LOW AND HIGH DYSKINETIC TREATMENTS INDUCE DIFFERENT MOTOR RESPONSES AND mRNA CHANGES IN CAUDATE-PUTAMEN IN THE 6-OHDA RAT MODEL OF PARKINSON’S DISEASE

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In patients affected by Parkinson’s disease, treatment with the dopamine precursor L-DOPA or D₁ dopamine receptor agonists is accompanied by motor side effects as fluctuations and abnormal involuntary movements (dyskinesia), whereas D₂/D₃ agonists produce only mild dyskinesia.

In order to clarify the neurochemical basis of dyskinesia, rats unilaterally lesioned with 6-hydroxidopamine (6-OHDA) were subchronically treated with L-DOPA (6 mg/kg i.p. x 19 days twice/day), the D₂/D₃ dopamine receptor agonist ropinirole (5 mg/kg i.p. x 19 days twice/day) and with the D₁ agonist SKF38393 (3 mg/kg s.c. x 19 days once/day).

Behavioural observation showed that while subchronic treatment with L-DOPA and SKF38393 induced both contralateral turning sensitization and AIMS, subchronic ropinirole induced contralateral turning sensitization but not AIMS.

mRNA levels of the early-gene zif-268 and of striatal peptides dynorphin (DYN) and enkephalin (ENK) were evaluated in the caudate-putamen (CPu), whereas mRNA for the enzyme GAD67 was measured in the globus pallidus (GP) of 6-OHDA lesioned rats by means of in situ hybridization histochemistry. 6-OHDA lesion increased ENK and decreased DYN mRNA levels leaving unaltered zif-268 mRNA in the CPu. Subchronic treatment with L-DOPA and SKF38393 induced a significant increase in zif-268, DYN and ENK mRNAs in the CPu. In contrast, subchronic ropinirole did not modify zif-268 and ENK mRNAs expression, whereas reduced DYN mRNA levels as compared to the vehicle treated, 6-OHDA lesioned CPu. In the GP, all subchronic treatments produced a similar increase in GAD67 mRNA levels.

Results suggest that turning sensitization and AIMS might represent two aspects of a gradual response, reflecting the differential severity of dyskinetic movement induced by treatments with high (L-DOPA and SKF38393) or low (ropinirole) dyskinetic potential. L-DOPA and SKF38393 subchronic treatments were associated with an increase in striatal markers of neuronal activity, whereas ropinirole did not produce any raise in striatal mRNAs, suggesting that an hyperactivity of striatal neurons might be correlated with the high dyskinetic potential of drugs. Moreover increased levels in GAD67 mRNA observed after all treatments in the GP suggest that changes in this area do not correlate to the dyskinetic potential but might rather represent an index of antiparkinsonian activity of treatments.