The implication of nigrostriatal dopaminergic degeneration in the pathogenesis of REM sleep behavior disorder


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Background and purpose: The pathogenesis of rapid eye movement (REM) sleep behavior disorder (RBD) is not clear despite its frequent association with Parkinson’s disease (PD). We investigated whether the nigrostriatal dopaminergic system is involved in the development of idiopathic RBD.

Methods: Fourteen patients with RBD, 14 patients with PD and 12 normal controls were included in the study. The diagnosis of RBD was confirmed on polysomnography. All the participants performed single-photon emission computed tomography imaging 3 h after injection of [123I]FP-CIT. During REM sleep of the RBD patients, each 30-s epoch was rated as tonic when there was at least 50% of tonically maintained chin electromyography (EMG) activity in the epoch. Phasic EMG activities were calculated as the percentage of 3-s mini-epoch containing phasic EMG events (leg and chin, separately).

Results: The RBD patients showed a trend of lower binding in the striatum than the normal controls ($P = 0.07$), and the significance was revealed in the putamen ($P = 0.02$). However, in 11 individual cases of the 14 RBD patients, the dopamine transporter (DAT) densities in the putamen still remained within the normal range. In the RBD patients, there was no correlation between EMG activities and DAT densities.

Conclusions: Nigrostriatal dopaminergic degeneration could be a part of the pathogenesis of RBD, but not essential for the development of RBD. The lack of correlation between RBD severity and DAT densities suggests that another pathogenic process not related to nigrostriatal dopaminergic transmission may be implicated in RBD.

Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by loss of normal REM sleep muscle atonia, dream-enacting behaviors and aggressive or violent dreams [1,2]. RBD occurs either as an idiopathic disease or in association with neurodegenerative diseases. It is particularly associated with synucleinopathy neurodegenerative disorders including Parkinson’s disease (PD), multiple system atrophy (MSA) and dementia with Lewy bodies (DLB) [3,4]. The presence of RBD has been reported in 33–60% of PD patients, 50–80% of DLB and even up to 80–95% of MSA patients [3,5]. In addition, patients with idiopathic RBD frequently develop degenerative disorders. Nearly 40% of patients with idiopathic RBD were eventually diagnosed as having PD [6], and in another series, 45–50% of idiopathic RBD patients developed neurological disorders including PD and DLB [3,4]. This tendency of RBD to precede the development of PD or other synucleinopathic disorders raises the possibility that the dopaminergic system may be involved in the pathophysiology of RBD.

However, other findings suggest that the dopaminergic system may not play a key role in the pathogenesis of RBD. Clonazepam, a highly effective drug in the treatment of RBD, exerts its effects partly through serotonergic actions with no definite influence on the dopaminergic system [7]. In addition, promipexole, a D2-D3 dopamine receptor agonist, has shown little effect on RBD-related symptoms in PD [8].

Therefore, in the present study, we investigated whether the nigrostriatal dopaminergic system is involved in the pathogenesis of idiopathic RBD by measuring dopamine transporter (DAT) density using FP-CIT single-photon emission computed tomography (SPECT). We also studied the relationship between the
polysomnographic RBD scores and the dopaminergic integrity in RBD patients to elucidate the significance of dopaminergic system in the development of RBD.

Methods

Subjects

We enrolled 14 patients with idiopathic RBD (11 men, three women) who did not have any known neurological disorders including PD. Idiopathic RBD was diagnosed based on the following minimal diagnostic criteria defined by the International Classification of Sleep Disorders; (i) presence of REM sleep without atonia on polysomnography (PSG); (ii) a history of sleep-related, injurious, potentially injurious or disruptive behaviors by history and/or the presence of abnormal REM sleep behavior documented during polysomnographic monitoring; (iii) absence of electroencephalography epileptiform activity during REM sleep; and (iv) the sleep disorder symptoms are not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use or substance use disorder [2]. Subjects’ mean age at RBD diagnosis was 66.6 ± 4.5 years, and the mean interval between subjects’ reported onset of RBD and diagnosis of idiopathic RBD was about 4.1 years. For the purpose of comparison, 12 age-matched and gender-matched subjects (mean age 63.3 ± 5.7 years, M:F = 2:1) and 14 patients with idiopathic PD (mean age 67.0 ± 4.1 years, M:F = 11:3) served as healthy and disease controls, respectively. None of the controls or early, idiopathic PD patients had any history of dream enactment behaviors. Patient with PD fulfilled the clinical diagnostic criteria for PD [9]. They were rated as being at Hoehn and Yahr stage I at the time of our study, and disease duration ranged from newly diagnosed through 4.1 years. The study protocol was approved by our Institutional Review Board. All subjects provided written informed consents.

Polysomnography (PSG) and electromyography (EMG) study

The 14 patients with idiopathic RBD underwent PSG to confirm the diagnosis of RBD. We used an Embla™ N 7000 (Embla, Reykjavik, Iceland) with standard electrodes and sensors. Electroencephalography, electrocystography, submental EMG and EMG of both anterior tibials muscles were recorded. Based on the criteria of Rechtschaffen and Kales [10], we scored every 30-s epoch of the nocturnal PSG. In evaluating the phasic and tonic EMG activities during REM sleep, we referred to an earlier study [11] with allowance for our modifications. We used 30-s epochs and 3-s mini-epochs instead of 20-s epochs and 2-s mini-epochs. Also, we calculated phasic leg EMG activities as well as submental ones. Each 30-s epoch was rated as ‘tonic’ when there was at least 50% of tonically maintained submental EMG activity in the epoch. Phasic EMG events were defined as bursts of EMG activity with amplitudes exceeding four times the atonic EMG baseline.

Dopamine transporter (DAT) image acquisition and analysis:

[123I]-FP-CIT SPECT images were acquired with a dual headed rotating γ-camera system (ADAC Forte; Philips Medical Systems, Milpitas, CA, USA) equipped with low-energy, high-resolution, parallel-hole collimators, 4 h after a bolus injection of 167–185 MBq of [123I]-FP-CIT. Data acquisition was performed in 128 × 128 matrices in a step-and-shoot with 60 steps for 180° and 25 s per step. Image reconstruction was performed using a filtered back projection algorithm with a Butterworth filter (cut-off frequency, 0.3 cycle/cm; order, 10), and attenuation was corrected using Chang’s method (coefficient of 0.12/cm). Reconstructed images were reoriented manually in the axial and transverse planes, to insure that the left and right striata were aligned, and were subsequently transferred to a personal computer for further analysis. All scan data were processed using SPM2 (The Welcome Department of Cognitive Neurology, Institute of Neurology, University College London) implanted in MATLAB 7.0 (Mathwork, Natick, MA, USA) and Analyze software packages (ver 7.0; Mayo Foundation, Rochester, MN, USA). Initially, a ligand-specific template for [123I]-FP-CIT in the standard space was created using [123I]-FP-CIT images of 12 healthy controls with standard procedure [12,13]. After that, standard regions of interest (ROIs) for the entire striatum, caudate, and putamen as well as occipital cortex serving as a reference region, were manually defined on [123I]-FP-CIT templates superimposed on a standard MRI (Fig. 1).

Specific binding of [123I]-FP-CIT to DAT in the striatum was semiquantitatively analyzed on normalized images with standard ROIs. The radioactivity for each standard ROI was extracted from the spatially normalized data. Specific radiotracer binding for DAT in each region was calculated as the ratio of radioactivity in the ROIs and occipital cortex [specific binding potential (BP) = ROIs/occipital cortex – 1].

Correlations between EMG activities and DAT densities

We evaluated correlations between tonic and phase (chin and legs) EMG activities on the PSG and regional
DAT densities in the caudate, putamen and striatum. Tonic EMG activity of each patient was defined as the percentage of tonic epoch during REM sleep. Phasic chin or leg EMG activities were calculated as the percentage of 3-s mini-epochs containing phasic EMG leg or chin events during REM sleep.

Statistical analysis

All numeric data were analyzed using the spss ver.12.0 (SPSS Inc, Chicago, IL, USA). Differences in the mean BP of [123I]FP-CIT for each region amongst the three groups (controls, RBD patients and PD patients) were assessed with one-way analysis of variance (ANOVA), and with Tukey’s protected t-test for post-hoc analysis with multiple comparisons. Furthermore, correlations between EMG activities and DAT densities were tested using the Pearson correlation analysis. The statistical significance of the tests was set at the $P < 0.05$.

Results

Polysomnographic findings

Table 1 shows polysomnographic findings for the 14 idiopathic RBD patients. The average duration and the percentage of REM sleep were 62.3 ± 28.9 min and 13.4 ± 6.0%, respectively. The tonic EMG activity was observed during 43.5 ± 18.4% of REM sleep time. Phasic chin and legs EMG activities increased during 19.9 ± 11.9% and 10.4 ± 6.7% of REM sleep time, respectively. Eight patients had five or more apneas or hypopneas per hour, whilst five patients had periodic limb movements of more than 15/h.

Table 1 Polysomnographic findings of 14 patients with RBD

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST (min)</td>
<td>338.2 ± 82.6</td>
</tr>
<tr>
<td>REM (min)</td>
<td>62.3 ± 28.9</td>
</tr>
<tr>
<td>REM (%)</td>
<td>13.4 ± 6.0</td>
</tr>
<tr>
<td>EMG activity during REM sleep</td>
<td></td>
</tr>
<tr>
<td>Tonic chin (%)</td>
<td>43.5 ± 18.4</td>
</tr>
<tr>
<td>Phasic chin (%)</td>
<td>19.9 ± 11.9</td>
</tr>
<tr>
<td>Phasic leg (%)</td>
<td>10.4 ± 6.7</td>
</tr>
<tr>
<td>PLMs/h</td>
<td>31.6 ± 44.1</td>
</tr>
<tr>
<td>AHI</td>
<td>14.9 ± 13.5</td>
</tr>
</tbody>
</table>

Tonic chin (%) denotes percent of 30-s epoch of REM sleep having at least 50% of tonically maintained chin EMG activity in the epoch; phasic chin (%) and leg (%) were calculated as the percentage of 3-s mini-epoch containing phasic EMG events in the leg and chin, respectively; REM, rapid eye movement; RBD, REM sleep behavior disorder; TST, total sleep time; EMG, electromyography; PLM, periodic limb movements; AHI, apnea-hypopnea index.

FP-CIT SPECT finding

In group comparison, the average DAT binding of FP-CIT in the striatum and subregions was significantly different amongst the groups (Table 2). The RBD group showed a decreasing trend in DAT binding of the striatum. When the RBD group was compared with controls, difference reached significance for the putamen but not for the caudate. Compared with the PD group, the RBD group had significantly higher DAT binding in the whole striatum and in each subregion, showing the largest difference in the putamen. DAT bindings of individual subject are presented in Fig. 2. In the whole striatum and each subregion, the DAT density in the majority of RBD patients (11 of 14) was within the normal range, as defined by mean – 1.96
standard deviation of normal data. In contrast, DAT density in the putamen in most early PD patients was below the normal range. Furthermore, the ratio of caudate to putamen FP-CIT uptake (C/P ratio) in the RBD patients did not differ significantly from ratios in the controls (1.33 ± 0.15 vs. 1.20 ± 0.09, \( P = 0.153 \)), in contrast with an increased C/P ratio in PD patients (1.65 ± 0.22, \( P < 0.001 \)),

Correlation between polysomnographic EMG findings and DAT density

In the correlation analyses between tonic or phasic EMG findings and DAT densities for the striatum and each subregion, no significant correlation was observed (Table 3), indicating that RBD severity is not related to the overall neuronal integrity of the nigrostriatal dopaminergic neurons.

Discussion

DAT is considered as a reliable biologic marker for neuronal integrity of the dopaminergic projections in the striatum, because in histological examination, DAT density is highly correlated with the number of intact dopaminergic neurons in the striatum. Furthermore, \([123I]-FP-CIT\) binds selectively to the DATs in the striatum with a high affinity, which means the specific binding of \([123I]-FP-CIT\) in the striatum can be used as an imaging biomarker for assessment of DA function in the striatum. Alterations in DA neuronal integrity imply changes in the status of pre-synaptic dopaminergic hypoactivity in the striatum. The DAT density in the striatum should decrease following degeneration of dopaminergic projections. In the case of pre-synaptic dopaminergic depletion, DAT density will be decreased by functional down-regulation regardless of structural changes, because synaptic dopamine is mainly regulated by pre-synaptic DATs. Thus, the imaging of DAT with \([123I]-FP-CIT\) or other radiopharmaceuticals has been utilized as a bioimaging method for pre-synaptic dopaminergic function. These techniques could be also applied to the idiopathic RBD patients without parkinsonian symptoms to investigate the possible

Table 2 \([123I]FP-CIT\) uptake of the patients with rapid eye movement sleep behavior disorder (RBD), Parkinson’s disease (PD) and healthy controls

<table>
<thead>
<tr>
<th>Density</th>
<th>Controls (n = 12)</th>
<th>RBD (n = 14)</th>
<th>PD (n = 14)</th>
<th>F-value</th>
<th>Significance (P-value)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate</td>
<td>4.38 ± 0.93</td>
<td>3.73 ± 1.16</td>
<td>2.67 ± 0.77</td>
<td>10.49</td>
<td>0.22, 0.016**, 0.001***</td>
</tr>
<tr>
<td>Putamen</td>
<td>3.61 ± 0.64</td>
<td>2.82 ± 0.92</td>
<td>1.63 ± 0.51</td>
<td>25.39</td>
<td>0.02*, &lt; 0.001**, &lt; 0.001***</td>
</tr>
<tr>
<td>Entire striatum</td>
<td>3.97 ± 0.76</td>
<td>3.24 ± 1.02</td>
<td>2.11 ± 0.61</td>
<td>17.24</td>
<td>0.073, 0.002**, &lt; 0.001***</td>
</tr>
<tr>
<td>C/P ratio</td>
<td>1.20 ± 0.09</td>
<td>1.33 ± 0.15</td>
<td>1.65 ± 0.22</td>
<td>27.44</td>
<td>0.153, &lt; 0.001**, &lt; 0.001***</td>
</tr>
</tbody>
</table>

Specific \([123I]FP-CIT\) uptake value (BP, binding potential) for the caudate nucleus, putamen and entire striatum was calculated as the ratio of total binding in the region to non-specific binding obtained from the occipital cortex (BP = region/occipital cortex – 1); values are averaged from right and left side and expressed as mean ± standard deviation; C/P, caudate to putamen uptake ratio; *P-value at post-hoc Tukey’s tests for controls versus RBD, RBD versus PD and controls versus PD are listed and significant group differences (\( P < 0.05 \)) are marked with asterisks (*); *significant in control versus RBD; **significant in RBD versus PD; ***significant in control versus PD.

Figure 2 Striatal dopamine transporter density measured by \([123I]-FP-CIT\) uptake in individual subjects. RBD, rapid eye movement sleep behavior disorder; PD, Parkinson’s disease. Each point represents the mean binding in the caudate, putamen and entire striatum (○ controls, ◯ RBD, ▲ PD). Values for each region represent the mean from both sides. The dopamine transporter density of the subregions in the majority of RBD individuals (11 of 14) remained above the lower normal limit (---, mean – 1.96 SD of normal data), although the group difference of \([123I]-FP-CIT\) binding in the putamen between rapid eye movement sleep behavior disorder patients and controls was significant. In contrast, \([123I]-FP-CIT\) bindings in each region of most PD patients were below the normal range.

standard deviation of normal data. In contrast, DAT density in the putamen in most early PD patients was below the normal range. Furthermore, the ratio of

Table 3 Correlation coefficients between DAT density and polysomnographic EMG activities

<table>
<thead>
<tr>
<th>Density</th>
<th>Tonic chin (%)</th>
<th>Phasic chin (%)</th>
<th>Phasic leg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate</td>
<td>0.102</td>
<td>0.167</td>
<td>-0.300</td>
</tr>
<tr>
<td>Putamen</td>
<td>-0.030</td>
<td>0.189</td>
<td>-0.112</td>
</tr>
<tr>
<td>Striatum</td>
<td>0.039</td>
<td>0.180</td>
<td>-0.212</td>
</tr>
</tbody>
</table>

Tonic chin (%) denotes percent of 30-s epoch of rapid eye movement sleep having at least 50% tonically maintained chin EMG activity in the epoch; phasic chin (%) and leg (%) were calculated as the percentage of 3-s mini-epoch containing phasic EMG events in the leg and chin, respectively; DAT, dopamine transporter; EMG, electromyography; \( P < 0.05 \).
involvement of the dopaminergic system. In this study, we demonstrated that the DAT densities in patients with idiopathic RBD decreased in the putamen, but not to the PD range. Previous studies using DAT or vesicular monoamine transporter imaging found similar reductions in dopaminergic terminals in the striatum [14–16]. However, most idiopathic RBD patients in the current study showed slightly reduced DAT densities, spanning the low normal ranges. Such densities are probably enough to maintain the motor coordination via striatonigral pathway, without parkinsonian symptoms. Furthermore, the pattern of reduction in idiopathic RBD patients’ DAT densities differs from that of PD patients, which is characterized by asymmetry and rostrocaudal gradient.

It has been documented that the high prevalence of RBD in PD, DLB and MSA and the presence of RBD preceding these diseases demonstrate an association between RBD and several neurodegenerative diseases [16–19]. Furthermore, frequent observation of histopathological features of synucleinopathy in the substantia nigra and locus ceruleus [5,20,21] also suggest that the degeneration of dopaminergic neurons is a possible RBD pathophysiology. Nevertheless, several findings raise the questions about the role of the nigrostriatal pathway in the pathogenesis of RBD. In a recent post-mortem study on a patient with idiopathic RBD, neuropathological findings included an α-synuclein pathology containing Lewy bodies as well as Lewy neuritis and neuronal loss [22]. However, the presence of α-synuclein pathology in this case was limited to the dorsal motor nucleus, medullary tegmentum and central raphe nucleus, sparing substantia nigra and locus coeruleus. This finding contrasts with the α-synuclein pathology of PD, DLB and MSA in which the involvement of the substantia nigra is characteristic. These findings raise some arguments against the idea that degeneration of the monoaminergic neurons in the substantia nigra and locus coeruleus is the primary cause of idiopathic RBD. The sparing of the substantia nigra in this study may explain why the pattern of decreased DAT density in RBD patients on [123I]-FP-CIT SPECT was different from that of PD patients. Also, the disappearance of Parkinsonism during RBD-related behaviors suggests that abnormal motor activities in RBD might be generated in the motor cortex through pyramidal tract bypassing the nigrostriatal dopaminergic system [8,23].

The other interesting finding in our study is that there was no relation between DAT densities and polysomnographic EMG activities during the REM sleep of RBD patients. Polysomnographic EMG activities during REM sleep in RBD might represent the severity of RBD [11,24]. Also, the phasic EMG activities are thought to reflect behavioral manifestations of RBD [25,26]. Thus, the current study showed that the DAT density in the striatum was not correlated with the clinical severity of RBD, in sharp contrast to the relationship between nigrostriatal dopaminergic integrity and the severity of symptoms in PD. We suggest that the muscle activities of RBD patients during REM sleep may not be influenced by the nigrostriatal dopaminergic pathway and thus that a different dopaminergic pathogenesis exists in RBD. This finding is, in a sense, contrary to the previous report that muscle activity during REM sleep was associated with decreased DAT densities in the striatum in patients with subclinical RBD [24]. In that report, it was argued that the reduction in striatal DAT might cause increased muscle activity during REM sleep in patients with subclinical RBD. There are differences between our study and the previous one in terms of study subjects and method used to measure muscle activities. The previous report examined normal controls and patients with subclinical RBD. Also, the previous report divided muscle activities into long-lasting and short-lasting, instead of using tonic and phasic muscle activities as in our study. Considering these differences, these two studies give rather contradictory explanations about the role played by the nigrostriatal dopaminergic system in the pathogenesis of RBD.

The current study may be limited by small sample sizes. Clinical follow-up and additional DAT examination of RBD patients might corroborate the findings of the current study.

In conclusion, only a small proportion of RBD patients showed the reduction of monoaminergic projects in the striatum that has been a universal finding in PD and other synucleinopathies. Furthermore, there was no correlation between muscle activities during REM sleep and striatal DAT densities in RBD patients. This data may suggest that neuronal degeneration of the nigrostriatal dopaminergic pathway could be involved, but is not essential for the development of RBD. Further longitudinal evaluation of the pre-synaptic dopaminergic system in idiopathic RBD patients may provide more understanding of RBD and associated synucleinopathies.

References


