Although both peripheral and brain cytokines can induce IDO activation, IDO regulation mainly occurs in the peripheral tissues rather than in the CNS (*32*). (2) Kynurenine is subsequently regulated by the second rate-limiting enzyme KMO. KMO contributes to the regulation of 3-HK expression and can be stimulated by inflammatory factors, subsequently increasing the production of downstream 3-HK and QUIN, which exhibit neurotoxicity (*33*). KMO displays functions analogous to IDO. (3) Neurotoxins produced in the KP include 3-HK, 3-HAA, and QUIN. A large amount of 3-HK produced by the peripheral tissue may easily cross the BBB and accumulate in the CNS due to its high liposolubility. Microglia and astrocytes in the CNS produce a small amount of indigenous 3-HK. Even in healthy circumstances, 3-HK and 3-HAA can produce a number of free radicals, subsequently causing oxidative stress and mitochondrial damage, which may directly induce CNS disorders. Moreover, in an inflammatory circumstance, the overexpression of KMO and 3-HK enhances downstream QUIN levels and causes more severe neurological damage (*17*). QUIN is an agonist of the NMDA receptor, which exhibits the same effects on the NR2A and NR2B subtypes. Although QUIN may promote the release of glutamate in neurons, it simultaneously also suppresses glutamate uptake by glial cells. These effects induce the overactivation of the NMDA receptor, further inducing excessive calcium influx (*34*). In other words, the overactivation of the NMDA receptor may generate superabundant reactive oxygen species. These effects finally result in comprehensive neuronal damage. Additionally, QUIN plays a role in triggering local CNS inflammation. It has been reported that QUIN is closely associated with a series of inflammatory processes in the CNS (*17*). Briefly, the neurotoxic effects of the KP are due to 3-HK, 3-HAA, and QUIN. (4) As the sole neuroprotective component of the KP, KA acts as an antagonist for three endogenous glutamate receptors, particularly for the NMDA receptor. The neuroprotective action of KA is due to the suppression of the neurotoxicity that is produced by the activation of the NMDA receptor by QUIN overactivation (*35*). Moreover, KA can also antagonize the noncompetitive α7-nicotinic acetylcholine receptor (α7-nAChR) and reduce the extracellular levels of glutamate and dopamine in the CNS (*36*). In this regard, the QUIN/KA ratio is commonly used as an index of glutamate receptor activation and neurotoxicity.

Reportedly, KESs, particularly IDO1, are closely associated with the neurological disease. Some previous studies reported that IDO1 overexpression enhances the ratio of kynurenine/tryptophan, thereby inducing depression-like behaviors in animals (*6-8*). Conversely, the suppression of IDO1 expression may alleviate such depression-like symptoms (*6*). Leraci *et al*. revealed that the activation of the KP induces cognitive impairment in rats, the mechanisms of which might be related to the decline in the levels of brain-derived neurotrophic factor (*37*). Other studies have reported that the KP is associated with stroke (*11*) and multiple sclerosis (*10*). Widner *et al*. found that the ratios of serum kynurenine/tryptophan and IDO1 increased and the activation of IDO1 is relevant to the cognitive impairment observed in patients with AD (*9*). Duan *et al*. found that IDO1 inhibitor can alleviate neurotoxicity associated with amyloid β and tau proteins in animal models of AD (*38*). They hypothesized that IDO1 inhibitor might exhibit neuroprotective effects on PD since PD is also an NDD with protein depositions (*38*). Currently, the effects of the KP on CNS diseases are complicated and remain unclear. Recently, Park *et al*. reported that antioxidant stress might be an essential mechanism underlying this effect. As a key enzyme in the KP, IDO1 plays a crucial role in the regulation of the KP. Hence, IDO1 should be considered a potential therapeutic target for neurological diseases (*39*).

4. Association between the KP and PD

Our preliminary data demonstrates that the tryptophan levels in the animal models of PD decreased, while the kynurenine levels enhanced, indicating the involvement of the KP in the pathophysiology of PD. These data implied that during the PD state, the KP is activated, which might be associated with a battery of neurotoxic effects. Early in 1992, Ogawa *et al*. reported that the levels of neurotoxic 3-HK in the putamen and substantia nigra significantly increased, while those of neuroprotective KA decreased in patients with PD (*40*). Later, Miranda *et al*. reported that the enhancement of the KA levels in animal brains resulted in resistance toward QUIN-mediated neurotoxicity and the protection of the dopamine neurons (*41*). Zadori *et al*. reported that the induction of KA production in the KP serves a neuroprotective function, contributing to the amelioration of PD symptoms (*42*). Recently, Perez Pardo *et al*. verified that TDO inhibitors can significantly improve PD symptoms and CNS inflammation in rotenone-induced PD models. These results provided further evidence concerning a key link between the KP and inflammatory mechanisms of PD (*12*). The aforementioned results prove that the KP is closely associated with the development and progression of PD.

Two factors, namely, aging and gut microbiota, are involved in the relationship between the KP and PD. Aging is the most important factor that affects the development and progression of PD; meanwhile, aging also plays a key role in the disorders of the KP.

Reportedly, the cerebral IPO activity increases with aging (*43*). Sustained stimuli from a low degree of inflammation and the IDO upregulation may influence some aging-related disease. For example, aging-related inflammation might trigger the activation of the KP and increase the risk of developing NDDs (*44,45*). Commonly, due to the existence of the BBB, inflammatory factors present in the peripheral organs and tissues have diminished direct influence on the CNS. However, in terms of the liposoluble nature of the KESs in the KP, they have the remarkable ability to affect the CNS by crossing the BBB. Therefore, we believe that the KP plays a key role in "delivering aging signal" from the periphery to the CNS, thereby contributing to the regulation of inflammatory processes in the CNS (*46,47*).

Another factor involved in the relationship between the KP and PD is the disturbance of the gut microbiota. From the viewpoint of the microbiota-gut-brain axis, the KP acts as a bridge between α-synuclein (α-syn) deposition and the gut microbiome. It is well established that α-syn accumulation Lewy body formation in dopaminergic neurons are the most important neuropathological characteristics of PD. α-Syn deposition has been reported to occur not only in the CNS but also in the intestine in patients with PD, as well as in older individuals without PD (*48*). Bu *et al*. reported α-syn deposition in the enteric nerves of older people without PD (*49*). Moreover, Devos *et al*. revealed that kynurenine present in the gut can easily cross the BBB and affect the KP metabolism in the brain (*50*). Some gut microbiota can even directly produce kynurenine and 3-HAA (*51*), which possibly cross the BBB and introduce neurotoxic effects in the CNS. Evidence indicates that the disturbance of the gut microbiota can affect the plasma concentration of KESs (*17*). Moreover, high QUIN levels in the abnormal KP under certain pathological conditions has been reported to be associated with α-syn deposition in the gut (*52*). A recent study suggested that α-syn deposition originates in the digestive tract and affects the brain *via* the vagus nerve pathway (*53*). These aforementioned reports seem to imply that the microbiota–gut–brain axis affects α-syn deposition *via* the KP; however, unfortunately, to the best of our knowledge, no studies so far have provided evidence indicating the direct association between the abnormal KP and α-syn deposition in the CNS and that the abnormal KP causes PD. Therefore, we speculate that aging, along with other pathological factors, may induce gut microbiota disturbance, subsequently activating the KP and producing a number of toxic KESs, which cross the BBB, ultimately inducing α-syn deposition (Figure 3).

5. IDO1 is a key target for regulation of the KP and PD

Compared with TDO, IDO is more widely distributed. IDO1 is widely expressed in the peripheral organs and tissues including the lung, blood vessels, and fat. IDO1 expression is upregulating with age. Moreover, the expression level of IDO1 is also positively correlated with the expression of aging markers, including p16 and p21 (*54*), as well as the expression of aging-related secretory phenotypes, including IL-6 and TNF-α (*55*). In the aging animal models, the expression level of IDO1 is also significantly upregulated, which accelerated the aging processes in these animals (*56*). Evidence shows that stimuli of low-degree sustained inflammation can induce IDO1 upregulation, which activate the KP and further increase the risk of NDDs (*44,45*). These

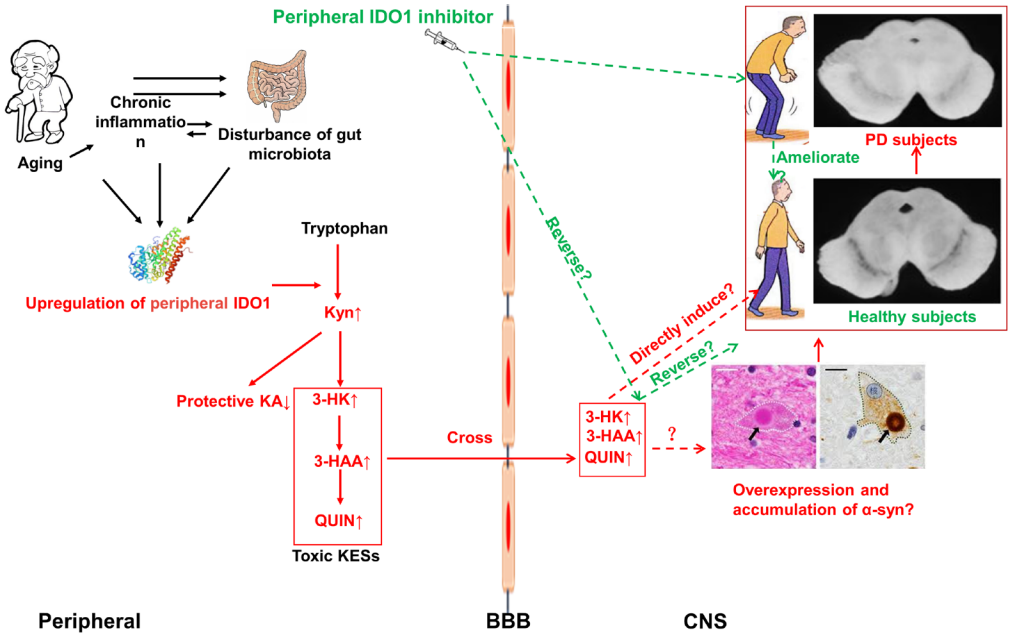

Figure 3. Potential mechanisms involved in the interactions between the KP and PD. Red represents the pathological changes induced by the KP, and green represents the protective effects conducted by the intervention of the KP with an IDO1 inhibitor.

studies confirmed that IDO1 is highly correlated with inflammation. However, presently, there is only direct evidence concerning increased IDO1 expression in AD (*17*), but not reported in PD. In terms of the indirect evidence, currently, Ning *et al*. employed a co-inhibitor of IDO1 and TDO to treat the rat PD models. They found that IDO1 suppression reduced the levels of inflammatory factors, increased the neuroprotective KA level, and alleviated the depletion of dopamine neurons in the rats' brain. Importantly, administration of IDO1 inhibitor significantly improved the motor symptoms in PD animals, and its efficacy is comparable to L-dopa (*13*). Sodhi *et al*. directly administrated an IDO1 inhibitor in the traditional 6-hydroxydopamine-induced PD rat models. They found that the behavioral performance in PD animals was significantly improved. The degrees of oxidative stress, inflammation, and mitochondrial damage in the CNS were also improved (*14*). These investigations suggest that IDO1 can be considered as a potential key target in the KP, which is closely involved in the development of PD. Hence, we hypothesize that the peripheral IDO1 activity increased with aging or under certain pathological conditions (like inflammation). Such activated IDO1 may stimulate the KP metabolism, resulting in the production of more toxic KESs, which might cross the BBB and cause neuronal damage in the CNS (*43*) (Figure 3). However, so far, several evidences in this hypothesis remain absent: (1) No direct evidence has elucidated that upregulation of IDO1 will affect cerebral α-syn deposition and dopamine neuron apoptosis in the PD subjects. (2) With respect to efficacy, only two studies verified the efficacy of IDO1 suppression against PD symptoms. However, these studies employed the simplest behavioral assessments in rodent PD animal. Investigations with more rigorous experimental design to verify the efficacy of IDO1 suppression are indispensable, for example, effects of IDO1 inhibitor on different stage of PD model, on nonmotor symptoms, and on different sorts of PD model (mouse, rat, and nonhuman primates). (3) What are the interactions between IDO1 suppression and conventional dopaminergic therapeutics; synergistic effects or canceling effects? To uncover the roles of the KP, particularly IDO1, in PD, several further investigations are expected to clarify these issues.

6. Concluding remarks

In this review, updated information regarding the roles of the KP in PD was provided. The results of Ning's study (*13*) got an inspiring result, that is, IDO1 inhibitor might achieve a "comparable" efficacy versus L-dopa, which is now still regarded as the golden standard medication for PD. We believe the KESs, particularly IDO1, are promising novel targets against PD, which are independent from the dopaminergic system and are seldom affected by the BBB. Once these novel targets are successfully verified and developed, they are the next-generation medications in treating PD. Clinicians can have more options other than the dopaminergic medications. Moreover, administration and regulation of such medicines will be very convenient, since they mainly act in the periphery and are seldom influenced by the BBB. Hence, the effects of the KP, KESs, particularly IDO1, on PD warrant further notice and investigation since it might bring a revolutionary progress in the PD treatment.

However, to uncover the secrets of the KP on PD, panoramic understanding and insights are indispensable. The following concerns should be fully addressed:

i) Expression and distribution of all the KP members, including KESs in the peripheral organs, and the CNS should be thoroughly clarified, particularly under the PD pathological conditions.

ii) Can KESs affect α-syn expression and deposition and further affect the apoptosis of dopamine neurons?

iii) Clinically, can intervention of KESs achieve amelioration of the PD symptoms, including motor and nonmotor symptoms? Finally, can it stop the PD progression?

iv) What are the interactions between intervention of KESs and conventional dopaminergic therapy? Can patients benefit from combining these two different medications, for example, achieve improvement of QOL and ADL?

Undoubtedly, at present, researches clarifying the effects of the KP on PD remain in the exploratory stage. Verifying the effects of the KP will still take a long time, even though the first light has risen.

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