Measurement of the dopaminergic degeneration in Parkinson's disease with $[^{123}\text{I}]\beta$-CIT and SPECT

Correlation with clinical findings and comparison with multiple system atrophy and progressive supranuclear palsy

T. Brücke$^{1,2}$, S. Asenbaum$^{1,2}$, W. Pirker$^1$, S. Djamshidian$^1$, S. Wenger$^1$, Ch. Wöber$^1$, Ch. Müller$^1$, and I. Podreka$^3$

University Clinic for 1Neurology and 2Nuclear Medicine, Vienna, 3Rudolfstiftung Hospital, Vienna, Austria

Summary. The cocaine derivative $[^{123}\text{I}]\beta$-CIT binds with high affinity to dopamine uptake sites in the striatum and can be used to visualize dopaminergic nerve terminals in vivo in the human brain with SPECT. It has been validated that the calculation of a simple ratio of specific/nondisplaceable binding during a period of binding-equilibrium in the striatum about 20 hrs after bolus injection of the tracer gives a strong and reliable index of the binding potential of dopamine uptake sites. Previous studies have shown that the dopaminergic deficit in patients with Parkinson's disease (PD) can clearly be visualized and quantified using this method. Our own results in a group of 113 patients with PD demonstrate a 45% loss of striatal $[^{123}\text{I}]\beta$-CIT binding in comparison to age corrected control values. Highly significant correlations of SPECT findings with clinical data obtained from the UPDRS rating scale such as akinesia, rigidity, axial symptoms and activities of daily living are demonstrated, while no correlation is found with tremor. The signal loss in a region comprising the whole striatum ranges from 35% in Hoehn/Yahr stage I to over 72% in stage V and is highly significantly correlated to the different stages of disease severity. A comparison of $[^{123}\text{I}]\beta$-CIT binding in the striatum contralaterally and ipsilaterally to the affected body side in 29 patients with hemiparkinson shows a loss of striatal binding of 41% contralaterally and 30% ipsilaterally. Results from subregional analyses in caudate and putamen show relative sparing of the caudate nucleus in PD. Data in 9 patients with multiple system atrophy (MSA) and 4 patients with progressive supranuclear palsy (PSP) are similar to the findings in PD although the differences between caudate and putamen are somewhat less marked.

These data demonstrate that the dopaminergic nerve cell loss in PD and other disorders with a dopaminergic lesion can be quantified with $[^{123}\text{I}]\beta$-CIT and SPECT and that hopefully a preclinical or very early diagnosis is made possible. Such studies might also open the way for a better evaluation of neuroprotective strategies in PD. It does not seem to be possible however to differentiate PD and MSA or PSP with this method in individual cases.
Introduction

Parkinson’s disease (PD) is a slowly progressing neurodegenerative disorder with a loss of dopaminergic neurons in the substantia nigra which leads to a loss of dopaminergic nerve endings and to a marked reduction of the dopamine content in the striatum. Dopamine transporters are located presynaptically on the plasma membrane of dopaminergic terminals and are thus lost in the process of degeneration (Pimoule et al., 1983; Janowsky et al., 1987; Maloteaux et al., 1988). Idiopathic PD is characterized by symptoms such as resting tremor, akinesia, rigidity and postural instability. Typically symptoms start asymmetrically on one body-side, gradually affect both sides and usually respond well to levodopa. Although these symptoms are very characteristic and sometimes make it possible to diagnose this disorder by just watching a patient as it is described in James Parkinson’s original monography (1817) the differential diagnosis with other extrapyramidal syndromes often can be very difficult. In a clinico-pathological study it was recently reported that the clinical diagnosis of PD was only correct in about 80% of the cases even when strict diagnostic criteria had been used (Hughes et al., 1992). It can only be speculated that this number would probably be lower in patients who are diagnosed by physicians who are less familiar with the disorder. Therefore there is a need for an objective diagnostic test for PD. Because the evaluation of disease progression based on clinical neurological examinations is often difficult due to the effects of antiparkinsonian treatment there is also a need for an objective measure of the dopaminergic nerve cell loss in vivo to evaluate possible neuroprotective strategies.

One way to visualize and measure dopaminergic nerve endings in the brain in vivo is to label the dopamine transporter either with positron- or with single photon emitting ligands. In vitro studies in postmortem human brain samples of PD patients had shown a loss of dopamine transporter binding with [3H]cocaine and [3H]GBR-12935 (Pimoule et al., 1983; Janowsky et al., 1987). These findings could be replicated in vivo with the PET ligand [11C]nomifensine (Aquilonius et al., 1987; Tedroff et al., 1988). Recently a group of cocaine analogs with very high affinity for the dopamine transporter and less nonspecific binding was described (Madras et al., 1989). PET studies with the [11C] labeled tropane analog WIN 35428 (CFT) also demonstrated reduced binding in patients with PD (Frost et al., 1993). 2-β-carbomethoxy-3-β-(4-iodophenyl)-tropane (β-CIT, RTI 55) is an iodinated analog of the originally described fluoro-derivative CFT with further increased affinity for monoamine transporters (Boja et al., 1991; Neumeyer et al., 1991) which has been extensively characterized in animal experiments (Innis et al., 1991; Scheffel et al., 1992; Shaya et al., 1992; Laruelle et al., 1993; Laruelle et al., 1994a) and its binding studied in postmortem human brain samples (Farde et al., 1994; Staley et al., 1994). SPECT studies with [123I] labelled β-CIT in patients with PD have shown that it is possible to visualize and quantify the loss of dopaminergic nerve endings in this disorder and that the results correlate well with clinical measures of disease severity, motor impairment and asymmetry of symptomatology (Kuikka et al., 1993; Brücke et al., 1993,