A provocative test as a new approach to preclinical diagnostics of Parkinson's disease and to assessment of degradations of nigrostriatal dopaminergic system

M. Ugrumov, **M. Ugrumov**, M. Ugrumov, M. Ugrumov, A. Kim, V. Safandeev, A. Kim, E. Pavlova
Laboratory of Neural and Neuroendocrine Regulations, Institute of Developmental Biology RAS, Russia

All the attempts to develop preclinical diagnostics of Parkinson`s disease, mainly by searching for biomarkers in biological fluids and the impairment of non-motor functions are unsuccessful. A drawback of this methodology is the search for markers in patients at the clinical stage without the guarantee that they are characteristic for the preclinical stage. Indeed, all the markers detected so far are nonspecific or semi-specific. Therefore, the development of preclinical diagnosis of PD remains a priority and is the objective of this study. We propose a provocative test as a new approach to the development of preclinical diagnosis of PD. This approach is successfully used in internal medicine. We have shown that systemic administration of α-methyl-p-tyrosine (αMPT), a reversible inhibitor of dopamine synthesis (provocative agent), to MPTP-treated mice at the presymptomatic stage of parkinsonism causes a reversible decrease in striatal dopamine to the threshold (30%) that is accompanied by a short-term appearance of motor disorders. In control, although the dopamine level decreases under αMPT administration, it does not reach the threshold and does not affect motor behavior. Although αMPT is used in clinics for the systemic treatment of pheochromocytoma and other needs, it causes peripheral side-effects. We have shown in MPTP-treated and control mice that these side-effects can be avoided if αMPT is administered intranasally. In addition, we determined the minimum doses of αMPT, which cause dopamine loss to the threshold and initiate motor disorders in presymptomatic mice at different levels of degradation of the nigrostriatal dopaminergic system (NDS). This means that the level of NDS degradation can be defined not only by PET, but also with easily available pharmacological approach using αMPT at the predetermined doses. Thus, we proposed a fundamentally new, this time specific technology for the early diagnosis of PD and the assessment of NDS degradation.