MITOCHONDRIAL FACTORS INVOLVED IN PARKINSON'S DISEASE BY MPTP TOXYCITY IN *MACACA FASCICULARIS* AND DRUG EFFECT

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The maximal rates (Vmax) of some mitochondrial enzyme activities related to energy transduction (citrate synthase, succinate dehydrogenase, malate dehydrogenase, NADH-cytocrome c reductase, succinate Coenzyme Q oxidoreductase, succinate cytochrome c reductase, cytochrome oxidase) and amino acid metabolism (glutamate dehydrogenase, glutamate-pyruvate- and glutamate-oxaloacetate- transaminases) were evaluated in non-synaptic and intra-synaptic ("light" and "heavy") mitochondria from cerebral cortex of *Macaca fascicularis* (*Cynomolgus* monkey) obtained by ultracentrifugation technique, as previously described (1). The different mitochondrial populations were isolated from the cerebral cortex of control and treated monkeys *p.o.* with dihydroergocriptine at a dose of 12 mg/kg/day, before and during the induction of a Parkinson's-like syndrome by MPTP administration (*i.v.*, 0.3 mg/kg/day for 5 days) (2).
The MPTP administration modified the activity of many enzymes related to the energy metabolism on selected types of mitochondria. The neurotoxin modified all the valued enzyme activities, mainly stimulating Kreb's cycle enzymes in intra-synaptic mitochondria. Instead, the treatment with MPTP, as a model of experimental Parkinson's disease, decreased the activities of Complex I-III and Complex IV enzymes only in "light" intra-synaptic mitochondria. Thus, the stimulation of the energy metabolism (increased activity of Kreb's cycle) due to the neurotoxin administration determined the increased production of available electrons for the electron transfer chain (ETC); neverthless, at the same time, the MPTP decreased the electron flux along the ETC. As a consequence, there was a decrease in ATP production and an increase in the formation of free radicals in excess, that could cause the damage of mitochondrial membranes.
The treatment by dihydroergocriptine promoted return to the steady-state levels of most enzymes, demonstrating a protective effect on these biochemical parameters. In particular, the drug was able to normalize the variations of enzymatic activities of all the enzymes related to glutamate metabolism, both in non-synaptic and intra-synaptic mitochondria. However, from a pharmacodynamic point of view, the drug mostly interfere at the level of intra-synaptic mitochondria on the enzyme activities of Kreb's cycle and ETC, counteracting the modifications induced by MPTP administration, showing a neuroprotective action, as previously observed (3).

1) Villa R.F., Gorini A., LoFaro A. and Dell'Orbo C. (1989) Cell. Mol. Neurobiol. 9:247-262.
2) Villa R.F., Arnaboldi R., Ghigini B. and Gorini A. (1992) Neurochem. Res. 17:1147-1154.
3) Villa R.F., Arnaboldi R., Ghigini B. and Gorini A. (1994) Neurochem. Res. 19:229-236.