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Review article

Emerging targets and new small molecule therapies in Parkinson's disease treatment

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ABSTRACT

Parkinson's disease (PD) is a common chronic degenerative disease of the central nervous system. Due to a rapidly aging society worldwide, PD morbidity is on the rise; however, the treatment of PD with conventional drugs carries serious adverse reactions and cannot fix the root cause of PD, the degeneration of dopaminergic neurons, which limits conventional drug usage in clinical practice. In recent years, research on the pathogenesis of PD and its clinical manifestations has led to the discovery of an increasing number of novel targets in PD, including several small molecule targeted compounds. In this paper, we analyze and summarize the most recently published PD literature and review several recently discovered novel targets in PD and their small molecule targeted pharmacologically active agents based on their mechanisms of action and pharmacodynamic profiles.

Contents

1. Introduction

Parkinson's disease (PD), also known as *paralysis agitans*, is a common chronic degenerative disease of the central nervous system. The morbidity of neurodegenerative diseases is on the rise

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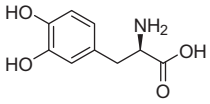
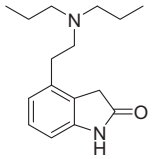
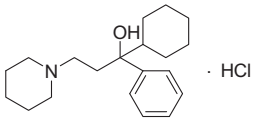
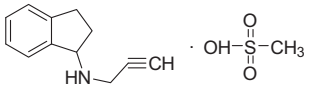
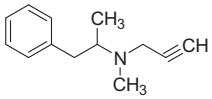
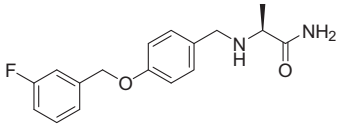
Table 1
Parkinson's disease commonly used drugs and their side effect

Types of drugs	Representative drug	Structural formula	Side effect	Reference
Dopamine compensatory agent	Levodopa		Cardiovascular symptoms and the 'on–off' phenomenon and the 'end of dose' phenomenon	10
Dopamine receptor agonist	Ropinirole		Lower limb edema, vomiting and convulsions, occasional symptoms of hypotension	11
Cholinergic inhibitor	Benzhexol		Mydriasis, blurred vision and severe extrapyramidal effects	12
	Rasagiline mesylat		Syncope, orthostatic hypotension, fall down, headache, joint pain, muscle pain, infection, etc.	13
MAO-B inhibitor	Selegiline		Anxiety and illusion, nausea, orthostatic hypotension, etc.	14
	Safinamide		New drug, the side effect is unknown	15
NMDA receptor antagonist	Amantadine		Hallucination, insomnia, excessive dreaming	16

due to an aging society worldwide. Up to 1/200 of individuals aged 65 or higher have PD, which makes PD one of the most common neurodegenerative diseases in middle-aged and elderly populations[1] and a serious threat to human health in the 21st century. PD is characterized by resting tremor, bradykinesia, myotonia and gait disorders with or without non-motor symptoms such as depression, constipation and sleep disorders. And PD is associated with the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), resulting in striatal depletion of the neurotransmitter dopamine (DA). The pathogenesis of Parkinson's disease is complex and remains to be fully elucidated. At present, there are two main aspects about the pathogenesis of Parkinson's disease, one is the α-synuclein, the other is the oxidative stress.[2,3] α-synuclein is a presynaptic neuronal protein that is linked genetically and neuropathologically to Parkinson's disease (PD). It is predominantly expressed in neurons of the central nervous system (CNS) where it localizes to presynaptic terminals in close proximity to synaptic vesicles. α-synuclein is mostly soluble in normal brain while the α-synuclein inclusions are detergent-insoluble in PD. α-synuclein may contribute to PD pathogenesis in a number of ways, but it is generally thought that its aberrant soluble oligomeric conformations which termed protofibrils are the toxic species that mediate disruption of cellular homeostasis and neuronal death, through effects on various intracellular targets, such as synaptic function.[4–6] The brain is particularly susceptible to oxidative damage due to its high level of polyunsaturated fatty acids and relatively low antioxidant activity, so oxidative stress plays an important role in the degeneration of dopaminergic neurons in Parkinson's disease (PD). It can disrupt the physiologic maintenance of the redox potential in neurons and interfere with several biological processes, ultimately leading to cell death. And some evidence have been found for oxidative damage to key cellular components in the PD substantia nigra.[7–9] In addition to this, environmental toxins, genetic and accelerated aging and other reasons can also lead to Parkinson's disease. At present, the conventional drugs for PD include levodopa (a dopaminergic drug), Ropinirole (Dopamine receptor agonists), benzhexol (a central cholinergic receptor blocker), Monoamine oxidase inhibitors Rasagiline and a number of other anti-PD drugs such as amantadine (Table 1). Levodopa enters the brain via active transport, where it is converted into DA. Levodopa is a pro-drug of DA and helps to restore patients' motor functions; however, oral levodopa can cause side effects, including gastrointestinal symptoms, cardiovascular symptoms and transient elevated liver enzymes, and its long-term use is associated with decreased treatment effects, peak dyskinesia, the on–off phenomenon and the 'end of dose' phenomenon (the effective action time of each drug was shortened, and the symptom with the regular fluctuation of blood drug concentration). Recent studies have shown that levodopa might have certain neurotoxic effects that accelerate the death of residual dopaminergic neurons.[10] Ropinirole is a non ergoline dopamine agonist and it can be suitable for the treatment of idiopathic Parkinson's disease. Ropinirole besides can improve parkinsonian bradykinesia, rigidity and tremor, but also can improve the ability of daily life of patients and depression, but long term use can lead to nausea, sleepiness, lower limb edema, abdominal pain, vomiting, convulsions, occasional symptoms of hypotension and bradycardia.[11] Benzhexol exerts its anti-PD effects by blocking striatal cholinergic receptors, inhibiting the excitation of cholinergic neurons and DA reuptake in synaptic-gaps and enhancing the effects of dopaminergic neurons. The