MOLECULAR CHANGES UNDERLYING DOPAMINERGIC DEFICIT COMPENSATION IN A PROGRESSIVE MPTP MONKEY MODEL

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Progressive loss of dopaminergic (DA) neurons in the substantia nigra (SN) \textit{pars compacta} is the major feature of Parkinson’s disease (PD).

Striatal dopaminergic depletion occurs several years before the onset of clinical signs. Nigro-striatal changes are admitted as the main compensatory mechanisms but modulation of the output nuclei of the basal ganglia might also play a relevant role.

We have developed a progressive monkey model of PD with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to investigate molecular changes associated with DA striatal depletion.

Monkeys were distributed in 4 groups based on motor severity: \textit{asymptomatic}, \textit{recovered} (after showing parkinsonian signs), \textit{parkinsonian}, and \textit{controls}.

DA depletion was evaluated by \textsuperscript{11}C-dihydrotetrabenazine (\textsuperscript{11}C-DTBZ) PET’s studies and post-mortem by immunohistochemistry for striatal DA transporter (DAT) and

\textit{in situ} hybridization striatal preproenkephalin (PPE) mRNA and glutamate decarboxylase mRNA in the globus pallidum and SN. Cytochrome oxidase activity was quantified in the subthalamic nucleus.

DAT immunohistochemistry revealed a gradual DA depletion in the MPTP-treated monkeys compared to controls (p< 0.01). \textit{Parkinsonian} monkey and \textit{recovered} monkeys showed a mean DAT reduction of 71\% and 48\% respectively, indicating that permanent motor features requires about 70\% denervation. All MPTP groups showed an increase in striatal PPE mRNA (p< 0.01) which was not paralleled by significant changes in the output nuclei activity.

These results suggests that increased striatal PPE is an early manifestation of dopaminergic depletion. On the other hand, it appears that intracellular activity in the output nuclei of the basal ganglia maintains within normal limits until dopamine depletion is very severe.