Real-time monitoring of MPTP-induced changes of striatal oxygen, glucose, lactate and movement in freely moving rats

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Chronic and/or acute administration of the neurotoxin MPTP to monkeys and small rodents has been widely used for obtaining in vivo models of Parkinson's disease (PD). MPTP is bioactivated by monoamine oxidase enzyme (MAO-B) to MPP^+ that inhibits the complex I of the mitochondrial respiratory chain, generating an overproduction of oxygen reactive species (ROS), and a reduction of ATP synthesis and energy metabolism impairment. Tissue oxygenation and dissolved oxygen play a key role in energy homeostasis and MAO-B activity, but is also involved in MPP formation and ROS production. This study aimed to perform a real time monitoring of neurochemical (oxygen, glucose and lactate) and behavioural (animal activity and movement) changes during a 3 days MPTP systemic administration in freely moving rats using micro- and bio-sensors, as well as microvibration sensor and manually recorded ethogram during the open field test. Glucose, lactate and oxygen sensors were stereotaxically implanted in the rat striatum and connected to a biotelemetric device, equipped with a microvibration sensor, able to record and send to a PC the animal physiological signals (Rocchitta et al., 2013). According to previous microdialysis study (Bazzu et al., 2013), MPTP was intraperitoneally administered for 3 consecutive days as follows: 25 mg/kg, 15 mg/kg, 10 mg/kg and all parameters were evaluated 1h before and 2 h after each neurotoxin injection. Glucose, lactate and oxygen levels significantly increased after the first MPTP administration, while a reduction of locomotor activity and stereotyped behavior was observed after neurotoxin injection. On day 2 and 3 a progressive reduction of glucose levels and locomotor activity was observed both before and after MPTP administration; on the contrary, lactate and oxygen levels resulted increased in comparison with the corresponding day 1 baseline values. Moreover, each MPTP administration induced a short-lasting increase of extracellular levels of oxygen but not lactate, probably due to the concomitant reduction of glucose levels. Preliminary in vitro experiments using a MAO-B- based biosensor demonstrated that increasing the O2 concentrations from 50 to 250 μM, determine an enhanced enzyme activity corresponding to a greater MPTP bioactivation into MPP^+ that consequently could lead to an increased neurotoxicity in vivo. On the basis of these observations and on the results obtained with microdialysis, a pre-treatment of 15 mg/kg of the MAO inhibitor (iMAO) pargiline was systemically administered to rats 30 minutes prior MPTP injection. In agreement with microdialysis results, pargiline pretreatment attenuated, but not completely reverted, the MPTP-induced changes in glucose and lactate levels. Pargiline administration ameliorates also rats locomotion and stereotype behavioral pattern observed during behavioral tests. On the other hand, pargiline pretreatment did not affect MPTP-related oxygen increase. In conclusion, the neurotoxin MPTP is able to induce a striatal increase of dissolved oxygen that could enhance the MAO-B activity, resulting in a boosting of MPTP neurotoxicity and increased energy metabolism impairment, as well as reduced locomotion and activity in rats. iMAO drugs, such as pargiline, could be used as preventing strategy, able to attenuate the damage caused by neurotoxins activation and to preserve mitochondrial respiratory chain complex I in order to compensate increased dissolved oxygen by aerobic energy metabolism with ATP synthesis and reduction of ROS formation.

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