Drug Development against Parkinson’s Disease

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Parkinson’s disease (PD) is currently the second most common neurodegenerative disease among the older population. The main problem in the treatment is that the exact etiology of the disease is not known, and it is not known what exactly initiates the neuronal damage process. There is still no drug that would effectively cure the disease. However, scientists are still trying to develop more effective pharmacotherapy by using new molecular targets based on relevant in vitro and in vivo models, and by using computer-aided design of drugs and other particles.

Keywords: computer modeling ; drugs ; in vitro models ; in vivo models ; neurodegeneration ; Parkinson’s disease

1. Parkinson's Disease

Parkinson’s disease (PD) is currently the second most common neurodegenerative disease among the older population. It is predicted that by 2030, the number of sick people will increase to 9 million. The diagnosis is based on the finding of at least two symptoms from among: tremor, rigidity, bradykinesia and postural instability, and is further confirmed by performing a histopathological examination which indicates the presence of Lewy bodies—protein aggregates composed of alpha-synuclein—which is a useful biomarker for in vitro research. The pathogenesis of PD is multifactorial. The accumulated proteins cause degeneration of dopaminergic neurons, especially in the substantia nigra (SN) area, which reduces the concentration of dopamine and weakens the dopaminergic transmission, leading to the motor symptoms characteristic of PD. In addition to the SN area, loss of neurons is observed in the basal ganglia, hypothalamus and olfactory bulb. It subsequently triggers the transmission disorders in other systems, namely the cholinergic, glutaminergic, adenosine, GABAergic, serotonergic, noradrenergic and histaminergic systems. Neuron degeneration also occurs as a result of oxidative stress, caused by disturbances in calcium regulation and mitochondrial, lysosomal and proteasome dysfunction. Degeneration of other non-dopaminergic systems produces non-motor symptoms of PD, for which dopamine replacement therapy brings no therapeutic effect[1][2].

2. Etiology

Due to the complexity of the disease, the etiology of PD is still not fully understood. It is found that environmental and genetic factors play an important role in its development. Age is the biggest risk factor: over 60 years of age, the risk of developing the disease fluctuates within 2%, while above 80 years, it increases to 4%. A higher proportion of cases is noticeable among men, and it is estimated that about 5% of cases are inherited. It has been studied that individual genes may be responsible for the disease. So far, 26 genes, which are referred to as PARK genes, have been associated with the disease, and their mutations have been shown to have a significant impact on the development of the disease. The reduction of parkin production or the production of mutant proteins leads to the accumulation of the toxic proteins and the degeneration of neurons. Mutations in parkin (PARK2), PINK1 (PARK6), DJ-1 (PARK7) and ATP13A2 (PARK9) have been shown to be responsible for the recessive form of adolescent PD, while mutations in SNCA (PARK1), which encodes the synuclein protein, and LRRK2 (PARK8) are responsible for the autosomal form of PD. Important mutations are also those related to the protein 35 (VPS35) and GBA1—the gene encoding β-glucocerebrosidase. These genes are involved in the processes that are usually disturbed in PD patients, such as mitochondrial metabolism, autophagy and proteostasis. Other risk factors related to the development of PD are mutations in the HLA-DQB1 gene and, above all, in the gene encoding the tau MAPT protein, the expression of which is used in various cell models[1].

3. Therapy

In the search for antiparkinsonian agents, interest is focused on several molecular targets. A noteworthy one is the adenosine A2A receptor. It has been investigated that the inhibition of this receptor increases the level of dopamine and improves signaling transmission. In animal models, blockade of A2A receptors has been proven to alleviate motor symptoms of the disease. It is likely to have neuroprotective effects as well [3][4].

An interesting molecular target is also monoamine oxidase B. In clinical studies, it has been shown that inhibition of these enzymes increases the level of dopamine in the brain by preventing its degradation. This has a positive effect on the motor and non-motor symptoms of PD, especially in the early stages of the disease[5].
Groundbreaking research focused on the polypyrimidine tract-binding (PTB) protein, which is responsible for turning genes on and off in the cell. In animal models, blockade of PTB has been shown to lead to the conversion of astrocytes into dopaminergic neurons, which restores normal dopamine transmission. This gives hope for an effective treatment that can cure PD permanently[6].

The treatment options for this disease are very limited as currently the treatment is mainly symptomatic, and the available drugs are not able to completely stop the progression of the disease but only to slow it down. There is still a need to search for new compounds with the most optimal pharmacological profile that would stop the rapidly progressing disease. The current knowledge of molecular targets is still incomplete, but new reports on them are constantly being sought. An increasing understanding of Parkinson's pathogenesis and the discovery of new molecular targets pave the way to develop new therapeutic agents. The use and selection of appropriate cell and animal models reflect pathogenic changes in the brain is a key aspect of this research. For this reason, it is proposed that the cell and animal models for PD studies reflect as much as possible the human pathophysiological and behavioral aspects of the disease.Examples of such *in vitro* models are the SH-SY5Y line, PC12, the LUHMES cell line as well as the 3D cultures that best reflect the complex biological mechanisms and processes of the human body. While, examples of *in vivo* models are toxin / pesticide models (e.g. 6-hydroxydopamine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, rotenone) and genetic models (e.g. α-synuclein, LRRK2)[7].

In addition, computer-assisted drug design methods are a promising approach to developing effective compounds with potential therapeutic effects. In silico methods use computer-based approaches to accelerate the lead hit identification and molecule optimization. These methods are widely known as computer-aided drug design techniques (CADD) and can be divided into two categories: ligand-based and structure-based approaches. The former can be implemented when the structure of the protein target is not known. However, if there is some data on the molecular target structure, the latter methods can be used. These techniques enable identifying common regions in a series of active and inactive molecules[8][9]. Some of these techniques, e.g., molecular docking, pharmacophore identification, structure-activity relationship (SAR), quantitative structure-activity relationship (QSAR) and combination methods, have been widely applied in the process of designing novel, selective ligands[10].

4. Conclusion

Therefore, thanks to advanced technology and the use of appropriate research models, it is possible to thoroughly understand the mechanisms of PD and to develop and test new drugs that may be effective in the treatment of PD.

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