Effect of a single dose of escitalopram on serotonin concentration in the non-human and human primate brain

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Abstract
Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed for treatment of psychiatric disorders. The exact mechanism underlying the clinical effects of SSRIs remains unclear, although increased synaptic serotonin concentrations have been hypothesized to be an initial step. [11C]AZ10419369 is a novel 5-HT1B receptor selective radioligand, which is sensitive to changes in endogenous serotonin concentrations. To assess whether a single dose of the SSRI escitalopram affects endogenous serotonin concentrations in serotonergic projection areas and in the raphe nuclei (RN), three cynomolgus monkeys and nine human subjects underwent PET examinations with [11C]AZ10419369 at baseline conditions and after escitalopram administration. In monkeys, the binding potential (BPND) was significantly lower post dose compared to baseline in dorsolateral prefrontal cortex, occipital cortex, thalamus, midbrain and RN (p < 0.05). In humans, the BPND tended to decrease in RN post dose (p = 0.08). In all serotonergic projection areas, the BPND was conversely higher post dose compared to baseline. The increase was significant in a combined region of all projection areas (p = 0.01) and in occipital and temporal cortex (p < 0.05). SSRIs are generally assumed to elevate endogenous serotonin concentrations in projection areas, evoking the antidepressant effect. In the present study, a single, clinically relevant, dose of escitalopram was found to decrease serotonin concentrations in serotonergic projection areas in humans. Hypothetically, desensitization of inhibitory serotonergic autoreceptors will cause the serotonin concentration in projection areas to increase over time with chronic administration. Thus, the findings in the present study might aid in understanding the mechanism of SSRIs’ delayed onset of clinical effect.

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Key words: [11C]AZ10419369, escitalopram, PET.

Introduction
Selective serotonin reuptake inhibitors (SSRIs) were introduced in the 1980s for treatment of depression and anxiety disorders. Although widely used, the exact mechanism underlying the antidepressive effect of SSRIs remains unclear. Using positron emission tomography (PET), it has been confirmed that SSRIs occupy the serotonin transporter (SERT) at clinical treatment (Meyer et al., 2004). A high occupancy of the SERT is achieved after a single dose (Lundberg et al., 2007), while the antidepressant effect requires several weeks of treatment. This observation indicates that inhibition of SERT is not the immediate cause of the antidepressant effect. However, despite decades of research on animal models, the downstream effects of SSRIs in the human brain are poorly understood.

The central serotonergic system originates in the raphe nuclei (RN). This nuclear complex can be divided into several subgroups, with primarily the dorsal raphe nucleus (DRN) projecting to cortical and striatal areas of the brain (Michelsen et al., 2008). It has long since been hypothesized that SSRIs increase the synaptic serotonin concentration in projection areas and that this increase is an initial step towards the antidepressive effect. This view has initially been supported by microdialysis studies in rodents showing that the extracellular serotonin concentration in brain raise 2- to 5-fold after acute systemic administration of a SSRI (for review, see Fuller, 1994). However, doses used in most experimental studies have usually been > 10-fold higher than the clinical doses administered for antidepressive treatment. Importantly, when doses corresponding to clinical treatment have been used, an increase in extracellular serotonin concentration in the RN has been observed, with little or no change in serotonin concentration in cortical regions.
There is, thus, a need for methodology allowing for direct examination of the effect of SSRI on serotonin concentration in the human brain.

Using PET, several attempts have been made to measure alterations in synaptic serotonin concentration after serotonergic challenges aiming to either raise or reduce serotonin concentration (for review, see Paterson et al., 2010), but results have been inconsistent. The recently developed radioligand $^{[11]} \text{C}\text{AZ10419369}$ binds selectively to the 5-HT$_{1B}$ receptor subtype (Maier et al., 2009) and has been validated for quantification of 5-HT$_{1B}$ receptors in both non-human primates and humans (Pierson et al., 2008; Varnas et al., 2011). The 5-HT$_{1B}$ receptor functions partly as an autoreceptor (Sari, 2004) and is therefore expected to be sensitive to alterations in endogenous serotonin concentration. Indeed, in non-human primates, $^{[11]} \text{C}\text{AZ10419369}$ has proven useful to study regional changes in endogenous serotonin concentration after administration of the serotonin-releasing compound, fenfluramine (Finnema et al., 2010, 2012).

An initial step towards the understanding of the mechanism of action of SSRIs in humans is to assess the effect of treatment on the endogenous serotonin concentration. Thus, the primary aim of the present PET study was to examine whether a single dose of the SSRI escitalopram changes the endogenous serotonin concentration in serotonergic projection areas and, if possible, in the RN. We used a change in the binding potential (BP$_{ND}$) of the radioligand $^{[11]} \text{C}\text{AZ10419369}$ as an indirect measurement of a change in serotonin concentration. In a first study, three monkeys were examined with PET and $^{[11]} \text{C}\text{AZ10419369}$, before and after administration of a high single dose of escitalopram. When a measurable effect of escitalopram on BP$_{ND}$ had been confirmed in monkeys, we subsequently examined nine human subjects, using a lower, clinically relevant dose.

**Materials and method**

**PET measurements in non-human primates**

**PET experimental procedures**

PET examinations were performed using the High Resolution Research Tomograph (HRRT; Siemens Molecular Imaging, USA), which, when using the point spread function, has a spatial resolution of approximately 1.5 mm full-width-half-maximum (Varrone et al., 2009). $^{[11]} \text{C}\text{AZ10419369}$ was prepared by N-methylation of the corresponding desmethyl precursor (AstraZeneca R&D, USA) using $^{[11]} \text{C}\text{methyl triflate}, as has been described earlier (Pierson et al., 2008).

Three female cynomolgus monkeys (Macaca fascicularis), weighing 3.3–5.1 kg, were included in the study. The PET experimental procedures were similar to those previously reported in detail (Finnema et al., 2012). In short, $^{[11]} \text{C}\text{AZ10419369}$ was administered i.v. in a sural vein of the monkey using a bolus infusion protocol (BI-protocol) with a $K_{bol}$ of 80–180 min. On each experimental day, one baseline PET measurement was followed by a PET measurement after i.v. administration of escitalopram. Two of the monkeys were examined on two experimental days each and one monkey on three experimental days. PET measurements were conducted for 123 min and were initiated 3 h apart (Fig. 1). A sterile solution of escitalopram oxalate salt in physiological buffer solution was infused i.v. over 30 min, starting approximately 45 min before the start of the BI-protocol.
of \( ^{11}C \text{AZ10419369} \). The dose of escitalopram (2.0 mg/kg) is expressed as relative to the free base. To minimize confounding carry-over effects between experiments, a minimum of 1 month elapsed between the experimental days for each monkey.

The mean combined radioactivity administered by bolus injection and infusion (decay corrected to time of bolus injection) was 298 MBq (range 208–363 MBq). The mean specific radioactivity at start of radioligand administration was 744 GBq/\( \mu \)mol, with a minimum of 312 GBq/\( \mu \)mol, corresponding to a mean administered mass of 0.21 \( \mu \)g with a maximum of 0.44 \( \mu \)g.

**PET data analysis**

Brain time activity curves (TACs) were obtained as previously described in detail (Finnema et al., 2012). Regions of interest (ROIs) were defined manually on the reoriented magnetic resonance (MR) images. The RN is a thin elongated structure and it is not possible to delineate the exact anatomical boundaries of the RN on MR images. Instead, a wider ROI, primarily including the localization of the DRN, was used for the rostral parts of the RN. ROIs were also delineated for the dorsolateral prefrontal cortex (DLPFC), the occipital cortex (OC), the caudate nucleus (CN), the putamen (Put), the thalamus (Thal), the globus pallidus (GP), the midbrain (MB), the hippocampus and the cerebellum (CB). \( B_{\text{PND}} \) was calculated during steady state conditions using the equilibrium method (63–123 min) with CB as the reference region (Finnema et al., 2012).

**Statistical analysis**

Regional \( ^{11}C \text{AZ10419369} \) \( B_{\text{PND}} \) values obtained during baseline and post-escitalopram conditions were evaluated using two-tailed paired \( t \) tests. The minimum level of significance was designated as \( p < 0.05 \) and the statistical analyses were performed in GraphPad Prism 5 (GraphPad Software Inc., USA).

### PET measurements in human subjects

**Study design**

The study was conducted at Karolinska Institutet, Stockholm, Sweden and was approved by the local Ethics and Radiation Safety Committees and the Medical Products Agency of Sweden. Ten control subjects were examined with PET and \( ^{11}C \text{AZ10419369} \). A baseline measurement and a measurement after oral administration of 20 mg escitalopram were performed on the same day, making each subject his own control (Fig. 1). The difference in \( B_{\text{PND}} \) of \( ^{11}C \text{AZ10419369} \) between the PET examinations was the primary end-point.

**Study subjects**

Ten males aged between 20 and 30 yr (25 ± 4.3, mean ± s.d.) were recruited by local advertisement. Only male subjects were included, as previous studies have shown that hormonal fluctuations in female subjects might affect the serotonin system (Jovanovic et al., 2006). The subjects were healthy according to medical history and physical examination including electrocardiogram, routine blood tests and magnetic resonance imaging (MRI) examination of the brain. Psychiatric symptoms were asked for via a structured questionnaire for screening of psychiatric diseases (The Mini International Neuropsychiatric Interview; Sheehan et al., 1998). A negative urine drug screen was required for inclusion and on the PET measurement day. All subjects gave verbal and written consent after receiving a description of the study.

**PET measurements**

Each subject participated in two PET measurements. One measurement was performed in the morning in drug-free conditions (baseline) and the other in the afternoon approximately 3 h after administration of a single oral dose of 20 mg escitalopram. As sleep might affect serotonin levels (Derry et al., 2006), wakefulness was controlled for and registered every 5 min throughout the PET measurements.

PET examinations were performed using the same HRRT PET system as in the monkey study and \( ^{11}C \text{AZ10419369} \) was prepared in an identical way. A plastic helmet was made individually for each subject and was used during each PET examination to minimize head movements and to ensure maintenance of the same head position in both measurements (Bergstrom et al., 1981).

For each examination, a saline solution containing \( ^{11}C \text{AZ10419369} \) with a radioactivity of 327–421 MBq (mean 401 ± 26 MBq) was injected in the antecubital vein as a bolus over 2 s. The specific radioactivity at the time of injection exceeded 278 GBq/\( \mu \)mol and the injected radioligand mass was <1 \( \mu \)g on all occasions. This low mass is not expected to cause any substantial mass effect of the
radioligand. Radioactivity in the brain was measured in a list mode fashion over 63 min. The 63 min acquisition time was chosen, as transient equilibrium is reached in the regions selected for the present study within this time-frame in humans (Varnas et al., 2011). The radioactivity from each PET measurement was reconstructed in a series of 32 time-frames (10 s × 8, 20 s × 5, 30 s × 4, 1 min × 4, 3 min × 4, 6 min × 7).

**Determination of escitalopram plasma concentrations**

Blood samples for determination of plasma concentrations of escitalopram were collected at the baseline PET measurement and at beginning, middle of and end of the escitalopram PET measurement. The mean of the three samples collected during the post-dose PET measurement was used as an estimate of the escitalopram concentration during the total post-dose PET acquisition time. The samples were analysed at the Department of Clinical Pharmacology, Karolinska Hospital, Huddinge, Sweden, using a LC-MS method slightly modified from methods published elsewhere (Juan et al., 2005; Kirchherr and Kuhn-Velten, 2006; Breaud et al., 2009). The limit of quantification with this method is 5 nmol/l.

**Protein binding of [11C]AZ10419369**

The protein binding in plasma of [11C]AZ10419369 was determined at both PET measurements to ensure that escitalopram administration did not change the free fraction of the radioligand. Venous blood samples for protein binding analysis were obtained 5–10 min before each radioligand injection. A previously described ultrafiltration method (Varrone et al., 2011) was then used to estimate the free fraction (\(f_p\)) of [11C]AZ10419369 in plasma.

**Regions of interest definition**

MRI T1-weighted images were acquired using a MR DISCOVERY 750 3T system (GE Medical Systems, USA). The MR images were realigned to the anterior–posterior commissure plane. ROIs were manually delineated on the realigned MR images for each subject by means of Human Brain Atlas software. As described for the monkeys, the RN cannot be visualized on the MR images. To ensure inclusion of the DRN, a wider region in the dorsal brain stem was defined for the rostral area of the RN. In addition, the following ROIs were depicted: the frontal cortex; the OC; the temporal cortex; the CN; the Put; the Thal; the CB. MR images were co-registered to averaged PET images using statistical parametric mapping software (SPM5; Wellcome Department of Cognitive Neuroscience, UK). ROIs were then transferred to the series of PET images to generate TACs. PET data were corrected for movement, using frame by frame motion correction as has been described before (Schain et al., 2012).

**Statistical analysis**

A two-tailed, paired \(t\) test was used to compare the \(BP_{ND}\) values before and after administration of escitalopram. A global ROI containing all depicted projection areas was initially used for the comparison. When an overall effect of escitalopram had been demonstrated in the global ROI, the \(t\) test was further applied to individual sub-regions. As projection areas can be viewed as a functionally homogenous region, corrections for multiple comparisons were not applied. Correlation of plasma concentration and degree of change in \(BP_{ND}\) values after escitalopram administration was tested with linear regression, using a least squares regression model. The statistical analysis was performed using SAS statistical software JMP 8 (SAS Institute, USA).

**Results**

**Non-human primates**

**Plasma concentrations**

Escitalopram was infused i.v. over 30 min, starting approximately 45 min (range 37–56 min) before the start of the BI-protocol of [11C]AZ10419369. The plasma concentration of escitalopram declined over time (Fig. 2). The mean escitalopram concentration was 2317 ± 839 nmol/l (mean, s.d.) at 5 min before [11C]AZ10419369 injection and 981 ± 125 nmol/l at 120 min after [11C]AZ10419369 injection. During the 60–120 min period, which was
The regional brain distribution of 

\[ \text{BPND} \]

was a numerically lower mean concentration of escitalopram was 44 nmol/l (range 774–1350 nmol/l). During the post-dose PET measurement, the mean plasma concentration of escitalopram was 44 ± 12 nmol/l (range 17–64 nmol/l; Fig. 2).

**Binding potential**

The regional brain distribution of 

\[ \text{[11C]AZ10419369} \]

was 95 ± 1.9% (mean, s.d.) at both the baseline and the post-dose PET measurement. Thus, there was no difference in the free fraction of the radioligand between the measurements.

**Protein binding of [11C]AZ10419369**

The mean plasma protein binding of 

\[ \text{[11C]AZ10419369} \]

was 95 ± 1.9% (mean, s.d.) at both the baseline and the post-dose PET measurement. Thus, there was no difference in the free fraction of the radioligand between the measurements.

**Binding potential**

There was a rapid increase in brain radioactivity after i.v. injection of 

\[ \text{[11C]AZ10419369} \]

in all of the subjects. The mean TACs in the CB and OC during the baseline and post-dose PET measurement are shown in Fig. 4a. The mean (n = 9) BPND at baseline varied between regions, from 0.62 in the Thal to 1.65 in the OC (Table 2). After escitalopram administration there was an increase in BPND in the global ROI representing all projection areas (p = 0.01). The BPND was also numerically higher in all individual projection regions post dose (Fig. 4b, c). In addition to the global ROI, the difference from baseline was statistically significant for the OC, temporal cortex and the combined ROI for all cortical regions (p < 0.05). Conversely, there was a trend towards a decrease in BPND in the RN (p = 0.08). The change in BPND in OC for each subject is illustrated in Fig. 4d.

**Adverse events**

All subjects but one reported adverse events. Except for one subject reporting severe headache, adverse events were mild to moderate in intensity. The most frequent adverse events reported were nausea (n = 4), other gastrointestinal side-effects (n = 4) and headache (n = 3). First announcements of adverse events were expressed 30 min after the escitalopram administration, but several adverse events did not appear until several hours after expected maximum concentration.

**Discussion**

In the present PET study, we measured the binding of 

\[ \text{[11C]AZ10419369} \]

in serotonergic projection areas and RN before and after administration of a single dose of escitalopram in monkey and human subjects. A change in the BPND of 

\[ \text{[11C]AZ10419369} \]

between the two experimental conditions was hypothesized to reflect a change in serotonin concentration. In monkeys, escitalopram caused a small, but significant, reduction in the binding of 

\[ \text{[11C]AZ10419369} \]

in most of the examined brain regions. In humans, there was a significant increase of BPND in serotonergic projection areas and a trend towards a decrease in RN. The results indicate that the serotonin concentration in serotonergic projection areas decrease after a single, clinically relevant dose of escitalopram in human subjects.

In monkeys, the reduction in the BPND was smaller than that previously obtained following a high dose of
(±)-fenfluramine [5.0 mg/kg; e.g. in the OC 12 ± 8% for escitalopram vs. 39 ± 8% for (±)-fenfluramine; Finnema et al., 2012]. This difference was expected, as previous microdialysis studies have shown that SSRIs cause less of an increase in serotonin concentrations than fenfluramine (Fuller, 1994). The small escitalopram-induced reduction in BP$_{ND}$ is consistent with previously reported reductions (16–30%) in radioligand binding after citalopram (4 mg/kg) in anaesthetized non-human primates using the PET-radioligands $[^{11}C]$P943 (Ridler et al., 2011) or $[^{11}C]$CUMI-101 (Milak et al., 2011). The measurable effect of escitalopram on $[^{11}C]$AZ10419369 binding in monkeys served as validation of the methodology before initiation of the subsequent study in human subjects.

In humans, a slight but statistically significant increase in BP$_{ND}$, indicating decreased serotonin concentration, was observed in several serotonergic projection areas after administration of escitalopram. The results are consistent with the effects seen in a study published during the course of the present study, where BP$_{ND}$ for the 5-HT$_{1A}$ receptor was measured in healthy volunteers with $[^{11}C]$CUMI-101 before and after i.v. administration of citalopram (Selvaraj et al., 2012).

In the study of 5-HT$_{1A}$ receptor binding with $[^{11}C]$CUMI-101, no significant or trend-level effect on the BP$_{ND}$ in the DRN could be demonstrated. In the present study on a small sample, there was a trend towards a decrease in BP$_{ND}$ in the RN. The ROI defined for the RN is a small region and, as such, the signal:noise ratio is lower in larger regions. Additionally, it is not possible to delineate the exact anatomical boundaries of the RN on MRI images. Thus, the region defined for the RN likely also includes some of the surrounding tissue, which will ‘dilute’ the radioactivity signal. These conditions increase the noise and might explain why the decrease in BP$_{ND}$ was not significant in the RN in human subjects.

Microdialysis studies in rodents have shown that the serotonin concentration in the RN increases after systemic administration of a SSRI (Bel and Artigas, 1992; Invernizzi et al., 1992; Hervas and Artigas, 1998), leading to an activation of 5-HT$_{1A}$ autoreceptors and decreased serotonin firing and release in projection areas. Furthermore, local administration of a SSRI in the RN leads to decreased serotonin concentrations in projection areas (Romero et al., 1996; Romero and Artigas, 1997). In rodents, when citalopram has been administered locally in the frontal cortex to increase the serotonin concentration, addition of a systemically administered SSRI has been shown to decrease the serotonin concentration in the same area (Romero and Artigas, 1997; Hervas and Artigas, 1998). The net effect of a SSRI on serotonin concentrations in the projection areas depends on the ‘sum’ of the local SERT occupancy, leading to increased
concentrations, and the decrease in serotonin firing and release, leading to decreased serotonin concentrations. It is possible that, after administration of a single dose of SSRI, the balance between the occupancy of the SERT and the decreased serotonin release in humans is such that the net effect is a decrease of the serotonin concentration in the projection areas.

Microdialysis studies have shown that high and low doses of SSRIs affect the serotonin concentrations in projection areas differently (Bel and Artigas, 1992; Invernizzi et al., 1992), indicating that appropriate doses should be used when aiming to assess the effect of clinical treatment. In the present study, monkeys were administered a 7-fold higher escitalopram dose than humans (2.0 mg/kg)

Table 1. Mean BP_{ND} of [^{11}C]AZ10419369 in three monkeys (seven observations) at baseline and after 2.0 mg/kg escitalopram

<table>
<thead>
<tr>
<th>Region</th>
<th>BP_{ND} baseline (mean ± s.d.)</th>
<th>BP_{ND} post dose (mean ± s.d.)</th>
<th>ΔBP_{ND} (% of baseline) (mean ± s.d.)</th>
<th>p value (matched pairs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLPFC</td>
<td>0.91 ± 0.12</td>
<td>0.80 ± 0.15</td>
<td>-12 ± 12</td>
<td>0.03*</td>
</tr>
<tr>
<td>OC</td>
<td>1.3 ± 0.09</td>
<td>1.1 ± 0.13</td>
<td>-12 ± 10</td>
<td>0.02*</td>
</tr>
<tr>
<td>CN</td>
<td>0.80 ± 0.20</td>
<td>0.73 ± 0.20</td>
<td>-9 ± 14</td>
<td>0.1</td>
</tr>
<tr>
<td>Put</td>
<td>0.91 ± 0.09</td>
<td>0.82 ± 0.17</td>
<td>-11 ± 14</td>
<td>0.1</td>
</tr>
<tr>
<td>Thal</td>
<td>0.88 ± 0.17</td>
<td>0.77 ± 0.18</td>
<td>-13 ± 8</td>
<td>0.005**</td>
</tr>
<tr>
<td>GP</td>
<td>1.8 ± 0.25</td>
<td>1.7 ± 0.35</td>
<td>-7 ± 10</td>
<td>0.08</td>
</tr>
<tr>
<td>MB</td>
<td>1.1 ± 0.10</td>
<td>1.0 ± 0.15</td>
<td>-11 ± 10</td>
<td>0.03*</td>
</tr>
<tr>
<td>HC</td>
<td>0.74 ± 0.09</td>
<td>0.65 ± 0.10</td>
<td>-12 ± 14</td>
<td>0.07</td>
</tr>
<tr>
<td>RN</td>
<td>0.45 ± 0.09</td>
<td>0.34 ± 0.11</td>
<td>-25 ± 16</td>
<td>0.002**</td>
</tr>
</tbody>
</table>

BP_{ND}, Binding potential; DLPFC, dorsolateral prefrontal cortex; OC, occipital cortex; CN, caudate nucleus; Put, putamen; Thal, thalamus; GP, globus pallidus; MB, midbrain; HC, hippocampus; RN, raphe nuclei.

* p < 0.05; ** p < 0.01.

Fig. 4. Effect of escitalopram (Escit) on [^{11}C]AZ10419369 receptor binding in human subjects. Time-course for regional brain radioactivity (%SUV) (a), regional binding potential (BP_{ND}) values (b), relative change in regional BP_{ND} (c) and individual BP_{ND} change in occipital cortex (OC). Mean and s.d., n = 9. Bsln, Baseline; CB, cerebellum; FC, frontal cortex; TC, temporal cortex; CN, caudate nucleus; Put, putamen; Thal, thalamus; RN, raphe nuclei. * p < 0.05; ** p < 0.01.
While we have interpreted the change in BPND as reflecting a change in serotonin concentration, a possible that escitalopram provides a measurable change in done before initiation of the human study to confirm were females. However, the study in monkeys was only males were included in the human part of the study. The participating monkeys, on the other hand in female subjects might affect the serotonin system, to administration of SSRIs. As hormonal fluctuations influence on the serotonin system and the response higher than the clinical range. 

In conclusion, the BPND of [11C]AZ10419369 increased in serotonergic projection areas after a single dose of escitalopram might explain why the clinical effect of SSRIs does not appear during the initial phase of treatment. In rodents, it has been demonstrated that the serotonin concentration in a cortical projection area is more or less unchanged after acute administration of clinically representative doses of SSRIs, due to 5-HT1A autoreceptor activation in the RN (Bel and Artigas, 1992, 1993; Invernizzi et al., 1992). With time, the 5-HT1A autoreceptors desensitize (Invernizzi et al., 1994) and serotonin concentrations increase (Bel and Artigas, 1993). This increase in serotonin concentrations may be temporarily matched by the delay of onset of the clinical effect observed in humans (for review, see Pineyro and Blier, 1999). Thus, the present observation of reduced serotonin concentration in projection areas after a single dose of escitalopram might explain why the clinical effect of SSRIs does not appear during the initial phase of the treatment. The study can be viewed as a first step towards an understanding of the mechanism of action of SSRIs in humans. However, subsequent studies are needed to evaluate the effect of SSRIs on serotonin concentrations after prolonged treatment. 

In conclusion, the BPND of [11C]AZ10419369 increased in serotonergic projection areas after administration of a single dose of escitalopram to human subjects. Conversely, there was a trend towards lower [11C]AZ10419369 binding to the 5-HT1B receptor in the RN after escitalopram administration. We conclude that the serotonin concentration decreases in serotonergic

### Table 2. Mean BPND of [11C]AZ10419369 in nine human subjects at baseline and after 20 mg escitalopram

<table>
<thead>
<tr>
<th>Region</th>
<th>BPND baseline (mean ± S.D.)</th>
<th>BPND post dose (mean ± S.D.)</th>
<th>ΔBPND (% of baseline) (mean ± S.D.)</th>
<th>p value (matched pairs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC</td>
<td>1.36 ± 0.17</td>
<td>1.43 ± 0.11</td>
<td>6 ± 7</td>
<td>0.05</td>
</tr>
<tr>
<td>OC</td>
<td>1.65 ± 0.31</td>
<td>1.74 ± 0.31</td>
<td>5 ± 5</td>
<td>0.01*</td>
</tr>
<tr>
<td>TC</td>
<td>1.14 ± 0.14</td>
<td>1.19 ± 0.09</td>
<td>5 ± 6</td>
<td>0.04*</td>
</tr>
<tr>
<td>CN</td>
<td>0.85 ± 0.11</td>
<td>0.90 ± 0.10</td>
<td>6 ± 10</td>
<td>0.1</td>
</tr>
<tr>
<td>Put</td>
<td>1.10 ± 0.14</td>
<td>1.15 ± 0.10</td>
<td>5 ± 8</td>
<td>0.08</td>
</tr>
<tr>
<td>Thal</td>
<td>0.62 ± 0.11</td>
<td>0.64 ± 0.07</td>
<td>6 ± 13</td>
<td>0.2</td>
</tr>
<tr>
<td>RN</td>
<td>1.09 ± 0.16</td>
<td>0.98 ± 0.11</td>
<td>-9 ± 13</td>
<td>0.08</td>
</tr>
<tr>
<td>Cortical regions</td>
<td>1.32 ± 0.17</td>
<td>1.38 ± 0.13</td>
<td>5 ± 5</td>
<td>0.01*</td>
</tr>
<tr>
<td>Subcortical regions</td>
<td>0.83 ± 0.10</td>
<td>0.87 ± 0.06</td>
<td>6 ± 8</td>
<td>0.07</td>
</tr>
<tr>
<td>All projection areas</td>
<td>1.29 ± 0.16</td>
<td>1.36 ± 0.12</td>
<td>5 ± 5</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

BPND, Binding potential; FC, frontal cortex; OC, occipital cortex; TC, temporal cortex; CN, caudate nucleus; Put, putamen; Thal, thalamus; RN, raphe nuclei.

* p < 0.05; ** p < 0.01.
projection areas after a single, clinically relevant dose of escitalopram. The observations may contribute to the understanding of the time-lag between SERT occupancy and the clinical effect of SSRIs.

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Statement of Interest

L.F. is an employee of AstraZeneca and affiliated with KI. C.H. has a consultancy agreement with AstraZeneca.

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