MPTP enhances its neurotoxicity by increasing extracellular oxygen levels in the striatum of freely-moving rats

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MPTP is a pro-neurotoxin widely used for obtaining *in vivo* models of Parkinosn's disease (PD). It has been shown that type B monoamine oxidase enzyme (MAO B), found in astrocytes, is responsible of MPTP bioactivation into MPDP metabolite, which decomposes into the neurotoxin MPP^+. In a previous microdialysis study (Bazzu at al., 2013) we demonstrated that MPTP, intraperitoneally administered for three consecutive days (25 mg/kg, 15 mg/kg, 10 mg/kg), initially induced a short-lasting increase of extracellular levels of glucose, lactate, pyruvate, lactate/pyruvate (L/P) and lactate/glucose (L/G) ratios in the striatum o freely-moving rats. Starting from day two, a progressive reduction of glucose and pyruvate levels with a concomitant further increase of extacellular lactate and L/P and L/G ratios, were observed. The MAO-B inhibitor pargyline (15 mg/kg), systemically administered before each MPTP injection, attenuated, but not completely reverted, the MPTP-induced changes in all studied analytes. In the present study we implanted, in the striatum of freely-moving rats, a glucose biosensor, a lactate biosensor and an oxygen microsensor, connected to a biotelemetric device for the realtime monitoring of neurochemical changes and movement as previoulsy-described (Rocchitta et al., 2013). By using the same protocol described in Bazzu et al. 2013, we confirmed the glucose and lactate changes observed by microdialysis and the protective role of pargyline and, for the first time, we studied the time-course of striatal extracellular oxygen (O_2). Indeed, MPTP administration led to an increase of oxygen on day 1 (+350%) , but also on day 2 and day 3. An increase of O_2 striatal baseline was observed day-by-day and a short-lasting oxygen increase after each MPTP administration (up to +550% of the day 1 baseline). Pargiline did not attenuated this phenomenon. Because molecular oxygen is a MAO B cofactor from which depends the bioactivation of MPTP, the striatal increase of O_2 could be responsible for increased production of MPP^+. For validating this hypothesis, we have constructed and characterized a biosensor, exploiting human MAO B enzyme activity *in vitro*. The enzyme is able to metabolize MPTP in the presence of molecular oxygen generating hydrogen peroxide (HP), electrochemically detectable on the surface of a Platinum electrode by applying an anodic potential of +700 mV vs Ag/AgCl. In the present study we have applied the paradigm of O_2 variations, as found *in vivo* experiments, going to evaluate changes in the current generated by the enzymatic production of HP. We have found that increasing the O_2 concentrations from 50 to 250 μM determined a 4-fold increase of HP production, which corresponds to an equimolar increase of MPP^+ production. The presence of pargyline inhibited the HP production as result of its MAO inhibitor (iMAO) activity *in vitro*. In conclusion, we can assume that the increase of O_2, which occurs i*n vivo* following the administration of the MPTP, could aggravate the damage through a boosting of MAO B activity, which results in a strong increase in MPP^+ production. This effect could be blocked by using a MAO inhibitor (iMAO), as pargyline, confirming that iMAO drugs could be used as preventing strategy, capable of containing the damage caused by neurotoxins activation.

Bazzu G et al (2013) *Brain Res.* 1538, 159-171
Rocchitta G et al (2013) *Anal Chem*. 85, 10282-10288.