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Sommario	Introduction: Parkinson?s disease (PD) is characterized by a chronic progressive loss of nigrostriatal dopaminergic neurons that is associated with chronic neuroinflammation. Current treatments for PD can significantly improve symptoms but do not cure the disease or slow its progression. An approach used in existing therapies is based on the inhibition of monoamine oxidase (MAO), enzyme involved in the metabolic degradation of dopamine. Although, preclinical studies showed that MAO-B inhibitors have neuroprotective activity in cellular and animal models of PD, clinical trials did not completely confirm this result. Therefore a large number of new molecules, with more potent MAO-B inhibitory activity and a possible neuroprotective effect, have been proposed to replace the pre-existing MAO-B inhibitors. The profile of the recent MAO inhibitor, SZV558, appears to be particularly interesting because of its pharmacodynamic, favorable for disease-modifying properties and its irreversible MAO-B enzyme bind. The enhancement of adult neurogenesis could be of great clinical interest in the management of neurodegenerative disorders. In line with this, the metformin, a well-known antidiabetic drug, has recently been proposed to promote neurogenesis and to have a neuroprotective effect on the neurodegenerative processes induced by the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-

tetrahydropyridine (MPTP) in a mice PD model. Although, PD has multiple origins, one hypothesis is that amphetamine-related drugs may be part of the wide array of factors leading to the dopaminergic neuron degeneration that causes the disease. These hypothesis are supported by different results that showed a persistent, long-term dopaminergic toxicity induced by 3,4-methylenedioxymethamphetamine (MDMA) in mice. Moreover, the MDMA, altering the dopaminergic transmission, may affect neurogenesis and synaptogenesis. On these basis, considering that the young brain is particularly sensitive to drug-induced neurotoxicity, the consumption of MDMA during the adolescence might increase the vulnerability of dopaminergic neurons. However, the use of amphetamine-related drugs by adolescent and young people is often combined with caffeinated energy drinks in order to amplify their stimulant actions. Although caffeine use is safe, the combined treatment of caffeine and MDMA increases not only the DA release but also the microglia and astroglia activation. Aims: During my Ph.D. I studied the influence of neuroprotective drugs, such as MAO inhibitors and metformin, or substances, such as caffeine, on the neurodegenerative effects of two dopaminergic toxins, MDMA and MPTP, in mice. 1. In the first phase of my study, I evaluated the neuroprotective activity of the new MAO-B inhibitor SZV558, compared with well-known rasagiline, in a chronic mouse model of MPTP plus probenecid (MPTPp), which induces a progressive loss of nigrostriatal dopaminergic neurons. 2. Previous results showed that when MDMA is associated with caffeine, a more pronounced degeneration in adolescent compared with adult mice was observed. To better clarify the molecular mechanism at the base of the different neurotoxic effect of this drug association at different ages, I evaluated the neuronal nitric oxide synthase (nNOS) expression, which plays a critical role in the integration of dopaminergic and glutamatergic transmissions, in the CPu of adolescent or adult mice treated with MDMA, alone or in combination with caffeine. 3. Finally, I investigated the neuroprotective effect of metformin against dopaminergic neurotoxicity induced by MDMA in the CPu and SNc of adult mice. Conclusions: These results demonstrated that the dopaminergic neurodegenerative process may be induced or conditioned by environment stressors or substances which influence, through different ways, the development of neurodegenerative mechanisms. In the present study I evaluated the effects of 3 substances, known as potentially neuroprotective, in combination with two different neurotoxins that affect the nigrostriatal dopaminergic system. The SZV558 MAO-B inhibitor and the metformin protected the nigrostriatal pathway, usually affected in PD, by MPTP- and MDMA- induced neurotoxicity, respectively. On the other hand, caffeine, administrated with MDMA, showed a neurotoxic potential depending on the age of consumers, confirming the vulnerability of adolescent brain to consumption of drug and substances that affected the dopaminergic system. In conclusion, the study of neurodegenerative processes may be relevant to understand the human pharmacology, the origin and development of neurodegenerative disease and to predict the neurotoxic effect of drug abuse.

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