Decreased $[^{18}F]$Spiperone Binding in Putamen in Idiopathic Focal Dystonia

Joel S. Perlmutter,1,5 Mikula K. Stambuk,4 Joanne Markham,6 Kevin J. Black,1,2,5 Lori McGee-Minnich,1 Joseph Jankovic,7 and Stephen M. Moerlein1,5

Departments of 1Neurology and Neurological Surgery, 2Psychiatry, and 3Medicinal Chemistry, 4Division of Biology and Biomedical Sciences, 5Mallinckrodt Institute of Radiology, and the 6Biomedical Computing Laboratory, Washington University School of Medicine, St. Louis, Missouri 63110, and 7Department of Neurology, Baylor College of Medicine, Houston, Texas 77030

In this study we have investigated the pathophysiology of two idiopathic focal dystonias: hand cramp with excessive cocontractions of agonist and antagonist hand or forearm muscles during specific tasks, such as writing, and facial dystonia manifested by involuntary eyelid spasms (blepharospasm) and lower facial and jaw spasms (oromandibular dystonia). We used positron emission tomography (PET) to measure the in vivo binding of the dopaminergic radioligand $[^{18}F]$spiperone in putamen in 21 patients with these two focal dystonias and compared the findings with those from 13 normals. We measured regional cerebral blood flow and blood volume in each subject and compared the findings with those from 13 normals. We measured regional cerebral blood flow and blood volume in each subject as well as the radiolabeled metabolites of $[^{18}F]$spiperone in arterial blood. A stereotactic method of localization, independent of the appearance of the images, was used to identify the putamen in all of the PET images. We analyzed the PET and arterial blood data with a validated nonsteady-state tracer kinetic model representing the in vivo behavior of the radioligand. An index of binding called the combined forward rate constant was decreased by 29% in dystonics, as compared with normals ($p < 0.05$). There were no significant differences between dystonics and normals in regional blood flow, blood volume, nonspecific binding, permeability–surface area product of $[^{18}F]$spiperone or the dissociation rate constant. These findings are consistent with a decrease of dopamine D$_2$-like binding in putamen and are the first demonstration of a receptor abnormality in idiopathic dystonia. These results have important implications for the pathophysiology of dystonia as well as for function of the basal ganglia.

Key words: dystonia; PET; spiperone; D$_2$-like receptors; putamen; blepharospasm; hand cramp

Dystonia is a syndrome of repetitive or sustained involuntary muscle contractions that frequently produce twisting, repetitive movements and abnormal postures (Fahn, 1988). Idiopathic dystonias are distinguished from secondary dystonias (such as those caused by birth injury, stroke, or drug reaction) by the lack of identifiable etiology (Calne and Lang, 1988) and can be classified by affected body part. Generalized idiopathic dystonia often begins in childhood, whereas focal dystonias more frequently start in adult life (Marsden and Harrison, 1974; Fahn, 1988; Greene et al., 1995). There are several types of idiopathic focal dystonia, including blepharospasm and hand cramp. Blepharospasm refers to spasms of involuntary eyelid closure that can be sufficiently severe to render a person functionally blind. Some patients also may have lower facial dystonic spasms; the combination is called cranial dystonia. Dystonic hand cramp is produced by excessive cocontractions of agonist and antagonist hand or forearm muscles during specific tasks, such as writing (writer’s cramp) (Sheehy and Marsden, 1982; Cohen and Hallett, 1988). Clinically, one might suspect that the idiopathic focal dystonias share a common pathophysiology, because there is frequent overlap of symptoms in individual patients (Jankovic et al., 1991), but the exact etiological relationship among the idiopathic focal dystonias remains unclear (Micheli et al., 1994) despite recent advances in genetics (Ozelius et al., 1989, 1992; Waddy et al., 1991; Bressman et al., 1994; Kramer et al., 1994; Greene et al., 1995).

Numerous reports have described structural abnormalities in basal ganglia contralateral to the symptomatic side in hemidystonic patients (Grimes et al., 1982; Demierre and Rondot, 1983; Pettigrew and Jankovic, 1985). Computed tomography (CT) and magnetic resonance imaging (MRI) have revealed putaminal lesions in patients with secondary dystonias (Marsden et al., 1985; Fross et al., 1987; Obeso and Gimenez-Roldan, 1988; Rutledge et al., 1988; Krauss et al., 1992; Bhatia and Marsden, 1994; Lee and Rinne, 1994), and we found an abnormality of blood flow and oxygen metabolism in the putamen contralateral to the side of the body affected by a post-traumatic paroxysmal hemidystonia despite completely normal brain MRI, CT, and angiography (Perlmutter and Raichle, 1984). Furthermore, high field-strength MRI demonstrated prolonged $T_2$ times in the lentiform nucleus in idiopathic torticollis (Schneider et al., 1994). Overall, these studies suggest that the putamen is a likely site of pathophysiology in dystonia.

Several lines of evidence suggest that abnormalities of dopaminergic pathways also play a key role in the underlying pathophys-
After adequate time allotted for decay of $^{15}$O, as much as 5 mCi of no-carrier-added $[^{18}F]$SP containing $<1$ ng of unlabeled ligand (specific activity $>2000$ Ci/mmol) was injected intravenously, and PET scans were begun immediately. Initial scans were 60 sec and increased up to 10 min to maintain adequate counts for statistical accuracy (Perlmutter et al., 1987). During these scans, $14$ arterial blood samples were collected to measure total radioactivity, and 11 of these samples were assayed in duplicate for the fraction of $[^{18}F]$ that represented unmetabolized $[^{18}F]$SP (Perlmutter et al., 1986). Subjects were observed continuously throughout the PET procedures. Some of the patients had minimal blepharospasm, but there were no other movements seen.

Data analysis. All volumes of interest (VOIs) were identified by an observer blinded to subject diagnosis. For each subject, we started with the same coordinates for the center of putamen identified on a stereotactic atlas of the brain (Talairach and Tournoux, 1988), then transferred these coordinates to the appropriate single PET slice by a stereotactic method of localization (Fox et al., 1985), and finally expanded the VOI to include putaminal activity on the slices immediately above and below. The same-sized region was outlined on all slices ($9 \times 5$ voxels), and then the regional values were averaged across the three slices and for the right and left putamen. A single hemispheric cerebellar value was averaged from left- and right-sided regions ($5 \times 5$ voxels each) identified on three PET slices. The VOIs were held in a constant position for all frames of the dynamic collection made after injection of $[^{18}F]$SP and for the CBV and CBF images. The $[^{18}F]$ tissue activity curves were decay-corrected to the time of injection of $[^{18}F]$SP. We calculated radioligand binding with a tracer kinetic model previously described (Perlmutter et al., 1986), validated (Perlmutter et al., 1989, 1991) and applied to human studies (Fox et al., 1985). Briefly, PET and arterial blood data were analyzed with a nonsteady-state two-compartment model to estimate the free fraction of radioligand in the cerebellum ($f_f$; dimensionless) as a measure of the nonspecific binding. This value was assumed to be the same in the putamen, and then a three-compartment, three-parameter nonsteady model was used to estimate the local permeability–surface area product (PS) for $[^{18}F]$SP at the blood–brain barrier, the combined forward rate constant (CFRC) of $[^{18}F]$SP (this equals the apparent maximum number of specific binding sites times the association rate constant of $[^{18}F]$SP for the specific sites) as well as the dissociation rate constant of $[^{18}F]$SP–receptor complex. The assumptions and limitations of this approach have been described in detail, including the test–retest variability of calculations of the relevant binding variables (Mintun et al., 1984; Perlmutter et al., 1986, 1987, 1989, 1991).

Statistical analyses. Results were compared between dystonics and normals with unpaired $t$ tests. Because there was only a comparison of mean values from a single VOI value, there was no correction for multiple comparisons.

RESULTS

No subject had a gross abnormality on MRI scan of the brain. Cerebellar blood flow and blood volume, putaminal blood flow and blood volume, and the measured free fraction of $[^{18}F]$SP in blood are listed in Table 2. There were no statistical differences between patients and normals. The typical time course of total radioactivity measured in the arterial blood after injection of $[^{18}F]$SP is shown in Figure 1. Most of the area under the curve is within the first few minutes, and it is necessary to sample this part of the curve adequately to permit accurate parameter estimation (Perlmutter et al., 1986). Nearly one-half of the radioactivity in arterial blood by 30 min after $[^{18}F]$SP injection represents radiolabeled metabolites of $[^{18}F]$SP rather than $[^{18}F]$SP itself, as shown in the inset of Figure 1. An example of the time-dependent measurements of regional radioactivity within the putamen (averaged left and right side) is demonstrated in Figure 2. The parameter estimation method finds the optimal estimates of the unknown variables to make the tracer kinetic model equations fit the observed tissue activity points. The closeness of fit of the model to the data also is shown in Figure 2.

Variables estimated from the tracer kinetic model, including the calculated free fraction of $[^{18}F]$SP in brain tissue, the permeability–surface area product (PS) for $[^{18}F]$SP in cerebellum, PS for $[^{18}F]$SP in striatum, and dissociation rate constant of $[^{18}F]$SP, are
Table I. Subject characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Type of dystonia</th>
<th>Age</th>
<th>Gender</th>
<th>Duration</th>
<th>Medications</th>
<th>Time of last oral medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cranial</td>
<td>48</td>
<td>M</td>
<td>6 yrs</td>
<td>trihexyphenidyl</td>
<td>6 hr</td>
</tr>
<tr>
<td>2</td>
<td>Cranial</td>
<td>54</td>
<td>F</td>
<td>4.5 yrs</td>
<td>hydralazine, clonazepam, levothyroxine btx/2 months ago</td>
<td>6 hr</td>
</tr>
<tr>
<td>3</td>
<td>Cranial</td>
<td>54</td>
<td>F</td>
<td>1.5 yrs</td>
<td>estrogen, progesterone, diclofenac, indepamide, verapamil btx/2 weeks ago</td>
<td>12 hr</td>
</tr>
<tr>
<td>4</td>
<td>Cranial</td>
<td>46</td>
<td>F</td>
<td>4 yrs</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Cranial</td>
<td>47</td>
<td>M</td>
<td>3 yrs</td>
<td>aspirin btx/5 months ago</td>
<td>24 hr</td>
</tr>
<tr>
<td>6</td>
<td>Cranial</td>
<td>48</td>
<td>F</td>
<td>3 yrs</td>
<td>clonazepam, orphenadrine btx/5 weeks ago</td>
<td>24 hr</td>
</tr>
<tr>
<td>7</td>
<td>Cranial</td>
<td>74</td>
<td>F</td>
<td>29 yrs</td>
<td>cimetidine</td>
<td>24 hr</td>
</tr>
<tr>
<td>8</td>
<td>Cranial</td>
<td>79</td>
<td>F</td>
<td>16 yrs</td>
<td>hydrochlorothiazide btx/4 months salicylate</td>
<td>24 hr</td>
</tr>
<tr>
<td>9</td>
<td>Cranial</td>
<td>66</td>
<td>F</td>
<td>6 yrs</td>
<td>none btx/5 years ago</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Cranial</td>
<td>54</td>
<td>F</td>
<td>6 yrs</td>
<td>none btx/6 months ago estrogen</td>
<td>24 hr</td>
</tr>
<tr>
<td>11</td>
<td>Cranial</td>
<td>54</td>
<td>F</td>
<td>1 yr</td>
<td>estrogen btx/5 weeks ago</td>
<td>24 hr</td>
</tr>
<tr>
<td>12</td>
<td>Cranial</td>
<td>73</td>
<td>M</td>
<td>1 yr</td>
<td>trihexyphenidyl</td>
<td>24 hr</td>
</tr>
<tr>
<td>13</td>
<td>Cranial</td>
<td>77</td>
<td>F</td>
<td>12 yrs</td>
<td>none btx/4 weeks ago estrogen, levothyroxine btx/4 months ago</td>
<td>24 hr</td>
</tr>
<tr>
<td>14</td>
<td>Cranial</td>
<td>55</td>
<td>F</td>
<td>2.5 yrs</td>
<td>none btx/4 weeks ago estrogen, levothyroxine btx/4 months ago</td>
<td>24 hr</td>
</tr>
<tr>
<td>15</td>
<td>Hand</td>
<td>38</td>
<td>F</td>
<td>10 yrs</td>
<td>none</td>
<td>24 hr</td>
</tr>
<tr>
<td>16</td>
<td>Hand</td>
<td>50</td>
<td>M</td>
<td>3 yrs</td>
<td>none btx/3 months ago</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Hand</td>
<td>59</td>
<td>F</td>
<td>15 yrs</td>
<td>propoxyphene, atenolol</td>
<td>24 hr</td>
</tr>
<tr>
<td>18</td>
<td>Hand</td>
<td>67</td>
<td>F</td>
<td>9 yrs</td>
<td>quinapril</td>
<td>24 hr</td>
</tr>
<tr>
<td>19</td>
<td>Hand</td>
<td>68</td>
<td>M</td>
<td>26 yrs</td>
<td>none btx/3 years ago</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Hand</td>
<td>25</td>
<td>F</td>
<td>4 yrs</td>
<td>none</td>
<td>24 hr</td>
</tr>
<tr>
<td>21</td>
<td>Hand</td>
<td>45</td>
<td>F</td>
<td>15 yrs</td>
<td>levothyroxine, estrogen, progesterone</td>
<td>24 hr</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>56</td>
<td>5 M, 16 F</td>
<td>8.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>14</td>
<td></td>
<td>7.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td>25–79</td>
<td></td>
<td>1–29</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Normals

<table>
<thead>
<tr>
<th>Patient</th>
<th>Type of dystonia</th>
<th>Age</th>
<th>Gender</th>
<th>Duration</th>
<th>Medications</th>
<th>Time of last oral medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td></td>
<td>21</td>
<td>M</td>
<td></td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td></td>
<td>53</td>
<td>F</td>
<td></td>
<td>nicotine patch</td>
<td>24 hr</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>76</td>
<td>M</td>
<td></td>
<td>hydrochlorothiazide, lovastatin, aspirin</td>
<td>24 hr</td>
</tr>
<tr>
<td>25</td>
<td></td>
<td>24</td>
<td>F</td>
<td></td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td></td>
<td>40</td>
<td>M</td>
<td></td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td></td>
<td>24</td>
<td>F</td>
<td></td>
<td>estrogen, progesterone</td>
<td>24 hr</td>
</tr>
<tr>
<td>28</td>
<td></td>
<td>67</td>
<td>F</td>
<td></td>
<td>gemfibrozil</td>
<td>24 hr</td>
</tr>
<tr>
<td>29</td>
<td></td>
<td>60</td>
<td>F</td>
<td></td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td>64</td>
<td>M</td>
<td></td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td></td>
<td>72</td>
<td>M</td>
<td></td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td></td>
<td>65</td>
<td>M</td>
<td></td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td></td>
<td>63</td>
<td>F</td>
<td></td>
<td>aspirin</td>
<td>24 hr</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>52</td>
<td>6 F, 6 M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>± SD</td>
<td></td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td>21–76</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

btx, Botulinum toxin A injections; F, female; M, male. There was no statistically significant difference between the ages of the dystonics and normals (p > 0.5, two-tailed t test).
There were no statistically significant differences between dystonics and normals except for the combined forward rate constant, which was ~29% lower in dystonics compared with normals (p < 0.05), as shown in Table 3. We found no significant difference between the combined forward rate constant for dystonic hand cramp and cranial dystonia (p > 0.2). It is important to note that a change in the combined forward rate constant is consistent with a change of the association rate constant, the maximum number of specific binding sites ($B_{max}$), or both. The parameter estimation of the dissociation rate constant has substantially more noise than for the combined forward rate constant.

This is indicated in Table 3 with the greater variance of the estimates of the dissociation rate constant compared with the variance of the estimates of the combined forward rate constant (i.e., higher mean coefficient of variation for the variable estimates). In part, this is attributable to the greater number of association rate events compared with dissociation events that occur during a 3 hr PET study. For this reason, we have chosen to report the combined forward rate constant as the index of binding rather than the binding potential (this equals combined forward rate constant/dissociation rate constant), which would incorporate the additional uncertainty of the dissociation rate constant.

**Figure 1.** Arterial blood radioactivity after $[^{18}F]$spiperone injection. This graph represents the measurements made from arterial blood samples in a single subject in this study. Total radioactivity was measured on 31 samples in a well counter cross-calibrated with the PET scanner, and the counts were decay-corrected to the time of radioligand injection. The horizontal axis is shown with a log scale to demonstrate that the majority of the area under the curve occurs in the first few minutes. To delineate this time–activity curve accurately requires frequent sampling at the beginning of the study. The inset graph demonstrates the fraction of radioactivity in blood that represents radiolabeled metabolites, which decreases to ~60% of the total activity and then remains nearly constant. The radiolabeled metabolites of $[^{18}F]$SP were measured as described in Materials and Methods.

**Figure 2.** Tissue activity curve for putamen. After $[^{18}F]$SP injection, 39 sequential PET scans were collected over 3 hr. The circles represent regional PET measurements of radioactivity averaged from the left and right putamen over the 3 hr. The measurements were cross-calibrated with the well counter used to measure blood radioactivity and then decay-corrected to time of radioligand injection. The solid curve represents the best fit of the tracer kinetic model equations to the observed tissue activity data. This model represents the behavior of $[^{18}F]$SP after injection within the field of view of the PET. The parameter estimation technique determines the optimal values of the unknown variables that yield the best fit of the model to the observed data. Each of the parameter estimations in this study converged to a single optimal solution.
estimate (Mintun et al., 1984; Perlmutter et al., 1986). The uncertainty or greater variance of the estimates for the dissociation rate constant limits the detection of statistical differences between groups.

Limitations imposed by potential radiation exposure of subjects and reduced brain penetration of $^{18}$FSP, as compared with other more promising radioligands (Moerlein et al., 1995), reduce the signal-to-noise ratio of PET-based measurements, which tends to increase the variance of the estimated unknown binding variables. To reduce the variance of the estimates, we combined data from the left and right putamen, thus doubling the regional counts to improve signal-to-noise by ~40%. This compromise obfuscates any potential side-to-side differences in a seemingly unilateral condition, such as hand cramp. However, numerous other physiological measurements in hand cramp patients have shown bilateral abnormalities (Panizza et al., 1989, 1990; Tempel and Perlmutter, 1993; Chen et al., 1995; Van Der Kamp et al., 1995), and many patients progress to bilateral hand cramp. Of course, there is no compelling reason to suspect that the patients with bilateral facial dystonia have a unilateral brain abnormality. Thus, we believe that this is a reasonable compromise, given the nature of the data.

Our findings are not likely to be affected by previous treatment of dystonia. Most hand cramp patients had not been treated before the PET, although most blepharospasm patients had previous local injections of botulinum toxin A but were not exposed to oral drugs (Table 1). The direct effects of the toxin probably are limited to the periphery, with blockade of presynaptic release of acetylcholine at the neuromuscular junction (Hamian and Walker, 1994) and minimal penetration of the blood–brain barrier (Black and Dolly, 1987). Although the numbers are small, we did not find a statistical difference in the combined forward rate constant between those patients treated with botulinum versus those not previously treated ($p > 0.2$). The effects of oral medications are not likely to have influenced these findings either. We compared the combined forward rate constant in dystonic patients treated only with botulinum or aspirin ($n = 9$) with normals meeting the same criteria ($n = 8$), and the CFRC was still lower for the dystonics (0.209 ± 0.058), as compared with the normals (0.270 ± 0.142).

**DISCUSSION**

We found decreased $^{18}$FSP binding in putamen in patients with facial or hand dystonia, the first demonstration of a receptor

| Table 2. Measured variables used in tracer kinetic modeling |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                             | Cerebellar CBF (ml/[100 gm min]) | Cerebellar CBV (ml/100 gm) | Putaminal CBF (ml/[100 gm min]) | Putaminal CBV (ml/100 gm) |
| Dystonics                   |                             |                             |                             |                             |
| mean                        | 71                          | 2.8                         | 80                          | 4.6                          |
| ± SD                        | 15                          | 1.0                         | 15                          | 1.5                          |
| (n = 21)                    |                             |                             |                             |                             |
| Normals                     |                             |                             |                             |                             |
| mean                        | 69                          | 2.3                         | 82                          | 4.7                          |
| ± SD                        | 10                          | 0.7                         | 14                          | 1.2                          |
| (n = 12)                    |                             |                             |                             |                             |

There were no statistically significant differences between dystonics and normals in any of these variables. CBV, Cerebral blood volume; CBF, cerebral blood flow; $f_1$ is a dimensionless ratio. CBF and CBV were measured with PET and $^{15}$O-labeled water and carbon monoxide, respectively. The free fraction of $^{18}$FSPiperone in arterial blood was measured using a microcentrifuge technique, as described in Materials and Methods.

| Table 3. PET measurements of $^{18}$Fspiperone binding in putamen: variables determined with parameter estimation and the tracer kinetic model |
|-----------------------------|-----------------------------|-----------------------------|
|                             | Free fraction in tissue ($f_2$) | Cerebellar PS (sec$^{-1}$) | Putaminal PS (sec$^{-1}$) | Putaminal dissociation rate constant (sec$^{-1}$) | Putaminal combined forward rate constant (sec$^{-1}$)$^*$ |
| Dystonics                   |                             |                             |                             |                             |                             |
| Mean                        | 0.0053                      | 0.038                       | 0.051                       | 0.00013                     | 0.20                        |
| ± SD                        | 0.0017                      | 0.0139                      | 0.016                       | 0.00007                     | 0.07                        |
| Mean COV                    | 3.3%                        | 4.4%                        | 3.4%                        | 68%                         | 29%                         |
| ± SD COV                    | 0.9%                        | 1.0%                        | 0.9%                        | 29%                         | 11%                         |
| (n = 21)                    |                             |                             |                             |                             |                             |
| Normals                     |                             |                             |                             |                             |                             |
| Mean                        | 0.0060                      | 0.036                       | 0.049                       | 0.00017                     | 0.28                        |
| ± SD                        | 0.0034                      | 0.0093                      | 0.012                       | 0.00011                     | 0.14                        |
| Mean COV                    | 3.4%                        | 4.5%                        | 4.3%                        | 80%                         | 43%                         |
| ± SD COV                    | 1.1%                        | 0.9%                        | 1.2%                        | 21%                         | 24%                         |
| (n = 12)                    |                             |                             |                             |                             |                             |

$^* p < 0.05$ comparing dystonics to normals with two-tailed $t$ test. There were no other significant differences between dystonics and normals. Mean COV, The mean of the SD of the variable estimate for each subject divided by the value of the estimated variable (this reflects the confidence of each individual value); ± SD COV, the SD of all of the subjects’ COVs; PS, permeability surface area produced for $^{18}$Fspiperone at the blood–brain barrier. $f_1$ is a dimensionless ratio. These variables were calculated using sequential PET measurements of regional radioactivity, PET measurements of regional CBF and CBV, blood measurements of the free fraction of $^{18}$Fspiperone in blood, and sequential measurements of total radioactivity and radiolabeled metabolites of $^{18}$Fspiperone in arterial blood with a three compartment model that represents the in vivo behavior of $^{18}$Fspiperone after interventive injection. These variables were calculated for a 1 cc tissue volume.
abnormality in idiopathic dystonia. This has important implications for the pathophysiology of dystonia as well as for the function of the basal ganglia.

Our findings must be interpreted cautiously, because \(^{18}F\)SP-specific binding is relatively nonselective. \(^{18}F\)SP-specific binding in the nonhuman primate putamen comprises \(~74\%\) to \(D_2\)-like and \(26\%\) to serotonergic \(S_2\) sites (Perlmutter et al., 1991). Furthermore, because \(^{18}F\)SP binds to \(D_2\)-like receptors, \(^{18}F\)SP binding could reflect a change in \(D_2\) or \(D_3\)-specific sites. \(D_4\) binding sites are less likely to be relevant, because they are much less numerous in primate putamen (Seeman et al., 1993).

Others have found reduced dopaminergic activity in dystonia consistent with the interpretation that reduced \(^{18}F\)SP binding reflects a change in \(D_2\)-like binding. For example, Playford et al. (1993) found a 15\% mean reduction of \(^{18}F\)dopa uptake in putamen (and not in caudate) in familial idiopathic dystonia. Others found decreased CSF homovanillic acid (HVA), a major metabolite of CNS dopamine, in one of two patients with cranial dystonia, suggestive of decreased dopamine turnover (Ashizawa et al., 1980), reduced dopamine in GPe (Jankovic et al., 1987) in one patient with cranial dystonia, and reduced striatal dopamine in one of two patients with generalized dystonia (Hornykiewicz et al., 1986). In dopa-responsive dystonia (DRD) there is a remarkable symptomatic response to levodopa. The more common autosomal dominant DRD is associated with a deficiency of an enzyme required for biosynthesis of a cofactor for tyrosine hydroxylase, the rate-limiting enzyme for dopamine production (Nygaard, 1995). The less common autosomal recessive form of DRD is caused by a defect in tyrosine hydroxylase (Knappska et al., 1995). Furthermore, acute blockade of \(D_2\)-like receptors with neuroleptics may produce acute dystonic reactions (Garver et al., 1976; Kolbe et al., 1981; Rupniak et al., 1986). Some parkinsonian patients develop dystonia as an early symptom, suggesting that dystonia may result from deficient dopaminergic transmission, because striatal dopamine deficiency produces parkinsonism (Wooten and Trueman, 1989). Similarly, some baboons develop a transient dystonic phase after intracarotid N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) injection has reduced striatal dopamine levels by \(>90\%\) (Perlmutter et al., 1993). Because most people with Parkinson’s disease (PD) do not have dystonia, there must be a difference between the nature of the striatal dopamine deficiency in parkinsonism and dystonia. Parkinsonism is associated with severe striatal dopamine deficiency and presumed secondary dysfunction at both \(D_1\)-like and \(D_2\)-like dopamine receptors, whereas we suggest a selective dysfunction of \(D_2\)-like mediated function in dystonia.

If decreased dopaminergic transmission in putamen produces dystonia, how does this fit with current models of basal ganglia function? One model describes multiple cortical–striato–pallido–thalamic–cortical loops with the cortical striate projection fibers of the motor loop predominantly targeting putamen (Alexander et al., 1986; Alexander and Crutcher, 1990; Gerfen et al., 1990; Gerfen, 1992). From there, two major pathways lead to the internal segment of the pallidum (GPI): (1) the direct pathway via inhibitory GABAergic fibers connecting striatum and GPI and (2) the indirect pathway, including inhibitory GABAergic neurons from striatum to the external segment of pallidum (GPE), inhibitory neurons projecting from GPe to subthalamic nucleus (STN), and excitatory neurons projecting from STN to GPI. Both the direct and indirect pathways converge on GPI, which then sends inhibitory GABAergic neurons to ventral anterior thalamus that projects via excitatory neurons to cortical areas, including premo-
involuntary movements in other parts of the body. Clinically, this is typical of dystonia, particularly when it first begins. At that time, involuntary postures and muscle spasms may occur only during a specific motor activity and not at rest. The involuntary spasms spread as the movement persists with the loss of “surround inhibition” (Mink and Thach, 1993). This commonly is seen in writer’s cramp, because the muscle spasms tend to spread from hand to wrist to arm as writing persists (Sheehy and Marsden, 1982). Under such circumstances, we propose that the “braking action” of the basal ganglia, important for inhibition of excessive movements, has gone awry.

Our findings do not explain all types of dystonia. People with PD may develop dystonia not only as an early manifestation of the disease but also in at least three different patterns associated with dopa replacement therapy. Dystonia may occur commonly in the lower extremities when the plasma dopa levels are low but also may occur when plasma levels peak. Finally, dystonia may occur as the effect of an individual dose begins or as it diminishes (Poewe et al., 1988). Proposing pathophysiological mechanisms for these three patterns of dystonia is difficult, given the uncertainty of the relative influence of the different dopamine receptor subtypes on subsequent activities of the direct and indirect pathways.

In summary, we have found a decrease in $^{[18F]}$SP binding in the putamen of patients with idiopathic adult-onset focal dystonias affecting the face or hand. There was no significant difference between patients with hand and facial dystonia, suggesting that there may be a common mechanism producing both conditions, consistent with the clinical impression that they share a similar pathophysiology (Jankovic et al., 1991). However, because we used large VOIs, our data do not exclude the possibility that different areas of putamen may have different degrees of decreased binding in the two types of dystonia. We propose that the pathophysiology of these dystonias reflects decreased activity in the $D_2$-like mediated function of the indirect pathway of the motor circuit in the basal ganglia. Additional studies with more specific radioligands should help to clarify the nature of this abnormality further. It also would be interesting to determine the relative activity of the putametal neurons projecting directly to GPe versus those projecting to GPi in animal models of dystonia.

REFERENCES


Gerfen CR (1992) The neostriatal mosaic: multiple levels of compartmental organization. Trends Neurosci 15:133–139.


