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

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We read with great interest the article by Kumar and colleagues recently published in *Brain* (Kumar et al., 2003). We addressed the same problem in a somewhat different way, correlating pharmacological parameters with PET findings (Linazasoro et al., 2004). Whereas we studied nine patients with Parkinson’s disease and motor fluctuations on whom an apomorphine test and PET studies using [¹⁸F]fluorodihydroxyphenylalanine (Fdopa) and raclopride were performed, Kumar and colleagues studied differences in the motor response to a levodopa dose on both body sides of patients with asymmetrical Parkinson’s disease. These authors conclude that the development of motor fluctuations is related to both levodopa treatment and dopaminergic terminal loss, which induce changes in presynaptic and postsynaptic mechanisms. This conclusion concurs with ours as well as with previously obtained data in clinical and pharmacological investigations.

In spite of this, there are some relevant differences in the results, such as the one related to the latency of levodopa to reach its peak effect. Along with the magnitude of the clinical response, this parameter is one of the hallmarks of the short-duration response that can be considered to be the pharmacological substrate of the wearing-off phenomenon (Obeso et al., 1997). Quite unexpectedly, Kumar and colleagues found that the onset of levodopa response was delayed on the more affected side in eight out of 11 cases. This conflicts with previous data. Indeed, a virtually universal observation in clinical practice is that patients with advanced and severe Parkinson’s disease exhibit an abrupt motor response after a levodopa or apomorphine challenge, a finding also observed in pharmacological studies. Sohn and colleagues encountered a shortening of the latency that correlated with the severity of the disease (Sohn et al., 1994) and Nutt and colleagues found that latency did not differ between the more and less affected arms in a group of Parkinson’s disease patients followed for 4 years (Nutt et al., 2002). Moreover, Kumar and colleagues found a correlation of marginal significance between the asymmetry of latency to onset and the asymmetry of tetrabenazine binding in the putamen. In sharp contrast with these results, we found that latency was related to the severity of Parkinson’s disease as assessed by clinical and PET studies. Hence, latency was positively correlated with the uptake of Fdopa in the putamen and caudate, whereas it was negatively correlated with the motor UPDRS and Hoehn and Yahr stage. We also observed a positive correlation between latency to peak effect and striatal raclopride binding, suggesting that postsynaptic mechanisms are also involved in the shortening of the latency.

The second discrepancy is related to the magnitude of the motor response, which is defined as the difference between the on and off conditions assessed by the Unified Parkinson’s Disease Rating Scale (UPDRS) or by timed tests. Several pharmacological studies have demonstrated that the magnitude is higher in patients with motor fluctuations than in stable responders (Nutt et al., 2002). Also, the magnitude is greater in the more affected body side in asymmetrical Parkinson’s disease patients (Rodríguez et al., 1994). In keeping with these findings, we have shown that the magnitude of the clinical response is a direct reflection of the severity of the disease, as it was positively correlated with basal motor UPDRS and Hoehn and Yahr stage and negatively with striatal Fdopa uptake (the greater the severity of Parkinson’s disease, the lower the uptake of Fdopa and the greater the magnitude of the clinical response). By contrast, the magnitude of the motor response was similar on the more affected side compared with the less affected side in the study of Kumar and colleagues.

Perhaps these discrepancies are more apparent than real and relate to methodological differences. Besides the characteristics of the patient population, it is likely that the use of levodopa instead of apomorphine and tetrabenazine instead of Fdopa may account, at least in part, for the differences observed. First, the mechanism of action of levodopa is quite complex. It depends on the peripheral metabolism of the drug and on its conversion to dopamine. Therefore, the analysis of the motor response to a levodopa challenge is considerably more complex than the
analysis of the same response to apomorphine, which acts directly on dopamine receptors after reaching the brain independently of the digestive system. Secondly, the location of the enzymatic conversion of levodopa to dopamine is a matter of debate, but it is possible that it occurs beyond the dopaminergic nigrostriatal system. Finally, the uptake of tetrabenazine reflects the status of denervation in the nigrostriatal system in a different way to Fdopa. Other factors, such as the possible influence of compensatory mechanisms from the contralateral hemisphere, cannot be excluded.

In summary, the wearing-off phenomenon may be considered as the clinical reflection of the short-duration response. The Kumar group and ourselves have reached the conclusion that factors related to disease severity and the administration of antiparkinsonian drugs, by acting on both pre- and postsynaptic mechanisms, may be involved in the origin of these pharmacological and clinical phenomena.

References