

Muscular mitochondrial respiratory chain dysfunction in a rodent model of Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative disease affecting the dopaminergic neurons of the substantia nigra. Aside from the central lesion, involvement of peripheral organs has been proposed as part of the complex clinical picture of the disease. The etiology is unknown in the majority of cases. Mitochondria and oxidative stress seem to play an important role in the process of neurodegeneration (Winkler-Stuck et al., 2005) and the origin and tissue distribution of the mitochondrial dysfunction in PD remains still a matter of controversy. It has to be clarified whether the mitochondrial dysfunction is restricted to specific structures in the brain or if mitochondria in other tissues than brain also show any involvement.

The central aim of this study was to evaluate whether and how changes in muscular mitochondrial oxidative metabolism occurred in the presence of on-going nigrostriatal degeneration in a rodent model of PD. Male Sprague-Dawley rats, weighing 200-250 g at the beginning of the experiment, received 6-hydroxydopamine (6-OHDA, n=11) or saline (sham, n=9) by direct injection into the right substantia nigra after stereotaxic surgery (Blandini and Armentero, 2012). Four weeks after surgery the gastrocnemius skeletal muscle was obtained from both ipsilateral and contralateral hindlimb to the cerebral lesion. Mitochondrial fraction from gastrocnemius was processed for citrate synthase and respiratory chain complexes (NADH-ubiquinone oxidoreductase, succinate dehydrogenase, rotenone-insensitive cytochrome c reductase, cytochrome oxidase) specific activities (expressed as nmol/min/mg of protein). A significant reduction in NADH-ubiquinone oxidoreductase specific activity was observed in both ipsilateral (39.77 ± 2.10 , $p < 0.01$) and contralateral (37.20 ± 2.32 , $p < 0.01$) gastrocnemius of 6-OHDA rats compared to sham rats (75.98 ± 6.62 , 73.60 ± 7.51 , respectively). Rotenone-insensitive cytochrome c reductase specific activity was significantly higher in both ipsilateral (198.07 ± 9.42 , $p < 0.01$) and contralateral (211.76 ± 13.26 , $p < 0.01$) gastrocnemius of 6-OHDA rats compared to sham rats (63.60 ± 6.44 , 64.69 ± 6.10 , respectively). No differences in mitochondrial enzyme activities were observed between gastrocnemius from ipsilateral and contralateral limbs; this is most likely due to the 'spill-over' of toxin crossing the midline during the injection of 6-OHDA (Sliwinski et al., 2005). The present study suggests a correlation, in PD, between the effects of the lesion to the substantia nigra and the observed skeletal muscle mitochondrial dysfunction. Skeletal muscle, like brain, is characterized by high dependence on oxidative metabolism. Our preliminary results support the hypothesis of a wide-spread mitochondrial alterations in PD. The origin of this defect is not known, but it is likely that direct oxidative damage on mitochondrial proteins plays an important role. Whether the alterations in muscle mitochondrial enzyme activities represent an adaptive response remains to be determined.

References

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