Citalopram Enhances Action Inhibition Systems in Parkinson’s Disease

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Introduction

Impulsivity in Parkinson’s disease (PD) is highlighted by the severity of impulse control disorders (ICDs). However, subtler impulsivity is common even in the absence of ICDs and is likely to be multifactorial. In addition to dopaminergic ‘overdose’ and structural changes in the frontostral circuits for motor control, we propose that changes in serotonergic projections to the forebrain also exacerbate the impairment of response inhibition. Enhancing central serotonin transmission with selective serotonin reuptake inhibitors (SSRIs) might therefore provide adjunctive treatment for behavioural impulsivity in Parkinson’s disease.

We investigated whether the SSRI citalopram reduces impulsivity and enhances neurocognitive systems mediating response inhibition in Parkinson’s disease. We studied two forms of inhibition: (1) restraint, using NoGo events; and (2) cancellation, in terms of the Stop-Signal Reaction Time (SSRT). There is strong preclinical evidence that serotonin plays an important role in regulating action restraint. In contrast, the link between serotonin and action cancellation is less well established. We tested three specific hypotheses.

Hypothesis 1: PD impairs both action restraint and cancellation.

Hypothesis 2: The effect of citalopram on behavioural performance depends on patients’ disease severity.

Hypothesis 3: The behavioural effect relates to the enhancement of inferior frontal cortical activation following citalopram.

Methods

Participants

• PD patients (N=21): right-handed.
• Controls (N=20): right-handed; no history of neurological or psychiatric disorders.

Table 1: Demographic data, clinical features and neuropsychological measures (means, SDs and p values of two-sample t tests)

<table>
<thead>
<tr>
<th>Items</th>
<th>PD</th>
<th>Control</th>
<th>P (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (M,F)</td>
<td>64.8 (6)</td>
<td>65 (6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>MMSE</td>
<td>29 (1)</td>
<td>29 (1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Years of disease</td>
<td>11 (5)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>UPDRS-III motor</td>
<td>21 (8)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr</td>
<td>1.9 (0.4)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Levodopa equivalent dose (LED, mg/day)</td>
<td>632.6 (310.6)</td>
<td>--</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>9.9 (5.5)</td>
<td>3.8 (3.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Simple reaction time (ms)</td>
<td>294 (53)</td>
<td>314 (72)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Choice reaction time (ms)</td>
<td>353 (47)</td>
<td>392 (70)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Drug and Design

• Double-blind randomised placebo-controlled crossover design
• Patients (sessions 26 days apart): 30mg citalopram (CIT) and placebo (PLA)
• Controls (one session): on drug
• CIT: SSRIs that increases extracellular cortical serotonin 4 fold
• Task and Stimuli: An integrated Stop-Signal and NoGo paradigm with 360 Go trials (75%), 40 NoGo trials (8%) and 80 Stop-Signal trials (SS, 17%, with ~50% accuracy).
• Go: Subject responded to a left/right black arrow (1000ms) with their right hand.
• NoGo: Subjects withheld a response to a red arrow (1000ms) and auditory tone.
• SS: A button press was cued by the left/right black arrow but signalled to stop by a colour change (to red) and auditory tone approx. after a variable delay. An online tracking algorithm maintained approx. 50% successful inhibition.

Results

• Behaviour (Table 2 & Fig.1A): Disease effect (Hypothesis 1: control vs. PD-PLA) and drug effect (Hypothesis 2: PD under CIT vs. PLA) were examined respectively with two-sample t-tests and repeated-measures ANOVAs with disease severity, age, LED, and plasma concentration of CIT as covariates.

• fMRI (Fig.1B): General linear models estimated brain responses to correct SS, Go and NoGo trials, commission errors (SS, NoGo and Go trials), and Go omission errors. Contrast maps of SS-Go and NoGo-Go were computed for each group and compared between groups (Hypothesis 1). We focused on the RIFG which showed inhibition-related activations in controls.

• Behaviour-fMRI (Fig.1C): Parameter estimates (betas) were pooled across controls and PD-PLA to create a disease contrast map. We focused on the RIFG which showed inhibition-related activations in controls.

• CIT-induced changes of SSRT and NoGo error correlated with the changes of inferior frontal cortical activation (p < 0.05).

Conclusion

• PD impairs both action restraint and cancellation.
• Effect of citalopram on behavioural impulsivity depends on the severity of PD and individual difference in inferior frontal cortical activation.

This study indicates the need for patient stratification in clinical trials and serotonergic treatments of impulsivity in PD.

References and Funding


This work was primarily funded by...