Do Dyskinesia and Pain Share Common Pathophysiological Mechanisms in Parkinson’s Disease?

Shen-Yang Lim, FRACP, Michael J. Farrell, PhD, Stephen J. Gibson, PhD, Robert D. Helme, PhD, FRACP, FFPMANZCA, Anthony E. Lang, MD, FRCPC, and Andrew H. Evans, FRACP

Abstract: Plastic changes within the striatum resulting from pulsatile dopaminergic stimulation are thought to lead to dyskinesia in patients with Parkinson’s disease (PD). The basal ganglia play a role in processing pain. We hypothesized that the plastic changes that lead to dyskinesia may also mediate pain responses. Our objective was to compare the change in pain sensitivity after levodopa administration between stable responders, fluctuators without dyskinesia, and dyskinetic patients, and to compare pain sensitivity between PD and healthy subjects. Fifty patients with PD were assessed with cold water immersion after overnight withdrawal of dopaminergic medications and again after a standard levodopa challenge, and carefully classified into stable responder (n = 12), fluctuator (n = 15), and dyskinetic (n = 23) groups. Twenty age-matched controls were also tested. PD patients “off”-medication had a lower threshold (P = 0.016) and tolerance (P < 0.0001) to cold pain compared to controls. After levodopa administration, dyskinetic patients experienced a large increase in cold pain threshold (48%) and tolerance (66%) that was absent in stable responders (P = 0.038 and P = 0.015); there was no significant difference in pain sensitivity change scores between the fluctuator and either the stable responder or dyskinetic groups. Our results suggest that dyskinesia and pain may share common pathophysiological mechanisms in PD.

Key words: Parkinson’s disease; parkinsonian pain; central pain; dyskinesia; sensitization

BACKGROUND

Approximately 50% of patients with Parkinson’s disease (PD) experience pain.1 The pain has been described in various categories1 but often occurs on the side with worse parkinsonism.2 The pathogenesis of PD-related pain is unclear, but in some patients it appears to relate to central dopaminergic mechanisms and improves in response to dopaminergic medications.3,4

Pain often fluctuates with parkinsonian motor disability1,4,5 and cross-sectional studies show that pain is more common in patients experiencing levodopa-induced dyskinesia (LID).2,6 Younger age at PD onset is a risk factor for chronic pain1,7 and younger patients are also prone to developing LID.8

Acute L-dopa challenges in PD patients have been reported to have no effect9,10 or to markedly increase pain threshold and tolerance.11–13 We postulated that the presence of LID may be an important factor in accounting for these mixed results. Our objective was to compare the change in pain sensitivity after L-dopa administration between stable responders, fluctuators without dyskinesia, and dyskinetic patients, and to compare pain sensitivity between PD and healthy subjects.

*Correspondence to: Dr. Andrew H. Evans, Department of Neurology, Royal Melbourne Hospital, Parkville 3050, Victoria, Australia E-mail: ae@pobox.com

"Potential conflict of interest: SYL was supported by a grant from Novartis Australia Pty Ltd. The other authors report no conflicts of interest.”

Received 10 October 2007; Accepted 2 April 2008

Published online 15 August 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22111

Vol. 23, No. 12, 2008, pp. 1689–1695
© 2008 Movement Disorder Society
METHODS

Subjects

A convenience sample of 50 patients with clinically diagnosed PD without dementia or clinical evidence of peripheral neuropathy were studied. Twenty healthy subjects matched for age (mean 63 ± 2) and sex (8 males, 12 females) were also studied. Written informed consent was obtained from each subject and the protocol was approved by the human research ethics committee of the Royal Melbourne Hospital.

Procedure

Subjects were asked to avoid taking analgesics on the day before, and of, testing. PD patients were examined in the morning after withdrawal of dopaminergic medications for at least 12 hours. Baseline (t1) assessments included the Unified PD Rating Scale (UPDRS), McGill Pain Questionnaire (MPQ), modified to include the question: “Do you commonly notice pain in association with your Parkinson disease?” Gracely box scales 14 and cold water immersion, after which a single dose of oral l-dopa was administered. The dose given was the patient’s usual morning dose plus an additional 50 mg. Patients were pretreated with domperidone. Cold water immersion was repeated once patients had reached a full “on” state at least 60 min after L-dopa (t2) and again at 6 hours post-L-dopa (t3). The hands were immersed in an ice-water bath (water temperature 1.0–2.0°C); on each occasion, the right hand was tested first followed by the left. Patients were instructed to say “yes” immediately on feeling a change in sensation from cold to “faintly painful.” The duration of time in seconds between hand immersion and when this occurred was recorded as the cold pain threshold. The hand was kept immersed until it became “intolerable” or 180 seconds had elapsed; whichever occurred first defined the cold pain tolerance. Patients were told that a maximum of 3 min would be allowed and if they reached this cutoff they would be asked to withdraw the hand; otherwise they were not privy to their threshold or tolerance results. Testing was carried out in a private room and no external cues were provided. Cold water immersion was administered only once in control subjects (right hand, then left hand), without L-dopa challenge, as L-dopa does not significantly change response to cold pain in this group. 11 PD patients were retested with the UPDRS motor examination (part III) when “on” (t2). Dyskinesia severity was scored by SYL (a movement disorders neurologist) using a scale modified from the Abnormal Involuntary Movements Scale (AIMS) and the Goetz scale, similar to previously described. 15 The AIMS was scored in the neck, trunk and each limb during: sitting still for 1 min, performing mental subtractions, and putting on a coat. Gracely scores were assessed every 30 min for 6 hours post-L-dopa by asking patients to rate spontaneous pain “right now” using box scales ranging from 0 to 20 for increasing pain intensity and unpleasantness, anchored by psychophysically determined word descriptors. 14 Pain that was clearly nociceptive in origin was not included. The Geriatric Depression Scale (GDS) and a wearing-off questionnaire were administered in the “on”-medication state; this questionnaire has been shown to be more sensitive than routine clinical assessment in detecting response fluctuations. 16 Patients were classified as “fluctuators” if they endorsed one or more items on the questionnaire, but did not exhibit dyskinesia during the L-dopa challenge. Patients were classified as “dyskinetics” if choreiform dyskinesia was judged by SYL to be present during the L-dopa challenge and independently confirmed from video-recordings by a blinded movement disorders neurologist (AHE). Patients who did not endorse any wearing-off symptoms and did not exhibit any dyskinesia were classified as “stable responders.” To ensure consistency, SYL sat with patients for the duration of the L-dopa challenge and administered all tests. Dopaminergic medication doses were calculated as L-dopa equivalent units (LEU), as previously described. 17

Statistical Analysis

SPSS version 12.0.1 was used. Mean values with standard error are reported. Significance was set at 0.05. One-way ANOVA was used to look for between-group differences in clinical characteristics. 2 χ test for independence was used to explore the relationship between group membership and categorical variables. Repeated-measures ANOVA was conducted to evaluate the impact of group membership, side with worse parkinsonism and time after L-dopa administration on pain threshold and tolerance. T-tests were used for post-hoc analyses. Pearson’s test for correlations was used to explore the relationship between potential explanatory variables and cold pain threshold and tolerance at t1, and percent change in threshold and tolerance from t1 to t2; to account for multiple comparisons, significance was set at 0.01.

RESULTS

Clinical Characteristics of PD Patients

Fifty patients were tested (Table 1). Dyskinetic patients had longer disease duration and higher daily
LEU. Mean GDS was 8 ± 1; 13 patients (26%) scored ≥10, indicating possible depression.

McGill Pain Questionnaire

Twenty-four patients reported commonly experiencing pain which they attributed to PD (48%). This proportion was 17, 60, and 57% for the stable responder, fluctuator, and dyskinetic groups (P = 0.04).

Healthy Controls

Cold pain threshold and tolerance were 22 ± 8 and 102 ± 16 in this group, compared with 10 ± 1 and 47 ± 7 in the overall PD patient sample (i.e., all three PD groups combined) at t1 [t(67) = 2.47, P = 0.016 for threshold; t(68) = 3.77, P < 0.0001 for tolerance]. A threshold result was not available for one control subject in whom cold immersion did not produce even faint pain after 3 min.

1-Dopa Challenge—Motoric Response

Mean UPDRS III “on,” Goetz and modified AIMS scores are given in Table 1. The mean t1 to t2 change in UPDRS III score was −4 ± 1 (−13%), −7 ± 1 (−26%) and −12 ± 2 (−39%) in the stable responder, fluctuator, and dyskinetic groups; the difference between the stable responder and dyskinetic groups was significant [F(2,47) = 5.29, P = 0.008; t(33) = −2.6, P = 0.01]. Six out of 23 patients were not aware of dyskinesia prior to the day of testing.

1-Dopa Challenge—Spontaneous Pain

Spontaneous pain that was not clearly nociceptive in origin diminished with L-dopa challenge (we defined this as a change of ≥6 points in the Gracely score for pain intensity and unpleasantness) in 21 patients (42%). This proportion was 17, 53, and 48% for the stable responder, fluctuator, and dyskinetic groups (P = NS).

1-Dopa Challenge—Evoked Pain (Cold Water Immersion)

Mean threshold and tolerance for each group at the three timepoints are shown in Tables 2 and 3. Using repeated-measures ANOVA, there was a time main effect for both threshold [F(2,94) = 3.87, P = 0.024] and tolerance [F(2,94) = 4.67, P = 0.012] and a side main effect for tolerance [F(1,47) = 4.18, P = 0.047] but not threshold. Importantly, there was a group-by-time interaction for both threshold [F(4,94) = 2.61, P = 0.041] and tolerance [F(4,94) = 2.61, P = 0.041], indicating a between-group difference in the change in threshold and tolerance in response to L-dopa (see Fig. 1). There was no interaction between side, time, and group.

The side main effect was due to lower mean tolerance on the side with worse parkinsonism (43 ± 6 vs. 53 ± 8). Post-hoc testing revealed that the time main effect was due to higher threshold and tolerance at t2 compared to t1 and t3 (P < 0.05). The group-by-time interaction for threshold was due to the dyskinetic
group having a greater percent change in threshold from t1 to t2 compared to stable responders (48 ± 12 vs. −4 ± 11, \( P = 0.038 \)), but the difference in percent change scores from t2 to t3 (−20 ± 7 vs. −1 ± 10) did not reach significance. The group-by-time interaction for tolerance was due to the dyskinetic group having a greater percent change in tolerance from t1 to t2 compared to stable responders (66 ± 20 vs. −14 ± 5, \( P = 0.015 \)), as well as from t2 to t3 (−27 ± 6 vs. −2 ± 5, \( P = 0.036 \)). The percent change scores for threshold (37 ± 19 from t1 to t2, −8 ± 11 from t2 to t3) and tolerance (28 ± 18 from t1 to t2, −13 ± 8 from t2 to t3) in fluctuators did not differ significantly from those of either the stable responder or dyskinetic groups.

There was a lack of correlation (using a threshold for significance at \( P < 0.01 \)) between age, disease severity (as defined by the UPDRS III “off” score) or disease duration, and baseline pain threshold and tolerance. There was also a lack of correlation between daily LEU, severity of dyskinesia or percent change in upper limb tremor score (derived from items 20 and 21 of the UPDRS) from t1 to t2, and the t1 to t2% change in threshold and tolerance. The percent change in UPDRS III score from t1 to t2 correlated significantly with the t1 to t2% change in threshold (\( r = 0.39, P = 0.005 \)), but not with the t1 to t2% change in tolerance (\( r = 0.27, P = 0.056 \)). There was no significant difference in the t1 to t2% change in threshold and tolerance when dyskinetic patients were dichotomized around the median value for percent change in UPDRS III score (37%), nor was there a difference in threshold and tolerance change scores when comparing the group with versus the group without reduction in spontaneous pain during L-dopa challenge.

**DISCUSSION**

Previous reports have indicated that PD patients in the “off” medication state are more sensitive to pain compared to healthy subjects.\(^9\,11\) The present data confirm these findings. Importantly, we found that after L-dopa administration, dyskinetic patients experienced a large increase in cold pain threshold (48%) and tolerance (66%) that was absent in stable responders.

Disease characteristics (presence or absence of dyskinesia), as well as differences in the modalities of pain tested, may therefore explain the mixed results in the literature regarding the effect of L-dopa on experimental pain in PD.\(^9\,\,13\) In keeping with the known evo-

### Table 2. Cold pain threshold (seconds) across the 3 timepoints

<table>
<thead>
<tr>
<th>Group</th>
<th>Side</th>
<th>“Off”-medication (t1)</th>
<th>Post-L-dopa (t2)</th>
<th>6 hours post-L-dopa (t3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable Responders</td>
<td>More</td>
<td>6.6 ± 1.4</td>
<td>6.2 ± 1.0</td>
<td>6.2 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>Less</td>
<td>8.6 ± 1.6</td>
<td>7.3 ± 1.4</td>
<td>6.8 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>7.6 ± 1.5</td>
<td>6.7 ± 1.1</td>
<td>6.5 ± 1.1</td>
</tr>
<tr>
<td>Fluctuators</td>
<td>More</td>
<td>9.7 ± 2.4</td>
<td>10.8 ± 2.6</td>
<td>9.6 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>Less</td>
<td>8.3 ± 1.6</td>
<td>11.5 ± 2.1</td>
<td>9.1 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>9.0 ± 1.9</td>
<td>11.2 ± 2.3</td>
<td>9.3 ± 1.9</td>
</tr>
<tr>
<td>Dyskinetics</td>
<td>More</td>
<td>10.6 ± 1.7</td>
<td>21.2 ± 6.4</td>
<td>11.6 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>Less</td>
<td>11.4 ± 1.7</td>
<td>16.2 ± 2.9</td>
<td>12.5 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>11.0 ± 1.7</td>
<td>18.7 ± 4.4</td>
<td>12.0 ± 2.1</td>
</tr>
</tbody>
</table>

More = Side more affected by parkinsonism.
Less = Side less affected by parkinsonism.

### Table 3. Cold pain tolerance (seconds) across the 3 timepoints

<table>
<thead>
<tr>
<th>Group</th>
<th>Side</th>
<th>“Off”-medication (t1)</th>
<th>Post-L-dopa (t2)</th>
<th>6 hours post-L-dopa (t3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable Responders</td>
<td>More</td>
<td>26.9 ± 4.0</td>
<td>23.1 ± 3.3</td>
<td>21.8 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>Less</td>
<td>41.6 ± 13.9</td>
<td>34.5 ± 13.5</td>
<td>36.0 ± 13.4</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>34.3 ± 8.6</td>
<td>28.8 ± 7.6</td>
<td>28.9 ± 7.5</td>
</tr>
<tr>
<td>Fluctuators</td>
<td>More</td>
<td>48.7 ± 14.6</td>
<td>57.7 ± 16.9</td>
<td>45.9 ± 14.7</td>
</tr>
<tr>
<td></td>
<td>Less</td>
<td>56.5 ± 16.8</td>
<td>65.8 ± 18.6</td>
<td>49.4 ± 14.9</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>52.6 ± 15.3</td>
<td>61.7 ± 17.7</td>
<td>47.7 ± 14.8</td>
</tr>
<tr>
<td>Dyskinetics</td>
<td>More</td>
<td>41.5 ± 7.7</td>
<td>80.6 ± 14.6</td>
<td>42.7 ± 9.6</td>
</tr>
<tr>
<td></td>
<td>Less</td>
<td>57.3 ± 12.4</td>
<td>76.2 ± 14.0</td>
<td>56.9 ± 11.7</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>49.4 ± 9.3</td>
<td>78.4 ± 13.4</td>
<td>49.8 ± 10.0</td>
</tr>
</tbody>
</table>

More = Side more affected by parkinsonism.
Less = Side less affected by parkinsonism.
Time:

PD induces plastic changes in basal ganglia circuits that can lead to the development of pharmacological sensitization and tolerance. Augmentation of motor response and dyskinesia are thought to be sensitization phenomena and wearing-off fluctuations result from the development of tolerance. Because the basal ganglia plays a role in processing nociceptive information, we hypothesized that plastic changes may also occur in pain responses in patients with dyskinesia. Parkinsonian monkeys with dyskinesia display pathological metabolic activity in limbic and associative-related structures and not simply in motor parts of the basal ganglia. In addition to its role in pain modulation, the mesolimbic dopamine system mediates reward and motivation, and sensitization of this system was recently demonstrated in a group of PD patients who compulsively overuse dopaminergic drugs and exhibit disabling dyskinesia. Taken together, we postulate that the increased pain threshold and tolerance observed in dyskinetic patients when “on” may reflect a process of sensitization to the analgesic and motivational effects of L-dopa. This is consistent with the finding that L-dopa reduces abnormal cold pain-induced overactivation of cortical areas involved in processing sensory-discriminative and affective-motivational dimensions of pain in PD patients. A role for movement-related motor cortex modulation of the somatosensory system is also possible; motor cortex stimulation in primates inhibits the homotopic region of the somatosensory cortex, and is a treatment for intractable neuropathic pain. Interestingly, overactivation of motor cortical areas (attributed to overactivity of basal-
ganglia thalamocortical outflow) has been shown in PD patients presenting mild dyskinesia after L-dopa administration.43

This was an intensive observational study monitoring responses for 6 hours after administration of L-dopa. The careful classification of patients into stable responder, fluctuator, and dyskinetic groups is a major strength of this study. In a routine clinical setting, under-recognition of mild dyskinesia and early response fluctuations is common, in part because of the need to rely on patients’ understanding and awareness of these phenomena.44

Several limitations need to be pointed out. First, only PD patients (not control subjects) were pretreated with domperidone, a peripheral dopamine2-receptor antagonist, to avoid peripheral dopaminergic side effects of L-dopa. There is no evidence to indicate that it has pain-promoting properties, but we cannot completely exclude this possibility. Second, for patient tolerability, only one modality of pain was tested; cold water immersion was chosen because cold pain threshold had only one modality of pain was tested; cold water immersion was chosen because cold pain threshold had previously demonstrated sensitivity to change after L-dopa challenge in PD patients.11 Third, although previous studies suggest that pain is more common in dyskinetic patients,26 we did not find dyskinetic patients to be more sensitive to or less tolerant of pain when “off”-medication compared to stable responders. The fact that almost all our dyskinetic patients had mild dyskinesia (and mild wearing-off – they performed no worse in the UPDRS motor assessment when “off” medication compared to stable responders) may be the most parsimonious explanation for this result. Fourth, it could be argued that normalization of hyperalgesia contrasts with development of (pathological) dyskinesia and argues against a common pathophysiology. Yet, augmentation of motor response to L-dopa (i.e., a greater degree of shift towards normal motor function) is also closely linked with dyskinesia and may reflect, at least in part, a process of pharmacological sensitization induced by chronic L-dopa treatment. It has even been posited that motor benefit and dyskinesia may not be dissociable.26 Finally, although no external cues were provided to subjects during cold water immersion, in accordance with the study protocol, it should be acknowledged that all tests were administered by SYL, who was not blinded to the study hypothesis.

In conclusion, the present data demonstrating improved pain response to L-dopa in patients with dyskinesia have potential implications for understanding pain mechanisms in PD and suggest that dyskinesia and pain may share common pathophysiological mechanisms in PD.

Acknowledgments: We thank the participants involved in this study for their time and patience. SYL was supported by the Royal Melbourne Hospital Victor Hurley Fund.

REFERENCES