Neurosci Bull February 1, 2010, 26(1): 66-76. http://www.neurosci.cn
DOI: 10.1007/s12264-010-0302-z

·Minireview·

Treatment strategies for Parkinson's disease

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Abstract: Parkinson's disease (PD) is caused by progressive degeneration of dopamine (DA) neurons in the substantia nigra pars compacta (SNpc), resulting in the deficiency of DA in the striatum. Thus, symptoms are developed, such as akinesia, rigidity and tremor. The aetiology of neuronal death in PD still remains unclear. Several possible mechanisms of the degeneration of dopaminergic neurons are still elusive. Various mechanisms of neuronal degeneration in PD have been proposed, including formation of free radicals, oxidative stress, mitochondrial dysfunction, excitotoxicity, calcium cytotoxicity, trophic factor deficiency, inflammatory processes, genetic factors, environmental factors, toxic action of nitric oxide, and apoptosis. All these factors interact with each other, inducing a vicious cycle of toxicity causing neuronal dysfunction, atrophy and finally cell death. Considerable evidence suggests that free radicals and oxidative stress may play key roles in the pathogenesis of PD. However, currently, drug therapy cannot completely cure the disease. DA replacement therapy with levodopa (*L*-Dopa), although still being a gold standard for symptomatic treatment of PD, only alleviates the clinical symptoms. Furthermore, patients usually experience severe side effects several years after the *L*-Dopa treatment. Until now, no therapy is available to stop or at least slow down the neurodegeneration in patients. Therefore, efforts are made not only to improve the effect of *L*-Dopa treatment for PD, but also to investigate new drugs with both antiparkinsonian and neuroprotective effects. Here, the advantages and limitations of current and future therapies for PD were dicussed. Current therapies include dopaminergic therapy, DA agonists, MAO-B inhibitor, COMT inhibitors, anticholinergic drugs, surgical procedures such as pallidotomy and more specifically deep brain stimulation of the globus pallidus pars interna (GPi) or subthalamic nucleus (STN), and stem cell transplantation.

Keywords: Parkinson's disease; treatment strategy; pharmacological neuroprotection

1 Advantages and limitations of current therapy

The diagnosis of Parkinson's disease (PD) generally relies on the clinical observation of 4 cardinal motor signs: tremor, rigidity, bradykinesia, and balance impairment or postural instability. These symptoms, typically the first three, can be improved by dopamine (DA) replacement therapy, and a "good" response to levodopa (*L*-Dopa) is mandatory for the diagnosis of the disease[1]. However, not all the parkinsonian motor symptoms can be adequately controlled with dopaminergic medication. Furthermore, non-motor features, such as dysfunctions in autonomic, cognitive and psychiat-

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Article ID: 1673-7067(2010)01-0066-11
Received date: 2009-03-02; Accepted date: 2009-11-02

ric systems, are also frequent and have become an important source of disability in patients. These non-motor features also tend to be poorly responsive to *L*-Dopa and may even be worsened by antiparkinsonian medications[2].

1.1 Dopaminergic therapy *L*-Dopa is the precursor of DA, and dopaminergic therapy was first introduced by Hornykiewicz in 1970. After 4 decades of universal usage, *L*-Dopa therapy remains a gold standard for the treatment of PD. Its major advantages include the relatively cheap price, and its ability to cross the blood-brain barrier after the conversion into DA. In the early stage of PD, *L*-Dopa is effective in ameliorating the motor symptoms, such as alleviation of akinesia or bradykinesia and rigidity, and partial response to tremor. This period is also known as the *L*-Dopa "honeymoon". Besides, *L*-Dopa is the only drug that has been reported to improve life expectancy[3]. However, this therapy also has limitations in various facets. Firstly, after long-term usage, disabilities in motor symptoms such as speech, gait, posture, and balance, tend to deteriorate despite of the optimal *L*-Dopa therapy[4]. Non-motor features of PD are also present during the treatment, such as hallucination, cognitive impairment, and orthostatic hypotension. Besides, "wearing off" or "on-off" fluctuations and dyskinesia tend to worsen with continuing *L*-Dopa exposure, in approximately 50% of the patients after 5-year medication. Moreover, it has been reported that *L*-Dopa may accelerate the neuronal degeneration by way of oxidative metabolism[5], although this proposition is still controversial today. Finally, *L*-Dopa can neither halt or retard the disease progression, nor reverse the PD-associated biochemical abnormalities.

1.2 DA agonists The pharmacological effects of DA agonists are achieved by direct stimulation of postsynaptic DA receptors in the striatum[6]. Different from *L*-Dopa, DA agonists such as pramipexole, ropinirole and pergolide[7], can delay the onset of motor fluctuations. Similarly, patients receiving combined treatment of cabergoline and *L*-Dopa[8] are 50% less likely to develop motor function problems than when receiving *L*-Dopa monotherapy. Although active on motor symptoms, DA agonists are less efficacious than *L*-Dopa and are relatively more expensive, especially the newest ones. For the side effects, sleep disturbances and cognitive problems such as confusion and hallucination occur more frequently, especially in the elderly and in those with pre-existing cognitive deficits. In patients whose symptoms are severe enough to disturb their social or work activities, symptomatic treatment with *L*-Dopa combined with DA agonist may be necessary. DA agonists not only reduce the need of *L*-Dopa in clinical benefit, but also independently exert neuroprotective effects in PD patients.

1.3 Monoamine oxidase-B (MAO-B) inhibitors Selegiline is a selective MAO-B inhibitor that prevents the breakdown of DA. If given in conjunction with *L*-Dopa, selegiline could reduce motor response fluctuations and decrease the dosage requirement for *L*-Dopa[9]. Besides, it attenuates parkinsonian motor symptoms and delays the need for *L*-Dopa treatment by several months[10]. However, it has no impact on *L*-Dopa–resistant motor or non-motor features. And there is growing concern about an increased risk of mortality in PD patients receiving combined treatment of selegiline and *L*-Dopa, although it has not been confirmed by other studies. Moreover, the therapeutic effects could be counteracted by its many neurotoxic metabolites. Thus, a novel MAO-B inhibitor rasagiline, is developed.

Rasagiline is a selective and irreversible inhibitor of MAO-B. Recently, it has been evaluated in phase III clinical trials as an adjunct to *L*-Dopa therapy or as a monotherapy for early stage of PD[11]. The results of the trial demonstrate that rasagiline is effective as a monotherapy in early stage of PD. However, further studies are required to evaluate the long-term effects of rasagiline in PD.

1.4 Catechol-O-methyl transferase (COMT) inhibitors The main metabolite of *L*-Dopa is 3-O-methyldopa, and COMT contributes a lot for this process. COMT inhibitors can increase the plasma half-life of *L*-Dopa, which allows a relatively larger amount of *L*-Dopa crossing the blood-brain barrier. Thus, the inhibitors would lead to a more constant level of *L*-Dopa in the brain and consequently increase "on" time and decrease "off" time[12]. Entacapone is the sole COMT inhibitor available worldwide, since the use of tolcapone (the first discovered COMT inhibitor) was suspended in several countries including the European Union and restricted in the United States due to its side effect of liver toxicity. However,

research still indicates that tolcapone widens the levodopa therapeutic window, even in patients who have not benefited from entacapone. Thus tolcapone is indicated before patients are referred for more invasive procedures[13].

1.5 Anticholinergic drugs Anticholinergic drugs are among the oldest and cheapest antiparkinsonian medications. They are useful adjuvants to *L*-Dopa treatment and are more effective in ameliorating the mild symptoms of tremor and rigidity without alterations in bradykinesia. However, anticholinergic drugs often produce many side effects, such as dry mouth, sweating inhibition, blurred vision, and urinary retention. Reactions in the central nervous system (CNS), such as confusion, dementia and psychiatric symptoms are also common and can be a particular problem in old patients. There are no data available concerning the effects of anticholinergics drugs on motor fluctuations, disease progression, or mortality. It is normally accepted that the anticholinergics drugs can antagonize the hyperactive cholinergic transmission, via blockade of postsynaptic muscarinic receptors, thereby restoring the balance between DA and acetylcholine (ACh) systems in the striatum. However, recent studies suggest that the underlying mechanisms are more complex than previously thought[14]. Extrastriatal and different neurotransmitter systems may be also involved in the effects exerted by antimuscarinic drugs.

The mostly used cholinergic antagonists include trihexyphenidyl, benztropine, biperiden, orphenadrin, and procyclidine. They are effective in the treatment of tremor and drooling, but have limitations in other signs and symptoms of PD.

Amantadine is another old and cheap antiparkinsonian drug, and has modest effects on parkinsonian motor features. Its mechanism has not been clearly delineated, but recently it has been recognized as a weak antagonist for *N*-methyl-*D*-aspartate (NMDA) receptors. It has gained great interest in the treatment of PD due to its antidyskinetic effects, probably related to the NMDA receptor antagonistic properties. The side effects of amantadine include confusion, hallucination, livedo reticularis and edema. NMDA receptor antagonists could potentially provide neuroprotective effects, and some reports suggest that amantadine may slow the rate of PD progression[15]. However, no clinical trials have been properly designed or performed.

1.6 Surgical procedures Currently, there has been a resurgence of interest in surgical procedures such as pallidotomy and more specifically deep brain stimulation of the globus pallidus pars interna (GPi) or subthalamic nucleus (STN), in treating PD patients with severe disabilities that cannot be satisfactorily controlled with available medical therapies[16]. Neurosurgical procedures are limited to the symptoms or *L*-Dopa-induced dyskinesias so troublesome that they cause disabilities at home or at work. Before *L*-Dopa treatment, stereotaxic lesions of the thalamus (thalamotomy) are efficient targets for the treatment of tremor. Chronic deep brain stimulation is an alternative way to destructive lesions, and seems to produce a functional lesion in the target area, perhaps by depolarization block. The advantages lie that the stimulation parameters can be titrated to yield an optimum response over time and that it is reversible if adverse effects occur. However, although tremor can be controlled, akinesia is not alleviated. While response fluctuations are reduced, potentially surgery-related important side effects can occur in 2%-5% of the patients, including mechanical defects and infection. Besides, deep brain stimulation can not slow the disease progression and thus does not prevent worsening of gait and balance, cognitive disturbances, hypophonia or dysphagia[17]. Moreover, it is expensive and requires expertise in diagnosis, imaging, stereotactic surgery, neurophysiology, microelectrode recording, and postoperative management of the stimulator system, all of which greatly limit its widespread applicability.

Transplantation of fetal dopaminergic cells can provide functional and biochemical improvement in animal models of PD[18]. Similar techniques have been applied in patients. PET scans have shown significant increases in (^{18}F) fluorodopa uptake in the area around the graft that has been maintained for at least 6 years in several patients. Long–lasting symptomatic improvement has been reported in a majority of the grafted patients, and in the most successful cases, it is possible to withdraw *L*-Dopa treatment. The main limitations of transplantation are the ethical, practical and safety issues concerning the tissue from aborted human foetuses and the large amount of tissue needed to obtain therapeutic effects.

Fetal nigral transplantation has been proved to be promising by open-label studies, but 2 consecutive placebo-controlled double-blind trials fail to meet their primary end point and have shown specific transplant-related side effects, such as off-medication dyskinesia[19]. Treatment with free-radical scavengers, caspase inhibitors or neurotrophic factors during the fetal cell preparation may improve DA neuron survival. Other approaches using stem cells and gene therapies are promising but have not been established to be effective or well tolerated in patients. Currently, no evidence has supported that these surgical procedures could improve *L*-Dopa resistant symptoms or life expectancy, or delay the disease progression.

In summary, currently available treatments to manage motor symptoms and motor complications are based on the DA replacement strategy and act by stimulating DA receptors (Table 1), consistent with the concept that striatal DA denervation plays a key role in the pathogenesis of motor symptoms. Non-dopaminergic medical treatments, such as anticholinergics, antiglutamate agents and surgical procedures, also have some antiparkinsonian effects but generally are used in a more restricted fashion, and no therapy provides more powerful antiparkinson effects than *L*-Dopa.

Table 1. Current therapeutic interventions to treat motor features of PD

Current therapeutic interventions
Drugs
Dopaminergic medications
L-Dopa
Dopamine agonists: apomorphine, bromocriptine, cabergoline, dihydroergocriptine, lisuride, pergolide, piribedil, pramipexole, ropinirole
MAO-B inhibitor: selegiline
COMT inhibitors: entacapone (tolcapone)
Non-dopaminergic medications
Antiglutamate: amantadine
Anticholinergic: benztropine, biperiden, orphenadrin, procyclidine, trihexyphenidyl
Surgery
Lesion: thalamotomy, pallidotomy, subthalamotomy
Deep brain stimulation: thalamus, pallidum, subthalamus nucleus
Restorative
Transplantation
Trophic factors (GDNF)
Stem cells
Gene therapies
Rehabilitation
Physical, occupational and speech therapy

2 Future therapy: pharmacological neuroprotection

Although the rate of nigral cell death is not exactly known, neuro-imaging techniques estimate that approximately 10% of the nigral cells die each year. Although the degenerative process is progressive, compensatory changes may develop, thus the deterioration is not a linear change. There is a gradual decline in the number of necrotic substantia nigra pars compacta (SNpc) and DA neurons of the basal ganglia with aging, even in the general population. In idiopathic PD, symptoms become apparent when 70%-80% striatal and approximately 60% nigral DA neurons are lost. Recent neuroimaging (PET and SPECT) and autopsy data indicate that there is a preclinical period of 4-5 years before the appearance of symptoms, with the disease progression relatively more rapid during the early phase than during the more advanced stage of the disease. Thus, it is possible to conduct neuroprotective intervention during the preclinical phase. The establishment of the neuroprotective strategy against PD should be based on the etiology and pathogenesis of dopaminergic cell death, as shown in Table 2[20].

2.1 DA agonists DA agonists can not only reduce the need for *L*-Dopa, but also have an independent neuroprotective effect. *In vitro* and *in vivo* studies have demonstrated their capacity to protect dopaminergic and non-dopaminergic neurons[21], and the DA agonists have emerged as important candidates for disease modification in PD. In tissue culture, DA agonists could enhance the growth of cultured DA neurons and protect them from a variety of toxins. *In vivo* studies indicate that these agonists can similarly protect nigrostriatal DA neurons from 6-OHDA and MPTP[22]. DA agonists can also protect non-dopaminergic neurons.

Table 2. Neuroprotective strategies against PD

Etiopathogenesis (multi-factorial)	Neuroprotective agents
Oxidative stress	Antioxidants: Vit E, Tea, CoQ, red wine, N-acetyl
	cysteine, ascorbic acid
	Scavengers: salicylic acid, flavonoids
Iron increase	Iron chelators: apomorphine, desferoxamine
DA decrease	DA agonists: pramipexole, ropinirole, quinpirole, pergolide cabergoline, apomorphine, bromocriptine,
NO synthesis	Inhibitors of NO synthase: 7-NI
Mitochondrial dysfunction	Creatine
↓Neurotrophic factors	Neurotrophic factors: GPI 1485, GM-1ganglioside, Glial cell-derived neurotrophic factor (GDNF)
Apoptosis	Bcl-2 over-expression, caspase 3 inhibitors,
Immunological mechanisms	Suppress immuno-reactions
Glutamatergic excitotoxicity	Glutamate antagonists: remacemide, amantadine
	Glutamate release inhibitors: riluzole
↑Inflammatory processes	Anti-inflammatory drugs: COX-2 inhibitors, aspirin
↑MAO-B activity	MAO-B inhibitors: selegiline, rasagiline
Adenosine increase	Adenosine antagonist: caffeine, KW-6002,
	SCH-58261, KF-17837, VER-11135
Other	Nicotine, modafinil, folate, estrogen, erythropoietine

Protective effects have been observed in a variety of agonists, including bromocriptine, pergolide, pramipexole, apomorphine and ropinirole, and it remains to be determined whether this is a class effect and if any of these agents offers benefits that are more potent or more relevant to the clinical situation in PD[23]. Recent clinical studies of pramipexole and ropinirole also indirectly evaluated the rate of disease progression in patients treated with DA agonists compared with those taking *L*-Dopa. Results show that initial treatment with pramipexole results in lower incidences of dyskinesias and wearing off compared with initial treatment with levodopa. Besides, initial treatment with levodopa results in lower incidences of freezing, somnolence, and edema and provided for better symptomatic control, as measured by the Unified Parkinson's Disease Rating Scale, compared with initial treatment with pramipexole. Both options result in similar quality of life. Levodopa and pramipexole both appear to be reasonable options as initial dopaminergic therapy for PD, but they are associated with different efficacy and adverse-effect profiles[24].

In vitro and *in vivo* data suggest that DA agonists exert neuroprotective effects via both DA receptor and non-DA receptor. Firstly, DA agonists exert a *L*-Dopa-sparing effect, thereby minimizing the formation of oxidative radicals derived from the metabolism of *L*-Dopa. This is the initial basis for considering that DA agonists might be neuroprotective in PD. Secondly, DA agonists might act as free radical scavengers in both *in vitro* and *in vivo* systems, thus providing protective effects. Thirdly, DA agonists may exert antioxidant effects through the activation of presynaptic autoreceptors. DA agonists may inhibit DA synthesis, release, and metabolism, thus decreasing free radical production and the risk of oxidative damage. Finally, it is also possible that DA agonists exert neuroprotective effects by preventing STN-mediated excitotoxicity. Physiological and metabolic studies indicate that the STN, which uses glutamate as its neurotransmitter, is overactive in PD. Also, DA agonists may provide neuroprotection via the anti-apoptotic effect.

R-Apomorphine (R-APO) is a DA D_1/D_2 receptor agonist acting both pre- and post-synaptically. Clinical trials in-

dicate that it can reduce 'on-off' oscillations and wean the patients from *L*-Dopa[25]. *In vitro* studies have shown R-APO to be a radical scavenger, a highly potent iron chelator and an inhibitor of membrane lipid peroxidation. R-APO has also been implicated in inhibition of brain and mitochondrial protein oxidation. More recently, apomorphine has been shown to induce trophic factors in cultured mesencephalic dopaminergic neurons. *In vivo*, R-APO can also exert neuroprotective properties against MPTP- and methamphetamine-induced PD at the dose of 5 mg/kg or higher. However, the possible neuroprotective and neurotrophic effects of R-APO in the 6-OHDA-lesion rat model of PD has not yet been addressed[26]. Besides, R- and S-APO can prevent the increase in mRNA levels of TNF-α, GDNF and cyclin B2 induced by MPTP, suggesting that besides the oxidative processes, inflammation is also inhibited. Moreover, it is reported that apomorphine has anti-apoptotic properties[27].

Intermittent subcutaneous injection of apomorphine has been proved to be effective and safe for outpatient usage to reverse off-state events that occur despite of the optimized oral therapy[28]. Long-term and open-label studies have demonstrated the persistent response to injectable apomorphine as a rescue therapy for up to 5 years. To keep up with the disease progression, an increase in the number of doses per day is required, while duration of benefit and dosage of each injection remain the same[29]. Recently, Stacy[30] suggests that apomorphine may have a greater potency than other DA agonists.

2.2 Nicotine or nAChR agonists In PD brain, there is a loss of nicotinic ACh receptors (nAChR). The report that nicotine treatment relieves some of the symptoms and the observation of a decreased incidence of PD with tobacco use (due to the nicotine in tobacco products) imply that nicotine or nAChR agonists may have antiparkinsonian and long-term neuroprotective effects[31]. However, there are multiple nAChR populations in the brain with different functional properties such as cognition and addiction. Therefore, identification of the subtypes involved in nigrostriatal dopaminergic activity is critical in the selection of therapeutic agents for symptomatic treatment and/or neuroprotection against PD.

In vitro studies indicate that nicotine can protect against glutamate cytotoxicity (NMDA receptor) by its inhibitory effect on nitric oxide (NO) formation. Another potential mechanism for nicotine-induced attenuation of excitotoxicity is via the production of growth factors (FGF-2 and BDNF). This effect appears to be mediated by α7 subtype nAChRs. Interestingly, the neuroprotection by nicotine depends on both the concentration and incubation period. In several cases, 0.5-24 h of pre-incubation with nicotine is required for neuroprotection, while others have reported successful neuroprotection by post-incubation with nicotine for 1 h. These discrepancies suggest that different mechanisms may be involved in the neuroprotective properties of nicotine in these model systems[32]. *In vivo* studies indicate that nicotine can prevent MPTP toxicity. The neuroprotective effects of nicotine in rats bearing 6-OHDA-induced nigrostriatal tract lesion have also been examined[33]. The neuroprotective effect of nicotine in rats is critically dependent upon the dosage and the application time, and is consistent with the activation of nAChRs, since a high dose of nicotine may desensitize its receptor, thus failing to exert neuroprotective effects. Interestingly, the effects of nicotine are present only in 8-10-month-old animals, not in 6-8-week-old animals, indicating that age may also be a factor for the production of neuroprotective effect by nicotine. Furthermore, neuroprotection is absent in α4 nAChR subunit knockout mice. α6 nicotinic receptors are present on nigrostriatal dopaminergic neurons and receptors containing this subunit may be vulnerable to nigrostriatal damage. α6 mRNA is highly expressed in catecholaminergic neurons and its level has been shown to increase in the SN following MPTP treatment in the monkey. Administration of α6 antisense mRNA into the rat brain by osmotic minipump could reduce the effect of nicotine on locomotor activity. These *in vivo* results suggest that activations of α6, α4β2 and possibly α7 subunits containing nAChRs play a major role in the production of neuroprotective effect by nicotine upon Parkinsonian-like damage. There is evidence indicating that nicotine may act as an antioxidant or prevent excitoxicity. Nicotine can also exert antiparkinsonian effects, since nicotine administration could induce an increase in DA release (perhaps due to the stimulation of presynaptic nicotine receptors).

Other epidemiological studies have shown that smoking can lessen the incidence of PD, indicating that smoke may contain neuroprotective chemicals[34].

2.3 Antioxidants Based on the oxidative hypothesis, administration of antioxidants could lower the oxidative stress, therefore slowing the degenerative process during PD. Coenzyme Q10 (CoQ) is an electron acceptor for complexes I and II of the electron transport chain. Coenzyme Q10, an endogenous lipophilic antioxidant, plays an indispensable role in ATP synthesis. The therapeutic value of coenzyme Q10 in PD and other neurodegenerative disorders is still being tested and the preliminary results are promising[35]. The activity of complex I is reduced in mitochondria from platelets of parkinsonian patients, with proportional reductions of CoQ. Administration of CoQ protects against MPTP toxicity in mice. In patients, CoQ increases plasma concentrations of vitamin and is well tolerated[36]. These findings suggest that chronic administration of CoQ in PD patients could improve mitochondrial electron transport chain function and reduce intracellular levels of free radicals, thus slowing disease progression.

Table 3 lists several agents currently under investigation of their potential neuroprotective effects, based on their capacities to modify mitochondrial dysfunction and oxidative stress. These agents are therefore promising candidates for neuroprotective drugs against PD.

2.4 Antagonists of glutamate receptors and glutamate release inhibitors Glutamate is a major excitatory amino acid in the CNS and acts through ionotropic glutamate receptors (iGluRs) or metabotropic glutamate receptors (mGluRs). Excessive release of glutamate is neurotoxic and numerous preclinical studies have demonstrated that antagonists of glutamate receptors and glutamate release inhibitors are neuroprotective. Since the neuronal activity is increased in the STN and the Gpi of parkinsonian animals and human, and the STN provides excitatory glutamatergic input to the Gpi, glutamate inhibition is promising in improving parkinsonism.

Table 3. Bioenergetic agents effective in PD models[37]

Agents	Proposed mechanisms
Coenzyme Q10	Cofactor of complexes I, II, III ; antioxidant
Creatine	Increases PCr; inhibits the MPT
Ginkgo biloba	Antioxidant; preserves mitochondrial function
Carnitine	Facilitates fatty acid transport; increases respiration
Nicotinamide	Precursor of NADH; inhibitor of poly-ADP-ribose polymerase
Lipoic acid	Coenzyme for α-ketoglutarate dehydrogenase; antioxidant

PCr: creatine/phosphocreatine; MPT: mitochondrial permeability transition pore; NADH: nicotinamide adenine dinucleotide.

Riluzole is a Na^+-channel blocker that preferentially stabilizes the inactivated conformation of the channel and displaces the voltage-inactivation curve to more hyperpolarized potentials. By blocking Na^+ channels, riluzole reduces neuronal excitability, energy demand and glutamate release[38]. Riluzole has been shown to produce neuroprotection in a number of *in vivo* models of neurodegenerative diseases in mice, rats and marmosets, suggesting a broad neuroprotective potential. Beneficial effects have been observed in the mouse MPTP-induced and the rat 6-OHDA-induced PD models. The novel neuroprotective mechanism of riluzole is the direct inhibition of protein kinase C. In a pilot study, the compound appeared to be well tolerated in patients with PD. Further studies are conducted to evaluate the effect of riluzole (50 mg bid) in patients with motor fluctuations and dyskinesia. Also, a large multicenter study has been initiated to evaluate the potential neuroprotective and neurorestorative properties of riluzole[39]. All these studies indicate a good tolerability to riluzole. However, it seems that riluzole could not provide any meaningful symptomatic benefit in patients with PD. Larger and more longitudinal studies are further needed.

Remacemide is a low-affinity NMDA antagonist and has been shown preclinically to have neuroprotective properties within a wide range of dosages[40]. Although study in patients with early PD came to a disappointing result, motor fluctuations in patients with advanced PD are diminishing, due to the remacemide treatment. Currently, no studies have been conducted to assess the effect of remacemide on PD progression, although one study indicates that remacemide has no ameliorating effect on Huntington's disease.

Amantadine has been used to treat PD for several decades. Recent studies indicate that amantadine improve the symptoms through inhibition of NMDA receptors.

However, its possible effects on disease progression have not been investigated[41]. Memantine, an NMDA receptor blocker, is under evaluation in PD patients based on the preliminary preclinical results[42,43].

Evidence suggests that group II mGluR activation may also offer protection against glutamate-mediated neurodegeneration. Recently, LY-379268, a systemically active group II agonist, has been shown to provide some protection in 6-OHDA models in rats[44]. New ligands with systemic activity have been developed in the past few years and further work is required to evaluate these agents in PD models.

2.5 Neurotrophic factors One particularly promising therapeutic and potentially neuroprotective approach is the application of neurotrophic factors, particularly GDNF[45,46]. GDNF inhibits *L*-Dopa-induced adverse effects, resulting in a 20% enlargement of nigral neurons and an increase of fibre density. Early studies have also demonstrated GDNF-induced protection and repair of the nigrostriatal system and functional improvement in monkey. GDNF also has neuroprotective actions in both young and aged rats. Neurturin (NTN) and GDNF have potent neuroprotective and neurorestorative effects on dopaminergic neurons. However, the severe delivery obstacles have limited their application in PD treatment[47].

2.6 Cyclooxygenase 2 (COX-2) inhibition Recently, increasing data have supported the hypothesis that inflammation plays a role in PD development[48]. Several studies have demonstrated that apart from the massive loss of dopaminergic neurons, conspicuous glial reaction and neuroinflammation also occur in PD brain, as manifested by elevated cytokine levels and up-regulation of inflammatory-associated factors such as COX-2 and iNOS. COX-2 inhibition has been shown to reduce neuroinflammation and neurodegeneration in animal models of PD. One pilot study employed [(11)C]-PK11195 PET to quantify neuroinflammation and evaluate the ability of COX-2 inhibition to reduce neuroinflammation in PD patients. In current practice, [(11)C]-PK11195 seems to be an unsuitable tracer for accurate or reliable quantification of neuroinflammation. Refinement of [(11)C]-PK11195 uptake analysis and, more importantly, further development of better tracers are necessary to enable accurate measurement of neuroinflammation and effects of anti-inflammatory treatment in patients[49].

In vitro and *in vivo* studies demonstrate that inhibition of COX-2 is neuroprotective, and non-steroidal anti-inflammatory agents can prevent MPP^+- and 6-OHDA-induced toxicity. Furthermore, MPTP-induced toxicity in rodents and human is associated with clustering of microglia around the dying cells in the SN.

2.7 Neuronal nitric oxide synthase (nNOS) and iNOS inhibitors In the early 1990s, it was reported that excessive nitric oxide (NO) produces neurotoxicity through combining with superoxide to form the harmful peroxynitrite anion. In recent 10 years, nNOS and iNOS inhibitors have been shown to be neuroprotective in ischemic[50] and PD[51] models. Changes in the transcription level of NOS1 are believed to play a role in the development of many diseases[52]. NOS inhibitors may be useful to treat *L*-Dopa-induced dyskinesia[53].

2.8 Adenosine receptor antagonists There is a high density of adenosine receptors in the striatum and several studies have shown that these receptors are localized on neurons containing GABA and enkephalin[54]. Adenosine receptor antagonists, such as caffeine, could improve the locomotor activity, while the agonists worsen the movement. In the past 5 years, several new molecules have been identified to be selective antagonists for A_{2A} subtype receptor, including KF-17837, KW-6002, SCH-58261 and VER-11135. These molecules can improve motor functions without provoking dyskinesia in MPTP-treated primates. More recently, the 8-substituted 9-ethyladenine (ANR) derivatives ANR 82, ANR 94, and ANR 152 have been characterized as new A_{2A} receptor antagonists, and they show high efficacy in *in vivo* models of PD[55].

2.9 Inhibition of apoptosis Recent evidence indicats that apoptosis plays a role in cell death in PD brain[56]. Also, mice over-expressing Bcl-2 are resistant to MPTP-induced neurotoxicity. Similar studies also demonstrate that mice with dominant-negative inhibition of caspase-1, Bax deficiency and p53 knockout are all resistant to MPTP-induced neurotoxicity. Adenoviral delivery of a caspase inhibitor, X-chromosome-linked inhibitor of apoptosis (XIAP) can protect the cell bodies, but not the terminals. It is also clear that MPTP can

activate c-jun N-terminal kinase (JNK), which then acts as a mediator of MPTP-induced apoptotic cell death[57]. Recently, it has been reported that inhibitors of JNK are neuroprotective[58]. For example, CEP-1347 can attenuate MPTP-mediated dopaminergic cell death. The effects seem reasonably modest and the compound fails to show trophic actions. However, whether it could effectively delay the PD progression-induced disability is currently under clinical investigations.

3 Conclusion

In summary, up to now, the treatment for PD remains essentially symptomatic. Although this approach is simple and effective during the early phases of the disease, the management of advanced PD is complicated due to the decline in the number of dopaminergic neurons, the development of motor complications, and the appearance of non-dopaminergic motor and non-motor features, resulting in significant morbidity and a shortened lifespan. There is good evidence indicating that the early use of DA agonists either alone or in combination with *L*-Dopa can prevent or retard the onset of motor complications. Also, considerable preclinical data have demonstrated the protective properties of DA agonists in a variety of *in vitro* and *in vivo* models. However, the results of clinical studies with pramipexole and ropinirole are not conclusive, and further studies are required. Nevertheless, the prospects for PD treatment have improved significantly over the past 5 years, greatly due to the development of basic science, a deeper understanding of the cause and pathogenesis of the disease, and improved model systems for the study of potentially neuroprotective drugs.

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帕金森氏病的治疗策略

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摘要：帕金森氏病(Parkinson's disease，PD)是由中脑黑质中多巴胺神经元变性，导致纹状体系统多巴胺(DA)含量下降引起的神经病变。其特征性症状包括震颤、僵硬和运动徐缓等。目前为止，帕金森氏病神经元死亡的病因仍不清楚。具体的神经变性机制包括自由基生成、氧化应激、线粒体异常、兴奋性中毒、钙中毒、营养因子不足、炎症过程、一氧化氮毒性和细胞调亡。这些因素相互增强形成恶性循环导致神经功能异常、萎缩, 最终导致多巴胺神经元死亡。大量实验提示在 PD 病理过程中，自由基的生成和氧化应激起关键作用。目前，药物疗法并不能治愈 PD。尽管左旋多巴(*L*-Dopa)替代疗法一直是控制 PD 症状的标准，但其只能缓解临床症状，并且 *L*-Dopa 长期治疗会引起多种副作用。目前尚无可行的疗法能遏制或减缓神经元变性。因此，研究不仅要致力于改善和延长 *L*-Dopa 对 PD 的治疗效果，还要研发兼具抗 PD 与神经保护功能的药物。本文综述了当前各种 PD 疗法的优缺点。这些疗法包括 DA 治疗、DA 激动剂、单胺氧化酶 -B 抑制剂、儿茶酚 -O- 甲基转移酶抑制剂、抗谷氨酸药、胆碱能药物、外科手术(深部大脑苍白球或丘脑术)和干细胞移植术等。同时，基于 PD 病理过程，对未来的药物神经保护作一展望。

关键词：帕金森氏病；治疗策略；药物神经保护