The Effect of SSRIs on the Binding of ^{18}F -FP-CIT in Parkinson Patients: A Retrospective Case Control Study

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Received: 5 February 2014 / Revised: 15 June 2014 / Accepted: 18 June 2014 / Published online: 3 July 2014
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Abstract

Purpose ^{18}F -FP-CIT [^{18}F -fluorinated *N*-3-fluoropropyl-2-beta-carboxymethoxy-3-beta-(4-iodophenyl) nortropane] is useful for detecting striatal dopamine transporter (DAT). Since FP-CIT shows relatively high affinities for DAT and serotonin transporter (SERT), its binding can be influenced by selective serotonin reuptake inhibitors (SSRIs). We aimed to evaluate the effect of SSRIs on the binding of ^{18}F -FP-CIT.

Methods In our ^{18}F -FP-CIT positron emission tomography (PET) data pool, images of 24 drug-naïve Parkinson's disease (PD) patients (62.6 ± 10.6 years), 111 PD patients taking SSRIs [escitalopram ($n=19$) and fluvoxamine ($n=20$)] or clonazepam ($n=72$), and 10 normal people were reviewed. PET images acquired 3 h after ^{18}F -FP-CIT injection were analyzed by an automated method using a predefined volume of interest (VOI) set of the striatum (ST), occipital cortex (OC), raphe nuclei (RN), and cerebellar cortex (CB). The uptake ratios (URs) of each VOI to the CB were compared among the groups.

Results The ST/CB URs of all PD groups were significantly lower than that of normal group. When adjusted for drug severity, ST/CB URs were higher in drug-naïve group but had no difference among antidepressant groups. Whereas OC/CB URs were not different among groups ($p>0.05$), RN/CB URs were significantly lower in SSRI groups than in non-SSRI groups ($p<0.001$) and showed similar results when adjusted for disease severity.

Conclusions PD patients taking SSRIs showed significantly decreased URs in the RN but not the OC. When adjusted for Hoehn and Yar (HY) score, ST URs were not different among antidepressant groups. This result suggests that the OC may be used as a reference region for the quantification of DAT binding in ^{18}F -FP-CIT PET images of PD patients taking SSRIs.

Keywords Parkinson's disease · Selective serotonin reuptake inhibitor · ^{18}F -FP-CIT · PET

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder that involves the degeneration of dopaminergic cells, resulting in a loss of dopamine transporters (DATs) in the striatum [1, 2]. Many studies have shown that DAT imaging is a sensitive means to detect the loss of striatal DATs (especially in the putamen) in PD, even in the earliest clinical motor stages of this disorder [3, 4]. Several radiotracers for DAT imaging have been successfully developed. Of these, ^{18}F -FP-CIT [^{18}F -fluorinated *N*-3-fluoropropyl-2-beta-carboxymethoxy-3-beta-(4-iodophenyl) nortropane] is useful for detecting the loss of striatal DAT in degenerative parkinsonisms, such as PD and atypical parkinsonism [5–7]. After its registration in 2008, the use of ^{18}F -FP-CIT has increased dramatically in Korea for both routine clinical and experimental studies [7]. Although it has been shown that visual analysis is sensitive enough to diagnose degenerative parkinsonism [6], the quantitative analysis of ^{18}F -FP-CIT positron emission tomography (PET) is employed in many centers as a supplementary tool for diagnosis and for experimental studies. Patients with PD are usually on various medications because psychiatric comorbidities such as anxiety and depression are common in PD. The possibility of alterations in the uptake and

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metabolism of DAT imaging by these medications remains [8–11]. Thus, it is important to evaluate the potential effects of drugs on DAT imaging with ^{18}F -FP-CIT.

It has been proposed that drugs with the following mechanisms may potentially influence FP-CIT (either ^{18}F - or ^{123}I -labeled) images: (1) drugs with affinity for monoaminergic transporters or that may influence the affinity of FP-CIT for monoaminergic transporters; (2) drugs that may influence the expression of DAT and serotonin transporter (SERT); (3) drugs with potential effects on the metabolism of FP-CIT and on cerebral blood flow [7, 12].

Several recent studies have shown that selective serotonin reuptake inhibitors (SSRIs) may influence the brain uptake and metabolism of ^{123}I - β -CIT, ^{125}I - β -CIT, and ^{123}I -FP-CIT single-photon emission computed tomography (SPECT) images [12–16]. Although ^{123}I -FP-CIT is more selective for DAT than β -CIT [12], ^{123}I -FP-CIT still labels SERT to some extent [17]. Striatal binding ratios are quantified as striatal binding over nonspecific binding in the occipital cortex (OC) or cerebellum, and since SERT is expressed not only in the striatum but also in the OC and cerebellum (although to a low extent), the blockade of FP-CIT binding to SERTs by SSRIs may lead to alterations in the striatal binding ratio. This may be problematic since SSRIs are the most commonly used antidepressants for PD patients, among whom 40–50 % suffer from depression [7].

^{18}F -FP-CIT has an almost identical molecular structure to ^{123}I -FP-CIT, except for the type and location of the labeled radionuclide, and thus has the same affinity for DAT and SERT as ^{123}I -FP-CIT [17]. However, unlike ^{123}I -FP-CIT, ^{18}F -FP-CIT does not metabolize into radiolabeled nor- β -CIT (which crosses the blood-brain barrier and may be taken up by the brain) [18, 19]. Due to its similarity to ^{123}I -FP-CIT, it can be hypothesized that the striatal binding ratio of ^{18}F -FP-CIT may also be influenced by SSRIs. However, this hypothesis has not been tested in humans and it is still possible that the effect of SSRI on ^{18}F -FP-CIT images may differ from that of ^{123}I -FP-CIT images, because there are also differences between the two radiopharmaceuticals (such as in metabolites).

With this background, we aimed to investigate the effect of SSRIs on the human brain tissue uptakes and binding ratios of ^{18}F -FP-CIT in striatal and reference regions.

Methods

Study Subjects

Between May 2010 and April 2012, 1,162 patients underwent ^{18}F -FP-CIT PET at the Asan Medical Center for the evaluation of parkinsonism. Of these, 430 patients were diagnosed with PD and had an available Hoehn and Yahr (HY) stage on their medical records. Among these cases, 111 PD patients taking

SSRIs [escitalopram ($n=19$, 64.7 ± 10.7 years, M:F=9:10) and fluvoxamine ($n=20$, 62.8 ± 11.0 years, M:F=6:14)] or clonazepam ($n=72$, 65.6 ± 9.5 years, M:F=31:41) along with antiparkinson drugs and 24 drug-naïve PD patients (62.4 ± 10.6 years, M:F=10:14) were enrolled in this study. Ten normal (healthy) people (65.5 ± 6.2 years, M:F=3:7) were also included. The 39 PD patients taking SSRIs were the group in question, while another 96 PD patients and 10 normal people were included for comparison.

The diagnosis of PD was based on the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [20]. Duration of the disease was defined as the time passed since the first presentation of the patient's symptom. All patients were evaluated by neurologists specializing in movement disorders and had available medical records. The severity of motor symptoms was assessed using the Unified Parkinson's Disease Rating Scale, Part III (UPDRS III) and the modified HY stage. Antiparkinsonian drugs had been discontinued for at least 12 h before ^{18}F -FP-CIT PET scanning and the medical records and patient history were thoroughly examined to ensure that no drug with affinity for the DAT was being administered. The institutional review board at our center approved the retrospective use of the clinical data for this study.

Radiopharmaceutical Synthesis

^{18}F -FP-CIT was synthesized with a protic solvent (*t*-butanol or *t*-amyl alcohol) as a reaction solvent and *N*-[3'-(tosyloxy)propyl]-2 β -carbomethoxy-3 β -(4'iodophenyl) nortropane as a precursor [21]. The radiochemical purity was greater than 98 % after purification by high-performance liquid chromatography and the mean specific activity was 6,475.0 mCi/ μmol (1,055.6–19,300.2) at the end of synthesis.

^{18}F -FP-CIT PET

^{18}F -FP-CIT PET was performed using a Biograph 40 TruePoint PET/CT camera (Siemens Medical Systems, Malvern, PA), which provides an in-plane spatial resolution of approximately 2 mm full width at half-maximum at the center of the field of view. Image acquisition was started 3 h after intravenous injection of ^{18}F -FP-CIT (185 MBq). Emission PET data were acquired for 10 min in the three-dimensional mode after brain CT, which was performed in the spiral mode at 120 kVp and 380 mA (reference standard) using the CARE Dose 4D program. ^{18}F -FP-CIT PET images were reconstructed from CT data for attenuation correction using the TrueX algorithm and an all-pass filter with a 336×336 matrix.

Image Analysis

For image analysis, image processing was performed with SPM2 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London) within MATLAB 6.5.1 for Windows (MathWorks, Natick, MA, USA) and MRICro version 1.37 (Chris Rorden, Columbia, SC, USA). The analyses were based on volumes of interest (VOIs), which were defined on the basis of a template in standard space. All reconstructed PET images were spatially normalized to the Talairach space by use of a standard ^{18}F -FP-CIT PET template to remove inter-subject anatomic variability [22]. The template was made in-house from ^{18}F -FP-CIT PET and T1-weighted MR images of 13 healthy people [four men and nine women, 55.2 ± 9.2 years (range, 41–70 years)] and the VOIs were drawn manually by an experienced nuclear medicine physician specializing in nuclear neurology, as described previously [22]. The following VOIs were drawn: 12 VOIs (bilateral ventral striatum, anterior caudate, posterior caudate, anterior putamen, posterior putamen, and ventral putamen) of the bilateral striatal subregions, VOIs of the OC and cerebellar cortex (CB), which were to be used as reference regions, and the VOI of the raphe nuclei (RN), which is a DAT-poor but SERT-rich region. The VOIs were drawn manually on a coregistered, spatially normalized, single T1-weighted MRI and ^{18}F -FP-CIT template. The VOI template in the standard stereotactic space was automatically applied directly to the spatially normalized individual PET images to analyze striatal ^{18}F -FP-CIT binding.

The activity concentration in each VOI was calculated and the 12 VOIs for the bilateral striatal subregions were summed and averaged according to their voxels as representative uptake values of striatal (ST) activity. The uptake ratios (URs) of the VOI activities (ST/CB, ST/OC, OC/CB, RN/CB, RN/OC) were calculated.

Statistical Analysis

To compare the general characteristics (age, gender, duration, and severity of disease) and URs among normal and PD groups, analysis of variance (ANOVA) and Kruskal-Wallis tests were used, according to normality tests. Spearman correlation was used to assess the correlation between disease duration and HY stage. Unadjusted and adjusted models with linear regression analysis were performed to assess the relationship between URs and disease severity, to compare URs between groups, and to adjust for disease severity. All statistical analyses were performed using the SPSS 17.0 statistical software package (IBM SPSS, New York, USA) and $p < 0.05$ was considered statistically significant.

Results

The clinical characteristics of the PD patients and the normal group are summarized in Table 1. No significant differences were seen for the age and gender of any of the groups. Drug-naïve patients had a less advanced disease status (shorter disease duration and lower HY stages) than the PD groups taking antidepressants [(SSRI: fluvoxamine, escitalopram), clonazepam] (all p values were either ≤ 0.001 or 0.01). There were no significant differences in disease duration or HY stages among the PD groups taking antidepressants. The duration of the disease correlated well with the HY stage ($\rho = 0.62$, $p = 0.01$).

ST/CB UR decreased with a longer disease duration (regression coefficient, -0.284 ; 95 % CI, -0.358 to -0.210 ; $p < 0.001$) or a higher HY stage (regression coefficient, -1.71 ; 95 % CI, -2.063 to -1.358 ; $p < 0.001$). OC/CB URs showed no significant change as the duration (regression coefficient, -0.004 ; 95 % CI, -0.01 to 0.001 ; $p = 0.081$) or HY stage (regression coefficient, -0.009 ; 95 % CI, -0.035 to 0.017 ; $p = 0.496$) increased. RN/CB URs also decreased with a longer duration (regression coefficient, -0.048 ; 95 % CI, -0.09 to -0.006 ; $p = 0.025$) or a higher HY stage (regression coefficient, -0.456 ; 95 % CI, -0.663 to -0.24 ; $p < 0.001$).

The URs of the normal and PD groups are summarized in Fig. 1.

The ST/CB URs of all PD groups (6.2 ± 2.1) were significantly lower than that of the normal group (11.7 ± 2.0) and the PD groups taking antidepressants had lower ST/CB URs than the drug-naïve PD group (all p values < 0.001). When adjusted for HY stage, ST/CB UR was higher in the drug-naïve group than the antidepressant groups (all p values $= 0.001$ – 0.003) except for the fluvoxamine group (p value $= 0.115$). There was no difference in ST/CB UR among PD groups taking antidepressants. When adjusted for duration of disease, similar results were found and the ST/CB UR was higher in the drug-naïve group than the antidepressant group (all p values $=$ below 0.001 – 0.028) except for the fluvoxamine group (p value $= 0.152$). The fluvoxamine and escitalopram groups had a significant difference as well ($p = 0.016$).

The OC/CB URs were not different among normal (1.6 ± 0.1), drug-naïve (1.6 ± 0.1), SSRI (1.6 ± 0.1), and clonazepam (1.6 ± 0.1) groups ($p = 0.736$).

RN/CB URs were significantly lower in the fluvoxamine (2.4 ± 1.2) and escitalopram (2.0 ± 0.8) groups than in the normal (3.4 ± 0.8), drug-naïve (3.6 ± 0.8), or clonazepam (3.2 ± 0.8) groups (all p values < 0.001). The non-SSRI groups had no significant differences in RN/CB URs. When adjusted for HY stage or duration of disease, the results were the same (all p values between SSRI and non-SSRI groups were < 0.001).

Figure 2 shows representative ^{18}F -FP-CIT PET ratio parametric images of normal people and patients with HY stage 2

Table 1 Clinical characteristics of the study subjects with Parkinson's disease (PD) and normal controls

	Normal (<i>n</i> =10)	Parkinson's disease (<i>n</i> =135)			<i>p</i> value	
		Drug-naïve (<i>n</i> =24)	Antidepressants			
			SSRIs		Non-SSRI	
			Fluvoxamine (<i>n</i> =20)	Escitalopram (<i>n</i> =19)	Clonazepam (<i>n</i> =72)	
Age (years)	65.5±6.2	62.6±10.6	62.8±11.0	64.7±10.7	65.6±9.5	0.547
Sex (M:F)	3:7	10:14	6:14	6:10	31:41	0.748
Symptom duration (years)	NA	1.1±0.6	4.7±3.4	5.4±4.8	5.6±4.1	<0.001 ^a
Modified HY score	NA	1.3±0.6	2.0±0.8	2.4±0.7	2.1±0.8	<0.001 ^b

SSRI selective serotonin reuptake inhibitor, HY Hoehn and Yahr

^a Drug-naïve group had a significantly shorter duration of disease than PD groups taking antidepressants (all *p* values ≤0.001). There was no significant difference in duration of disease among patients taking antidepressants

^b Drug-naïve group had a significantly lower HY score than PD groups taking antidepressants (all *p* values were either <0.001 or 0.01). There was no significant difference in duration of disease among patients taking antidepressants

PD (drug-naïve, fluvoxamine, citalopram, and clonazepam groups) at striatal and midbrain levels.

Discussion

The main result of our current study is that the OC/CB URs of ¹⁸F-FP-CIT were not different among normal and PD patient groups regardless of SSRI use, and that RN/OC and RN/CB URs significantly decreased in PD patients taking SSRIs. There was no difference in ST/CB UR among PD groups taking antidepressants, when adjusted for HY stage. To our knowledge, this is the first study to assess the effect of SSRIs on ¹⁸F-FP-CIT PET in human brains, although it was performed in a retrospective manner.

In most clinical studies, the striatal binding of FP-CIT can be simply quantified by a ratio of striatal specific uptake over nonspecific uptake in the cerebellar or cerebral cortex (such as the OC). Since SERT is present (in decreasing order) in the RN, hypothalamus, striatum, limbic cortex (which includes the cingulate gyrus and amygdala), and OC [23], SSRIs may theoretically influence the UR of the striatum to the reference region, such as the OC, by blocking the binding of FP-CIT to SERTs in the reference region. Studies on rats by Booij et al. [24] have shown that an SSRI can displace ¹²³I-FP-CIT binding in the OC but not in the cerebellum. Another study by Booij et al. [12] on healthy humans with ¹²³I-FP-CIT SPECT found that paroxetine (an SSRI) affects the ST/OC UR but not the ST/CB UR. That study suggested that although the SERT expression is low in both the OC and cerebellum, the expression is higher in cerebral cortical areas. A previous preclinical study by Shin et al. [25] showed that the use of fluvoxamine (an SSRI) in mice increased the ST/OC UR on ¹⁸F-FP-CIT PET, which is in line with previous studies with ¹²³I-FP-CIT or

β-CIT SPECT. In our current study, however, the OC/CB UR of ¹⁸F-FP-CIT was not influenced by the use of SSRIs, which contradicts other reported findings with ¹²³I-FP-CIT SPECT scans that found a decrease in the OC/CB [12].

One explanation for this discrepancy is that the SERT expression level in the OC is even lower than anticipated. Another possible explanation is that the radiometabolites of the two radiotracers and SSRIs used in both studies may result in a different influence of radiotracers on occipital uptake. ¹⁸F-FP-CIT has an almost identical molecular structure to ¹²³I-FP-CIT and the same affinity for DAT and SERT as ¹²³I-FP-CIT [17]. However, unlike ¹⁸F-FP-CIT, ¹²³I-FP-CIT is metabolized into radiolabeled nor-β-CIT by cocaine N-demethylation by microsomal cytochrome P-450 3A. This ¹²³I-radiolabeled nor-β-CIT crosses the blood-brain barrier and has a relatively high affinity for SERT compared with FP-CIT [18, 19]. Occipital uptake on ¹²³I-FP-CIT SPECT may reveal SERT binding of ¹²³I-FP-CIT and its metabolite ¹²³I-FP-CIT, in addition to nonspecific binding. However, we cannot exclude the possibility that the small sample size of our study did not reveal the effect of SSRIs on SERT binding of ¹⁸F-FP-CIT in the OC, although such an effect is probably small.

In our present findings, ST/CB URs decreased with a longer duration or a higher HY stage of the disease. This is in line with previous studies showing that the dopamine transporter activity correlates with the stage of Parkinson's

Fig. 1 a Uptake ratios (URs) of the striatum (ST), occipital cortex (OC), and midbrain raphe nuclei (RN) to the cerebellar cortex (CB) in the normal and Parkinson's disease (PD) groups. b–e URs are again presented by grouping PD patients according to drug use. Those *p* values that are statistically significant are shown. SSRI stands for selective serotonin reuptake inhibitor

Fig. 2 Representative ^{18}F -FP-CIT PET ratio parametric images of normal people and patients with Hoehn and Yahr stage 2 Parkinson's disease (drug-naïve, fluvoxamine, citalopram, and clonazepam groups) at the levels of the striatum and midbrain. The color scale (ranging from 0 to 12) reflects the ^{18}F -FP-CIT PET uptake of the region compared with that

of the cerebellum (color scale 1). Striatal uptake ratios of patients with Parkinson's disease were significantly lower than those of normal people. The uptakes of the raphe nuclei of the midbrain in patients taking fluvoxamine and escitalopram are notably and significantly lower than those of the others (arrows)

disease [26, 27]. When adjusted for HY stage or disease duration, there was no difference in ST/CB UR among PD groups taking antidepressants, indicating that the differences in the ST/CB URs were not due to a particular drug use. ST/CB UR was higher in the drug-naïve group than the antidepressant groups and indicates that drug-naïve patients were in a relatively earlier phase of PD than other PD patients on medication with a same HY stage. The HY stages are complained to be too broad, and although widely accepted, it has many weaknesses [28]. It is likely that even patients with the same HY stage PD in our study had disease severities that were widely variable.

Previous studies using ^{123}I - β -CIT SPECT have shown that the ST/CB UR increased significantly after SSRI administration [13, 14, 16], whereas ST/CB URs were not different among patients taking antidepressants in our study. The difference in the affinity for SERT between the two tracers may be the reason for the different findings. Peripheral blockage of SERTs by SSRIs resulted in increased β -CIT availability in the brain. Although the expression of SERT in the cerebellum is very low, it may not be negligible [29]. Consequently, the combination of increased β -CIT availability and decreased SERT availability in the cerebellum may lead to the increased UR of the striatum to the cerebellum. Booij et al. [12] have also found that paroxetine does not influence the UR of the striatum to the cerebellum on ^{123}I -FP-CIT SPECT.

The use of SSRIs also decreased RN/CB or RN/OC URs in our study subjects. This decrease is mainly because most of the neurons in the RN of the midbrain are serotonergic. The decrease in the RN/CB UR we observed is in line with previously reported data showing that FP-CIT has a moderate

affinity for SERTs and labels them in vivo [17, 30]. However, there is also the possibility that the decrease in the RN/CB UR was caused by a downregulation of SERT related to depression. Although there seems to be an aging effect in the RN/CB, there were no significant differences in the ages of the studied groups and the effect of aging was probably insignificant in our present study series.

As mentioned above, the ST/CB UR differed with the disease severity, as anticipated. The fact that OC/CB UR remained uninfluenced by the disease status implies that it has a good feature for a reference region. Like ST/CB UR, RN/CB URs also decreased with a longer duration or a higher HY stage of the disease. This finding is probably due to the fact that patients with more advanced disease had a higher percentage of SSRI administration. In our present study, escitalopram and fluvoxamine were among the SSRIs evaluated. It is likely that other SSRIs have the same effect on ^{18}F -FP-CIT PET scans, although further studies are needed to confirm this supposition.

A major limitation of this study is that it is not based on a paired test, which would have compared URs observed from the same subject before and after the administration of SSRI. A further prospective study will be needed to confirm our current findings. Another limitation is that most of the enrolled patients, with the exception of the drug-naïve group, were taking other drugs such as antiparkinson drugs or anti-hypertensives along with SSRIs or clonazepam. Although it is unlikely that antiparkinson drugs significantly influence DAT imaging [31] or that other drugs taken by the elderly will cross the blood-brain barrier, we cannot exclude the small possibility that other drugs being taken by the patients may have

influenced the image findings. Another minor limitation is that since patient drug history was assessed based on medical records and on histories taken by a trained professional, there is a very small possibility that the patients were taking SSRIs without our knowledge.

Conclusions

PD patients taking SSRIs show significantly decreased URs in the RN but not the OC, when compared with normal, drug-naive, and clonazepam groups. When adjusted for HY stage, ST URs were not different among antidepressant groups, although the drug-naive group had higher ST URs than other groups, reflecting the heterogeneity within HY stages.

This result suggests that the OC may be used as a reference region for the quantification of the DAT binding ratio in ^{18}F -FP-CIT PET images of PD patients taking SSRIs, although it is unclear whether the decreased URs in the RN resulted from SSRI occupancy or a depression-related down-regulation.

Conflict of Interest Minjung Seo, Minyoung Oh, Minjung Cho, Sun Ju Chung, Chong Sik Lee, and Jae Seung Kim declare that they have no conflict of interest.

Ethical Standard All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. The institutional review board at our center approved the retrospective use of the clinical data for this study.

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