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Normative data of dopaminergic neurotransmission functions in substantia nigra measured with MRI and PET: Neuromelanin, dopamine synthesis, dopamine transporters, and dopamine D_2 receptors

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ABSTRACT

The central dopaminergic system is of major importance in the pathophysiology of Parkinson's disease, schizophrenia, and other neuropsychiatric disorders. In the present study, the normative data of dopaminergic neurotransmission functions in the midbrain, consisting of neuromelanin, dopamine synthesis, dopamine transporters and dopamine D_2 receptors, were constructed using magnetic resonance (MR) imaging and positron emission tomography (PET). PET studies with L-[β-^{11}C]DOPA, [^{18}F]FE-PE2I and [^{11}C]FLB457 and MRI studies were performed on healthy young men. Neuromelanin accumulation measured by MRI was compared with dopaminergic functions, dopamine synthesis capacity, dopamine transporter binding and dopamine D_2 receptor binding measured by PET in the substantia nigra. Although neuromelanin is synthesized from DOPA and dopamine in dopaminergic neurons, neuromelanin accumulation did not correlate with dopamine synthesis capacity in young healthy subjects. The role of dopamine transporters in the substantia nigra is considered to be the transport of dopamine into neurons, and therefore dopamine transporter binding might be related to neuromelanin accumulation; however, no significant correlation was observed between them. A positive correlation between dopamine D_2 receptor binding and neuromelanin accumulation was observed, indicating a feedback mechanism by dopaminergic autoreceptors. Discrepancies in regional distribution between neuromelanin accumulation and dopamine synthesis capacity, dopamine transporter binding or dopamine D_2 receptor binding were observed in the substantia nigra.

Introduction

The central dopaminergic system is of major interest in the study of the pathophysiology of Parkinson's disease, schizophrenia, and other neuropsychiatric disorders. Both pre- and postsynaptic dopaminergic functions can be estimated by positron emission tomography (PET) with the use of several radiotracers (Ito et al., 2008). The substantia nigra plays a particularly important role in the dopaminergic system. In a previous study, we showed that dopamine synthesis capacity (one of the presynaptic dopaminergic functions) and dopamine transporter (another of the presynaptic dopaminergic functions) were found in the substantia nigra (Ito et al., 2008). Binding to dopamine D_2 receptors in the substantia nigra was also observed (Ito et al., 2008).

Recently, neuromelanin-sensitive magnetic resonance (MR) imaging was developed to visualize the nuclei of the monoaminergic neurotransmission system including the substantia nigra and locus ceruleus

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(Sasaki et al., 2008). Neuromelanin is synthetized by Fe^{3+}-mediated catalysis of DOPA and dopamine in cytosol, and it is permanently stored in lysosomes (Sulzer et al., 2000). Since neuromelanin is the major iron storage in neurons (Zecca et al., 2001), it can be visualized by MR imaging due to shortened T1. Neuromelanin is thought to protect neurons from oxidative stress, and DOPA/dopamine adducts that are not accumulated in neuromelanin granules promote neurodegeneration (Sulzer et al., 2000). Changes in neuromelanin accumulation in some neuropsychiatric diseases have been investigated using MRI. Reduction of neuromelanin accumulation in the substantia nigra in Parkinson's disease was reported, suggesting depletion of neuromelanin-containing neurons (Sasaki et al., 2006). A significantly greater neuromelanin accumulation in the substantia nigra in schizophrenia was also reported, suggesting an increase in dopamine in the nigrostriatal dopaminergic system as well as the mesocortico-limbic dopaminergic system (Shibata et al., 2008). Altogether, the findings in these studies pointed to the possibility that neuromelanin accumulation in the substantia nigra may be one of the biomarkers of presynaptic dopaminergic functions in neuropsychiatric diseases.

In the present study, normative data of dopaminergic neurotransmission functions in the midbrain, consisting of neuromelanin, dopamine synthesis, dopamine transporters and dopamine D_2 receptors, were constructed using MRI and PET. Neuromelanin accumulation measured by MRI was compared with dopaminergic neurotransmission functions, dopamine synthesis capacity (L-[β-^{11}C]DOPA), dopamine transporter binding ([^{18}F]FE-PE2I) and dopamine D_2 eceptor binding ([^{11}C]FLB457) as measured by PET. Regional distributions of neuromelanin accumulation, dopamine synthesis capacity, dopamine transporter binding and dopamine D_2 receptor binding in the midbrain were also investigated in detail.

Materials and methods

Subjects

Eleven healthy men (23.4 ± 1.6 years of age [mean ± SD], Group 1) and ten healthy men (25.0 ± 5.8 years of age [mean ± SD], Group 2) were recruited. The subjects were free of somatic, neurological and psychiatric disorders according to their medical history and MR imaging of the brain. No histories of current or previous drug abuse were revealed by interviews. The study was approved by the Institutional Review Board of the National Institute of Radiological Sciences, Chiba, Japan. Written informed consent was obtained from all subjects.

Experimental MRI procedures

MR imaging studies were performed with a 3.0-T MR scanner (Siemens AG, Munich, Germany) for all subjects. T1-weighted images were acquired by three-dimensional MPRAGE sequence (TR: 2300 ms, TE: 2.98 ms, flip angle 9°; field of view: 256 mm, acquisition matrix size: 256 × 256, slice thickness: 1.2 mm). Neuromelanin-weighted images were acquired with a 2D fast-spin echo sequence (TR: 550 ms, TE: 11 ms, echo train length: 3, NEX: 5, field of view: 200 mm, matrix size: 448 × 311, resolution: 0.45 × 0.64 mm, slice thickness: 2.5 mm, number of slices: 14 (no gap, interleaved)). Image slices were located around the cerebral peduncle, parallel to a plane tilting at 20° to a transaxial plane including anterior and posterior commissures.

Experimental PET procedures

All PET measurements were performed with SET-3000GCT/X (Shimadzu Corp. Kyoto, Japan) (Matsumoto et al., 2006), which provides 99 sections with an axial field of view of 26 cm. The intrinsic spatial resolution was 3.4 mm in-plane and 5.0 mm full-width at half maximum (FWHM) axially. Image reconstruction was carried out by filtered-back projection algorithm. With a Gaussian filter (cutoff frequency: 0.3 cycle/pixel), the reconstructed in-plane resolution was 7.5 mm FWHM. Data were acquired in three-dimensional mode. Scatter correction was done by hybrid scatter correction method based on acquisition with dual-energy window setting (Ishikawa et al., 2005). A 4-min transmission scan using a^{137}Cs line source was performed to correct for attenuation.

Group 1 subjects

Two PET scans with L-[β-^{11}C]DOPA and [^{18}F]FE-PE2I were performed sequentially on group 1 subjects. First, dynamic PET scanning was performed for 89 min after intravenous rapid bolus injection of L-[β-^{11}C]DOPA. Then, 90 min later, dynamic PET scanning was performed for 90 min after intravenous rapid bolus injection of [^{18}F]FE-PE2I. The frame sequence consisted of seven 60-sec frames, five 120-sec frames, four 180-sec frames, twelve 300-sec frames for L-[β-^{11}C]DOPA, and nine 20-sec frames, five 60-sec frames, four 120-sec frames, eleven 240-sec frames and six 300-sec frames for [^{18}F]FE-PE2I. The radioactivity injected was 346–398 MBq and 167–206 MBq for L-[β-^{11}C]DOPA and ^{18}F]FE-PE2I, respectively. Specific radioactivity was 34–281 GBq/μmol and 72–455 GBq/μmol for L-[β-^{11}C]DOPA and [^{18}F]FE-PE2I, respectively. L-[β-^{11}C]DOPA was preferred for dopamine synthesis measurements because a previous study indicated that fraction of metabolites of [^{11}C]DOPA in blood was lower than that of [^{18}F]DOPA (Ito et al., 2006).

Group 2 subjects

The PET scan with [^{11}C]FLB457 was performed on group 2 subjects. Dynamic PET scanning was performed for 90 min after intravenous rapid bolus injection of [^{11}C]FLB457. The frame sequence consisted of nine 20-sec frames, five 60-sec frames, four 120-sec frames, eleven 240-sec frames, and six 300-sec frames for [^{11}C]FLB457. The injected [^{11}C]FLB457 radioactivity was 219–235 MBq and the specific radioactivity was 114–450 GBq/μmol.

Calculation of parametric images

For neuromelanin-weighted MR images, the neuromelanin accumulation index (I_{NM}) was calculated on a voxel-by-voxel basis as follows (Sasaki et al., 2006):

$$I_{NM} = \frac{S_{SN}}{S_{dSCP}} - 1$$

where S_{SN} and S_{dSCP} are the signal intensity in the substantia nigra and decussation of superior cerebellar peduncles, respectively.

For PET studies with L-[β-^{11}C]DOPA, the dopamine synthesis index (I_{DA}) was calculated on a voxel-by-voxel basis as follows (Dhawan et al., 2002; Hoshi et al., 1993; Ito et al., 2007):

$$I_{DA} = \frac{\int_{t_1}^{t_2} C_T(t)dt}{\int_{t_1}^{t_2} C_R(t)dt} - 1$$

where C_T is the radioactivity concentration in a brain region, and C_R is the radioactivity concentration in a brain region with no irreversible binding. The occipital cortex was used as a region with no irreversible binding, as this region is known to have the lowest dopamine concentration (Brown et al., 1979) and lowest aromatic L-amino acid decarboxylase (AADC) activity (Lloyd and Hornykiewicz, 1972). Integration intervals (t_1 to t_2) of 29–89 min, representing late portions of the time-activity curves, were used (Ito et al., 2006).

For PET studies with [^{18}F]FE-PE2I and [^{11}C]FLB457, the binding potentials (BP_{ND}) for dopamine transporters and dopamine D_2 receptors, respectively, were calculated by the reference tissue model method