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Modeling Parkinson's Disease Using Exogenous Neurotoxins (Literature Review)

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Abstract: In recent years, there has been an increase in the prevalence of neurodegenerative diseases, one of which is Parkinson's disease (PD), characterized by progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta of the brain and leading to patient disability and significant financial costs for their treatment and rehabilitation. In this regard, understanding environmental factors causing this disease, developing adequate experimental models for studying pathogenesis and searching for strategies to prevent its development, as well as possible neuroprotective drugs, has fundamental scientific significance. Although some researchers believe that the main factors in PD development are genetic mutations and population aging, numerous studies prove that PD can be caused by exposure to a number of toxic substances entering the organism from the environment. This review will examine the main exogenous neurotoxins causing PD development and consequently used for modeling this disease in animals and cell cultures, as well as their mechanisms of action, advantages and disadvantages of specific models.

Key words: Parkinson's disease, neurotoxins, pesticides, modeling, oxidative stress, environmental factors.

Introduction.

Parkinson's disease (PD) is a chronic progressive neurodegenerative movement disorder characterized by irreversible and selective loss of dopaminergic neurons [1]. PD belongs to socially significant diseases. This is explained by its wide prevalence and significant financial costs for patient treatment and rehabilitation. Despite decades of research, PD remains an incurable disease. Pharmacological treatment of PD is focused on replacement therapy that restores dopamine levels [2].

In 1817, English physician James Parkinson first described PD symptoms in detail in his work "An Essay on the Shaking Palsy." This event correlates with the beginning of the industrial and chemical revolution in Europe in the late 18th and early 19th centuries. Although many PD symptoms were described and published before Parkinson's publication, they were not distinguished as a separate disease. In this regard, there is a hypothesis that PD prevalence before the beginning of the 19th century was extremely low and a sharp increase in PD cases occurred parallel to the

industrial revolution [3].

There are numerous epidemiological and experimental studies proving the relationship between PD incidence and exposure to ecotoxicants. Additionally, a connection has been shown between increased PD risk and other environmental factors, including well water consumption, rural residence, farming, certain types of diets, and exposure to agricultural chemicals [4–6]. However, some researchers associate increased PD incidence with increased life expectancy and population aging [7]. The aging process is associated with impairment of the body's antioxidant system and cellular mitochondrial dysfunction [8].

It is known that in most cases, the debut of sporadic PD is observed at age 50-60 years. Logically, increased life expectancy will lead to increased PD incidence and prevalence. However, due to the fact that clinical diagnostic criteria for PD appeared only in the late 1980s and before this time neurologists did not recognize clear differences between PD and other nosological forms of parkinsonism [9], it is not possible to clearly track the relationship between life expectancy and PD incidence. On average, over the past 40 years, the PD incidence rate remains more or less constant [10].

The most likely scenario appears to be the combined influence of these two factors – aging and ecotoxicant exposure on increased PD incidence. The probability of developing PD has clear familial inheritance and is associated with mutations in at least 6 genes. Identification of genes such as SNCA or PARK1, encoding alpha-synuclein (α-syn) protein, opened keys to molecular mechanisms involved in PD pathogenesis [2]. Nevertheless, 90% of PD cases are sporadic and cannot be attributed only to genetic factors, suggesting that PD has multifactorial etiology [3].

Clinical features of PD syndrome include motor dysfunction, including resting tremor, rigidity, akinesia (or bradykinesia) and postural instability. However, motor symptoms begin to manifest when at least 60% of dopaminergic neurons die and dopamine content in the striatum decreases by 80-85% [4].

Although PD research is rapidly advancing, the involved pathogenetic molecular mechanisms are still unclear, and the etiology of this disease is complex. One of the leading factors in PD pathogenesis is oxidative stress (OS), which manifests as excessive generation of reactive oxygen species (ROS) and decreased levels of endogenous antioxidant defense systems, primarily in dopamine-producing neurons of the substantia nigra (SN) pars compacta of the midbrain [5]. A significant source of ROS is impaired mitochondrial functional activity [6].

Experimental data indicate that ROS formed during dopamine metabolism, as well as decreased glutathione levels and high iron and calcium levels in the SN, make a significant contribution to dopaminergic neuron loss in the brain in PD [7]. Additionally, the brain contains high concentrations of polyunsaturated fatty acids, which under OS conditions form lipid peroxides and toxic products [8]. In addition to neuron loss, the main neuropathological feature of PD is the presence of Lewy bodies in neurons, which are eosinophilic cytoplasmic inclusions containing α-syn aggregates [9].

Understanding and studying the neurodegeneration process in PD is aided not only by clinical but also experimental studies. Experimental PD models differ in objects and inductors that trigger the neurodegeneration process.

Identification of genes associated with PD served as the basis for targeted studies of molecular signals causing the disease. Moreover, studying these genes provided a rational basis for disease modeling in cells or animals through genetic manipulations. Animals are most often the object for genetic models. These models, mimicking genetic changes observed in PD patients [2], were developed for organisms such as rodents, worms, Drosophila and fish (Danio rerio) [11]. Methods used include gene knockout, overexpression or expression of mutated forms of PARK-1 (i.e., α-syn or its mutations A53T, A30P and E46K) or knockdown of DJ-1, PINK or LRRK2 and others.

Nevertheless, most existing genetic models do not demonstrate typical dopaminergic neuron degeneration in the SN, indicating the complex and not fully understood genetic component of this disease development. Additionally, genetic mutations cause less than 10% of PD cases and cannot explain many clinical and pathological features observed in patients with idiopathic form. This proves the important role of other factors in PD development, one of which is exposure to toxic substances from the environment.

Models Using Neurotoxins

To date, models using neurotoxins as inductors of dopaminergic neuron death remain generally accepted and most adequate. Used neurotoxins differ in mechanism of action and in this regard, choosing the most suitable one, as well as adequate cell culture for in vitro experiments, animal species and strains for in vivo experiments, is an important task in PD study.

Models based on using this substance were developed to understand the role of mitochondrial inhibition in PD development and to test various neuroprotective strategies or to observe consequences of dopamine content reduction in various brain areas with consequent changes in their functional activity. This model has two disadvantages. First,

MPTP induces acute or subacute neurodegeneration, which does not correspond to the chronic progressive process in PD, and second, as in the case with 6-OHDA, Lewy body formation is not observed [8].

Methods of rotenone administration to rats and mice include direct infusion into the SN, systemic intraperitoneal or intravenous injection. To achieve a more natural method of neurotoxin exposure similar to environmental exposure, oral, dermal or subcutaneous administration is used [10]. Systemic chronic administration (more than 5 weeks) of rotenone causes specific dopaminergic neuron degeneration with α-syn inclusion formation. Additionally, high rotenone doses lead to striatal neuron degeneration without SN involvement, demonstrating the same degeneration pattern as with manganese and carbon monoxide exposure in primates and humans. Since the enteric nervous system and olfactory bulbs of the brain are nervous structures most susceptible to environmental pollutant exposure, compounds acting locally on these nervous structures cause PD-like pathology appearance and its progression to the CNS through synaptically-connected structures [3]. However, the main disadvantage of this model is that chronic rotenone administration leads to multisystem damage not characteristic of PD [7].

Like MPTP and rotenone, it inhibits the mitochondrial electron transport chain, leading to OS development and subsequent stepwise apoptosis of dopaminergic neurons .Additionally, paraquat can induce neurotoxic effects through other mechanisms. It is known that paraquat-induced reduction in mitochondrial complex I activity is preceded by respiratory dysfunction in the brain. Paraquat exposure leads to ROS formation in complex III of the electron transport chain, as shown in the Drosophila model system .

Paraquat induces nitric oxide (NO) production in the brain by activating nitric oxide synthase and inhibits antioxidant activity of some enzymes, which in turn leads to increased reactive oxygen and nitrogen species content. Laboratory studies on animal PD models showed that paraquat causes dopaminergic neuron death in the SN with chronic low-dose exposure [2].

Cell Models. In vitro systems are very effective tools for screening and identifying potential neurotoxic compounds among numerous environmental chemicals to which humans are exposed. They also provide numerous opportunities for studying cellular and molecular effects of toxic substances and searching for compounds capable of reducing their negative effects.

For example, on PC12 and SH-SY5Y neuronal cell cultures, it was shown that aluminum, copper and iron, as well as some pesticides, initiate structural transformation and α-syn fibrillation [8]. Numerous studies showed that xenobiotics induce OS; thus, OS development due to numerous pesticides and insecticides exposure was shown on primary cultures of rodent cerebellar granular neurons on human neuroblastoma culture cells SH-SY5Y due to heavy metal exposure in primary cultures of mesencephalic neurons after ethylene-bis-dithiocarbamate fungicide exposure.

In vitro experiments also showed that xenobiotics cause glial reactivity, i.e., glial cell proliferation, which is a crucial stage of the brain inflammatory process. After subchronic mercury compound exposure on aggregated brain cell cultures, microgliosis and astrogliosis processes are observed without any signs of neuronal damage .

General Mechanism of Neurotoxin Action in PD Modeling

One common mechanism of action of the described neurotoxins is inhibition of NADH-ubiquinone oxidoreductase I, also known as mitochondrial electron transport chain complex I, and free radical formation, leading to cellular OS development. At the same time, postmortem examination of SN neurons in patients with sporadic PD showed mitochondrial dysfunction and OS. Additionally, similar changes are observed in PD patient platelets.

Many toxic substances cause α-syn aggregation and fibrillation. Interestingly, rotenone causes α-syn accumulation and release from intestinal neurons into extracellular space [3]. Desplat and colleagues showed that α-syn is transported between cells in co-culture from host neurons to grafted neurons. Thus, neurotoxin exposure induces α-syn spreading and accumulation in the central nervous system.

Finally, exogenous neurotoxins can cause pro-inflammatory signal release. PD patients show enhanced inflammatory reactions with microglial activation and inflammatory cytokines . The inflammatory process may include activation of brain immune cells (microglia and astrocytes), which release inflammatory and neurotoxic factors, which in turn leads to neurodegeneration [8]. Extracellular α-syn may also contribute to inflammatory reaction occurrence.

Conclusion

Modeling specific diseases is necessary for better understanding of their pathogenesis and developing new therapeutic strategies. A model rarely displays all aspects of the disease under consideration, especially when pathophysiology and disease etiology are not fully clear, as in the case of PD.

Exogenous neurotoxins may play an important role in PD pathology appearance and progression, especially in the idiopathic form of this disease. This can be confirmed by the fact that in most cases, the first signs of PD development

are decreased sense of smell (due to olfactory bulb damage, for example, with inhalational neurotoxin exposure) and gastrointestinal tract dysfunction (due to enteric nervous system damage with oral neurotoxin intake).

In vitro and in vivo studies showed that pathological process spreading and progression from structures most vulnerable to neurotoxins – olfactory bulbs and enteric nervous system – can occur through α-syn release and transcellular transfer. In this regard, using exogenous neurotoxins as inductors of neurodegenerative processes in PD modeling appears justified. These models contribute to elucidating cell death mechanisms and consequently allow developing and testing neuroprotective substances.

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