THE EFFECT OF ARMENIAN VIPER VENOM ON GLOBUS PALLIDUS NEURONS IN A ROTENON MODEL OF PARKINSON'S DISEASE

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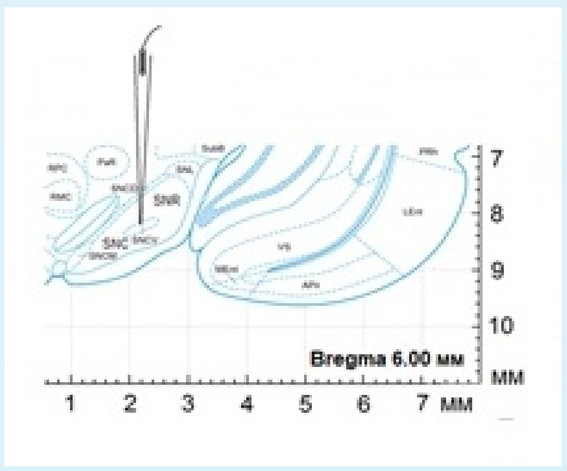
Introduction

Parkinson's disease (PD) is a chronic progressive brain disease characterized by nigrostriatal degeneration and impairment of basal ganglia functions, particularly the globus pallidus. In PD, neurons of the compact part of the substantia nigra most intensively die, which are associated with brain structures related to the central regulation of movement programming, in particular, with the globus pallidus. With PD, neurons in the globus pallidus are damaged, as a result of which dopamine, which is responsible for motor functions in the human body, ceases to be produced. At the moment, there is no high neuroprotection of PD, therefore, for this, extremely relevant prospects for the treatment of diseases remain. Of particular interest are animal venoms, which act as pronounced protectors in many pathological conditions of the body. Based on this, the task was set to study the effect of the venom of the Armenian viper *Montivipera raddei (MR*) on the morphofunctional state of globus pallidus neurons using the rotenone model of PD.

Methods

The study was carried out on sexually mature white rats weighing 200–250 g. Morphohistochemical studies were carried out by the method of detecting the activity of Ca 2+ -dependent acid phosphatase, developed by I.B.Meliksetyan. This method is based on the detection of intracellular phosphorus-containing compounds that occupy key positions in metabolic energy processes. The animals were divided into the following groups: intact rats (group 1, n=5) and experimental rats: unilaterally injected with rotenone in the “medial forebrain bundle” (group 2, n=5) with intramuscular injection of saline every other day for 2 weeks and sustained until the acute experiment 4 weeks, and injected with rotenone unilaterally similarly to group (2) in combination with intramuscular injection of *Montivipera raddei* venom every other day for 2 weeks and sustained for 4 weeks (group 3, n=5). Intracerebral injections of rotenone were performed under pentobarbital anesthesia (40 mg/kg, intraperitoneal). *Montivipera raddei* venom injections (at a dose of 10% of LD50 = 1.6 mg/kg, i.e. 0.16 mg/kg) were performed one day after the administration of rotenone.



Scheme of the experiment on the intracerebral administration of rotenone into the medial forebrain bundle

Results

Data analysis revealed that nerve cell lesions in the globus pallidus are abiotrophic in nature. Neuronal damage is accompanied by a decrease in phosphatase activity in the cytoplasm and chromatophilic substance lysis. Long processes react in such neurons, but their phosphatase activity is reduced. Various types of cell atrophy are revealed against a background of normal cells (Fig. 1 D-F). Thus, rotenone intoxication causes abrupt morphological and metabolic changes in intracellular structures, as well as in the globus pallidus. This is a reversible condition in the early stages of the disease.

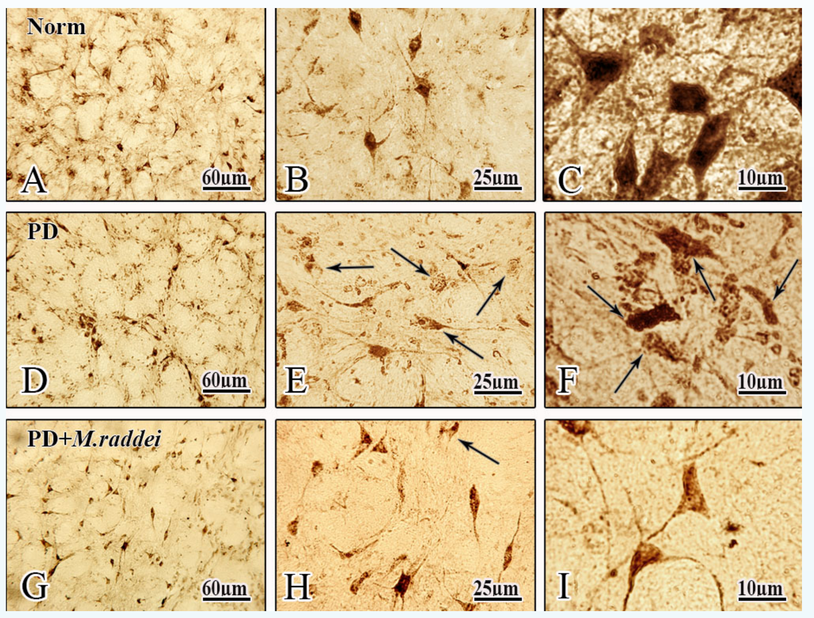


Figure 1. Frontal slices of the globus pallidus of the rat’s brain (A-C - control (Norm); D-F - under conditions of rotenone intoxication (PD); G-I - under conditions of regular administration of small doses of Montivipera raddei venom (PD + M.raddei) (black arrow - chromatolysis)). Method for detecting Ca2+-dependent acid phosphatase activity. Magnification: ×160 (A, D, G); ×400 (B, E, H); ×1000 (C, F, I).

When compared to a Parkinson's disease model, small doses of *Montivipera raddei* venom caused positive changes in the structural properties of neurons in the globus pallidus - neurons that have retained their shape and size are revealed (Fig. 1 G-I). In most of them, against the background of hyperchromic cytoplasm, light-colored centrally located nuclei stand out, which is typical for the norm. In most cells, long processes with high acid phosphatase activity react, which indicates that their connections with neighboring cells and other areas of the brain are preserved. Against the background of cells that have retained their shape and size, affected degenerated neurons are occasionally detected that have lost their shape and size, without processes (Fig. 1 H). Compared to the rotenone model of PD, an increase in phosphatase activity in the cytoplasm of cells is observed, which indicates an increase in metabolism, which was disturbed as a result of rotenone intoxication.

Conclusion

Thus, in PD, dopaminergic neurons in the globus pallidus are damaged and undergo atrophy. Deepening the process can lead to their disappearance. Under the influence of low doses of MR poison, positive changes in structural properties are observed in neurons of the globus pallidum in comparison with the PD model

The obtained data suggest that small doses of Armenian viper venom *Montivipera raddei* act as a neuroprotective agent, which requires further research to identify the mechanisms of action of therapeutic doses of *Montivipera raddei* venom and proposals for the treatment of Parkinson’s disease.