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ORIGINAL INVESTIGATION

Serotonin transporter occupancy induced by paroxetine in patients with major depression disorder: a ^{123}I-ADAM SPECT study

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Abstract
Rationale To assess the paroxetine-induced serotonin transporter (SERT) occupancy (SERTocc) using in vivo ^{123}I-ADAM SPECT.
Objectives ^{123}I-ADAM SPECT was used to investigate the SERTocc induced by paroxetine in major depression disorder (MDD) patients, to compare the SERT availability in drug-free MDD patients and healthy volunteers, and to study the relationship between paroxetine plasma concentrations (Cp) and SERTocc.
Materials and methods Measures of SERT availability by means of ^{123}I-ADAM SPECT were obtained in ten MDD patients before and after 4- to 6-week treatment with paroxetine 20 mg/day. ^{123}I-ADAM SPECT measures of SERT availability from a group of ten previously studied age-matched healthy volunteers were used for comparison. The relationship between percentages of SERTocc and paroxetine Cp was studied using an E_{max} model.
Results Mean SERTocc values were 66.4±9.5% in midbrain, 63.0±9.6% in thalamus, and 61.3±10.9% in striatum. No significant differences in SERTocc were found among these three regions. No significant differences in mean SERT availability were found in any region between drug-free MDD patients (midbrain=1.14±0.15; thalamus=0.85±0.13; striatum=0.70±0.07) and healthy volunteers (midbrain=1.19±0.22; thalamus=0.96±0.14; striatum=0.67±0.15). The E_{max} model returned a $SERTocc_{max}$=70.5% and a Cp_{50}=2.7 ng/ml.
Conclusions Using ^{123}I-ADAM SPECT, treatment with paroxetine 20 mg/day leads to more than 60% SERTocc on average in cerebral regions with known high SERT density. Data from this study do not support the existence of SERT availability differences between drug-free MDD patients and healthy volunteers. Finally, the E_{max} model is suitable for the study of paroxetine Cp relationship to ^{123}I-ADAM SPECT-measured SERTocc. This approach may be useful for pharmacokinetic–pharmacodynamic relationships in drug development.

Keywords ^{123}I-ADAM SPECT · Serotonin transporter · Serotonin transporter availability · Major depression disorder · Paroxetine · Occupancy · Pharmacology

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Introduction

The serotonergic neurotransmitter system is involved in the regulation of a wide range of psychological, behavioral, and

biological functions (Williams 1994). Several lines of evidence suggest that disturbances in central serotonin function may play an important role in mood disorders. Serotonin levels in the synaptic cleft are mainly regulated by the activity of the presynaptic serotonin transporter (SERT), which has become the target for most antidepressants. Dysregulation of SERT expression or function, leading to a decreased serotonergic neurotransmission, has been proposed to play an essential function in the physiopathology of major depressive disorder (MDD) (Owens and Nemeroff 1994). The selective serotonin reuptake inhibitors (SSRIs) are thought to alleviate depressive symptoms through inhibition of the SERT function and subsequent increment of serotonin concentration in central nervous synapses.

Nowadays, it is possible to study the SERT function in living humans by means of either positron emission tomography (PET) or single photon emission computed tomography (SPECT).

The decision of using either PET or SPECT mainly depends on the availability of radioligands, colocation of the technique in sites with access to target patient populations, and budget. SPECT has the advantage over PET of having a lower cost and wider availability, but until recently, the only radioligand available for SERT imaging with SPECT, the ^{123}I-β-CIT, lacked selectivity, showing high affinity also for the dopamine transporter (Laruelle et al. 1993). Recently, our group characterized in healthy volunteers a selective SPECT radioligand for SERT, the ^{123}I-ADAM [2-((2-((dimethyl-amino)methyl)phenyl)thio)-5-iodophenylamine] (Catafau et al. 2005). Evidence that this radioligand is suitable for measuring SERT occupancy (SERTocc) induced by the SSRI citalopram in healthy volunteers and in patients has also been reported (Erlandsson et al. 2005; Herold et al. 2006). However, despite paroxetine being a widely used SSRI for the treatment of MDD patients, to the best of our knowledge, there are no published data on the degree SERTocc is induced by therapeutic doses of this drug in MDD patients by means of ^{123}I-ADAM SPECT.

Besides the selection of the neurotransmission imaging technique (i.e., PET or SPECT), requirements for the accurate SERTocc measurement in the target patient population also deserve consideration. Receptor or transporter occupancies are calculated as the percentage of difference between the available number of receptor or transporters measured after treatment with respect to those initially available in a drug-naïve or drug-free condition in the same subject. However, scanning a patient in the naïve- or drug-free condition is difficult and too often unfeasible. For this reason, calculation of receptor occupancies using the mean receptor availability value from a control group is extensively used in the literature either using SPECT (Knable et al. 1997; Dresel et al. 1999; Tauscher et al. 1999a) or PET (Gefvert et al. 1998; Kapur et al. 1999; Talvik et al. 2004). The control group can either be an independent group of patients with the same characteristics as the target population or a group of healthy subjects under the assumption that there are no differences in receptor or transporter availability between healthy subjects and the patient population.

In this study, ^{123}I-ADAM SPECT was used to investigate the degree of SERTocc induced by a therapeutic dose of paroxetine (20 mg/day) at steady state in patients with MDD. As secondary objectives, the SERT availability in drug-free MDD patients and healthy subjects was compared, and differences in the drug-induced SERTocc calculated using SERT availability values from different populations (own patient, drug-free MDD patient group mean, and healthy volunteer group mean) were investigated. Finally, the relationship between paroxetine plasma concentrations (Cp) and SERTocc was explored.

Materials and methods

Subjects

Patients with MDD were recruited from the clinical setting after being evaluated by an expert psychiatrist. Inclusion criteria consisted of: (1) the existence of a major depressive episode, single or recurrent, according to DSM-IV; (2) a minimal score of 18 in the Hamilton scale for depression (HAMD) of 17 items (Hamilton 1960); and (3) absence of any active antidepressant treatment during a minimum of 6 months before admission. Main exclusion criteria were the existence of severe organic illness, drug abuse, other concurrent psychiatric pathologies, and treatment with psychotropic drugs that could affect the serotoninergic system. Doses of benzodiazepines equivalent to 10 to 20 mg/day of diazepam were allowed. Patients diagnosed as bipolar depressives were also excluded. Normal physical examination and review of systems were required. In women, pregnancy was excluded by means of a urine pregnancy test (Clearview HCG II, Unipath Limited, Bedford, UK). The study was approved by the local ethics committees and the Ministry of Health and performed in accordance with the Declaration of Helsinki (1964). All subjects signed a written informed consent before their inclusion in the study.

A total of ten Caucasian patients, four men and six women, mean age 36±10.8 years (range 20–53 years), were included in the study. Five of them were first MDD episode. Mean episode duration was 4.4±1.6 months. Nine patients completed the whole study protocol, but one of them voluntarily refused to continue before the second SPECT session.

Data from ten previously studied healthy volunteers, seven men and three women, mean age 36.2±10.5 years (range 28–65 years) (Catafau et al. 2005), were used to investigate differences with the pretreatment (i.e., drug-free) condition SERT availability of patients. Paroxetine-induced SERTocc in MDD patients was also calculated using the mean SERT availability value from this group of age-matched healthy volunteers to compare with the SERTocc values obtained using the SERT availability data from either the own patient or the whole drug-free MDD patient group.

Study design

Each subject underwent two SPECTs, the first one was after 3.2±2.5 days of inclusion in the study, in a drug-free condition before initiating treatment ($SPECT_{pre\text{-}t}$), and the second one was after 4–6 weeks (39.0±6.1 days) of treatment with paroxetine 20 mg/day postoperatively ($SPECT_{post\text{-}t}$).

Severity of the MDD was assessed by means of HAMD both at inclusion (pretreatment) and within the week of the posttreatment SPECT day. A HAMD score decrease of ≥50% from the pretreatment score was considered as clinical response.

During the posttreatment SPECT session, one blood sample was collected from each patient, and paroxetine Cp was measured using high-performance liquid chromatography with fluorescence detection (Brett et al. 1987).

SPECT procedure

On each SPECT day, four multimodality SPECT/MRI markers (MM303, IZI Medical Products, Baltimore, MD, USA), each filled with approximately 0.074 MBq of ^{123}I, were attached to the subject's head at the level of the temples and mastoids to allow for SPECT and MRI coregistration and realignment of SPECT images. To minimize radiation exposure to the thyroid gland, potassium perchlorate (8 mg/kg) was administered orally up to 20 min before radioligand injection. SPECT images were acquired on a triple-head Prism 3000S camera (Philips) fitted with ultra-high-resolution fanbeam collimators, and using a 360° circular orbit, step-and-shoot mode every 3°, on a matrix size of 128×128 pixels. SPECT acquisition started 240 min after intravenous injection of 170.7±25.3 MBq of ^{123}I-ADAM (MAP-Finland, OY) flushed with 20 ml of saline serum.

Each subject underwent an MRI on the day of each SPECT scan for coregistration and region of interest (ROI) drawing and placement. A superconductive 1.9 T system (Prestige 2T, GE) with a head coil was used. An axial, three-dimensional spoiled gradient-echo slab was positioned to include the entire head, and images were acquired with the following parameters: repetition time 25 ms, echo time 6 ms, flip angle 28°, field of view 25×25 cm, matrix size 256×256, section thickness 2 mm with no interslice gap, and 1NEX. Pixel size was 0.97 mm in the transaxial direction and 2 mm in the axial direction.

The previously studied healthy volunteer group had undergone the same SPECT and MRI procedures.

Image analysis

Images were reconstructed using a filtered-backprojection algorithm with a Butterworth filter (exponent=5.0; cuttoff frequency=0.4 cycles/pixel). Pixel sizes were between 2.46 and 2.53 mm on each slice and 3.6 mm in the axial direction. Chang's algorithm was applied for attenuation correction (μ=0.1 cm^{-1}). Fiducial markers were used to coregister SPECTs to the corresponding MRIs using a six-parameter (three translations and three rotations) rigid body transformation by minimizing the least squares of the distance of the corresponding marker positions. Postdose MRI scans were coregistered to the pretreatment MRI scans with a mutual information-based algorithm using SPM2 software package. Then, ROIs were manually drawn in cerebellum, midbrain, thalamus, and striatum only on the pretreatment MRI and were translated to the posttreatment MRI and corresponding SPECT scans.

Quantification was performed using the tissue ratio method, which was previously reported to correlate to the simplified reference tissue method (Catafau et al. 2005). The specific uptake ratio (SUR) was calculated as measurement of the specific-to-nonspecific partition coefficient at each time point as: $[(R-C)/C]$, where R is the mean counts in a cerebral region, and C is the mean counts in the region of reference (cerebellum). SERTocc between the pretreatment and posttreatment scans was calculated as: $100 \cdot \left[\left(SUR_{pre-t} - SUR_{post-t}\right)/SUR_{pre-t}\right]$, where $SUR_{pre\text{-}t}$ and $SUR_{post\text{-}t}$ represent the SUR calculated at pretreatment and posttreatment, respectively. SERTocc was also calculated using the mean SUR value from both the group of drug-free MDD patients ($SERTocc_{MDD}$) and the group of previously studied healthy volunteers ($SERTocc_{HV}$).

An E_{max} model was fitted to describe the relationship between the mean %SERTocc of all regions studied and paroxetine Cp, as: $\%SERTocc = [(\%SERTocc_{max} * Cp) / (Cp_{50} + Cp)]$, with $\%SERTocc_{max}$ being the maximum SERTocc and Cp_{50} being the plasma concentration of paroxetine associated with 50% of $SERTocc_{max}$.

Statistical analysis

All statistical analyses were carried out using the SPSS software (version 14.0; SPSS) for Windows. A one-way ANOVA was applied to compare SERTocc in the different regions (midbrain, thalamus, and striatum) and also to

compare mean SERTocc using different pretreatment SUR (SERTocc, $SERTocc_{HV}$, and $SERTocc_{MDD}$). Paired *t* tests were applied to compare SUR in healthy volunteers and drug-free MDD patients. A significance level of 5% was considered for all analyses.

Results

Paroxetine-induced SERTocc

Individual SERTocc values and percentage of decrease in the HAMD score are presented in Table 1. The mean SERTocc was 66.4±9.5% (53–80%) in midbrain, 63.0±9.6% (48–74%) in thalamus, and 61.3±10.8% (42–75%) in striatum. No statistically significant differences were found in SERTocc values among these three regions (ANOVA test, F=0.589, df=26, p=0.562). ^{123}I-ADAM SPECT images showing the decrease in midbrain-specific uptake after treatment in a representative patient are shown in Fig. 1.

Seven patients showed clinical response to treatment. The two nonresponder patients (patient numbers 2 and 4) showed similar SERTocc ranges to the responders (Table 1). No linear correlation between SERTocc and %HAMD decrease was found [R^2=0.057 (midbrain), R^2=0.027 (thalamus), R^2=0.006 (striatum)].

SERT availability in drug-free MDD patients and healthy volunteers

The mean SUR values measured in the midbrain, thalamus, and striatum from both the group of MDD patients in the drug-free condition (pretreatment) and the group of healthy volunteers are presented in Table 2. No statistically significant differences were found between these two groups for any of the regions studied (paired *t* test; midbrain: p=0.52; thalamus: p=0.09; striatum: p=0.62). Individual midbrain SERT availabilities expressed as SUR values from the healthy volunteers and MDD patients before and after treatment are shown in Fig. 2.

Table 1 SERT occupancy (%SERTocc) and percentage of HAMD (%HAMD) reduction for each of the MDD patients studied

Subject	%SERTocc midbrain	%SERTocc thalamus	%SERTocc striatum	%HAMD reduction
1	71.3	55.3	68.6	62.5
2	80.1	73.1	75.8	31.6
3	77.6	73.3	73.4	61.1
4	64.6	47.7	51.8	34.8
5	53.1	53.6	42.1	57.9
6	71.0	74.2	54.0	60.0
7	57.3	65.5	61.2	63.2
8	60.0	64.9	65.5	60.0
9	N.A.	N.A.	N.A.	N.A.
10	56.3	59.6	59.6	50.0

Patient number 9 underwent only the pretreatment scan (see text)
N.A. Not available

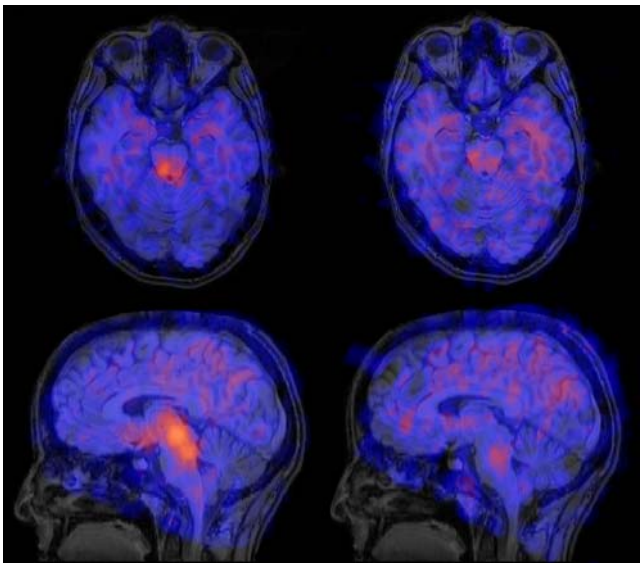

Fig. 1 Coregistered MRI and ^{123}I-ADAM SPECT images from a representative MDD patient (number 6) at baseline (*left*) and after a 6-week treatment with paroxetine 20 mg/day (*right*). Note the decrease in midbrain uptake between the two scans, both on axial (*top*) and sagittal slices (*bottom*), corresponding to 71% SERTocc

Comparison of SERTocc measurement methods

The SERTocc values measured using different pretreatment SUR values, i.e., the individual value from the same subject (SERTocc), the mean value from the drug-free MDD patient group ($SERTocc_{MDD}$), and the mean value from the healthy volunteer group ($SERTocc_{HV}$), for each of the cerebral regions studied are also shown in Table 2. No statistically significant differences were found among these three calculation methods for any of the regions studied (ANOVA test; midbrain: F=0.055, df=26, p=0.947; thalamus: F=0.460, df=26, p=0.637; striatum: F=0.079, df=26, p=0.924).

Paroxetine plasma levels and SERTocc

Mean paroxetine Cp on the day of the posttreatment SPECT was 30.8±15.0 ng/ml (14.0–50.0 ng/ml). The E_{max} model was fitted to describe the relationship between the mean SERTocc values (average of all regions studied) and paroxetine Cp. Using the data obtained from this model, the estimated $SERTocc_{max}$ was 70.5%, and the Cp_{50} value found was 2.7 ng/ml (Fig. 3).

Table 2 Mean SUR values from healthy volunteers and MDD patients, and mean %$SERT_{occ}$ values in MDD patients calculated using baseline data from different populations

Region	SUR_{HV}	$SUR_{pre\text{-}t}$	$SUR_{post\text{-}t}$	$\%SERT_{occ}$	$\%SERT_{occ\text{-}MDD}$	$\%SERT_{occ\text{-}HV}$
Midbrain	1.19±0.22	1.14±0.15	0.38±0.14	66.4±9.5	66.3±12.2	67.8±11.6
Thalamus	0.96±0.14	0.85±0.13	0.32±0.10	63.0±9.6	62.6±11.3	66.8±10.0
Striatum	0.67±0.15	0.70±0.07	0.27±0.10	61.3±10.8	60.5±13.9	58.9±14.5

SUR_{HV} SUR values from the previously studied healthy volunteer group
$SUR_{pre\text{-}t}$ SUR values at pretreatment from MDD patients
$SUR_{post\text{-}t}$ SUR values at posttreatment from MDD patients
$\%SERT_{occ}$ $\%SERT_{occ}$ calculated using the own patient $SUR_{pre\text{-}t}$
$\%SERT_{occ\text{-}MDD}$ $\%SERT_{occ}$ calculated using mean $SUR_{pre\text{-}t}$ from the whole group of MDD patients
$\%SERT_{occ\text{-}HV}$ $\%SERT_{occ}$ calculated using the mean SUR value from the healthy volunteer group

Discussions

Paroxetine-induced SERTocc

In this study, paroxetine-induced SERTocc in MDD patients measured by ^{123}I-ADAM SPECT is reported for the first time. A 4- to 6-week treatment with a therapeutic dose of paroxetine 20 mg/day induced more than 60% SERTocc on average in cerebral regions with known high SERT density. These SERTocc values are in overall agreement with those reported in the two previous ^{123}I-ADAM SPECT studies with citalopram in healthy volunteers (Erlandsson et al. 2005) and MDD patients (Herold et al. 2006). Herold et al. (2006) reported an average 61% SERTocc in midbrain induced after 7 days of treatment with 10 mg citalopram in n=13 MDD patients showing citalopram Cp of 25.2± 7.9 ng/ml (range 12.1–38.4). This SERTocc value is slightly lower than the average 66% SERTocc found in midbrain in the present study, although probably, the 20 mg paroxetine dose used would correspond to a higher citalopram dose of about 20–30 mg. Furthermore, Erlandsson et al. (2005) found 60–80% SERTocc in most healthy volunteers on the range of citalopram doses and Cp equivalent to the 20 mg paroxetine dose. In both studies, a high variability in the SERTocc values was reported. The coefficients of variance of SERTocc values found in the present study were: 14.3% in midbrain, 15.2% in thalamus, and 17.8% in striatum. The wide SERTocc range found in the present study (42–80%) is in close agreement with the SERTocc range of 37–88% found in Herold et al. (2006). As discussed in Erlandsson et al. (2005), it seems unlikely that intersubject variability in the ^{123}I-ADAM SPECT measurement could influence the SERTocc value variability because the same subject was used as at his own control for SERTocc calculations. Moreover, similar variability was found in the present study when using the mean of either the healthy

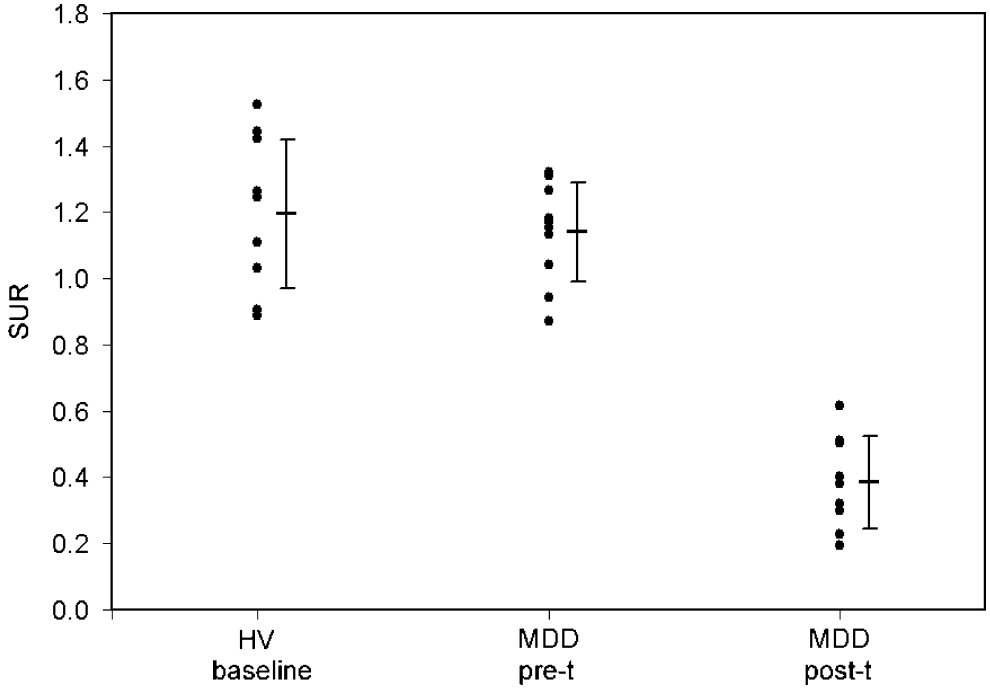

Fig. 2 Individual midbrain SERT availability expressed as SUR values for the healthy volunteers (*HV*) at baseline and MDD patients both at pretreatment (*pre-t*) and posttreatment (*post-t*)

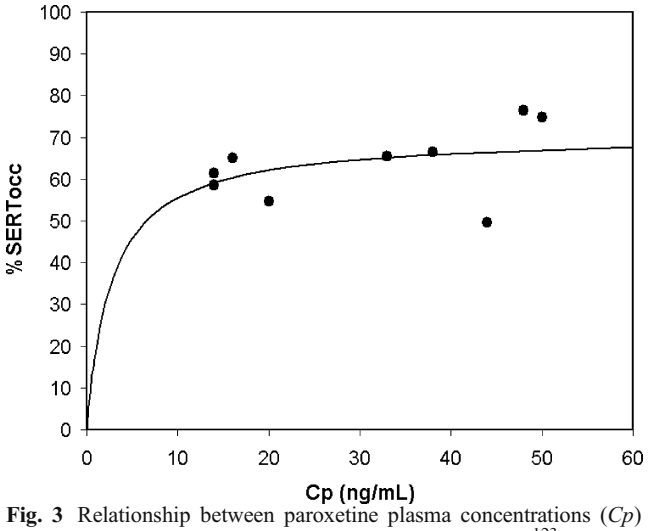

Fig. 3 Relationship between paroxetine plasma concentrations (*Cp*) and SERT occupancy (*%SERTocc*) measured by means of ^{123}I-ADAM SPECT on the nine MDD patients who completed the study. *Points* represent the individual SERTocc values (average of all regions), and the *line* is the fit to the E_{max} model (see text)

volunteers or the group of MDD patients for SERTocc calculations (67.8±11.6% vs 66.3±12.2%, respectively). Our group previously reported a test–retest variability of ^{123}I-ADAM SPECT of 13±11% in midbrain, 16±13% in thalamus, and 19±18% in striatum (Catafau et al. 2005). This intrasubject variability probably accounts for the variability of ^{123}I-ADAM SPECT-calculated occupancies. Moreover, the known high intersubject variability in paroxetine Cp for a given dose (Normann et al. 2004) may also play a role.

Lower SERTocc values were previously reported using the less selective SPECT SERT ligand ^{123}I-β-CIT. Using this ligand, 40% thalamus–hypothalamus SERTocc had been reported after 1 week on fluoxetine 60 mg/day (Tauscher et al. 1999b) and 50% hypothalamus–midbrain area SERTocc after 1 week on 20 to 60 mg of citalopram (Pirker et al. 1995). SERTocc measured in diencephalon by ^{123}I-β-CIT SPECT has been reported to be 29% after 1- to 3-week treatment with paroxetine 20 mg/day and 23.4% after a 6-week treatment period (Kugaya et al. 2004). It is likely that at least part of the ^{123}I-β-CIT signal arises from the dopamine and norepinephrine transporter affinities, making more difficult the interpretation of the SERTocc values with this ligand.

On the other hand, PET studies usually report higher SERTocc values for equivalent doses of SSRIs. Using ^{11}C-McN5652 as a SERT ligand, 82±14% SERTocc was found in n=5 patients with social phobia after 3–6 months of treatment with paroxetine 20–40 mg/day (Kent et al. 2002), and using ^{11}C-DASB, 83 and 77% SERTocc were reported after 4-week treatment with paroxetine 20 mg/day (n=8) and citalopram 20 mg/day (n=4), respectively (Meyer et al. 2001). Altogether, these data suggest that the SERTocc measurements highly depend on the technique employed, particularly the radioligand used. Among the SPECT ligands for SERT, ^{123}I-ADAM seems to provide the closest values to PET. Nevertheless, caution should be taken when comparing SERTocc among different studies.

Seven out of the nine patients included in the present study showed clinical response. The present study design is not optimal for the identification of a SERTocc threshold for clinical efficacy because a single therapeutic dose was used and the sample size was not empowered for efficacy. However, from the data found in this study, it seems that SERTocc would not be related to SSRI response, in agreement with what has already been suggested in other neuroimaging studies (Meyer et al. 2001; Kent et al. 2002; Herold et al. 2006). Further studies with larger sample sizes and wider range of doses are needed to reach definitive conclusions on the relationship between SERTocc values and antidepressant response to SSRIs.

SERT availability in drug-free MDD patients and healthy volunteers

Postmortem neuroanatomical studies, as well as neuroimaging studies, have shown controversial results when comparing SERT densities between MDD patients and controls (for a review, see Stockmeier 2003). Whereas some authors have found reductions of SERT in MDD patients compared to controls, others have found increases or failed to find any differences. A summary of the neuroimaging findings is given in Table 3. The radioligand and technique used seem not to account for the controversial results because inconsistencies have been reported even with the same methodology (Table 3). However, other methodological aspects, such as the ROI sizes and locations, camera used, and finally the sample sizes and characteristics of the patient populations, have to be taken into account. Finally, it may be possible that SPECT and PET techniques are not sensitive enough to detect subtle changes in SERT availabilities.

Previous SERT availability comparisons between MDD patients and healthy volunteers have been made without distinction on the therapeutic response to treatment in MDD patients. Higher platelet serotonin concentrations, probably related to an overexpression of SERT, have been reported in depressed patients with poor therapeutic outcome (Figueras et al. 1999). Therefore, it could be speculated that SERT differences, if present, might be more related to the therapeutic response than to the MDD diagnosis. Neurotransmission imaging has provided controversial results also when comparing SERT availabilities between responder and nonresponder MDD patients. For example, Kugaya et al. (2004) reported higher SERT availability in responders, whereas Herold et al. (2006) and Cavanagh et al. (2006) did not find differences between responders and nonresponders.

Table 3 Published PET and SPECT studies of SERT availability in MDD patients compared to healthy volunteers

Reference	Technique	Radioligand	MDD (*n*)	Controls (*n*)	Cerebral region	SERT in MDD vs HV
Malison et al. 1998	SPECT	^{123}I-β-CIT	15	15	Brainstem	Decrease
Dahlstrom et al. 2000	SPECT	^{123}I-β-CIT	31[a]	10	Hypothalamus midbrain	Increase
Meyer et al. 2001	PET	^{11}C-DASB	12	17	Striatum	No changes
Ichimiya et al. 2002	PET	^{11}C-McN5652	7[b]	21	Midbrain	No changes
					Thalamus	Increase
Ahonen et al. 2004	SPECT	^{123}I-ADAM	10	14	Midbrain	No changes
Newberg et al. 2005	SPECT	^{123}I-ADAM	7	6	Midbrain	Decrease
Kugaya et al. 2004	SPECT	^{123}I-β-CIT	23	23	Diencephalon	No changes
					Brainstem	No changes
Meyer et al. 2004a	PET	^{11}C-DASB	29[c]	35	Striatum	No changes
Meyer et al. 2004b	PET	^{11}C-DASB	20	20	Prefrontal cortex	No changes
					Anterior cingulated	No changes
					Thalamus	No changes
					Caudate putamen	No changes
Herold et al. 2006	SPECT	^{123}I-ADAM	21	13	Midbrain	No changes
Parsey et al. 2006	PET	^{11}C-McN5652	25	43	Midbrain	Decrease
					Amygdala	Decrease
Staley et al. 2005	SPECT	^{123}I-β-CIT	32	32	Brainstem	No changes
					Striatum	No changes
					Diencephalon	Decrease[d]

[a] Depressive children and adolescents
[b] n=7 MDD patients from a total of n=13 patients with mood disorders
[c] n=29 MDD patients without comorbid diagnoses from a total of n=51 patients
[d] Only in women (22% decrease in depressed vs healthy women and less than 1% decrease in depressed men vs healthy men)

The small number of nonresponders in the present study made a proper statistical treatment of the data difficult. However, the mean SERT availability from the two nonresponder patients (1.14±0.01) seemed not to differ from the mean SERT availability from the seven responder patients (1.14±0.17). More experience is therefore needed to understand the role of SERT imaging as a marker of either MDD diagnosis or clinical response in MDD patients.

Comparison of SERTocc measurement methods

The fact that no differences were found in SERTocc values calculated using different pretreatment SUR (own subject, MDD patient group, and healthy volunteer group) simplifies the procedure because a pretreatment drug-free scan is often difficult to be obtained in MDD patients. In this study, the healthy volunteer group values were obtained in the same center where the patient population was scanned, using the same method. This is the recommended procedure to follow if the baseline scan from the own patient or the drug-free group of patients is difficult to obtain because quantitative values may vary depending on the methodology used. Healthy volunteer data from the literature or from other centers would only be suitable for these purposes if the radioligand, instrumentation, image processing, and quantification analysis are exactly the same to be applied in the patient population. Keeping this in mind, results from the present study suggest that the mean SUR values from a healthy volunteer group can be used for SERTocc calculations because it can be assumed that no differences in ^{123}I-ADAM SPECT-measured SERT availabilities are present between these two populations. This simplifies the procedure and makes it more widely available.

Paroxetine plasma levels and SERTocc

In the present study, 4- to 6-week treatment with paroxetine 20 mg/day in MDD patients leads to Cp ranging from 14 to 50 ng/ml. These Cp values are within the reported ranges of stable plasma levels induced by this paroxetine dose (4–358 ng/ml, Normann et al. 2004). Therefore, the variability found in paroxetine plasma concentrations in the present study can be explained by the already-known intersubject variability.

SERTocc values have been reported to relate to paroxetine Cp following an E_{max} model (Meyer et al. 2001; Kent et al. 2002). Therefore, this model was applied to the present data to study such a relationship. However, the results of the model fitting reported in the present study have to be interpreted with caution because all patients were on the same therapeutic paroxetine dose of 20 mg/day. This may explain that most SERTocc values were distributed in the saturated (flat) part of the curve limiting the model fitting, given the absence of observed values in the

initial (ascending) part of the curve (Fig. 3). The estimated maximum paroxetine SERTocc of 71% is lower than those previously reported with SSRIs using either ^{123}I-ADAM SPECT (Erlandsson et al. 2005, 84%), ^{11}C-McNeal (Kent et al. 2002, 100%), or ^{11}C-DASB (Meyer et al. 2001, 83%). However, these other studies included a wider range of plasma concentrations in the model, and the higher plasma concentrations could have contributed to the higher maximum SERTocc values found. Maximum SERTocc values lower than 100% are contrary to the complete occupancy postulated in receptor-binding models based on the law of mass action (Nyberg et al. 2002). These low reported SERTocc max values should therefore be explained by technical factors (e.g., image processing methods and quantification methods) rather than by biological factors. Despite the differences in the reported $SERTocc_{max}$ values, the Cp_{50} found in this study (2.7 ng/ml) is in close agreement with the Cp_{50} reported by Kent et al. (2002) (2.9 ng/ml) and consistent with the high affinity of paroxetine to SERT. This consistency in Cp_{50} values despite different $SERTocc_{max}$ is remarkable because Cp_{50} is the useful value for drug tailoring and drug development.

Conclusions

Using ^{123}I-ADAM SPECT, the measured SERTocc induced by 4- to 6-week treatment with paroxetine 20 mg/day in MDD patients is more than 60% on average in cerebral regions with known high SERT density. The fact that (1) drug-free MDD patients showed similar SERT availability than healthy volunteers and that (2) similar SERTocc values were obtained using the pretreatment data from either the own patient, the mean MDD patient group, or the mean healthy volunteer group simplifies the procedure and makes it more available. Results from this study support the paroxetine plasma concentration relationship to SERTocc following an E_{max} model, which may be used for pharmacokinetic–pharmacodynamic relationships in drug development.

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