MPTP effects on oxygen, glucose and lactate striatal levels and neuroprotective role of pargyline on energy metabolism in MPTP model of Parkinson's disease

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The loss of dopaminergic neurons of *Substantia Nigra pars compacta* in Parkinson's disease is related to oxidative stress, mitochondrial dysfunction and impaired energy metabolism (Serra et al., 2000; Halliwell et al., 1992; Olanow et al., 2007). The neurotoxin MPTP, known to induce a significant dopaminergic neurodegeneration, is converted into MPP^+ by MAO-B in glial cells interfering with Complex I of the mitochondrial electron transport chain. This leads the dopaminergic cell to impaired glucose metabolism and energetic deficit because of reduced ATP production (Miele et al., 1995). The aim of this study was monitoring oxygen, glucose and lactate levels by means of amperometric micro- and bio-sensors, integrated to a wireless telemetric system, in order to evaluate real-time effects of sub-chronic MPTP administration on physiological metabolism in the brain of freely moving rats.

In addition, we also deemed of interest the study of neuroprotective role of pargyline, (MAO-inhibitor), on dopamine and energy metabolism in MPTP-induced parkinsonism. This study was carried out by an innovative microdialysis approach for the simultaneous monitoring of striatal dopamine (DA) and energy substrates, in freely moving animals, using asymmetric perfusion flow rates on a dual microdialysis probe (Bazzu et al., 2011).

Adult male Wistar rats (280-330 g) were used in this study. Oxygen was electrochemically reduced at -400 mV vs Ag/AgCl reference electrode on carbon-epoxy sensor surface. Glucose and lactate detection was attained by glucose oxidase or lactate oxidase-based biosensors polarized at +700 mV vs Ag/AgCl reference electrode. Oxygen microsensors, glucose and lactate biosensors, and microdialisys probes were stereotaxically implanted in the right striatum of rats. Systemic MPTP was administered for three consecutive days as follows: 25 mg/Kg (day 1), 15 mg/Kg (day 2) and 10 mg/Kg (day 3). Pargyline (15 mg/Kg/day i.p. for 3 days) was administered 40 minutes prior the MPTP dose to a second group of animals. Striatal levels of catecholamines were quantified by means of HPLC-EC. Glucose, lactate, pyruvate and L/P ratio were electrochemically and spectrophotometrically evaluated.

Oxygen, glucose and lactate baseline of 60 minutes was recorded every day before MPTP administration. The first MPTP administration led to an increase of oxygen, glucose and lactate concentrations. On Day 2 and Day 3 a further increase of oxygen and lactate amounts was found, compared to both basal and after MPTP administration levels recorded on Day 1. Conversely, glucose showed a statistically significant decrease either in basal levels or following MPTP administration.

These energy metabolism results were confirmed during microdialisys experiments, where the first dose of MPTP induced an increase in dopamine concentrations in both groups; while the second and third doses reduced striatal DA only in animals without pargyline pre-treatment. Furthermore, animals treated only with MPTP showed a progressive decrease in glucose and pyruvate levels, and an increase in striatal lactate and of L/P ratio. Pargyline pre-treatment resulted in a reduced glucose and pyruvate loss as well as lactate and L/P ratio increase in the rat striatum.

These in vivo results showed MPTP-related mitochondrial dysfunction with consequent loss of DA and energy impairment. They also suggest that in MPTP-related mitochondrial dysfunction oxygen and glucose cannot be normally used by neurons. Moreover, the increased production of lactate reflects a switch towards anaerobic metabolism. Pargyline pre-treatment showed a neuroprotective effect preventing the bioactivation of MPTP and preserving neuronal dopamine and energy metabolism.

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