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.

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.


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 (SNC) 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-
the sympathizing system, which are mostly located in the lateral neostriatum and NA.

In human subjects, Volkow et al3 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]-iodobenzamide (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 striatum;9 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, . . . , IBIn) was transformed...
into a figure on a two-dimensional plane by plotting IBI<sub>k</sub> against IBI<sub>k-1</sub>. The length of the transverse axis (T) is affected by both the sympathetic and parasympathetic blockades, whereas the length of the longitudinal axis (L) is affected only by the parasympathetic blockade. Thus, log10 (LxT) is a cardiac vagal index (CVI), whereas the L/T ratio is a cardiac sympathetic index (CSI). These two indices have been demonstrated to be more reliable than conventional measures including spectral analysis. The advantages of the geometric method include: 1) controlled respiration or other maneuvers are not required, and 2) as few as 100 interbeat intervals are sufficient for the assessment.

The power spectral density (PSD) analysis of heart rate variability (HRV) was calculated by fast fourier transformation. The three spectral components are defined as follows: very low frequency (VLF, 0 to 0.04 Hz), low frequency (LF, 0.04 to 0.15 Hz), and high frequency (HF, 0.15 to 0.40 Hz). The HF power of HRV represents an index of cardiac parasympathetic (vagal) activity, whereas LF power represents an index of vasomotor sympathetic activity, or both sympathetic and vagal activities. The LF/HF ratio has been proposed as an index of relative sympathetic modulation or increased sympathetic activity, or both sympathetic and vagal activities. The LF/HF ratio has been proposed as an index of relative sympathetic modulation or increased sympathetic activity, or both sympathetic and vagal activities. The LF/HF ratio has been proposed as an index of relative sympathetic modulation or increased sympathetic activity, or both sympathetic and vagal activities. The LF/HF ratio has been proposed as an index of relative sympathetic modulation or increased sympathetic activity, or both sympathetic and vagal activities.

**Data Acquisition and Data Analysis**

A personal computer was used to receive and process signals. The data acquisition (DAQ) card used in this study was PCI-1200 (National Instruments, Austin, TX). It has eight channels of analog input with software-programmable gain and 12-bit analog-to-digital (A/D) conversion capability. The sampling rate of data acquisition was 120 Hz.

Colin BP-508 signals were output through two channels. The BP and HR signals were obtained from the serial output port, whereas the arterial pulse signals were obtained from the analog output. The acquired signals were recorded, stored, and analyzed by a specially designed and validated software written in LabVIEW (National Instrument).

**Statistics**

Pearson’s correlation was used to assess the relationships between the mean values of systolic BP, diastolic BP, HR, CSI, CVI, HF, LF, LF/HF, and the St/Fc ratios and age. The t test was used to compare the mean values of cardiovascular variables between the following categorical groups: gender, history of smoking, alcohol drinking, and exercise. Multiple linear regression was used to analyze the relationship between the St/Fc ratios and the cardiovascular variables while adjusting the possible confounding factors. All analyses were performed using the SPSS computer package (SPSS Inc., Chicago, IL). P values of less than .05 were considered statistically significant.

**Results**

As shown in Table 1, the St/Fc ratio of striatal dopamine D<sub>2</sub>/D<sub>3</sub> binding was negatively correlated with systolic BP (P < .04), HR (P = .006), and positively correlated with CVI (P = .003), HF power (P = .03), and LF power (P = .01), but not significantly correlated with diastolic BP (P = .07), CSI (P = .92), or LF/HF ratio (P = .08). Age correlated positively with systolic BP (r = 0.44; P = .01) and diastolic BP (r = 0.43; P = .01), and negatively with HF power (r = −0.47; P = .005), LF power (r = −0.40; P = .02), and CVI (r = −0.39; P = .02), but not significantly with HR (r = 0.20; P = .26), CSI (r = 0.26; P = .14), or LF/HF ratio (r = 0.17; P = .34). None of the indices of cardiovascular activity was significantly different between categorical groups including gender, history of smoking, alcohol drinking, and exercise.

The St/Fc ratio was not significantly correlated with age (r = −0.15; P = .40). In addition, the St/Fc ratio was not significantly different between categorical groups including gender (t = 0.14; P = .89), history of smoking (t = −1.07; P = .29), alcohol drinking (t = −0.69; P = .49), and exercise (t = −0.33; P = 0.75).

To further explore the obviously confounding effect of age on cardiovascular variables, we performed multiple linear regression analyses with cardiovascular variables as the dependent variables and the St/Fc ratio and age as the explanatory variables. The results of our regression analyses are shown in Table 2. The St/Fc ratio and age were the significant explanatory variables for CVI (P = .005; P = .04) and LF power (P = .02; P = .03). The St/Fc ratio was also the significant predictor for HR (P = .01), whereas age was the significant predictor for systolic BP (P = .02), diastolic BP (P = .02), and HF power (P = .01).

### Table 1. The correlation between D<sub>2</sub>/D<sub>3</sub> receptor binding and cardiovascular activity

<table>
<thead>
<tr>
<th>Indices of cardiovascular activity</th>
<th>I&lt;sup&gt;123&lt;/sup&gt;-IBZM SPECT (St/Fc ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>−0.35</td>
</tr>
<tr>
<td>DBP</td>
<td>−0.31</td>
</tr>
<tr>
<td>HR</td>
<td>−0.46</td>
</tr>
<tr>
<td>CVI</td>
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</tr>
<tr>
<td>CSI</td>
<td>−0.02</td>
</tr>
<tr>
<td>HF</td>
<td>0.36</td>
</tr>
<tr>
<td>LF</td>
<td>0.43</td>
</tr>
<tr>
<td>LF/HF</td>
<td>−0.31</td>
</tr>
</tbody>
</table>

CSI = cardiac sympathetic index; CVI = cardiac vagal index; DBP = diastolic blood pressure; HF = high frequency power; HR = heart rate; LF = low frequency power; SBP = systolic blood pressure.
Table 2. Results of linear regression among D2/D3 receptor binding, age, and cardiovascular activity

<table>
<thead>
<tr>
<th>Indices of cardiovascular activity</th>
<th>I123-IBZM SPECT (St/Fc ratio)</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>0.29</td>
<td>0.07</td>
</tr>
<tr>
<td>DBP</td>
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<tr>
<td>HR</td>
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<td>0.01</td>
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<tr>
<td>CVI</td>
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<td>CSI</td>
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</tr>
<tr>
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</tr>
<tr>
<td>LF/HF</td>
<td>0.29</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

Discussion

This study revealed that the ratio of striatal dopamine D2/D3 receptor binding correlates negatively with supine resting systolic BP and HR, and correlates positively with supine resting HF power, LF power, and CVI. In addition, our regression analysis revealed that the resting HR, CVI, and LF power are all significantly correlated with striatal D2/D3 receptor binding.

The LF power may be influenced by both sympathetic and parasympathetic inputs. Under resting conditions, vagal tone prevails and variations in heart period are largely dependent on vagal modulation. In the supine resting state, LF and HF powers are correlated with each other. Dividing LF power by HF power (the LF/HF ratio) rules out the parasympathetic component and leaves us a value that is more influenced by sympathetic nervous activity than LF power. Vagal and sympathetic activities constantly interact. It has been reported that, in the resting state, both persistent and white coat hypertensive subjects have lower HF and LF powers and greater LF/HF ratios, indicating greater sympathetic-to-parasympathetic activities, compared to normotensive subjects. In addition, our regression analysis also revealed that the St/Fc ratio is a significant predictor for resting CVI in healthy subjects. Therefore, our results seem to indicate that striatal D2/D3 receptor binding correlates positively with greater parasympathetic modulation, and thus also correlates negatively with resting systolic BP and HR.

The correlation between the St/Fc ratio and systolic BP is no longer significant after adjusting for age. Blood pressure is not regulated by HR alone. Rather, BP is also regulated by the central and peripheral nervous systems, as well as the responsiveness of vascular smooth muscles, the heart, and the kidneys. Age is associated with profound changes in the cardiovascular responses to autonomic nerve activity and changes in the sensitivity of these end organs to neurotransmitters. In this study, the correlations between age and both systolic BP (β = 0.39; P = 0.02) and diastolic BP (β = 0.39; P = 0.02) are stronger and more significant than those between the St/Fc ratio and both systolic BP (β = −0.29; P = .07) and diastolic BP (β = −0.25; P = .12). However the St/Fc ratio is a significant predictor for resting CVI and LF in this study, which are mainly determined by the parasympathetic tone. The tonic BP at rest is mostly determined by the parasympathetic activity of the arterial baroreflex loop. Therefore, striatal dopamine activity may partially modulate the resting BP through parasympathetic nervous activity. But the interaction between striatal dopaminergic activity and the BP should be cautiously explored by more detailed experimental studies involving larger samples.

These results are consistent with previous studies documenting that central DA activity is reduced in SHR and that the dopaminergic activity of the caudate nucleus is normalized while attenuating the development of hypertension in the SN-lesioned SHR. Lin et al also reported that activation of dopaminergic receptors within the caudate–putamen complex facilitates reflex bradycardia in rats. In rats, feedback from peripheral baroreceptors may affect the striatal dopamine release. Striatal dopamine release can be increased by increasing the carotid BP with phenylephrine injection, and decreased by lowering the carotid BP with bilateral carotid occlusion. These results indicate that the striatal DA receptor may play a role in mediating the homeostasis of cardiovascular activity. Our study is one of the few studies in humans focusing on striatal dopaminergic involvement in cardiovascular regulation.

The SN and the VTA contain DA neurons that form the mesotelencephalic DA pathway, which in turn innervates the striatum, cerebral cortex, and limbic system. The DA neurons within the SN–VTA region have been suggested to be involved in the preparation, organization, and initiation of goal-directed behaviors such as drinking, feeding, and sexual behaviors. Stimulating these neurons elicits changes in HR and BP, suggesting that the SN–VTA region is likely involved in modulating the cardiovascular responses that accompany goal-directed behaviors. Mogenson and Yang have also reported that the activation of mesostriatal dopaminergic neurons has a modulating effect on the relay of information from the amygdala and hippocampus to the NA. For example, activation of accumbal neurons by stimulation of the amygdala or hippocampus can be attenuated by stimulating dopaminergic cells in the VTA. A similar attenuating effect of excitatory inputs to the NA can be produced by exogenous application of dopamine to accumbal neurons. The NA, in addition to its connections with the basal ganglia, nucleus of the solitary tract, and the ventrolateral medulla of the brain stem, is also reciprocally connected with limbic structures. The NA may play a role in regulating species–specific behaviors, emotional reactions, motivational processes, and autonomic outflows. The demonstration of dopamine’s neuromodulatory role in the NA and the NA’s role in emotional arousal and cardiovascular regulation suggests that the mesostriatal dopaminergic system may modulate the cardiovascular and behavioral components of emotional re-
sponses by modifying the relay of information between limbic structures and the NA.28

Our results are not entirely consistent with the findings of previous studies on the pressor responses to central DA stimulation in animals2 or in human subjects.5 These studies showed that phasically stimulating the central DA system result in increased striatal DA release, BP, and HR. Van den Buuse2 speculated that it is possible that the central DA system does not actually mediate the pressor response, but just alters the sensitivity of cardiovascular reflexes, such as the baroreceptor–HR reflex, to modulate the effects of other systems on BP.

The present study has several limitations. First, this is an association study. Because it does not rely on an experimental manipulation of the dopaminergic tone to induce the changes in cardiovascular activity, the causal relationship between striatal dopaminergic activity and cardiovascular activity can not be confirmed. Second, SPECT imaging with [123I]-IBZM ligand competition only provides a relative measure of the actual changes in DA concentration. It is possible that the measurements are underestimates of the actual DA changes.30 Third, D2 receptors are found at both presynaptic and postsynaptic sites in the brain. Separate measurements of the receptors are needed in future studies. Fourth, the measurement of cardiovascular activity of HRV by the geometric method and spectral analysis is indirect and limited. Direct nerve recordings by either microneurography or noradrenaline spillover studies are better and should be included in future work. Fifth, the relatively small sample size makes adequate statistical adjustments more difficult. Further studies involving larger samples are necessary for validating the current findings. Sixth, this study included only healthy subjects. We do not know whether similar results can be obtained in patients with abnormal BPs or how different antihypertensive medication classes could impact results. Further experimental studies involving case control are recommended to explore those issues.

In conclusion, this study documents the striatal dopaminergic involvement in cardiovascular regulation in human subjects. Striatal dopamine D2/D3 receptor binding was found to positively correlate with greater parasympathetic modulation, and thus also negatively correlated with resting HR.

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References