NIGROSTRIATAL DOPAMINE DENERVATION DECREASES STRIATAL ADENOSINE LEVELS. A_{2A} RECEPTOR ANTAGONISM INCREASES STRIATAL GLUTAMATE OUTFLOW

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Striatal adenosine A_{2A} receptors are involved in the regulation of the indirect striatum output pathway that controls motor activity. The aim of our study was to first identify modifications in striatal adenosine and glutamate concentrations in a model of Parkinson's disease (PD): the unilaterally 6-hydroxydopamine (6-OHDA) denervated rat. 6-OHDA was injected in the left medial forebrain bundle (MFB). Fourteen days after 6-OHDA lesion, rats were implanted with vertical microdialysis probes in the intact and lesioned dorsolateral striata. Twenty-four hours after probe implantation, microdialysis samples were collected from awake and freely moving rats. Glutamate and adenosine concentrations in the dialysate were determined by HPLC systems coupled with a fluorimetric detector. Fifteen days after 6-OHDA lesion, extracellular adenosine levels were 0.017±0.002 µM in the intact striatum and 0.011±0.002 µM in the denervated striatum (-35%) (n=14). Two-way ANOVA followed by post hoc Fisher's LSD test showed that the extracellular adenosine concentration was significantly lower in the denervated striatum ($F_{1,256}$ =15.5, $p<0.0001$). Extracellular glutamate levels were 0.92±0.21 µM in the intact striatum and 0.92±0.14 µM in the denervated striatum. Two-way ANOVA showed that glutamate outflow was not modified by the 6-OHDA lesion. A further aim of the study was to evaluate the effect of the selective A_{2A} receptor antagonist SCH 58261 on glutamate outflow in dopamine (DA) denervated striatum and in the intact one (Fig.1). Extracellular glutamate concentration, measured as percentage variation of the mean of the first five determinations, was evaluated in both the striatum correspondent to the intact side and to the 6-OHDA infused side of 15 rats. SCH 58261 (50 nM) administered through the microdialysis probe significantly decreased extracellular glutamate levels in the intact striatum (87.14±1.63, -13%; Student's *t* test: $p<0.024$) while the extracellular glutamate level in the denervated one (243.25±25, +143%; Student's *t* test: $p<0.004$) increased significantly. Two way ANOVA, calculated for the two factors: time-course and 6-OHDA lesion, showed that both factors were statistically significant ($F_{10,316}=2.86$,$p<0.00201$; $F_{1,316}=27.33$, $p<0.0000001$) and that there was a significant interaction between time-course and treatment with 6-OHDA ($F_{10,316}=3.53$, $p<0.000203$).
In the present model of PD, fifteen days after 6-OHDA infusion, dopamine extracellular concentrations are depleted by 91% (Pinna et al., *Neuropharmacol*., in press). Since adenosine extracellular concentrations are decreased of only 35%, it is envisaged that a residual adenosinergic tone accounts for activation of the indirect striatal output pathway. Antagonism of A_{2A} receptors located on the cellular bodies of the indirect output pathway can account for the increase of striatal glutamate outflow. It is envisaged that the increased glutamate outflow contributes to the beneficial effect of the A_{2A} antagonism in PD. In fact, A_{2A} antagonists have been recently described as beneficial in the control of motor disturbances in the model of PD induced by MPTP (Kanda et al., *Ann. Neurol*., 43, 507, 1998). The decreasing effect of A_{2A} antagonism on glutamate release is ascribed to antagonism of A_{2A} receptors located on glutamatergic cortico-striatal terminals. It is envisaged that this last effect is relevant to the neuroprotective effects described for A_{2A} antagonists in several models of ischemia (Pedata et al., *Ann. NY Acad. Sci*., 939, 74, 2001)

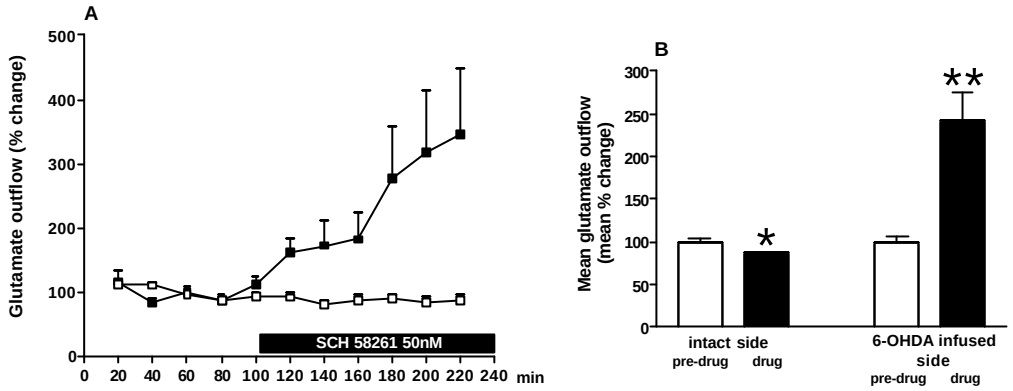

Fig.1: Effect of SCH 58261 (50 nM) on the time-course of glutamate outflow in the intact striatum and in the striatum corresponding to the 6-OHDA infused side. Each point is the mean±s.e. of *n*=15 animals. Values are expressed as percentage variations of the mean of the respective first five determinations. Full statistical analysis by two-way ANOVA is described in the text. In FIG 3 B the histograms show the effect of SCH 58261 (50 nM) on the mean percentage glutamate outflow in the intact and in the striatum corresponding to the 6-OHDA OHDA infused side before and after drug administration. Black bar: pre-drug samples; white bar: SCH 58261 treated samples. Student's *t* test: *p<0.024; **p<0.004 versus pre-drug values.