Activation of striatal dopamine receptors by psychostimulants: chemical anatomy, autonomic and behavioural effects

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ABSTRACT

Pharmacological activation of dopamine neurotransmission can be assessed by Positron Emission Tomography (PET) studies of changes in the binding of radioligands for dopamine D_2 receptors. The present thesis focuses on the use of this activation method to study receptor mapping, receptor pharmacology and behavioural aspects related to perturbation of dopamine neurotransmission in humans and animal models.

This thesis first describes the use of PET to map the distributions of dopamine $D_{2/3}$ and D_1 receptors in pigs and in monkeys, frequently used models for dopamine activation studies. As in humans, pigs and monkeys had a negative rostro-caudal gradient in the *t*-maps calculated from the statistical contrast between the normalized binding maps for D_1 and $D_{2/3}$ receptors. A positive rostro-caudal gradient for $D_{2/3}$ binding was observed only in monkeys. These results suggest a relative predominance of D_1 over $D_{2/3}$ receptors in the limbic striatum in mammals. In monkeys, $D_{2/3}$ receptors were more predominant in the motor striatum; the apparent lack of gradients in ^{11}C-raclopride binding in pig striatum might be attributed to their less sophisticated associative and motor circuits as compared to primates.

The effects of the psychostimulant 3,4-methylenedioxy-methamphetamine (MDMA, "Ecstasy") on cerebral blood flow (CBF) and dopamine receptor availability were tested. Unlike most previous studies of d-amphetamine, MDMA evoked a progressive decline of butyrophenone (^{11}C-NMSP) binding. MDMA-evoked hyperthermia correlated with increased CBF brain structures linked to central regulation of body temperature. These results suggest that the co-release of dopamine and serotonin by MDMA may influence the patterns of binding changes in living striatum.

ADHD is a highly prevalent pediatric neuropsychiatric disorder which is presently treated with psychostimulants. The effects of methylphenidate (0.3 mg/kg, p.o.) on the binding of ^{11}C-raclopride was measured by PET in nine young ADHD patients. There was a negative correlation between the magnitude of methylphenidate-evoked decline in ^{11}C-raclopride binding and the severity of inattention and impulsivity, measured by a continuous performance test. Thus, the dopamine activation paradigm was successfully used as a tool to link behavioural disturbance with reduced dopamine neurotransmission in patients with ADHD.

Together, these findings highlight PET as a method for linking behavioural, autonomic and pharmacological aspects of dopaminergic activation with segregated striatal circuits.