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Dopamine transporter binding in females with panic disorder may vary with clinical status

Eduard Maron [a,b,*], David J. Nutt [b,c], Jyrki Kuikka [d], Jari Tiihonen [e]

[a] Department of Psychiatry, University of Tartu, Raja 31, Tartu 50417, Estonia
[b] Department of Community Based Medicine, University of Bristol, Bristol, UK
[c] Department of Neuropsychopharmacology and Molecular Imaging, Imperial College London, London, UK
[d] Department of Clinical Physiology and Nuclear Medicine, University of Kuopio, Kuopio, Finland
[e] Department of Forensic Psychiatry, University of Kuopio, Kuopio, Finland

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ABSTRACT

Background: To date the involvement of dopamine system in neurobiology of panic disorder (PD) has been not investigated by imaging studies in humans. In this study, we evaluated the binding potential of dopamine transporter (DAT) in striatum of patients with PD.
Methods: Subjects comprised seven female patients with current PD, seven female PD patients in remission and seven female healthy controls, matched by age. Striatal DAT binding was evaluated using single-photon emission computed tomography and [^{123}I]nor-β-CIT tracer.
Results: Significantly higher DAT binding in striatum was detected in remitted PD females as compared with both currently ill PD and control females. The females with current PD demonstrated non-significant lowering in striatal DAT binding as compared with healthy controls. The correlation analysis in total sample of female patients showed significant and inverse relationship between striatal DAT binding characteristics and severity of panic symptoms.
Conclusions: This is first report showing that DAT binding in striatum may depend on the clinical status in females with PD. Our data suggest that increased level of DAT may contribute to stability of remission; however, the exact involvement of dopamine system in PD pathogenesis requires further investigations. The preliminary results of current study should be confirmed by other independent studies and should also be extended to include male patients.

1. Introduction

Panic disorder (PD) is a prevalent and potentially disabling condition characterized by recurrent panic attacks and associated fearful anticipation of panic or its consequences and frequently developing agoraphobia (DSM-IV, ICD-10). There are increasing efforts to identify the neurobiological substrate underlying the onset and development of PD. During last decades the serotonin (5-hydroxytryptamine, 5-HT) system became the main candidate for such research which pointed to a strong involvement in the PD pathogenesis (Maron and Shlik, 2006). The impact of 5-HT system in the pathophysiology of PD was recently supported by some brain-imaging studies. Particularly, it was shown by two positron emission tomography (PET) studies that patients with symptomatic PD have significant reduction of 5-HT1A receptors in midbrain raphe as well as in various postsynaptic brain regions, including the amygdala, and the orbitofrontal, temporal and cingulate cortices (Neumeister et al., 2004; Nash et al., 2008). In contrast, PD patients in remission after SSRI treatment demonstrated a degree of normalization in 5-HT1A receptor functioning, but there remained a reduction in the density of 5-HT1A receptors in the raphe region, suggesting the trait nature of these alterations (Nash et al., 2008). Furthermore, the results of our recent study showed that the patients with current PD, mostly females, had significantly lower 5-HTT binding in the midbrain raphe, in the temporal lobes, and in the thalamus than the healthy controls. On the contrary, the patients with PD in remission had normal 5-HTT-binding properties in the midbrain and in the temporal regions, but still a significantly lower thalamic 5-HTT binding (Maron et al., 2004).

Dopamine (DA) – another important monoamine with crucial role in several neuropsychiatric disorders – has been less investigated in PD. An overactivity in response to the DA agonist, apomorphine was demonstrated in patients with PD as compared with depressive patients, but not with healthy subjects (Pitchot et al., 1992; Pichot et al., 1995). Clinical trials showed only suggestive evidence for therapeutic efficacy of bupropion, a DA and noradrenaline re-uptake inhibitor, in treatment of PD (Simon et al., 2003). To our knowledge, so far there have been no brain-imaging studies

* Corresponding author. Address: Department of Psychiatry, University of Tartu, Raja 31, Tartu 50417, Estonia. Tel.: +372 7 318800; fax: +372 7 318812.
E-mail address: Eduard.Maron@kliinikum.ee (E. Maron).

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of the function of DA system in PD. In order to better understand the involvement of DA system in PD we re-analyzed our previous data on [^{123}I]nor-β-CIT imaging in a PD sample but this time focusing on binding in the striatum where this tracer gives an estimate of the availability of the DA transporter [DAT] (Maron et al., 2004).

2. Methods and materials

The pooled striatal DAT binding was evaluated in seven female patients with current PD (mean age 35.7 ± 16.8), seven female patients with PD in remission (mean age 33.4 ± 14.3) and in seven matched healthy females (mean age 35.1 ± 5.3) as previously described (Maron et al., 2004). According to Mini International Neuropsychiatric Interview (M.I.N.I. 5.0.0) assessment none of the patients had a lifetime or current diagnosis of major depression, bipolar disorder, or psychotic disorder or a history of suicidal attempts, with the exception of one remitted female patient who had a history of a single depressive episode. Two females with current PD and six females in remission had previously received treatment with antidepressants. However, all of them were medication free at least 4 months before the neuroimaging study. The remitted females had shorter lifetime period suffering under PD then currently ill females (5.1 ± 4.8 years vs 11.7 ± 12.9 years), however, this difference was not significant. The mean duration of remission in panic attacks-free females was 12.4 ± 6.6 months.

Single-photon emission computed tomography (SPECT) was performed with iodine-123 labeled 2 β-carbomethoxy-3β-(4-iodophenyl) or [^{123}I]nor-β-CIT as radioligand. Nor-β-CIT is an analogue of β-CIT with a higher affinity to both 5-HTT and DAT and well-characterized kinetics (Bergström et al., 1997; Hiltunen et al., 1998). A single dose of 185 MBq of [^{123}I]nor-β-CIT was diluted in a volume of 10 ml of physiological saline and slowly injected into the right antecubital vein in a dark and quiet imaging room. Whole head serial scans (5 min, 6 h, 24 h after injection of tracer) were performed on a Siemens Multi SPECT 3 gamma camera with fan-beam collimators (Kuikka et al., 1993). The imaging procedures were carried out at the Department of Clinical Physiology and Nuclear Medicine of Kuopio University Hospital in Kuopio, Finland. The patients were transported from Tartu to Kuopio in groups of three to four patients.

The SPECT scans were decay-corrected and reconstructed with Butterworth-filtered back-projection in a 128 × 128 matrix with a pixel size of 3 × 3 mm, and were attenuated-corrected with Chang's algorithm (Kuikka et al., 1993; Hiltunen et al., 1998). The imaging resolution was 8–9 mm. Regions of interest were the striatum and the cerebellum as a reference region. The specific binding of nor-β-CIT to DAT in striatum was manually drawn and calculated using a reference region model. The main assumptions of this model are that the distribution volume of nonspecifically bound ligand is the same for both target and reference tissues, and that the delivery of tracer from arterial blood is the same in both regions (Acton et al., 1999). We used a graphical method to estimate the specific binding as a distribution volume ratio between striatum and cerebellum minus 1 from the slope of the time–activity curves (Logan et al., 1990). The intraclass correlation coefficient for striatum was (0.79) with good agreement between the repeated studies in healthy subjects (Lehto et al., 2008).

3. Statistical analysis

One-way analysis of variance (ANOVA) with striatal DAT binding values as dependent variables; groups as a fixed factor; and age as covariate was performed (STATISTICA 8). The level of significance was set at $p < 0.05$ with a two-tailed test. Correlations were estimated with Pearson product–moment correlation analysis. The SPECT analyses were done without knowledge of the anamnestic data of the subjects.

4. Results

The females with current PD had significantly higher scores on the both Panic Disorder Severity Scale (PDSS) and the Hamilton Anxiety Scale (HAM-A) than the females in remission (for PDSS: 8.9 ± 2.3 vs 2.3 ± 1.1, $p = 0.002$ and for HAM-A: 17.7 ± 6.1 vs 10.4 ± 4.4, $p = 0.03$, respectively). In addition, the females with current PD evaluated themselves on a Visual Analogue Scale of anxiety (VAS) as more anxious immediately before the scan procedure than the females in remission (52.6 ± 24.5 vs 28.6 ± 17.7, respectively), but this difference was not statistically significant ($p = 0.16$).

The volume of distribution demonstrated significant difference in the [^{123}I]nor-β-CIT binding to striatal DAT between the three female groups ($F(2.17) = 6.98$; $p = 0.006$ two-tailed; (Fig. 1)). Particularly, DAT binding were significantly higher in the group of remitted PD females than in the symptomatic female PD group (2.72 ± 0.27 vs 2.21 ± 0.29, respectively; $F(1.11) = 10.78$, $p = 0.007$; (Figs. 1 and 2)). Furthermore, remitted PD females showed markedly higher DAT binding in striatum as compared with control females (2.43 ± 0.17; $F(1.11) = 5.23$, $p = 0.04$). However, no significant difference in striatal DAT binding was seen between symptomatic PD and control female groups ($F(1.11) = 2.76$, $p = 0.12$).

Correlation analysis in total group of female patients showed inverse relationship between binding characteristics in the striatal DAT and the PDSS ($r = -0.60$, $p = 0.025$), but this correlation remained non-significant in remitted females ($r = -0.48$, $p = 0.28$) or in females with current PD ($r = 0.36$, $p = 0.42$). There was no

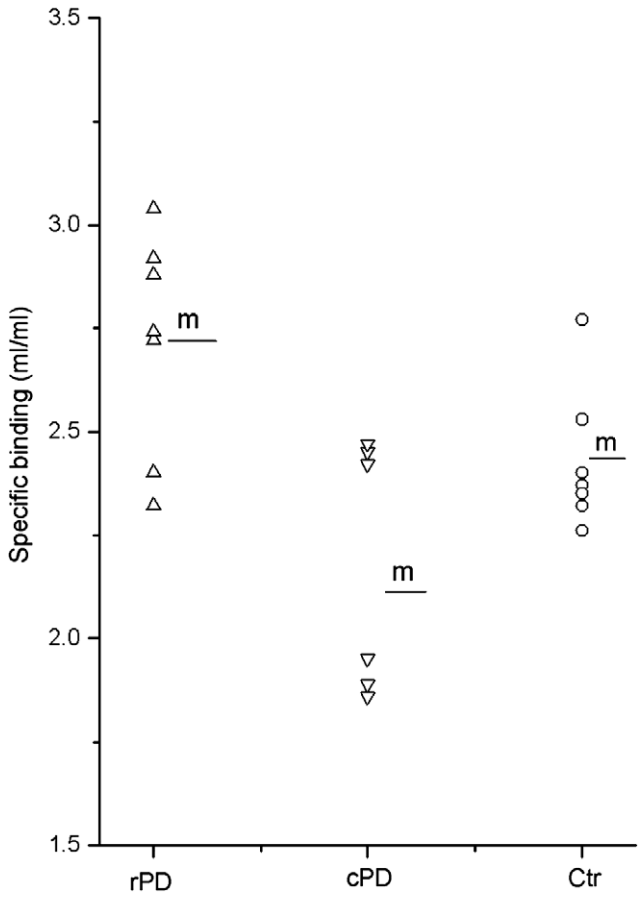

Fig. 1. Scatterplot of DAT binding in the striatum. Ctr – healthy female volunteers, cPD – females with current PD, rPD – females in remission, *m* – mean value.