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# Pharmacology of Nilotinib in the Treatment of Parkinson's Disease Caused by New Pathology

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## Abstract

*Parkinson's disease (PD) is still not curable and controllable, which needs to find new pathology of PD and effective drugs to treat. To study the new pathology of PD, ten rats composed of half sex as an experimental group were injected with 5 μg α-synuclein monomer into the substantia nigra in every rats. In the second day after injection, the four main symptoms of PD appeared in the rats to demonstrate that the standard animal models of PD were established and lasted at least for more than 3 months or became deteriorating of PD. For the drug experiments of rats by using the same 5 μg α-synuclein injected into the substantia nigra, one week later, after the symptoms stabilized, every experimental rats were intraperitoneally administered with 0.3 mg nilotinib solution every morning once a day for 30 consecutive days. Importantly, these treatments could eliminate all symptoms of PD, and then the rats gradually showed no stiffness, shaking, foot flipping, or dragging and exhibited strong feet, the ability to walk and run, and smooth fur. After 30 days, treatments were stopped, and the rats continued to show no symptoms of PD and healthily survived. Since the symptoms of PD were induced by injecting 5 μg α-synuclein into the rats, now no symptoms of PD indicated the elimination of α-synuclein monomer in the rats under the help of nilotinib. The rat experimental results had demonstrated the PD caused by injecting 5 μg α-synuclein was a new pathological process by α-synuclein to block dopamine functional channels (DFCs) reducing the values of functionalization factor (f) and functional dopamine (GD) content, independent on the content of dopamine and the apoptosis of dopamine neurons in the rats. The pharmacology of nilotinib used to cure the PD caused by new pathology was by clearing α-synuclein to unblock DFCs and increase the values of f and GD content..*

**Keywords:** *Dopamine Molecular Channels - DMCs, functional dopamine (GD), dopamine functionalization factor (f), PD, nilotinib, pharmacology*

## Introduction

Parkinson's disease (PD), a kind of neurological disorder diseases, includes four main symptoms [1]: resting tremor [2], muscle stiffness [3], motor retardation [4], abnormal gait and postural instability, and many possible complications, and other severe syndromes caused by disease-relieving drugs such as symptom fluctuation, switching phenomenon, dyskinesia, end-dose dystonia, and mental problems to make patients' lives extremely difficult, and them often feel that life is worse than death. PD is a long-term, chronic, severe, torturous, and easily disabled disease [1].

After a large number of observations, experiments and clinical practices for more than 200 years, it is generally believed that the pathological signs of Parkinson's disease are the loss of dopaminergic neurons in the substantia nigra compact area and the appearance of Lewy bodies in the remaining dopaminergic neurons [2]. However, the history of Parkinson's disease research and treatment shows that drugs that prevent or slow the progression of Parkinson's disease have still not been discovered [1]. More than 200 years ago, James Parkinson's hope in 1817 that "some treatment process may be discovered soon, and through this process, the progression of Parkinson's disease may be prevented" has yet not to be realized [3].

The research history of PD also implied that we did not have enough understanding of the nature of Parkinson's disease and didn't know enough about the pathology of Parkinson's disease. Dopamine function can only occur when dopamine molecules effectively interact with dopamine receptors, if its strength was strong enough, no symptoms of PD did appear in the living body. In the interstitial area of the substantia nigra synaptic cells of the living body, dopamine molecules effectively bind to their receptors in posterior membrane cells, causing the structural conformation changes of the dopamine receptors, which produces the first messenger function of the neurotransmitter dopamine, and then by coupling via G protein causes the second messenger function of the neurotransmitter dopamine. Then, it transmits information and control functions through the mode of next G-protein coupling and slow synaptic transmission way of neurotransmitter to produce dopamine functions, which are closely related to the pathology and treatment of Parkinson's disease [4,5].

The intensity of the first messenger of neurotransmitter dopamine depends on three items: 1) the content of dopamine molecules, 2) the content of dopamine receptors, and 3) the effective binding state between dopamine molecules and their receptors. The second item is the content of dopamine receptors, which is related to the content of dopamine cells in the posterior membranes. It is generally believed that there is no clinical problem about the content of dopamine receptors in Parkinson's disease. If the level of dopamine receptors constitutes a problem, such as from a cause by physical injury or other factors, patients generally die quickly. The first item is the content of dopamine molecules, which involves the content of dopamine cells in the anterior membrane.

Clinically, it is generally believed that there are problems from the content of dopamine molecules leading to Parkinson's disease. At present, in clinic, it is based on dopamine neuron apoptosis pathology to explain the problem of dopamine content, which is called the old pathology of Parkinson's disease [2]. The old pathological signs displayed the loss of dopaminergic neurons in the compact substantia nigra and the appearance of Lewy bodies in the remaining dopaminergic neurons. Because of dopamine neuron cell apoptosis, the current apoptotic dopamine cells cannot be revived, according to current opinion, the early-stage Parkinson's disease cannot be cured, and the late-stage Parkinson's disease is difficult to control.

The third item is the effective binding state of dopamine molecules with their receptors. In the synaptic space, dopamine receptors are embedded in the cell membranes of the posterior membrane cells of dopamine neurons. The outer port of the dopamine receptor (i.e. the extra-cellular direction of the posterior membrane cell), which is shaped like a large mouth of a funnel. The dopamine receptor outer port is the active site of dopamine receptor agonists, but it is not the active site of dopamine molecules. The active site of the dopamine molecules is located in the middle of the dopamine receptors [6], which is similar to the bottom of the small mouth of funnel structure. At this site, the cavity structure of dopamine receptor becomes smaller and has a strong interaction with dopamine to cause the conformation change of dopamine receptor structures and produce the first messenger effect of neurotransmitter dopamine [6]. In dopamine receptors, we had discovered dopamine molecular channels, including dopamine functional channels (DFCs) and protective channels (DPCs) [7-9]. The dopamine molecules located at the outer port of dopamine receptors in the interstitial space of synaptic cells, through the DFCs, reach the active sites of the receptors and effectively bind to the dopamine receptors, and to produce the neurotransmitter dopamine first messenger. Then, through the coupling of dopamine receptor G protein, the neurotransmitter dopamine second messenger is activated, and then through the slow synaptic transmission mode of neurotransmitter, it transmits information and control functions, regulates various motor functions, cognitive thinking activities and other processes (that is, the functions of dopamine), which is closely related to the pathology of Parkinson's disease [4,5]. When harmful molecules or harmful proteins block DFCs, dopamine molecules cannot pass through the DFCs and cannot reach the active sites in their receptors. Therefore, at this condition (i.e. the blockage of DFCs), even though dopamine molecules are sufficient enough, they cannot effectively bind with their receptors, and cannot cause the conformation changes of dopamine receptor structures, i.e, not to produce the first messenger effect of neurotransmitter dopamine. Therefore, by α-synuclein monomer to block DFCs, the decrease or loss of dopamine functions causes PD, which was suggested as new pathology of PD [7-9].

In the old pathology of dopaminergic apoptosis in PD, the pathological features were the loss of dopaminergic neurons in the substantia nigra compact area and the appearance of Lewy bodies in the remaining dopaminergic neurons, in which α-synuclein monomer was the main component of Lewy bodies in dopaminergic neurons. If α-synuclein monomer could be eliminated, the increase of Lewy bodies would be controlled, which might prevent the development of PD. In the new pathology of PD, α-synuclein monomer could block DFCs, which was the main origin to cause PD. If α-synuclein monomer could be eliminated, then the DFCs could be opened up, and the PD caused by the new pathology could be cured. In this article, we reported that the use of nilotinib could clear the α-synuclein monomer located in the substantia nigra of the interstitial space of synaptic cells, and cure PD caused by the new pathology of α-synuclein blocking the DFCs.

## Materials and experiments

### Animal experiments using α-synuclein

α-synuclein contains 140 residues:
(TKEGVLYVGSKTKEGVVHGVATVAEKTKEQVTNVGGAVVT-GVTAVAQKTVEGAGSIAAATGFVKKDQLGKNEEGAPQEGILEDMP-VDPDNEAYEMPSEEGYQDYEPEA140), and is a structure of fiber [10-14]. α-Synuclein (purity > 95%; 0.5 mg/mL in Tris solution) was purchased from Shanghai Chu-peptide Biotechnology Co., Ltd. The experimental animals were Sprague-Dawley rats purchased from the Animal Center of Kunming Medical University. Rats were raised in cages and weighed between 200 and 250 g.

Ten rats composed of half sex as an experimental group were injected with 5 μg α-synuclein (monomer solution) into the substantia nigra in every rats. In the second day after injection, the experimental rats had four main symptoms of PD appeared to demonstrate the standard animal models of PD established in the rats, which lasted at least for more than 3 months or became deteriorating of PD [9]. Blank solution was performed by injecting no-α-synuclein solution as a control to exclude the effects of injection and solution reagents.

In the experiments, we used chloral hydrate (0.1 g/mL) Tianjin Guangfu Fine Chemical Research Institute as an anesthetic reagent. Rats weighing 200-250 g were anaesthetised with approximately 0.8 mL chloral hydrate. After the experimental rats were completely comatose, the skin where the white matter of the rat was located (the back corner of the eye was moved backward by 0.5 cm, the boundary between the two nostrils was shifted to the right by 0.2 cm, and the thickness was 0.5 cm) was slightly enlarged. A hole approximately the size of a soy bean was created in the base of the skull. When injected, the needle entered 0.8 cm into the brain, and the injection tube was held in the substantia nigra for 30 s.

### Animal experiments using nilotinib

Nilotinib was purchased from J & K Scientific Ltd. (purity > 99%), and no further purification was required. Its solution was formulated with distilled water, with a concentration of 0.3 mg/mL; the pH was adjusted to 6.0 with HCl solution. PD was established in rats by injecting 5 μg α-synuclein (monomer solution) into the substantia nigra as described above. Symptoms of PD appeared the next day. One week later, after symptoms stabilized, each one of eight rats of half sex was intraperitoneally administered with 1 mL nilotinib solution every morning about at 10:00 once a day for 30 consecutive days. Each of other four PD experimental rats was intraperitoneally administered with 1 mL no-nilotinib solution to monitor their symptoms of PD for comparison with the rats treated with nilotinib. After administration, the states of the rats were observed using the four symptoms of PD..

## Results

### New pathology of PD demonstrated by the rats injected with α-synuclein

When the experimental rats were injected with 5 μg α-synuclein (monomer solution) into their substantia nigra, in the second day after injection, they had four main symptoms of PD: (1) resting tremors, (2) muscle stiffness, (3) bradykinesia, and (4) gait abnormalities and postural instability to demonstrate the standard animal models of PD established [15,16]. These symptoms in the

rats lasted at least for more than 3 months or became deteriorating of PD, which proved the injected 5 μg α-synuclein could not be removed by their bodies themselves without the help of drug molecules. On the second day after injection, the rats could not experience apoptosis in dopamine neurons, because the literature reported that the rats injected α-synuclein fibre like Lewy bodies of α-synuclein into, after more than three months, shew apoptosis in dopamine neurons [17], and they suffered from the symptoms of PD after their apoptosis in dopamine neurons.

Lewy bodies were derived from α-synuclein mutation, or excessive accumulation of α-synuclein lead to the formation of oligomer, polymer, fiber state and Lewy bodies, to produce toxic form of α-synuclein [17], which promotes dopamine cell death [18]. α-Synuclein monomer was believed no toxicity to dopamine neurons [17,18]. Therefore, except us, nobody had carried out animal experiments with α-synuclein monomer. We used α-synuclein monomer to block DFCs in rats to establish the standard symptoms of PD. Furthermore, the PD of the rats, caused by injecting 5 μg α-synuclein monomer into their substantia nigra, could be cured by using nilotinib, as described below, to further prove no apoptosis in dopamine neurons of the experimental rats, because apoptotic dopaminergic cells cannot be repaired or revived with nilotinib.

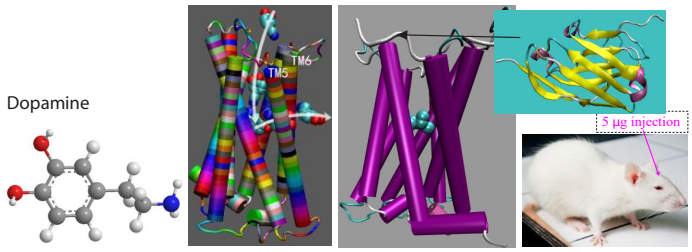


*Figure 1: Dopamine molecular channels including dopamine functional channels (DFCs) and dopamine protective channels (DPCs), and the structure of α-synuclein. In animal experiments of rats, 5 μg α-synuclein was injected into the substantia nigra of rats to block DFCs directly to cause PD without any apoptosis in dopamine neurons.*

In dopamine receptors, there are dopamine molecular channels, including DFCs and DPCs, as shown in (Figure 1) [7,8]. When α-synuclein monomer was injected into the substantia nigra of the experimental rats shown in (Figure 1), it could block DFCs in the experimental rats to lead to reduction of functionalization factor (f) [19], according to the formula of GD = $f \times$ TD [7,8], then reducing the content of GD to cause PD of the rats by new pathology of PD. In the formula of GD = $f \times$ TD [7,8], GD is the content of functional dopamine; TD is the content of total dopamine, expressed as a percentage; and f is the dopamine functionalization factor, which refers to the ratio of total dopamine converted to functional dopamine, normalized to 1 as its value for normal healthy persons. Our experiments clearly demonstrated that α-synuclein could block DFCs in experimental rats and cause PD since TD had no problem. After DFCs were blocked by α-synuclein, α-synuclein could also induce other effects, such as causing apoptosis in dopamine neurons and resulting in deteriorating PD in the experimental rats. Therefore, based on the DFCs and use of α-synuclein monomer, we established the standard rat model of PD without apoptosis in dopamine neurons.

In new pathology of PD, the reduction of GD content is caused by the reduction of (*f*) value due to α-synuclein blocking DFCs within dopamine receptors to cause; while in old pathology of PD, the reduction of GD content is caused by the reduction of TD content produced from apoptosis of dopaminergic neurons in the substantia nigra compact area. Therefore, in science, PD is caused by the reduction of GD content and identically expressed with the same symptoms in both new and old pathologies of PD, which is the nature (or essence) of PD.

## The Pharmacology for Nilotinib Used to Treat PD caused by New pathology

Nilotinib was used for the treatment of leukaemia [20,21]. Some researches had suggested it seemed effective for treating PD [22-26]. However, its mechanism had not yet been elucidated. The reported researches did not study the effect of nilotinib on PD caused by new pathology.

In our work to study the effect of nilotinib, total twelve experimental rats with the standard symptoms of PD were used, after injection of 5 μg α-synuclein (monomer solution) into each substantia nigra. One week later, until symptoms stabilized, among twelve experimental rats, eight rats of half sex were designed as the treatment group, each of which was intraperitoneally administered with 1 mL nilotinib solution (0.3 mg nilotinib) every morning about at 10:00 once a day for 30 consecutive days. Other four PD experimental rats were used as the controlled group, each one of which was intraperitoneally administered with 1 mL solution (no nilotinib) to monitor their symptoms of PD in comparison with the experimental rats treated with nilotinib.

Figure 2 showed the states of the rats of PD before (left) and after treatment (right) with nilotinib. The eight experimental rats of PD showed similar features during treatment. From day 3, symptoms of stiffness in the PD rats were significantly alleviated, and their movement was increased. On day 7, their hind leg dragging was significantly alleviated. The injections were continued once a day for 1 month, and various symptoms of PD in the experimental rats were eliminated completely, such that the experimental rats became the healthy states similar to those without injection of 5 μg α-synuclein. Importantly, this treatment eliminated all symptoms

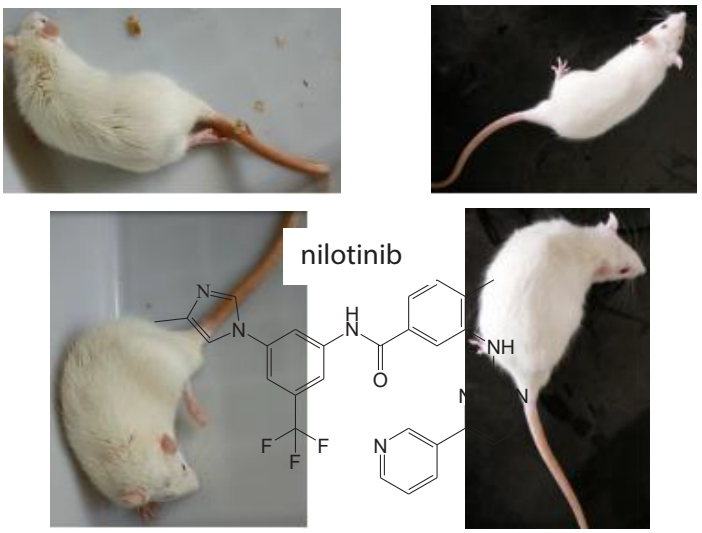


*Figure 2:* Molecular structure of nilotinib (middle). In pictures of left panel, before the rats of PD treated with nilotinib, the four main symptoms of PD in the rats appeared; while in the pictures of right panel, after the rats of PD treated with nilotinib, they returned to healthy states due to removing all symptoms of PD.

(TKEGVLYVGSKTKE GVVHGVATVAEKTKEQVTNVGGAVVT-GVTAVAQKTVEGAGSIAAATGFVKK DQLGKNEEGAPQEGILED-MPVDPDNEAYEMPSEEGYQDYEPEA140),

of PD in the experimental rats; the rats showed no stiffness, shaking, foot flipping, or dragging and exhibited strong feet, the ability to walk and run, and smooth fur. After 1 month, injection of nilotinib was stopped, and the cured rats maintained their healthy states both without using any drugs and without symptoms of PD. However, the controlled group of four experimental rats of PD maintained their standard symptoms of PD, almost not changing any symptoms and states. Thus, these findings demonstrated that nilotinib eliminated the injected 5 μg α-synuclein, to mean, eliminated the substance blocking DFCs, restored the functions of DFCs, increased the values of f and GD content to have cured their symptoms of PD.

In our experiments, healthy rats were used, and no endogenous α-synuclein or Lewis bodies had accumulated in the rats, except just only once injection of 5 μg α-synuclein monomer. In contrast, in patients with PD, Lewis bodies accumulated, and various types of α-synuclein proteins aggregated in the substantia nigra besides α-synuclein monomer. In addition, new α-synuclein was produced every day, so the content of α-synuclein continued to increase in patients with PD. Thus, the states of patients were quite complex. Therefore, the effects of oral nilotinib on disease control in humans might not be as obvious as in our current study, because nilotinib was used only to remove α-synuclein monomer, and other states of α-synuclein were not sure to be eliminated. However, we were sure this drug did help to alleviate the disease, because it could eliminate α-synuclein monomer in the substantia nigra. Pharmacologically, nilotinib promoted the clearance of α-synuclein monomer, opened up DFCs, increased the content of GD, and cured the PD caused by new pathology, independent of both the dopamine content (TD) and the apoptosis and recovery of dopamine neurons.

The controlled group of four PD experimental rats maintained their standard symptoms of PD. Even though the experimental rats were healthy, without the help of drugs, the α-synuclein injected into the rats could not be eliminated by their bodies themselves. The injected α-synuclein could have additional effects by experiencing apoptosis in dopamine neurons in the rats and worsen the states of PD besides maintaining the symptoms of PD caused by new pathology.

It was unclear whether animal models of PD required large numbers of apoptotic dopamine neurons, as would be expected from our prior understanding of the old pathology of PD and observations made in patients with late-stage disease. However, during the initial stages of the disease, patients might not experience obvious apoptosis of dopamine neurons. Therefore, the use of animal models requiring large numbers of apoptotic dopamine neurons as standard animal models of PD had been misleading and had jeopardised research and treatment of PD. Moreover, the diagnosis of PD was on detection of symptoms, not by an analysis of cell apoptosis. When a number of apoptotic dopamine neurons happened, total dopamine content was reduced, but this might not decrease largely the content of functional dopamine, if the value of functionalization factor (*f*) was high. Accordingly, it was necessary to use the content of functional dopamine as a standard to diagnose PD, which involved detection of f (in this paper just presenting qualitative analysis) closely related to the states of DFCs besides considering apoptosis in dopamine neurons. Therefore, the blockage of DFCs and the apoptosis of dopamine neurons were two key origins to cause PD.

## Conclusions

Our animal experiments with α-synuclein monomer had verified new pathology of PD. The injected α-synuclein monomer blocked DFCs in the rats to make dopamine not bind with its receptors. Consequently, in the rats, dopamine could not effectively bind with its receptors, not to lead to changing the conformation of the receptor structures, and not to start the neurotransmitter dopamine first messenger, then resulting in the weakening or loss of dopamine functions to cause PD, which was new pathology of PD. In the new pathology of PD, DFCs were blocked by α-synuclein to reduce the value of f and the content of GD, contrarily, in the old pathology of PD, the reduction of content of GD was caused by the reduction of TD content resulted from apoptosis of dopaminergic neurons in the substantia nigra compact area. PD was caused by the reduction of content of GD in both pathologies, so that the same symptoms of PD were expressed in either new or old pathology to cause. In the new pathology of PD, although dopamine existed sufficient enough, it could not perform its functions to cause PD. Therefore, in the new pathological process, PD had nothing to do with dopamine content and the apoptosis or the regeneration of dopamine neurons.

The animal experiments with nilotinib had demonstrated that nilotinib could be used to completely cure PD caused by new pathology. Since PD of the rats was caused by injecting 5 μg α-synuclein monomer into the substantia nigra, the PD of the rats was cured to show clearing the 5 μg α-synuclein. Therefore, the pharmacology of nilotinib in the treatment of PD caused by new pathology was to remove the injected 5 μg α-synuclein, open up DFCs, improve the value of f, increase the content of GD and then cure the PD caused by new pathology, which was regardless of the apoptosis and regeneration of dopamine neurons as well as the content of TD. Our animal experiments were easily repeated to prove the reliability of all experiments. In addition, because α-synuclein monomer was the main composition of Lewy bodies, based on the old pathology of PD, by using nilotinib to eliminate α-synuclein monomer and control increasing of Lewy bodies in the substantia nigra compact area, we might expect to slow the development of PD.

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