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A PET study with [11-C]raclopride in Parkinson's disease: preliminary results on the effect of amantadine on the dopaminergic system

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Abstract Amantadine has been proved to be beneficial in Parkinson's disease. Although it is still uncertain which neurochemical events are modified at therapeutic doses, an increase in dopaminergic tone secondary to NMDA receptor blockade and a direct inhibition of the glutamatergic overactivity have been suggested to be involved in its clinical effects. The aim of this study was to evaluate the effects of amantadine on the dopaminergic system by measuring the in vivo binding of [11-C]raclopride to D2 dopamine receptors in the basal ganglia of 6 patients with idiopathic Parkinson's disease. Each patient underwent a PET study, before and after 14 days of treatment with amantadine (200 mg/day). Repeated treatment with therapeutic doses of amantadine induced a moderate increase in the in vivo binding of [11-C]raclopride in the putamen of PD patients. This observation indicates that in PD patients, 200 mg/day amantadine does not produce an increase in extracellular levels of dopamine sufficiently to inhibit raclopride binding or that, if present, is it masked by a concurrent increase in receptor availability, as recently reported in rat striatum.

Amantadine is an old drug, available for decades, originally used for treatment and prophylaxis of influenza. It is also beneficial in drug-induced parkinsonism, Parkinson's disease, head injury, dementia, multiple sclerosis, cocaine withdrawal, morphine tolerance, and neuroleptic malignant syndrome. Amantadine is indicated in the early phase of Parkinson's disease when mild to moderate akinesia and rigidity are the major symptoms. However, amantadine may be beneficial in treating refractory dyskinesia and in controlling motor fluctuations induced by levodopa. Recently, a role in neuroprotection has been proposed [1].

Amantadine acts on the dopaminergic, serotoninergic and noradrenergic systems, blocks monoaminoxidase A, and seems to raise beta-endorphin/beta-lipotropin levels. Recently it has been shown that amantadine acts as a non-competitive antagonist of *N*-methyl-D-aspartate (NMDA) glutamate receptors, binding the so-called PCP (phenylcyclidine) site inside the cation channel of the receptor [2]. Although it is still uncertain which neurochemical events are modified at therapeutic doses, an increase in dopaminergic tone secondary to NMDA receptor blockade and a direct inhibition of the glutamatergic overactivity have been suggested to be involved in its clinical effects in Parkinson's disease. The possible mechanisms mediating the increase of dopaminergic tone include: increase in dopamine concentration due to inhibition of dopamine reuptake; increase in dopamine release from dopaminergic nerve endings; increase of dopa decarboxylase activity; increase of dopamine transporter (DAT) activity; and inhibition of NMDA-evoked release of acetylcholine [3, 4]. The use of positron emission tomography (PET) with [11-C]raclopride allows the in vivo assessment of dopamine D2 receptor expression within the basal ganglia of living subjects and the modification in synaptic dopamine concentration induced by pharmacological or behavioural stimulation [5]. The aim of this study was to evaluate the effect of a 2-week treatment with therapeutic doses of amantadine on D2 receptor expression by measuring the in vivo binding of [11-C]raclopride, in the basal ganglia of patients with Parkinson's disease. In order to avoid the confounding effects of a concurrent increase of dopa decarboxylase activity, PET studies were performed 14-16 h after the last intake of levodopa.

We recruited 7 patients with idiopathic Parkinson's disease, diagnosed according to UK Parkinson's Disease Society Brain Bank criteria. The patients underwent a baseline PET study (PET-I). A total of 6 subjects (mean age, 65±8 years; 5 women; Hoehn-Yahr stages, 2-2.5; duration of disease, 8±5 years; levodopa dosage, 614 ±377 mg/day) completed the study by undergoing the post-treatment PET study (PET-II), while 1 subject refused to undergo the post-treatment PET study. Levodopa treatment was stopped 14-16 h before each PET study. After PET-I, patients started amantadine treatment at the dose of 200 mg/day.

Raclopride PET studies were performed with an 18-ring tomograph (GE Advance). Patients received an intravenous injection of 5 ml saline solution containing approximately 1.07 ± 05 nmoles raclopride (mean doses, 250 ± 55 MB/kg). Immediately after tracer injection, 35 sequential scans were acquired in 3D mode, for a total scanning time of 60 minutes. Reconstructed images were transferred to a SYNSPARC workstation for imagine processing. Images of each temporal frame were realigned using SPM 96. Regions of interest (ROIs) were defined on the first PET study and then copied onto the second PET study after realignment of the two PET studies using dedicated software. The definition of cortical and cerebellar ROIs were performed on summed images standardised as follows: 6 circular ROIs (diameter, 12 mm) were drawn on the cerebellum (3 ROIs each hemi-

sphere with exclusion of the vermis). For the analysis of basal ganglia, circular ROIs (12-mm diameter, 3 on each hemisphere) were drawn on PET images acquired between 90 and 120 that provide an optimal visualisation of caudate nucleus and putamen. ROIs were positioned on the three image planes showing the highest basal ganglia radioactivity concentration. Time-activity curves were generated for each ROI. Raclopride binding potential (BP) was calculated from the equilibration striatum to cerebellum radioactivity ratio, using data integrated from 20 to 40 minutes after tracer injection. Statistical analysis was performed using sum-rank test for paired data when comparing BP values assessed before and after amantadine treatment (i.e. PET-I vs. PET-II). Bonferroni correction was applied for multiple comparisons. In addition, row data were transformed into rank values and used to calculate a generalised linear model to assess the effect of condition (i.e before and after amantadine therapy), regions and their interaction on raclopride BP values. Chronic treatment with amantadine increased the mean values of [11-C]raclopride BP in the putamen and caudate nucleus of the 6 patients who completed the study.

Discussion

The use of positron emission tomography (PET) and [11-C]raclopride allows the vivo assessment of dopamine D2 receptor expression within the basal ganglia of living subjects but also the modification in synaptic dopamine concentration induced by pharmacological or behavioural stimulation. Using this technique it has been demonstrated that ketamine, a non-competitive NMDA antagonist, inhibits the in vivo binding of [11-C]raclopride in the brain of normal volunteers, by increasing striatal dopamine concentration [6]. Repeated treatment with therapeutic doses of amantadine increased the in vivo binding of [11-C]raclopride in the putamen of all our patients with PD. These preliminary results indicate that in PD patients, 200 mg/day amantadine does not increase extracellular levels of dopamine sufficiently to inhibit [11-C]raclopride binding or that, if present, it is masked by a concurrent increase in receptor availability. The increase of D2 receptor binding of raclopride, according to the experimental results [7, 8], could be the in vivo evidence of D2 receptor expression and density in rat striatum, induced by administration of either amantadine or other non-competitive NMDA antagonist. Other patients are under study in the aim to confirm these results. Whether the lack of increase in dopamine release is due to the reduced number of dopaminergic nerves in PD patients, or to different intracerebral concentrations of amantadine at clinical doses, remains to be clarified in subjects with normal dopaminergic nerve endings.

References

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