PET imaging of neocortical monoaminergic terminals in Parkinson’s disease

R.-M. Marié1,2,3, L. Barré1,2,4, P. Rioux2, P. Allain1,2,4, B. Lechevalier2,3, and J.-C. Baron1,2

1CYCERON, 2INSERM Unit 320, 3Service de Neurologie Déjérine, Centre Hospitalo-Universitaire, and 4CEA DSV/DRIPP, University of Caen, France

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Summary. Post-mortem neurochemical studies in Parkinson’s disease (PD) have shown that, in addition to the typical nigro-striatal dopamine denervation, there exists a concomitant neocortical monoamine fibre deafferentation (of variable severity) whose role in motor, and especially in associated cognitive and affective impairment, remains elusive. We have extensively examined whether PET imaging with 11C-S-Nomifensine (11C-NMF), a radioligand of the dopamine and norepinephrine presynaptic reuptake sites which has been used so far to investigate the striatum, could provide a method for assessing in vivo the neocortical monoamine terminal loss in PD; previously, this has been a little addressed and controversial issue. To this end, we prospectively selected a highly homogeneous sample of nine non-demented, non-depressed idiopathic PD patients with mild to marked side-to-side asymmetry in motor impairment. In addition to recovering the previously-reported correlations with putaminal 11C-NMF specific uptake asymmetries, the clinical motor asymmetries also significantly correlated in the clinically expected direction to neocortical (especially frontal) 11C-NMF asymmetries, suggesting the monoamine neocortical denervation might play a direct role in motor impairment in PD. These results demonstrate that it is possible to assess in vivo the neocortical monoamine terminal loss, and to elucidate its potential role in the complex cognitive and affective impairment, in both PD and atypical degenerative parkinsonism.

Keywords: Positron Emission Tomography, dopamine, norepinephrine, 11C-nomifensine, reuptake sites.

Introduction

The hallmark of Parkinson’s disease (PD) is a loss of dopaminergic neuron cell bodies in the zona compacta of the substantia nigra, leading to striatal dopamine (DA) denervation (Bernheimer et al., 1973) evidenced post
mortem as a dramatic reduction of both DA concentration and presynaptic DA reuptake sites more marked for the putamen than for the caudate nucleus (Kish et al., 1988; Hirai et al., 1988; Niznik et al., 1991). A major advance in the pathophysiological approach to PD took place ten years ago, when it became possible to assess in vivo the degree and distribution of nigro-striatal DA denervation by means of positron emission tomography (PET) and $^{18}$F-6-Fluoro-L-DOPA ($^{18}$F-DOPA) (see Brooks, 1993 for review).

In addition to nigro-striatal DA denervation, post-mortem studies in PD have documented a reduction in neocortical DA concentration and fibre density, indicating that the mesocortical DA system is also consistently affected, though to a more variable extent (Jellinger, 1991). Although it is widely assumed that the clinical expression of PD is explained by the nigro-striatal dopamine denervation, a contribution from the meso-cortico-limbic DA cell loss has long been speculated, especially for cognitive and/or affective impairment (Scatton et al., 1982; Gaspar et al., 1991; Jellinger, 1991). For instance, experimental studies in the normal monkey have shown that prefrontal DA fibres are implicated in cognitive (especially mnemonic and executive) functions (Sawaguchi and Goldman-Rakic, 1991). Since post-mortem studies are inherently poorly-suited to investigate clinical correlations of this kind, a method for assessing in vivo the neocortical DA fibre density would be of considerable help. Although theoretically possible with PET and $^{18}$F-DOPA on biochemical grounds (Firnau et al., 1987), this has in practice been hampered by the high “background” noise due to brain entry of circulating labeled metabolites (Miletich et al., 1993).

In addition to DA cell loss, there also exists in PD a constant loss (though of variable magnitude) of locus coeruleus norepinephrine (NE) cells (Jellinger, 1991). Accordingly, reductions in both the density of NE fibres and the concentration of NE in the cerebral cortex have been reported in PD post-mortem (Javoy-Agid et al., 1989; Gaspar et al., 1991). This system is held to subserve attentional processes in the monkey (Arnsten and Goldman-Rakic, 1985) and the locus coeruleus seems particularly affected in demented PD patients (Jellinger, 1991). Since both the DA and the NE presynaptic reuptake sites in the frontal cortex have been characterized post-mortem in normal humans (Hitri et al., 1991, 1994; Bäckström and Marcusson, 1990) (though not evaluated in PD), in vivo imaging of these monoamine terminals with a positron-labelled reuptake inhibitor would be an attractive approach.

Based on successful $^3$H-Nomifensine in vitro autoradiographic investigations (Scatton et al., 1985), a PET method to assess in vivo the density of striatal presynaptic DA reuptake sites by means of $[^{11}]$C-Nomifensine ($^{11}$C-NMF) has been previously developed (Aquilonius et al., 1987; Tedroff et al., 1988). Nomifensine is a catecholamine reuptake inhibitor which has high affinity for both the DA and the NE reuptake sites, with more than a 100-fold lower affinity for the serotonin reuptake sites (Schacht and Leven, 1984). However, because of the virtual absence of NE innervation to the striatum, the $^{11}$C-NMF method essentially assesses the DA reuptake sites in this structure (Aquilonius et al., 1989). Thus, results of PET $^{11}$C-NMF studies in PD have been consistent with post-mortem findings, showing a marked reduction