NeuroImage: Clinical 12 (2016) 41–46

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Occupancy of pramipexole (Sifrol) at cerebral dopamine D2/3 receptors in Parkinson's disease patients

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ARTICLE INFO

Article history:
Received 22 April 2016
Received in revised form 7 June 2016
Accepted 8 June 2016
Available online 09 June 2016

Keywords:
Parkinson's disease
Pet
Fallypride
Pramipexole
Agonist
Dopamine receptors
Occupancy

ABSTRACT

Whereas positron emission tomography (PET) with the antagonist ligand [^{18}F]fallypride reveals the composite of dopamine D2 and D3 receptors in brain, treatment of Parkinson's disease (PD) patients with the D3-prefering agonist pramipexole should result in preferential occupancy in the nucleus accumbens, where the D3-subtype is most abundant. To test this prediction we obtained pairs of [^{18}F]fallypride PET recordings in a group of nine PD patients, first in a condition of treatment as usual with pramipexole (ON-Sifrol; 3 × 0.7 mg p.d.), and again at a later date, after withholding pramipexole 48–72 h (OFF-Sifrol); in that condition the serum pramipexole concentration had declined by 90% and prolactin levels had increased four-fold, in conjunction with a small but significant worsening of PD motor symptoms. Exploratory comparison with historical control material showed 14% higher dopamine D2/3 availability in the more-affected putamen of patients OFF medication. On-Sifrol there was significant ($p < 0.01$) occupancy at [^{18}F]fallypride binding sites in globus pallidus (8%) thalamus (9%) and substantia nigra (19%), as well as marginally significant occupancy in frontal and temporal cortex of patients. Contrary to expectation, comparison of ON- and OFF-Sifrol results did not reveal any discernible occupancy in nucleus accumbens, or elsewhere in the extended striatum; present methods should be sensitive to a 10% change in dopamine D2/3 receptor availability in striatum; the significant findings elsewhere in the basal ganglia and in cerebral cortex are consistent with a predominance of D3 receptors in those structures, especially in substantia nigra, and imply that therapeutic effects of pramipexole may be obtained at sites outside the extended striatum.

1. Introduction

Levodopa and direct agonists at striatal dopamine D2/3 receptors are the mainstay treatment for motor symptoms of Parkinson's disease (PD). Among the most important dopamine agonists in clinical practice are the benzothiazole pramipexole, the dipropylaminoethyl indole ropinirole, its thiophen homologues rotigotine, piripedil, and the dibenzoquinoline apomorphine; all of these medications are characterized by partial selectivity for D3 over the more abundant D2 receptors. In the case of pramipexole, this preference is reported to be as high as 100-fold in favor of D3 receptors (Millan et al., 2002). At least in rodent models of PD, pramipexole is neuroprotective against nigrostriatal degeneration (Joyce et al., 2004; Lao et al., 2013, Kim et al., 2015), although there is little evidence of disease-modifying effects of treatment of PD patients with pramipexole (Schapira et al., 2013), or conversely that levodopa exacerbates disease progression (Fahn, 2005). Nonetheless, clinical use of pramipexole and other direct agonists is favored in younger patients with PD (<70 years), and pramipexole in particular is considered to have an antidepressant effect in PD patients (Barone et al., 2010), in addition to its alleviation of motor symptoms, suggesting a particular link between D3 receptor activation and favorable treatment responses.

On the other hand, treatment with dopamine agonists, and to a lesser extent also levodopa, can evoke a variety of undesirable neuropsychiatric side-effects, including sleepiness and visual illusions, as well as delusions; one study reports that pramipexole is more likely than other agonists to evoke hallucinations and confusion (Kulisevsky and Pagonabarraga, 2010). Pramipexole and other direct agonists have been particularly implicated in iatrogenic impulse control disorders,

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http://dx.doi.org/10.1016/j.nicl.2016.06.007

including compulsive gambling, sexual behavior, buying and binge-eating. In one study of nearly 200 PD patients taking oral pramipexole, 42% developed impulse control disturbances (Garcia-Ruiz et al., 2014), versus 14% in a larger cross-sectional study (Weintraub et al., 2010). Indeed, preclinical studies show an effect of pramipexole in the probabilistic discounting paradigm, which is an index of risk-taking (Rokosik and Napier, 2012). Similarly, in a functional fMRI study of healthy young adults, pramipexole enhanced the BOLD signal change in the nucleus accumbens associated with anticipation of monetary reward, whilst reducing the apparent top-down regulation by the prefrontal cortex (Ye et al., 2011).

Autoradiographic studies of human brain indicate that D3 receptors predominate over D2 receptors in the basal forebrain and in the striosome compartment of the nucleus accumbens, are of intermediate proportion in the ventral putamen, but comprise <10% of D2/3 receptors in the caudate nucleus (Murray et al., 1994); the occurrence of this dorsal-ventral gradient of D3 distribution in human brain is confirmed by positron emission tomography (PET) displacement studies using the D3-prefering agonist [^{11}C]-PHNO (Narendran et al., 2006). Recent autoradiographic studies in transgenic D2-knockout mice confirmed that D3-sites normally contribute to approximately 20% of the binding of the D2/3 antagonist ligand [^{18}F]fallypide in ventral striatum, but are nearly absent in dorsal striatum (Mukherjee et al., 2015).

Given the apparent proclivity of pramipexole to influence reward and salience, and given its particular affinity for the D3 receptors in the limbic striatum, it is a matter of interest to determine the therapeutic occupancy of pramipexole at its targets in human brain. Indeed, impairment of impulse control in Parkinson's disease patients has recently been attributed to the D3-agonist selectivity of pramipexole (Seeman, 2015). Competition binding assays by PET afford estimates of the therapeutic occupancy for CNS drugs, which have proven informative in the case of antipsychotic medications for the treatment of schizophrenia. Such studies established the concept of therapeutic occupancy window at dopamine D2/3 receptors for obtaining antipsychotic efficacy (<65%; Farde et al., 1988) without provoking extrapyramidal side effects, which typically occur when blockade exceeds 80% (Kapur et al., 1995). This competition paradigm has since been extended to PET studies of antipsychotic occupancies at multiple receptor types, in support of the concept of atypicality (Mamo et al., 2007), and to measuring antipsychotic occupancy at the relatively less abundant extra-striatal dopamine D2/3 receptors (Vernaleken et al., 2008). However, hardly anything is known about the converse case, i.e. therapeutic occupancy of dopamine receptor agonists in the treatment of PD; oral treatment with the dopamine agonist lisuride at an effective antiparkinsonian dose (1 mg p.d.) displaced 19% of [^{11}C]raclopride binding in the putamen of PD patients (Antonini et al., 1994), whereas in another study, a low dose of the agonist apomorphine (0.03 mg/kg) decreased [^{11}C]raclopride binding, by 9% in the more intact putamen, and by 15% on the side contralateral to the main symptoms, suggesting an increase in affinity state in the dopamine-denervated striatum (de la Fuente-Fernández et al., 2001). A [^{11}C]FLB-457 PET study of five healthy middle-aged volunteers showed 10–20% occupancy at extra-striatal D2/3 receptors after challenge with 0.25 mg pramipexole (Ishibashi et al., 2011), but striatal binding could not be calculated with that ligand.

In the present study we undertook to measure dopamine D2/3 receptor availability in striatum and extrastriatal regions of patients with idiopathic PD using the high affinity antagonist ligand [^{18}F]fallypride, which is equally affine at D2 and D3 sites (Mukherjee et al., 2015). We predicted that receptor availability should be higher at medication-free baseline than under treatment as usual with pramipexole, and tested our hypothesis that occupancy by pramipexole should be higher in the limbic striatum and extra-striatal regions than in the putamen and caudate nucleus, in proportion to the relative abundance of D3 sites. In an exploratory study, we also assessed disease and treatment effects by comparison with historical [^{18}F]fallypride PET data from a healthy age-matched control group.

2. Methods

Nine patients with PD were recruited from the Department of Neurology, Ludwig-Maximilians University, Munich and from the Max Planck Institute of Psychiatry, Munich. Nine healthy control subjects were selected as an historical control group (Rominger et al., 2012; Jansen et al., 2014) so as to obtain optimal age- and demographic matching. Subjects were excluded if they had any history of substance abuse or other psychiatric disorders or any serious medical condition (other than PD) requiring treatment with CNS medications. The study protocol was approved by the local clinical institutional review board and complied with the declaration of Helsinki. Written informed consent was obtained from all participants after the procedures had been fully explained. Healthy volunteers had a single [^{18}F]fallypride scan at the Department of Nuclear Medicine. Patients had a baseline scan at 48–72 h after cessation of pramipexole treatment and a second [^{18}F]fallypride PET scan two weeks later, while under treatment with pramipexole as usual.

[^{18}F]Fallypride was synthesized as described previously (Rominger et al., 2010). A 15-minute transmission scan with a rotating [^{68}Ge] point source was followed by a 3-hour dynamic 3D emission recording, initiated immediately upon beginning the administration of [^{18}F]fallypride (mean dose 250 MBq) as a slow intravenous bolus. The dynamic recording consisted of 39 time frames (3×20 s, 3×1 min, 3×2 min, 3×3 min, 21×5 min, 2×8 min and 4×10 min; 180 min in total), which were recorded with an ECAT EXACT HR + PET (Siemens/CTI, Knoxville, TN, USA). During emission and transmission scans, the subjects' heads were comfortably immobilized within the aperture using a foam cushion. The tomograph acquired 63 contiguous transaxial planes, simultaneously covering 15.5 cm in the axial field of view, with 4.0 mm centre of field resolution (full width at half maximum). Dynamic image data were reconstructed as 128×128 matrices of $2.1 \times 2.1 \times 2.4$ mm voxels by 3D filtered back-projection using a Hann filter with a cut-off frequency of 0.5 Nyquist units. Final data were corrected for decay, randoms, dead time and scatter. Emission recordings were checked for motion between fraqmes, and then registered and normalized to an in-house standard brain [^{18}F]fallypride template in MNI coordinates using the SPM5 routines (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (version 7.1, MathWorks Inc., Natick, MA, USA). Details of the image analysis procedure are reported elsewhere (Rominger et al., 2012; Cumming et al., 2013). The sum of frames 9 to 13 (8–19 min) was used as source image for normalization the individual PET image using the SPM coregistration and normalization procedures. We then applied a cerebellum template (excluding the vermis) to the dynamic volumes using the program amide (http://amide.sourceforge.net) to calculate the time-activity-curve of the reference region. Using PMOD (PMOD technologies, Zurich, Switzerland) we then calculated voxelwise parametric maps of the [^{18}F]fallypride binding potential (BP_{ND}), using a linear graphical method (Logan et al., 1996) relative to cerebellum, as previously described for [^{18}F]fallypride (Mukherjee et al., 2002). Templates for caudate nucleus, posterior and anterior putamen, nucleus accumbens, thalamus, globus pallidus, insular and temporal cortex and the pituitary gland, were applied to the individual parametric maps in order to obtain the mean BP_{ND} by region. We used an in-house template for the striatum and its subdivisions (la Fougère et al., 2010) and the Wake Forrest University Pick Atlas for other regions (Maldjian et al., 2003).

[^{18}F]Fallypide PET scans were obtained from nine neurologically normal control subjects of mean (SD) age 63 ± 6 years who had participated in earlier studies (Rominger et al., 2012; Jansen et al., 2014). In an exploratory study, the spatially normalized mean parametric maps from the patients with PD (OFF condition) and the healthy control group were compared (subtraction analysis). The threshold for significant difference was arbitrarily set at 0.5 units of BP_{ND}. For statistical comparisons with predictable outcomes (i.e. UPDRS III scores and prolactin levels would increase in the OFF condition) we used the Student's 1-tailed *t*-test