

Correlation Between Striatal Dopamine D₂/D₃ Receptor Binding and Cardiovascular Activity in Healthy Subjects

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Background: The relationship between the striatal dopaminergic system and cardiovascular activity is not well known. The aim of this study is to investigate the relationship between striatal D₂/D₃ receptor binding and cardiovascular activity.

Methods: The striatal D₂/D₃ receptor binding of 34 healthy volunteers was assessed by the single-photon emission computed tomography (SPECT) imaging method with the [¹²³I]-iodobenzoamide (IBZM) ligand. The ratio of the radioactivity in the striatum (St) and the frontal cortex (Fc) (St/Fc ratio) was used as the marker for striatal D₂/D₃ receptor binding. Their cardiac autonomic functions were measured by continuously monitoring their heart rate and blood pressure (BP) in supine position during 10 min.

The heart rate variability (HRV) was analyzed by spectral analysis and the geometric method.

Results: The St/Fc ratio of striatal dopamine D₂/D₃ receptor binding correlated negatively with heart rate (HR), and positively with cardiac vagal index (CVI) and low frequency (LF) power in healthy subjects who were in a supine resting position.

Conclusions: Striatal dopamine D₂/D₃ receptors may play a part in cardiovascular regulation. Am J Hypertens 2006;19:964–969 © 2006 American Journal of Hypertension, Ltd.

Key Words: Striatal dopamine D₂/D₃ receptor binding, heart rate, blood pressure, healthy subjects.

Dopamine (DA), through different dopamine receptor subtypes, regulates cardiovascular functions by acting on the central and peripheral nervous systems, vascular smooth muscles, the heart, and the kidneys.¹ Dopamine “D₂-like” (D₂, D₃, and D₄) receptors, rather than “D₁-like” (D₁ and D₅) receptors, are involved in the central nervous system (CNS) regulation of blood pressure (BP).^{1,2} The D₂ receptors are found mainly in the striatum, olfactory tubercle, and nucleus accumbens (NA) where they are expressed by γ -aminobutyric acid (GABA)-ergic neurons.³ They are also found in the substantia nigra pars compacta (SN) and the ventral tegmental area (VTA), where they are expressed by dopaminergic neurons.³ Thus, D₂ receptors are found at both presynaptic and postsynaptic sites in the brain.

In the serial animal studies by Van den Buuse,² stimulating the VTA, the region of origin of the mesolimbic/mesocortical dopamine system in the brain, evokes a phasic

increase in BP that may be attenuated by pretreatment with the dopamine D₂ receptor antagonist, but not with the D₁ antagonist. In studies on genetic hypertension in the spontaneously hypertensive rat (SHR), partial depletion of brain dopamine by central treatment of the prehypertensive SHR with the catecholamine neurotoxin inhibits the subsequent development of hypertension in these rats.² Discrete lesions in the substantia nigra (SN), but not in the VTA, can also attenuate the development of hypertension,² suggesting that overactivity of the nigrostriatal pathway may be involved in the increase in BP in the SHR. However, functional studies have shown functional dopaminergic deficit in the SHR. The SHR showed reductions in striatal dopamine release and upregulated D₂ receptor expression.² The serial studies on animals by Sutoo and Akiyama⁴ also showed that calcium ions reduce BP through a central, calcium/calmodulin-dependent dopamine-syn-

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thesizing system, which are mostly located in the lateral neostriatum and NA.

In human subjects, Volkow et al⁵ reported that intravenous administration of methylphenidate, a dopamine transporter blockade, significantly increases heart rate (HR) and both systolic and diastolic BP. The methylphenidate-induced increases of striatal DA, which can be demonstrated by single-photon emission computed tomography (SPECT) with decreased dopamine D₂ receptor availability, correlated significantly with elevated BP. However, conventional neuroleptics are dopamine antagonists that block the central dopamine D₂ receptors and may cause dysregulated hyperactivities of the sympathetic nervous system in neuroleptic malignant syndrome, resulting in increased HR and elevated BP.⁶

Because controversy exists among animal studies on the role of brain dopamine in BP control and because few human studies have been done, the aim of this study was to investigate the relationship between striatal D₂/D₃ receptor binding and cardiovascular activity of human subjects using SPECT.

Methods

Study Population

Thirty-four health subjects, 14 men and 20 women, were recruited from the community by research advertisements. They were diagnosed as being healthy by a physician. Their mean age was 37.1 ± 12.3 years old (range 20 to 62 years) and their mean educational level was 14.8 ± 2.8 years (range 9 to 22 years). Experienced psychiatrists used the Chinese version of Mini International Neuropsychiatric Interview (MINI)⁷ to exclude individuals with any psychiatric morbidity. Their histories of smoking, alcohol intake, and exercise were recorded. All participants were free from the use of any medication or illegal substances and all refrained from tobacco, caffeine, and alcohol use on the day of the study.

The Ethical Committee for Human Research at National Cheng Kung University Medical Center had approved the study protocols. The procedures were explained to all subjects and informed consent was obtained.

Measurement of Brain Dopamine D₂/D₃ Receptor

The radioligand [¹²³I]-iodobenzoamide (IBZM) has been demonstrated to have high affinity and sensitivity for dopamine D₂ receptors.⁸ Each subject's thyroid gland was protected by taking 9 mL of Lugol's solution 12 h before SPECT examination with [¹²³I]-IBZM. For brain SPECT imaging, each subject was intravenously administered 185 MBq (5 mCi) of [¹²³I]-IBZM in a quiet environment about 10 min after setting up the intravenous line. Imaging was initiated approximately 120 min later. We used a triple-headed rotating gamma camera (Siemens Medical Systems, Hoffman Estates, IL) with ultra-high-resolution fan-

beam collimators. This camera yields an image resolution of approximately 8.5 mm full width half maximum (FWHM). The SPECT images were acquired over a 360° circular rotation, 120 steps, 50 sec/step, in a 128 by 128 by 16 matrix. The images were then reconstructed using Butterworth and Ramp filters (cutoff frequency = 0.3 Nyquist; power factor = 7) with attenuation by the Chang method. The reconstructed transverse images were re-aligned parallel to the canthomeatal line. The slice thickness of each transverse image was 2.89 mm. Acquisition of each SPECT image required about 35 min.

For semiquantitative analyses, six consecutive transverse slices on which the striatum was best visualized were combined to obtain a 17.34-mm thick slice. Then the regions of interest (ROIs) were placed over the striatum and the frontal cortex. All of the subjects underwent magnetic resonance imaging (MRI) (Sigma CV-I, 1.5 tesla, General Electric System, Milwaukee, WI). The MRI was used as a reference for defining the areas of striatum on the SPECT images. An experienced nuclear medicine specialist who was blind to the subjects' data drew the ROIs manually based on the individual MRIs. The sizes of all the ROIs were at least twice that of FWHM. The ratio of the radioactivity in the striatum (St) and the frontal cortex (Fc) (St/Fc ratio) was derived by dividing the average counts per pixel in the striatum by the average counts per pixel in the frontal cortex. The St/Fc ratio was used as the marker for striatal D₂/D₃ receptor binding. In this study, we used the frontal cortex as the reference site because: 1) the density of D₂ receptors is negligible in the region compared to the striatum⁹; and 2) [¹²³I]-IBZM activity in the neocortex is equal to the nonspecific activity in the striatum.¹⁰ In the present study, the brain SPECT imaging was performed on each participant starting at 10 AM. All participants completed cardiovascular activity measurements and underwent brain SPECT imaging within 2 consecutive days.

Measurement of Resting BP and Heart Rate

A full 20-min period of recumbent acclimatization preceded the cardiovascular measurements that started at 10 AM. Beat-to-beat BP of the left radial artery and HR were monitored for 10 min while subjects remained in the supine position. The BP and HR were continuously monitored using Tonometry BP Monitor (Colin BP-508, Colin Co., Komaki-City, Aichi, Japan) and input into a computer console. The referential BP was recorded by a sphygmomanometer cuff over the right brachial artery and measured at intervals of 2.5 min. Whenever the tonometry BP measurement was questionable or failed, cuff measurement for calibration was automatically started.

The cardiac autonomic function (CAF) was calculated by the geometric method, which is based on short-term measurements of interbeat interval (IBI).¹¹ Briefly, the sequence of IBI (IBI₁, IBI₂, . . . , IBI_n) was transformed

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