Letters to the Editor

Reply to: PET studies and physiopathology of motor fluctuations in Parkinson’s disease

Chong S. Lee and Ajit Kumar

1Pacific Parkinson’s Research Centre, Vancouver Hospital and Health Sciences Centre, 2Departments of Physics and Astronomy and 3TRIUMF, University of British Columbia, Vancouver, BC, Canada
Correspondence to: Dr Chong S. Lee, Pacific Parkinson’s Research Centre, M36, Purdy Pavilion, UBC Hospital, 2221 Wesbrook Mall, Vancouver, BC V6T 2B5, Canada. E-mail: cslee@interchange.ubc.ca
DOI: 10.1093/brain/awh229

We agree that the most interesting and unexpected finding in this study is the shorter latency to the onset of levodopa response on the less affected side than on the more affected side. This shorter latency to the onset on the less affected side reflects our consistent observations that the time–response curve of tapping rates on the more affected side appears as a down-shift of the curve on the less affected side, accounting for later onset and earlier offset on the more affected side.

The most characteristic changes in response fluctuations to levodopa are the greater magnitude and further left-shift of the time–response curve (with earlier onset, peak response time and decay) (Nutt, 1990). Although mechanisms of these response changes are not clearly understood, current evidence suggests that response fluctuations can be attributed to both presynaptic and postsynaptic factors. However, interpretation of data from clinical and pharmacological studies exploring mechanisms of response fluctuations is notoriously complicated, largely because of the difficulty in (i) separating the effects of dopamine (DA) terminal loss and drug treatment, and (ii) separating presynaptic and postsynaptic effects. For instance, since Parkinson’s disease is a slowly progressive degenerative disorder, a strong correlation exists between the duration of disease and the duration of drug treatment. Thus, longitudinal study does not solve the problem in delineating the effects of DA terminal loss from the effects of drug treatment. Furthermore, both presynaptic and postsynaptic factors are influenced by either DA terminal loss or drug treatment (Gerfen et al., 1990; Lee et al., 2000; Guttman et al., 2001). Therefore, comparisons of pharmacodynamic parameters of levodopa and in vivo [$^{11}$C]dihydroetetrabenazine (DTBZ) PET measures between the two sides in patients with asymmetrical Parkinson’s disease provide a unique opportunity to gain insight into the role of DA terminal loss in the development of response fluctuations. This is because DTBZ is a presynaptic marker for in vivo PET studies, which is relatively resistant to regulatory changes (Vander Borght et al., 1995), and the drug treatment is not a variable in side-to-side comparisons of patients with asymmetrical Parkinson’s disease.

We recognized that our finding of longer latency to onset on the more affected side was at variance with observations in cross-sectional and longitudinal studies. To explain this discrepancy, we analysed our data carefully and compared them with published data in the literature, detailed in the discussion of our report (Kumar et al., 2003). Sohn and colleagues reported, in a cross-sectional study, that symptom duration correlated significantly and negatively with the peak response time (i.e. latency to the peak response) of levodopa, but not with that of apomorphine (Sohn et al., 1994), in agreement with other cross-sectional studies (Colosimo et al., 1996). The authors suggested that the presynaptic factor plays a role in determining the peak response time of levodopa based on its correlation with symptom duration and the disparity between apomorphine and levodopa responses. However, this conclusion requires scrutiny. First, symptom duration, which was used as an index of disease severity, also correlates with treatment duration. Using the Hoehn and Yahr staging as another marker for disease severity would not be helpful because of the correlation between disease severity and symptom duration. Secondly, a shorter peak response time of levodopa, but not of apomorphine, was used as evidence for the pathogenic role of DA terminal loss in the response fluctuations. However, postsynaptic factors as well as presynaptic factors may influence the kinetics of DA in the striatum (Bordet et al., 1997; Thompson et al., 2000; Zapata and Shippenberg, 2002) and hence the pharmacological actions of levodopa, but not apomorphine. Thus, it is more likely that the disparity between our findings and those of Sohn and colleagues reflects treatment effects. This view is consistent with the finding of no significant difference between the more and less affected arms despite a 30% reduction in the peak response time over a 4-year period (Nutt et al., 2002).

We explored this issue further by using pharmacological methods. In our study, we demonstrated evidence that the inferred EC50 was higher on the more affected side than on the less affected side (Kumar et al., 2003). In a longitudinal study, the EC50 for tapping rates increased over time without
significant changes in the magnitude (Contin et al., 1994). There was significant correlation between the EC50 and severity of symptoms, duration of disease and duration of levodopa therapy (Contin et al., 1993). If the EC50 increases, the onset of the levodopa response is expected to be delayed, rather than shortened, in accordance with our unexpected finding of longer latency to the onset on the more affected side.

Current data suggest that the magnitude is determined not only by the severity of DA terminal loss but also by the drug treatment, as evidenced by observations during drug holidays (Nutt et al., 1994). Our data showed that the magnitude on the more affected side was greater or smaller than, or similar to, that on the less affected side.

We agree with Linazasoro and Leenders’ view that the discrepancy in PET observations might result from methodological differences—using different tracers and, more importantly, the study design. We believe the disparity between cross-sectional and within-subject comparisons may well indicate the effects of treatment.

References


