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 D_1 dopamine receptor agonists is accompanied by motor side effects as fluctuations and abnormal involuntary movements (dyskinesia), whereas D_2 /D_3 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 D_2/D_3 dopamine receptor agonist ropinirole (5 mg/kg i.p. x 19 days twice/day) and with the D_1 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 controlateral turning sensitization and AIMs, subchronic ropinirole induced controlateral 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.