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SHORT COMMUNICATION

Effects of age on dopamine D_2 receptor availability in striatal subdivisions: A high-resolution positron emission tomography study

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Abstract

The purpose of the present study was to examine the relationship between age and dopamine D_2 receptor availability in striatal subdivisions of young and middle-aged healthy subjects using high-resolution positron emission tomography (PET) with [^{11}C]raclopride to better characterize the nature of age-related decrements in striatal D_2 receptor availability. Twenty-four healthy volunteers completed 3-Tesla magnetic resonance imaging and high-resolution [^{11}C]raclopride PET scans. The analyses using linear and exponential models revealed that age had a significant negative correlation with D_2 receptor availability in the post-commissural putamen (postPU) and that D_2 receptor binding in the postPU decreased significantly more with age than in the ventral striatum, suggesting subregional differences in age-related changes in D_2 receptor binding. The postPU, which belongs to the sensorimotor striatum, may be particularly vulnerable to the effects of age in young and middle-aged subjects.

1. Introduction

The brain dopamine system, which plays a crucial role in motor and cognitive functions, has been reported to be vulnerable to the effects of aging (Volkow et al., 2000). Previous in vitro and in vivo studies have indicated a significant decline in striatal dopamine D_2 receptor density with age (Severson et al., 1982; Rinne et al., 1990; Antonini et al., 1993; Wong et al., 1997; Volkow et al., 1998; Ichise

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et al., 1998; Ishibashi et al., 2009). The precise mechanism of the decline is not yet clear; however, age-related losses in D_2 receptor binding are functionally significant in that they are associated with impaired performance on specific neuropsychological tasks and with decreased frontal metabolism in healthy individuals (Volkow et al., 1998, 2000).

A limitation of the previous studies is that D_2 receptor density was assessed mainly at the level of the striatum as a whole. The striatum is a heterogeneous structure that includes several anatomic and functional subdivisions such as the associative, limbic, and sensorimotor striatal territories (Martinez et al., 2003). Considering the complex functional role of dopamine within the striatum, it is hypothesized that subregional differences exist in terms of the effects of age on D_2 receptor density. In fact, in previous in vitro studies using human autopsy brain tissue, the decrease of [^{3}H]spiroperidol binding with increasing age was most prominent in substantia nigra and putamen (Rinne, 1987), and the average percentage decrease per decade of D_2 receptor binding density, as measured by the Bmax, was not the same within striatal regions (Rinne et al., 1990).

With advances in high-resolution imaging techniques, an analytical approach that captures the functional subdivisions of the striatum with the use of the D_2 receptor radiotracer was recently developed and has been used to localize the availability of D_2 receptors within striatal subdivisions (Mawlawi et al., 2001; Martinez et al., 2003; Kegeles et al., 2010). Hence, in the present study, we examined the relationship between age and dopamine D_2 receptor availability in five striatal subdivisions in young and middle-aged healthy adult subjects using high-resolution positron emission tomography (PET) instrumentation with [^{11}C]raclopride in order to better characterize the nature of age-related decrements in D_2 receptor availability.

2. Materials and methods

2.1. Subjects

The study protocol was approved by the Institutional Review Board of the Gachon University of Medicine and Science, and all procedures used in the study were conducted in accordance with international ethical standard, Declaration of Helsinki. Informed consent was obtained from all subjects after a full explanation of the study procedure.

Twenty-four healthy volunteers (11 men, 13 women) participated in the study. Twenty-one subjects were those included in a previous study on the relationship between personality traits and dopamine D_2 receptor availability (Kim et al., 2011), and three were newly recruited subjects. Their mean age was 35.8 ± 9.5 years (range = 24–54, median = 32.5). All subjects were right-handed. They underwent a complete medical, neurological, and psychiatric examination in order to ensure the absence of disease. The psychiatric evaluation included lifetime and current DSM-IV axis I diagnoses that were determined by the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) (First et al., 1996). Exclusion criteria included a past or present psychiatric or neurological disorder, alcohol or substance abuse, medical conditions such as immunologic, metabolic, and cardiovascular disorders, and a history of head trauma with loss of consciousness. Urine tests were performed for opiates and methamphetamines before the PET scans. With regard to the use of nicotine, four subjects were smokers and they smoked three or fewer cigarettes per day. They did not meet the DSM-IV criteria for nicotine dependence or withdrawal. Pregnancy was excluded using urine pregnancy tests before the PET scans. All participants had normal 3-Tesla magnetic resonance imaging (MRI) scans evaluated by a radiologist.

2.2. HRRT-PET and MRI imaging

All subjects completed PET scanning using the High Resolution Research Tomograph (HRRT) system (Siemens Molecular Imaging, Knoxville, TN). Emission data were collected as listmode data in the 3-dimensional (3-D) mode during the 60 min after the injection of [^{11}C] raclopride. The tracer [^{11}C]raclopride was synthesized as previously described by methylation of the desmethyl precursor using [^{11}C] iodomethane (Fei et al., 2004). A saline solution of 527.25 ± 37.00 MBq [^{11}C]raclopride, with a specific activity at the time of injection of 62.16 ± 24.42 GBq/μmol, was injected as a bolus into an intravenous line. Transmission scans using ^{137}Cs were used to correct for attenuation of the emission scans. The 3-D ordinary Poisson ordered-subset expectation maximization (OP-OSEM3D) algorithm, which was accelerated by parallelized computations (Hong et al., 2007), was used for the reconstruction. The 19 frames (2 × 30 s, 4 × 60 s, 2 × 90 s, 2 × 210 s, and 9 × 300 s) were reconstructed from the listmode data. A total of 207 planes covering an axial field of view of 25.2 cm (axial sampling of 1.22 mm) were generated for each time frame. The in-plane and axial resolutions were 2.52 and 2.57 mm full-width half-maximum at the center of the field of view, respectively. Attenuation, scatter, and decay time correction were estimated and applied to each frame.

To permit accurate delineation of the brain regions for data analysis, each subject underwent an MRI scan using a 3-Tesla scanner (Magnetom Verio; Siemens, Germany). A magnetization-prepared rapid acquisition gradient echo 3D T1-weighted sequence with 1 mm thickness was performed. For the volumetric analysis, whole brain and striatal volumes were measured. The whole brain volume was measured from the MRI images segmented as gray matter, white matter, and cerebrospinal fluid using statistical parameter mapping software (SPM8). The striatal volume was measured using the software 3D Slicer. Two trained raters participated in the procedure. The intraclass correlation coefficient for the interrater reliability of the volume of interest procedure was 0.99. In order to normalize individual differences due to brain size, the measured striatal volume was adjusted by the whole brain volume. The MRI scan of each subject was coregistered to his or her PET scan using SPM8 in order to draw the regions of interest (ROIs) of the striatum in an efficient and reliable manner. The spatial normalization of the coregistered MRI images of each subject was performed on the Montreal Neurological Institute template using SPM8 and the estimated transform was applied to the corresponding PET images. ROIs were drawn on each individual's normalized MRI. ROIs were manually drawn tightly on the boundary of the structure. The striatum was divided into 5 anatomic ROIs, including the ventral striatum (VST), the pre-commissural dorsal caudate (preDCA), the pre-commissural dorsal putamen (preDPU), the post-commissural caudate (postCA), and the post-commissural putamen (postPU), as proposed (Mawlawi et al., 2001; Martinez et al., 2003). Based on their cortical and subcortical connections, the preDCA, the preDPU, and the postCA are classified functionally as belonging to the associative striatum, the postPU captures the sensorimotor striatum, and the VST corresponds to the limbic striatum (Mawlawi et al., 2001; Martinez et al., 2003). The cerebellum was used as the region of reference for the analysis without arterial blood sampling.

Time-activity curves were generated for each ROI by averaging the dynamic PET images, which were coregistered to the corresponding MRI images. Activities from the left and right regions were analyzed separately. The distribution volume ratio (DVR) for [^{11}C]raclopride was obtained on the basis of the Logan graphical method (Logan et al., 1996). The DVR can be calculated without plasma sampling using Logan graphical modeling with reference