The role of dopamine and serotonin in cervical dystonia

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THE RELATIONSHIP BETWEEN THE DOPAMINERGIC SYSTEM AND DEPRESSIVE SYMPTOMS IN CERVICAL DYSTONIA

E. Zoons, M.A.J. Tijssen, Y.E.M. Dreissen, J.D. Speelman, M. Smit, J. Booij

ABSTRACT

Introduction: Cervical dystonia (CD) is associated with tremor/jerks (50%) and psychiatric complaints (17-70%). The dopaminergic system has been implicated in the pathophysiology of CD in animal and imaging studies. Dopamine may be related to the motor as well as non-motor symptoms of CD.

Hypothesis: CD is associated with reduced striatal dopamine D_{2/3} (D2/3) receptor and increased dopamine transporter (DAT) binding. There are differences in the dopamine system between CD patients with and without jerks/tremor and psychiatric symptoms.

Methods: Patients with CD and healthy controls were neurologically and psychiatrically examined. Striatal DAT and D2/3 receptor binding were assessed using [123I]FP-CIT and [123I]IBZM SPECT, respectively. The specific striatal to non-specific binding ratio (binding potential; BP_{ND}) was the outcome measure.

Results: 27 CD patients and 15 matched controls were included. Nineteen percent of patients fulfilled the criteria for a depression. Striatal DAT BP_{ND} was significantly lower in depressed compared to non-depressed CD patients. Higher DAT BP_{ND} correlated significantly with higher scores on the Unified Myoclonus Rating Scale (UMRS). The striatal D2/3 receptor BP_{ND} in CD patients showed a trend towards lower binding compared to controls. The D2/3 BP_{ND} was significantly lower in depressed compared to non-depressed CD patients. Both in patients and controls there was a significant correlation between DAT and D2/3R BP_{ND}.

Conclusion: Alterations of striatal DAT and D2/3 receptor binding in CD patients are mainly related to depression. DAT BP_{ND} correlates significantly with scores on the UMRS, suggesting a role for dopamine in the pathophysiology of tremor/jerks in CD.
INTRODUCTION

Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Idiopathic cervical dystonia (CD; dystonia of the neck) is the most common form. Approximately 50% of CD patients suffer from myoclonus (jerks) or tremor of the head. It has been hypothesized that patient with tremor/jerks have a more severe phenotype with segmental spreading of dystonia and more often an underlying genetic cause. One of the regions hypothesized to be involved in the pathophysiology in tremor/jerks in dystonia is the nucleus of Cajal which gets information projected from the substantia nigra pars compacta, implicating the dopaminergic system.

Over the last years there is an increasing awareness for non-motor symptoms in CD patients. In a significant number of dystonia patients (17-70%) current psychiatric complaints, mainly depressive symptoms and anxiety disorders have been described. Lifetime prevalence has been reported to be up to 91.4%. It is hypothesized that motor and psychiatric symptoms have a common underlying biochemical etiology. Several studies have implicated a role for the dopaminergic system in the pathophysiology of dystonia. A hyperdopaminergic system, defined as an increased concentration of synaptic dopamine, is an attractive hypothesis in dystonia. In animal models for inherited forms such as myoclonus dystonia (M-D) and DYT1 dystonia a hyperdopaminergic system has been confirmed.

Human studies showed lower striatal dopamine D_{2/3} (D2/3) receptor binding in patients with CD, writer’s cramp and M-D. According to the competition model, this decreased D2/3 receptor binding is compatible with higher concentrations of synaptic dopamine and occupancy of more postsynaptic D2/3 receptors, a reduced number of these receptors, or a combination of both. Increased levels of synaptic dopamine may lead to upregulation of the dopamine transporter (DAT) to ensure more reuptake of endogenous dopamine. However, previous imaging studies investigating DAT binding have not found differences between dystonia patients and controls. Recent animal studies have shown that the dopaminergic tone is probably regulated by the amount of DATs presented at the presynaptic cell membrane. This could explain that no abnormalities in DAT binding have been found, while there still are clues towards a hyperdopaminergic system, i.e. there are more DATs present but they are occupied by the higher level of intrasynaptic dopamine.
The dopaminergic system is also implicated in psychiatric conditions, especially in major depression. Two positron emission tomography (PET) studies found decreased striatal DAT binding in patients with major depression.\textsuperscript{18,19} Striatal DAT binding is also negatively related to depressive symptoms in patients with Parkinson’s disease.\textsuperscript{20} Previous nuclear imaging studies in dystonia did not correct for psychiatric symptoms.

To further establish the role of dopamine in dystonia and comorbid psychiatric symptoms, we performed a study in which we imaged both the presynaptic striatal DAT, as well as the postsynaptic striatal D2/3 receptors in the same sample. Our hypothesis was that CD is associated with reduced striatal D2/3 receptors and increased striatal DAT binding. Furthermore, we investigated if there were differences in the dopamine system between patients with and without jerks/tremor and between patients with and without psychiatric symptoms.

**MATERIAL AND METHODS**

**Subjects**
We included patients with idiopathic CD who had been diagnosed by an experienced neurologist in the past. Neurological examination and additional tests (laboratory tests, genetic tests and conventional imaging) did not reveal signs of acquired or inherited dystonia (including dopa-responsive dystonia). Inclusion criteria were CD that had been stable for at least one year during botulinum neurotoxin (BoNT) treatment on the Tsui scale.\textsuperscript{21} Age had to be between 35 and 80 years. BoNT injections were administered at the day of SPECT scanning or a maximum of 7 days prior to/after scanning. This applied for both scans. Scans were acquired within 3 to 7 days of each other. Exclusion criteria were other relevant neurological conditions at inclusion or in the past, treatment with deep brain stimulation (DBS), use of antidepressants in the past 6 months, symptomatic therapy for dystonia other than BoNT and low dosages of benzodiazepines, use of medication with a known dopaminergic or serotonergic effect\textsuperscript{22}, and pregnancy or lactation. Patients were allowed to use other medications, e.g. antihypertensive drugs. Healthy age- and sex-matched subjects (searched through flyers in the hospital) served as control group. Controls had a normal neurological examination and no self-reported history or family history of dystonia, myoclonus or psychiatric illness. Written informed consent was obtained in all subjects and the study was approved by the local medical ethics committee.
Scoring neurological and psychiatric symptoms

The neurological examination of patients was videotaped and blindly scored by two independent clinicians. Dystonic symptoms were scored using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)\textsuperscript{23} and the Tsui scale\textsuperscript{21}. Myoclonic symptoms were scored using the Unified Myoclonic Rating Scale (UMRS).\textsuperscript{24} The independent scores on Tsui and TWSTRS revealed good agreement between the two observers (>0.80 Intraclass Correlation Coefficients, two-way mixed, absolute agreement, average measures). The independent scores on the UMRS had a Intraclass Correlation Coefficient of 0.73. The average score of the two experts on the Tsui, TWSTRS and UMRS was used in the statistical analysis. Subjects filled in several questionnaires concerning psychiatric symptoms at home. The psychiatric interview, performed by a trained investigator (EZ; YD), consisted of the Mini International Neuropsychiatric Interview (MINI)-Plus and several questionnaires concerning symptoms of depression and anxiety. For this study we incorporated the results of the Beck Depression Inventory (BDI; home questionnaire) and Montgomery-Asberg Depression Rating Scale (MADRS; incorporated in psychiatric interview) for depression and the Liebowitz Social Anxiety Scale (LSAS; home questionnaire) and the Beck Anxiety Inventory (BAI; home questionnaire) for anxiety. Subjects were judged to have a depressive disorder when they fulfilled the according criteria on the MINI and/or had a MADRS score ≥ 20 points or BDI score ≥ 14 points. These cut off values correspond to moderate-severe depression. Subjects were judged to have an anxiety disorder when they fulfilled the according criteria on the MINI-Plus and/or had a BAI score ≥ 16 points or LSAS score ≥ 30 points. These cut off values correspond to moderate-severe anxiety.

SPECT imaging

All participants received 300 mg potassium iodide to block thyroid uptake of free radioactive iodide before administration of the tracer. For the DAT study, subjects received a mean dose of 100 MBq of \textsuperscript{[123]}I-FP-CIT intravenously (produced according to GMP criteria by GE Healthcare) as a bolus.\textsuperscript{25} Scans were performed 3 hours after bolus injection to visualize and quantify the specific DAT binding in the striatum.\textsuperscript{26} For visualizing striatal D2/3 receptor binding, subjects received a 56 MBq bolus of \textsuperscript{[123]}IIBZM intravenously (produced according to GMP criteria by GE Healthcare) followed by continuous infusion of 14 MBq/h of \textsuperscript{[123]}IIBZM until the end of the scan to achieve unchanging regional brain activity levels.\textsuperscript{27,28} Acquisition of the images was started 2 hours after the bolus injection.\textsuperscript{27,29} SPECT studies were performed using a 12-detector single-slice brain-dedicated scanner (Neurofocus 810, which is an upgrade of the Strichmann Medical Equipment) with a full-width at half-maximum resolution of approximately 6.5 mm, throughout the 20-cm field-of-view. After positioning of the
subjects with the head parallel to the orbitomeatal line, axial slices parallel and upward from the orbitomeatal line to the vertex were acquired in 5 mm steps. An average of 15 slices was acquired in a 64x64 matrix. Scanning time was 3.5 minutes per slice for \(^{[123]}\text{FP-CIT}\) and 5 minutes per slice for \(^{[123]}\text{IBZM SPECT}\). The energy window was set at 140-178 keV. Images were reconstructed in 3-D mode and analysed blindly by one observer (EZ). For the \(^{[123]}\text{FP-CIT SPECT}\) images, fixed regions of interest (ROIs) for caudate nucleus and putamen were positioned on the four consecutive axial slices with highest striatal activity, as earlier described. The activity in the separate ROIs was combined to reflect average activity in the caudate nucleus (left + right), putamen (left + right) and whole striatum bilaterally. The cerebellum was used as reference region by positioning a ROI, as earlier described. For the \(^{[123]}\text{IBZM images}\), fixed ROIs for the striatum were positioned as earlier described. The four slices with the highest striatal activity were pooled together and the average activity was calculated. On the same four slices a ROI was positioned on the occipital cortex as reference region for the IBZM tracer. For both scans specific to non-specific binding ratios were calculated as

\[ \frac{\text{activity in ROI} - \text{activity in reference region}}{\text{activity in reference region}} \]

representing the binding potential \((BP_{ND})\). \(^{[123]}\text{BP}_{ND}\) is a combined measure of the density of available neuroreceptors and tracer affinity to the neuroreceptor.

**Statistical analysis**

The Mann-Whitney U test and Kruskal-Wallis test were used to assess differences in receptor/transporter binding ratios \((BP_{ND})\) between different groups of subjects. The Kruskal-Wallis test was also used to assess differences in baseline characteristics between patients with and without jerks/tremor and controls. Chi-square and Fishers exact test were used to assess dichotomous variables.

Linear regression was used to assess if differences in baseline characteristics explained differences in \(BP_{ND}\), both between patients with and without jerks/tremor, and between dystonia patients and healthy controls. Linear regression was also used for assessing relationships between \(BP_{ND}\) and motor and psychiatric scores and between motor and psychiatric scores. Multicollinear variables were avoided by categorizing motor and psychiatric symptoms and not using more than one of such variables in the model. Analyses were carried out using SPSS version 20 and differences were considered significant at \(p<0.05\).
RESULTS

Clinical characteristics

We included 27 CD patients (15 with jerks/tremor and 12 without) and compared them to 15 age- and gender-matched healthy controls. Due to technical difficulties 1 [123I]FP-CIT SPECT scan of a control and 3 [123I]FP-CIT scans and 1 [123I]IBZM scan of patients had to be removed from the analysis. Baseline characteristics are depicted in Table 1 for subjects in which at least one scan was available for analysis. Patients with jerks/tremor were slightly, but not significantly, younger than patients without jerks/tremor and controls. Tsui scores were slightly higher in patients with jerks/tremor. UMRS scores were significantly higher in patients with tremor/jerks, but even 10 patients classified as having no tremor/jerks occasionally exhibited myoclonus with UMRS scores around 1-2. Psychiatric co-morbidity was common in CD patients (17/27 patients; 63%). There was no significant difference in psychiatric co-morbidity between patients with and without tremor/jerks. There was no correlation between motor scores and psychiatric co-morbidity, excluding multicollinearity in further regression models. Two out of 14 controls (14%) fulfilled the criteria of a psychiatric diagnosis (1 for alcohol abuse in the past and 1 scored 34 on the LSAS meeting the criteria of social anxiety disorder).

[123I]FP-CIT SPECT – dopamine transporter imaging

There was no difference between DAT BPND in the whole striatum between CD patients (3.48; IQR 3.01-3.84) and controls (3.64; IQR 3.33-3.99; p=0.41) or in the caudate nucleus (p=0.58) or putamen (p=0.38) separately. DAT BPND was comparable between patients with and without jerks/tremor for the whole striatum (p=value 0.24), caudate nucleus (p=0.33) and putamen (p=0.37). Neither Tsui (p=0.86) nor TWSTRS (p=0.56) explained the variance in DAT BPND. However, UMRS scores contributed significantly to differences in DAT BPND (p=0.04, rs = 0.19).

CD patients with co-morbid depression had lower DAT BPND (3.02; IQR 2.51-3.39) in the whole striatum compared to patients without a depression (3.54, IQR 3.34-4.03; p=0.05). This difference was also present in the caudate nucleus (DAT BPND 3.00; IQR 2.58-3.51) vs. 3.84 (IQR 3.51-4.24; p= 0.02)). DAT BPND was also lower in the putamen of patients with a depression compared to patients without, but this did not reach statistical significance (p=0.14). There was no significant difference in DAT BPND between CD patients without a co-morbid depression and controls (DAT BPND 3.54 (3.34-4.03) vs. 3.64 (IQR 3.33-3.99); p=0.86 for whole striatum). No differences were found between patients with and
without psychiatric co-morbidity and with and without an anxiety disorder. Scores of CD patients on the BDI (p=0.90), MADRS (0.29), LSAS (0.81) or BAI (0.44) did not contribute to differences in DAT BPND in the whole striatum.

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CD with jerks/tremor (n=15)</th>
<th>CD without jerks/tremor (n=12)</th>
<th>Controls (n=15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>62 (53-67)</td>
<td>52.5 (44.5-60)</td>
<td>61 (56-62)</td>
<td>0.06</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>7 (47%)</td>
<td>5 (42%)</td>
<td>7 (47%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Tsui, median (IQR)</td>
<td>8 (6.5-12)</td>
<td>7.8 (5.4-13.5)</td>
<td>N/A</td>
<td>0.79</td>
</tr>
<tr>
<td>TWSTRS Total, median (IQR)</td>
<td>16.5 (14.5-21)</td>
<td>14.5 (13.5-20.5)</td>
<td>N/A</td>
<td>0.59</td>
</tr>
<tr>
<td>UMRS, median (IQR)</td>
<td>12.5 (7-19)</td>
<td>1.3 (0.5-2.4)</td>
<td>N/A</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychiatric disorders, n (%)</td>
<td>9 (60%)</td>
<td>8 (67%)</td>
<td>2 (13%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anxiety disorders, n (%)</td>
<td>7 (47%)</td>
<td>6 (50%)</td>
<td>1 (7%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Depression, n (%)</td>
<td>2 (13%)</td>
<td>3 (25%)</td>
<td>0 (0%)</td>
<td>0.13</td>
</tr>
<tr>
<td>BDI, median (IQR)</td>
<td>5 (2-8)</td>
<td>4.5 (2.25-8.5)</td>
<td>2 (0-3)</td>
<td>0.02</td>
</tr>
<tr>
<td>MADRS, median (IQR)</td>
<td>2 (0-4)</td>
<td>3.5 (0-8.5)</td>
<td>1 (0-2)</td>
<td>0.06</td>
</tr>
<tr>
<td>LSAS, median (IQR)</td>
<td>11 (5-34)</td>
<td>16 (5.5-40.25)</td>
<td>4 (1-8)</td>
<td>0.02</td>
</tr>
<tr>
<td>BAI, median (IQR)</td>
<td>6 (4-10)</td>
<td>4 (0.25-11)</td>
<td>1 (0-1)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CD = cervical dystonia; IQR = interquartile range; LSAS = Liebowitz Social Anxiety Scale; MADRS = Montgomery Asberg Depression Rating Scale; n = number; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; UMRS = Unified Myoclonic Rating Scale; y = year

Since age and sex are known to have an effect on DAT BPND as measured with $[^{123}I]$FP-CIT SPECT$^{34-36}$, and age differed slightly between groups, they could be potential confounders. Therefore, we corrected for these factors for the striatum as a whole, which did not change any of the results (regression coefficients and p-values are depicted in Table 2). Correcting for the occurrence of depression only slightly changed the correlation between DAT BPND and UMRS scores (p=0.04 before correction and 0.06 after correction).

### $[^{123}I]$IBZM SPECT - dopamine D$_{2/3}$ receptor imaging

There was a trend towards lower striatal D2/3 receptor BPND in patients with CD (0.84; IQR 0.63-0.99) compared to controls (0.91; 0.79-1.12; p=0.14). There was no difference in D2/3 receptor BPND between patients with and without jerks (p=0.54). Scores on the Tsui (p=0.92), TWSTRS (p=0.74) or UMRS (p=0.67) did not contribute to differences in D2/3 receptor BPND.
Patients with psychiatric symptoms did not differ in D2/3 receptor $\text{BP}_{\text{ND}}$ from patients without (p=0.20), nor did patients with an anxiety disorder differ from patients without (p=0.72). Patients with a depression had a significantly lower D2/3 receptor $\text{BP}_{\text{ND}}$ (0.56, IQR 0.48-0.72) compared to patients without (0.89; IQR 0.70-1.01; p-value 0.008). There was no significant difference in D2/3 receptor $\text{BP}_{\text{ND}}$ between CD patients without a co-morbid depression and controls ($\text{BP}_{\text{ND}}$ 0.89 (IQR 0.70-1.00) vs. 0.91 (0.79-1.12); p=0.43). In CD patients scores on BDI (p=0.25), MADRS (0.82), LSAS (0.36) or BAI (0.70) did not contribute to D2/3 receptor $\text{BP}_{\text{ND}}$.

Since age and sex are known to have an effect on D2/3 receptor $\text{BP}_{\text{ND}}$ we corrected for these factors. This did not change the result between patients and controls (p=0.09 before and after correction) or between patients with and without jerks (p=0.66 before correction and 0.44 after correction).

Because of the surprising finding of a large difference in D2/3 receptor $\text{BP}_{\text{ND}}$ between patients with and without co-morbid depression we separately also corrected the D2/3 receptor $\text{BP}_{\text{ND}}$ for the occurrence of depression. Before correction there was a regression coefficient of -0.12 between patients and controls (95% CI -0.25-0.02; p-value 0.09) and after correction there was a regression coefficient of -0.06 (95% CI -0.19-0.07; p-value 0.34).
DAT-D2/3 receptor ratio

In patients with a lower striatal DAT BP$_{ND}$, there was a trend towards a lower striatal D2/3 receptor BP$_{ND}$ (regression coefficient 0.93 (95% CI -0.30-2.14); p-value 0.13). The same trend was found in controls (regression coefficient 1.03 (95% CI -0.55-2.61); p-value 0.18). When patients and controls were combined this resulted in a statistically significant correlation between striatal DAT and D2/3 receptor BP$_{ND}$ (regression coefficient 0.98 (95% CI 0.12-1.84); p-value 0.03; figure 1). This correlation was not caused by an age effect. When plotting the binding potential and age in graphs in both cases the fit lines are almost horizontal but with a trend towards decreasing BP$_{ND}$ at higher age (R2 Linear 0.028 for D2/3 receptor and R2 Linear 0.015 for DAT).

**Figure 1.** The correlation between DAT and D2/3 receptor BPND in both patients (black circles) and controls (grey circles). The D2/3 receptor BPND is shown on the x-axis, and the DAT BP is shown on the y-axis. Every black or grey circle is an individual study subject. Values are depicted only for subjects in which both a DAT and D2/3 receptor scan was performed.

**DISCUSSION**

This study showed a strong relation between depressive symptoms and striatal DAT and D2/3 receptor binding alterations in CD patients. Furthermore, the relation between DAT BP$_{ND}$ and scores on the UMRS suggests a role for dopamine in the pathophysiology of tremor/jerks in CD.

In line with previous studies no difference in striatal DAT binding was detected between patients and controls. Differences in DAT binding are likely to be small, but can still be clinically significant. The fact that we did not find a difference in striatal DAT binding can
have different explanations. First, it might mean that there is no difference in the number of DATs. Second, there could be a hyperdopaminergic system that cannot be detected with DAT imaging. Two recent animal studies hypothesized that dopaminergic tone is regulated by the amount of DATs presented at the presynaptic cell membrane. More intrasynaptic dopamine would lead to more DATs to bind dopamine. In that case, the amount of DATs free to bind [123I]FP-CIT might be stable and no difference will be found in DAT BPND. Lastly, it could mean there is a difference in intrasynaptic dopamine but [123I]FP-CIT is less sensitive to detect the reflection of differences in dopaminergic concentrations compared to [123I]IBZM.

We did find a strong trend towards a reduced striatal D2/3 receptor binding in patients with idiopathic CD compared to controls. This could be consistent with a hyperdopaminergic state in the striatum and/or with a reduced number of D2/3 receptors. Previous reports have been ambiguous about D2/3 receptor binding in dystonia, although reduced binding has been more commonly reported.

The existence of depressive symptoms within the group of CD patients was associated with a significant difference in striatal D2/3 receptor and DAT BPND. There was no significant difference in DAT or D2/3 receptor BPND between non-depressed CD patients and controls. Moreover, when we corrected for co-morbid depression, there was no difference in D2/3 receptor BPND anymore between patients and controls indicating that changes in the dopamine system of CD patients may be mainly correlated with depressive symptoms and not with dystonia per se. Psychiatric symptoms, more specifically anxiety and depression are common in dystonia. In our cohort, 63% of patients had psychiatric symptoms. This is on the high end of the 17–70% range reported in literature in observational cohort studies. Molecular imaging studies in depression and anxiety disorders have shown abnormalities in both striatal DAT as well as D2/3 receptor binding. Most studies in major depressive disorder (MDD) reported decreased striatal DAT binding compared to controls. In anxiety disorders decreased DAT binding has also been described, although less consistently. Results on striatal D2/3 receptor binding in patients with depression and anxiety have been ambiguous. Abnormalities have been found, but differences with controls were smaller than observed in studies on DAT binding and both decreased and increased binding have been described. Striatal DAT binding in depressed Parkinson’s patients has found to be reduced compared to non-depressed Parkinson’s patients and binding in the caudate nucleus was negatively related to the severity of depressive symptoms in patients with Parkinson’s disease. We also observed that decreased DAT binding in the caudate nucleus was related to depressive symptoms in CD. Another recent study investigated striatal DAT availability in different groups of patients with movement disorders and...
found normal DAT binding in dystonia patients with an inverse correlation between DAT availability in the left putamen and severity of both anxiety and depression. They hypothesized that dysfunction of the basal ganglia-thalamo-cortical circuits underlies both motor and psychiatric manifestations in movement disorders. We hypothesize that the differences we found in striatal DAT and D2/3R binding, are mainly driven by the psychiatric symptoms in dystonia. However, an effect of motor symptoms cannot be completely ruled out, especially since a recent study found different spatial reorganization of putaminal D2/3 receptor binding between patients with blepharospasm and hand dystonia. We were unable to measure spatial redistribution due to the limited spatial resolution of SPECT imaging. The least we can say is that psychiatric symptoms play an important role in abnormalities in the dopamine system of patients with CD and should be taken into account in future imaging studies. It could be that patients who suffer from both motor and psychiatric symptoms have a more severe phenotype in which dopamine plays a more important role.

There was no difference in D2/3 receptor or DAT binding between CD patients with and without tremor or jerks. DAT binding did however correlate with scores on the UMRS. This is probably caused by the fact that most patients classified as having no jerks (10/12) did have some mild jerks or tremor. As stated above, the nucleus of Cajal, which receives input from the substantia nigra pars compacta, has been hypothesized to play a role in the occurrence of tremor and jerks in dystonia. Biochemical changes in this region may lead to changes in DAT binding and tremor or jerks in CD patients. However, this area is too small to assess in-vivo in humans.

The other interesting finding is the positive correlation between DAT and D2/3 receptor binding. This is not consistent with the competition model. It is likely that the competition model only applies to acute interventions and not to chronic disease conditions such as dystonia. The relation between DAT and D2/3 receptor binding has not been extensively studied in healthy controls and in different conditions, although a recent study showed a significant positive correlation between striatal DAT and D2/3 receptor binding in healthy controls, using the same radiotracers we used.

This study has several limitations. Use of dopaminergic or serotonergic medication was an exclusion criterion in our study. This could have excluded patients with severe psychiatric complaints, which could have led to an underestimation of the effect of psychiatric symptoms on DAT and D2/3 receptor binding. Patients in our study did receive BoNT injections and were allowed to use low dosages of benzodiazepines. Furthermore, since subjects were on average 50-60 years old most of them used medication for other conditions. BoNT is a locally working neurotoxin without systemic effects of which the
effect is noticeable after one week. Before this effect could occur both scans were made. It is therefore unlikely that BoNT had a direct effect on striatal DAT or D2/3 binding ratios. We cannot rule out a placebo effect of the BoNT injections, such an effect has not been investigated before. There are some indications that benzodiazepines have an effect on D2/3 receptor binding in the striatum and dorsolateral prefrontal cortex. However, this has only been investigated with high enough dosages of lorazepam to cause sedation. Patients in our study used a low dosage of oxazepam or clonazepam. Therefore, we do not think this has influenced our results significantly. [123I]FP-CIT is derived from cocaine and metabolized by cytochrome P450 type 3A (CYP3A) in the liver. The same enzyme also metabolizes most drugs. Therefore, at least theoretically many drugs might influence [123I]FP-CIT metabolism and possibly striatal DAT binding. For most drugs a potential effect has not been investigated. The only potential influence we found was codeine, which was used by one of our patients in a combination drug with acetaminophen to treat pain (acetaminophen 500 mg + codeine 10 mg three times daily). Opioid abuse, including abuse of codeine, was associated with lower DAT binding in the striatum. In one study DAT binding correlated with the amount of opioids used. It is unlikely that a low dosage of codeine in one patient influenced our results. Even less is known about interactions between drugs and [123I]IBZM binding. Another potential weakness of this study is the fact that we did not correct for other factors that might influence the dopamine system, e.g. smoking, season and amount of sunlight exposure. All of these factors have been hypothesized to influence the dopamine system, although the relationship is still under debate in for example smoking. Our study group is too small to correct for every factor that could potentially influence the dopamine system. Also, with the technique we used it is only possible to measure adequately DAT and D2/3 receptors in the striatum. Therefore, we cannot exclude dopaminergic changes elsewhere in the brain. Lastly, the significant number of scans that had to be excluded from the analysis is a limitation. We had some technical difficulties during the course of this study, leading to poor scan quality. Taking this in regard we still have the largest SPECT imaging study in patients with dystonia thus far and were the first to find that depressive symptoms likely explain differences in striatal DAT and D2/3 receptor BP\textsubscript{ND} between CD patients and controls.
REFERENCES


The dopaminergic system in cervical dystonia


Chapter 3


