Norepinephrine transporter occupancy by nortriptyline in patients with depression: a positron emission tomography study with (S,S)-[18F]FMeNER-D2

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Abstract

Norepinephrine transporter (NET) plays important roles in the treatment of various neuropsychiatric disorders, such as depression and attention deficit hyperactivity disorder (ADHD). Nortriptyline is a NET-selective tricyclic antidepressant (TCAs) that has been widely used for the treatment of depression. Previous positron emission tomography (PET) studies have reported over 80% serotonin transporter occupancy with clinical doses of selective serotonin reuptake inhibitors (SSRIs), but there has been no report of NET occupancy in patients treated with relatively NET-selective antidepressants. In the present study, we used PET and (S,S)-[18F]FMeNER-D2 to investigate NET occupancies in the thalamus in 10 patients with major depressive disorder taking various doses of nortriptyline, who were considered to be responders to the treatment. Reference data for the calculation of occupancy were derived from age-matched healthy controls. The result showed approximately 50–70% NET occupancies in the brain as a result of the administration of 75–200 mg/d of nortriptyline. The estimated effective dose (ED50) and concentration (EC50) required to induce 50% occupancy was 65.9 mg/d and 79.8 ng/ml, respectively. Furthermore, as the minimum therapeutic level of plasma nortriptyline for the treatment of depression has been reported to be 70 ng/ml, our data indicate that this plasma nortriptyline concentration corresponds to approximately 50% NET occupancy measured with PET, suggesting that more than 50% of central NET occupancy would be appropriate for the nortriptyline treatment of patients with depression.

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Key words: Depression, norepinephrine transporter, nortriptyline, occupancy, positron emission tomography.

Introduction

Norepinephrine pathways in the brain play important roles in the regulation of cognitive functions such as attention, memory, mood, motivation, and vigilance. Norepinephrine transporter (NET) serves as one of the main targets of the treatment of various neuropsychiatric disorders, such as depression and attention deficit hyperactivity disorder (ADHD) (Nestler et al., 2008). Although depression consists of various symptoms, and is considered to be a heterogeneous disease (Harald and Gordon, 2012), some symptoms such as psychomotor-slowing and decreased concentration are reportedly related to the norepinephrine system. Antidepressants acting on NET play critical roles in the treatment of depression, particularly in patients who present with significant levels of these symptoms (Frazer, 2000; Brunello et al., 2002; Uher et al., 2009; Dell’Osso et al., 2011; Kasper et al., 2011).

Nortriptyline is a tricyclic antidepressant (TCA) that has been widely used for the treatment of depression.
In particular, nortriptyline is regarded as a relatively NET-selective antidepressant because its binding affinity for NET is much higher than that for the other monoamine transporters such as serotonin transporter (5-hydroxytryptamine transporter: 5-HTT) and dopamine transporter (Owens et al., 1997; Frazer, 2000, 2001; Vaishnavi et al., 2004; Gillman, 2007). Furthermore, it has been reported that there is a minimum effective level in the plasma concentration of nortriptyline in terms of clinical response, and also a maximum plasma concentration owing to a high incidence of side effects, although this may not necessarily be applicable to all patients (Baumann et al., 2004, 2005; Hiemke et al., 2011).

Recent advancements of suitable positron emission tomography (PET) radioligands for NET such as (S,S)-[18F]FMeNER-D2 and [11C]MRB have made it possible to evaluate in vivo NET occupancy in the brain by psychotropic drugs. In nonhuman primates, atomoxetine, a selective NET inhibitor used for the treatment of ADHD, showed dose-dependent occupancies for NET using [11C]MRB (Gallezot et al., 2011) and (S,S)-[18F]FMeNER-D2 (Seneca et al., 2006). This was also demonstrated for clomipramine, a TCA, using (S,S)-[18F]FMeNER-D2 in a monkey study (Takano et al., 2011).

We previously reported NET occupancies by nortriptyline in healthy human volunteers (Sekine et al., 2010), and in patients with major depressive disorder (MDD) by milnacipran (Nogami et al., 2013), a serotonin norepinephrine reuptake inhibitor (SNRI), using (S,S)-[18F]FMeNER-D2. The current study aimed to measure NET occupancies in the brain of patients with MDD taking various clinical doses of nortriptyline by using PET with (S,S)-[18F]FMeNER-D2. This is because our previous nortriptyline study only included normal volunteers with single oral administration, and we were unable to investigate the effects of high doses for ethical reasons. Moreover, there has been no report of NET occupancy in patients treated with relatively NET-selective antidepressants. Therefore, in this study, we explored the relationship between clinical daily doses of nortriptyline and its plasma concentrations, and central NET occupancies in MDD patients. We further estimated the NET occupancy corresponding to the reported minimum therapeutic level of plasma nortriptyline (Baumann et al., 2004, 2005; Hiemke et al., 2011).

Method

Subjects

Ten patients (8 men and 2 women; mean age, 40.1 yr; standard deviation [s.d.], 8.4 yr; range, 28–55 yr) fulfilling the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria for MDD were recruited from facilitated psychiatric hospitals and clinics. They had no other history of major medical illnesses. All patients were taking a variety of clinical doses of nortriptyline (mean, 122.5 mg/d; s.d., 39.9 mg/d; range, 75–200 mg/d) as an antidepressant. No other antidepressants were used, but some of them were taking benzodiazepines for anxiety or insomnia. Experienced psychiatrists evaluated the patients’ symptoms using the 21-item Hamilton Rating Scale for Depression (HAM-D) on the same day as the PET examinations. All of the patients were considered as responders to nortriptyline treatment with a mean HAM-D score of 7.3 (s.d., 4.7), and they had taken the drug for at least 1 month.

Age-matched healthy subjects (8 men and 3 women; mean, 39.6 yr; s.d., 9.1 yr; range, 23–55 yr) participated in the study as a control group. All healthy subjects were free of any somatic, neurological, or psychiatric disorders, and they had no history of current or previous drug abuse.

Studies were performed and analyzed at the National Institute of Radiological Sciences (NIRS, Japan). All participants provided written informed consent before participating in the study, which was approved by the Ethics and Radiation Safety Review board at NIRS.

PET procedures

(S,S)-[18F]FMeNER-D2 was synthesized by fluoromethylation of nor-ethyl-reboxetine with 18F-bromofluoromethane-D2 as previously described (Schou et al., 2004), yielding a radiochemical purity of higher than 95%.

An ECAT EXACT HR+ (CTI-Siemens, USA) PET scanner system was used with a head fixation device (Fixter, Sweden) to minimize head movement. A transmission scan for attenuation correction was performed using a 68Ge/68Ga source.

After an intravenous bolus injection of (S,S)-[18F]FMeNER-D2, regional brain radioactivity was measured from 120 to 180 min (10 min × 6 frames). Injected radioactivity averaged 188.3 (s.d., 4.4) MBq for the patient group and 190.5 (s.d., 5.9) MBq for the reference group, and specific radioactivity averaged 255.2 (s.d., 155.3) GBq/μmol for the patient group and 295.8 (s.d., 180.2) GBq/μmol for the reference group at the time of injection.

Magnetic resonance (MR) images of the brain were acquired with a 1.5 Tesla MR scanner, Gyroscan NT (Philips Medical Systems, The Netherlands). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin transverse sections (TE: 9.2 ms; TR: 21 ms; flip angle: 30 degrees; field of view: 256 mm; acquisition matrix: 256 × 256; slice thickness: 1 mm). The MRI results revealed no apparent structural abnormalities.

Plasma concentration of nortriptyline

Venous blood samples were taken to measure the plasma concentrations of nortriptyline just before and after the PET scan. The average values of these two samples were used in this study. The plasma concentrations
of nortriptyline were determined by gas chromatography-mass spectrometry with a lower limit of quantification of 20.0 ng/ml (Mitsubishi Chemical Medience Corporation, Japan).

**Data analyses**

All emission scans were reconstructed with a Hanning filter (cutoff frequency: 0.4 cycle/pixel). All MR images were coregistered to the PET images using the software package PMOD (PMOD Technologies, Switzerland). Volumes of interest were drawn manually on summed PET images with reference to coregistered MR images, and were defined for the thalamus and caudate on three consecutive slices in the transverse plane (Fig. 1). Regional radioactivity was calculated for each frame, corrected for decay, and plotted vs. time.

(S,S)-[18F]FMeNER-D2 bindings were expressed as binding potentials relative to non-displaceable binding (BPND) (Innis et al., 2007). BPND of (S,S)-[18F]FMeNER-D2 in the thalamus was calculated using the area under the curve (AUC) ratio method (Arakawa et al., 2008). We used the caudate as a reference brain region because of its negligible NET density (Donnan et al., 1991; Schou et al., 2005; Logan et al., 2007). In the AUC ratio method, BPND can be expressed as:

$$\text{BPND} = \frac{\text{AUC}_{\text{thalamus}}}{\text{AUC}_{\text{caudate}}} - 1,$$

where AUC_{thalamus} is the area under the time–activity curve of the thalamus and AUC_{caudate} is the area under the time–activity curve of the caudate. An integration interval of 120–180 min was used in this method.

The occupancies of NET were calculated by the following equation:

$$\text{Occupancy} = 100 \times \left( \frac{\text{BP}_{\text{reference}} - \text{BP}_{\text{nortriptyline}}}{\text{BP}_{\text{reference}}} \right),$$

where BP_{reference} is BPND of the mean of age-matched healthy control subjects and BP_{nortriptyline} is BPND of the patients with nortriptyline treatment.

The relationships between dose or plasma concentration and occupancies of NET were modeled by the following equation:

$$\text{Occupancy} = 100 \times \frac{C}{(E50 + C)},$$

where C is the dose or plasma concentration of nortriptyline, and E50 is the dose or plasma concentration required to induce 50% occupancy (Suhara et al., 2003; Takano et al., 2006).

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where $$\text{BP}_{\text{reference}}$$ is BPND of the mean of age-matched healthy control subjects and $$\text{BP}_{\text{nortriptyline}}$$ is BPND of the patients with nortriptyline treatment.

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Finally, we further explored the relationships between residual symptoms represented by HAM-D scores and the NET occupancies using Spearman’s signed rank correlation. Total scores of 21-item HAM-D (HAM-D-21) and 6-item HAM-D (HAM-D-6: depressed mood, feelings of guilt, work and interests, general somatic symptoms, psychic, and psychomotor retardation) (Bech, 2006) extracted from HAM-D-21 were used for the correlation analysis. This is because HAM-D-6 has been reported to be more valid as an outcome measure to see the dose–response relationship than the full HAM-D in clinical trials of antidepressants (Bech et al., 2004, 2006).

**Results**

Data of the healthy subjects and patients are listed in Tables 1 and 2, respectively. MRI and summed PET images of a patient taking 150 mg/d of nortriptyline and a normal subject are displayed in Fig. 1. The mean BPND value of healthy subjects was 0.61. The relationships between administered daily dose, or plasma concentration of nortriptyline, and NET occupancy in the thalamus are shown in Figs. 2 and 3. The estimated effective dose (ED50) and concentration (EC50) required to induce 50% NET occupancy were 65.9 mg/d and 79.8 ng/ml, respectively.

In respect of the relationships between residual symptoms and NET occupancies, we found no significant correlations between the total scores on the HAM-D-21 or HAM-D-6 and the NET occupancies in the thalamus.
Table 1. Data of healthy control subjects

<table>
<thead>
<tr>
<th>Healthy subjects</th>
<th>Gender</th>
<th>Age</th>
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<tr>
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</tr>
<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
<td>M</td>
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</tr>
<tr>
<td>4</td>
<td>M</td>
<td>34</td>
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</tr>
<tr>
<td>5</td>
<td>M</td>
<td>39</td>
<td>0.62</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>39</td>
<td>0.63</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>40</td>
<td>0.56</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>43</td>
<td>0.54</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>49</td>
<td>0.71</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>49</td>
<td>0.68</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>55</td>
<td>0.49</td>
</tr>
</tbody>
</table>

BPND: BPND in the thalamus.

\(p = -0.241, \quad p = 0.503 \) for HAM-D-21 and \(\rho = -0.338, \quad p = 0.340 \) for HAM-D-6). Furthermore, no significant correlations were observed between the NET occupancies in the thalamus and the duration of illness or that of nortriptyline medication (duration of illness: \(\rho = -0.248, \quad p = 0.489 \) for HAM-D-21 and \(\rho = -0.167, \quad p = 0.645 \) for HAM-D-6; duration of nortriptyline medication: \(\rho = 0.139, \quad p = 0.701 \) for HAM-D-21 and \(\rho = 0.025, \quad p = 0.946 \) for HAM-D-6).

Discussion

In the present study, we investigated the occupancies of NET with various doses of nortriptyline, a drug that is chronically administered to patients with MDD. All of them were considered to be responders according to the in-charge physicians, and six of them were in remission (HAM-D \(\leq 8 \)). The results showed approximately 50-70% NET occupancies in the brain after the administration of 75-200 mg/d of nortriptyline.

Nortriptyline is a secondary amine TCA, and a NET-selective antidepressant that has more than 10-fold higher affinity to NET than 5-HTT (Owens et al., 1997; Frazer, 2000; Vaishnavi et al., 2004; Gillman, 2007). Although in recent years selective serotonin reuptake inhibitors (SSRIs) and SNRIs have been the first-line medications for MDD, TCAs have equivalent, or in some cases, higher responder rates than SSRIs (Anderson, 1998, 2000; Nierenberg et al., 2003). Furthermore, along with desipramine, nortriptyline has the most pharmacologically desirable characteristics as a NET inhibitor, and it is also safe when co-administered with either monoamine oxidase inhibitors or SSRIs (Gillman, 2007). Thus, nortriptyline still commands an important role in the treatment of depression.

Previous PET studies have reported 5-HTT occupancy to be over 80% in patients with depression who have responded clinically to SSRIs (Meyer et al., 2001, 2004; Suhara et al., 2003). The same level of 5-HTT occupancy was also reported with clomipramine (Suhara et al., 2003) and duloxetine (Takano et al., 2006) in terms of their clinical use for depression. Recently, Lundberg et al. (2012) demonstrated that patients in remission from depression showed lower than the proposed 80% 5-HTT occupancy associated with various antidepressants including TCAs (amitriptyline and clomipramine) and SSRIs (citalopram, fluoxetine, sertraline, and venlafaxine).

In contrast, there have been only a few studies to examine central NET occupancy by antidepressants. In our preliminary study of NET occupancy with nortriptyline for normal subjects (Sekine et al., 2010), we measured the NET occupancies resulting from single doses of nortriptyline (up to 75 mg) in 6 healthy young men, and found that ED50 was 76.8 mg and concentration (EC50) was 59.8 ng/ml 5 h after a single oral administration. In our recent work, Nogami et al. (2013) examined both 5-HTT and NET occupancy in MDD patients treated with an SNRI, milnacipran. Estimated ED50 for 5-HTT was 122.5 and 149.9 mg for NET, and with milnacipran at 100 mg, the dose most commonly administered to MDD patients induces about 40% of occupancy in both 5-HTT and NET. However, it has been reported that higher doses of milnacipran such as 150 mg/d can lead to better improvement (Kanemoto et al., 2004; Hayashi et al., 2007).

With regard to nortriptyline, many previous investigations have suggested curvilinear relationships between plasma concentrations of nortriptyline and clinical response in patients with depression (Asberg et al., 1971; Sjoqvist et al., 1971; Sorensen et al., 1978; Perry et al., 1985, 1994; DeVane et al., 1991; Jerling et al., 1994), although some reported no correlation between the plasma nortriptyline levels and therapeutic effect (Burrows et al., 1972). As a result of this previous research, guidelines for therapeutic drug monitoring of psychotropic drugs (Baumann et al., 2004, 2005; Hiemke et al., 2011) claimed that the minimum therapeutic level of plasma nortriptyline was 70 ng/ml. Applying the data to the present study, our results indicate that this plasma nortriptyline concentration corresponds to 47% NET occupancy, suggesting that approximately 50% of central NET occupancy by nortriptyline would be necessary for the treatment of depression.

The ED50 and EC50 values in this study, i.e. 65.9 mg/d and 79.8 ng/ml, respectively, were different from those of our previous study (76.8 mg and 59.8 ng/ml, respectively) on healthy subjects (Sekine et al., 2010). The differences in ED50 and EC50 values between these two studies might be partly attributable to the different study protocols and different subjects: our current study involved chronic administration and depressed patients, whereas our previous study involved acute administration and healthy subjects. In addition, dose ranges were different between these two studies: our patients with depression were taking moderate-to-high doses of nortriptyline, whereas our previous study (Sekine et al., 2010) included...
healthy volunteers taking only low doses of nortriptyline for ethical reasons, which might cause different curve fitting.

We found no correlation between HAM-D-21 and HAM-D-6 total scores and NET occupancies, which may imply that depressive symptoms associated with norepinephrine, have been resolved in our responders to nortriptyline treatment, and the residual symptoms might be related to other factors, including different molecular systems. However, our current study evaluated patients only at one point in the responding phase of nortriptyline medication, and further studies are needed on the change of symptoms in relation with NET occupancy.

There are several limitations in this study. First, we recruited patients with MDD chronically treated with nortriptyline, and we used the data from healthy subjects as reference BPND. An autoradiography study reported a reduction in NET in the locus coeruleus (LC) in patients with depression (Klimek et al., 1997); however, no PET study has reported a comparison of NET BPND between patients with MDD before treatment and normal controls. This could cause over- and under-estimation of occupancies. Second, we included patients with different durations of nortriptyline medication, ranging from 38 to 450 d. We cannot exclude the possibility that different periods of medication can cause different functional changes in NET, since down-regulation (Bauer and Tejani-Butt, 1992; Zhu and Ordway, 1997; Zhu et al., 1998; Zavosh et al., 1999; Benmansour et al., 2004) as well as up-regulation (Biegon, 1986; Shores et al., 1994) and no change (Cheetham et al., 1996) of the transporter have all been reported in animal studies with chronic administration of NET inhibitors such as desipramine. However, for example, it was reported that such a down-regulation occurs at earlier stages of treatment and the change reached a maximal change after 3 wk, with no further down-regulation (Benmansour et al., 2004).

Thus, the range of duration of medication with

<table>
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<th>Age</th>
<th>NTP dose (mg/d)</th>
<th>NTP plasma conc. (ng/ml)</th>
<th>BPND</th>
<th>HAM-D-21</th>
<th>HAM-D-6</th>
<th>DOI (M)</th>
<th>D-NTP (D)</th>
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<td>175.4</td>
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<td>160</td>
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<td>0</td>
<td>0</td>
<td>100</td>
<td>450</td>
<td>MIL</td>
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</table>

F: female; M: male; NTP: nortriptyline; Conc.: concentration; BPND: BPND in the thalamus; HAM-D-21: total score of 21-item Hamilton Depression Scale; HAM-D-6: total score of 6-item Hamilton Depression Scale; DOI: duration of illness (months); D-NTP: duration of nortriptyline medication (days); AD: antidepressants; PAX: paroxetine; MIL: milnacipran; MAP: maprotiline; SER: sertraline; FLV: fluvoxamine; AMO: amoxapine; CLM: clomipramine; MIA: mianserin.
nortriptyline in our study (38–450 d) may not have had a large effect on NET function, if it is present at all. Nevertheless, there has been no in vivo human study on the change in NET function after chronic administration of a NET inhibitor. In addition, the involvement of NET in the symptomatology, as well as the pathophysiology of MDD, should be explored in detail by a prospective study examining unmedicated patients with MDD and the time-course of treatment.

Finally, because an age-related decline of NET BPND (Ding et al., 2010) has been reported, we took it into consideration in the current study. However, the gender effect on NET BPND is not clear and has to be clarified in future.

In conclusion, we measured NET occupancies in MDD patients treated with nortriptyline, a relatively NET-selective TCA, using PET with (S,S)-[18F]FMeNER-D2. NET occupancy was approximately 50–70% at daily doses of 75–200 mg. Considering the reported minimum therapeutic level of plasma nortriptyline, more than 50% of central NET occupancy would be appropriate for the nortriptyline maintenance treatment of patients with MDD.

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Statement of Interest

The authors declare that no financial support or compensation has been received from any individual or corporate entity for research or professional service, and there is no personal financial holding that could be perceived as constituting a potential conflict of interest.

References


Norepinephrine transporter occupancy by nortriptyline


