J Neural Transm (2011) 118:1659–1660
DOI 10.1007/s00702-011-0728-0

EDITORIAL

Mechanisms underlying and medical management of L-Dopa-associated motor complications

Manfred Gerlach · Peter Riederer · Dieter Scheller

Motor complications, particularly motor fluctuations such as wearing-off, on–off phenomena, and several different types of dyskinesia such as peak-dose, diphasic, wearing-off, chorea, dystonia and athetosis (collectively called dyskinesia) seem to be an inevitable consequence of L-Dopa (L-3,4-dihydroxyphenylalanine, levodopa) therapy of patients suffering from Parkinson's Disease (Jankovic 2005; Müller and Russ 2006). However, not all patients develop dyskinesia even after long periods of treatment suggesting that specific deteriorations or adaptations occur in one group of patients but not in the other. The present understanding of the underlying mechanisms of those differences is far from being known. The stage of the illness (degree of dopaminergic degeneration and loss of nigrostriatal projections) as well as the dose and frequency of L-Dopa treatment have been considered as essential contributors to the induction and expression of the involuntary movements. Age of the patients at onset of the symptoms and the speed of progression are further aspects. The statement by Iravani and Jenner (2011, this issue), "the cause of L-Dopa-induced dyskinesia remains to be fully elucidated", seems to suggest that we are indeed only at the beginning of the understanding of the mechanisms. The knowledge on pre- and post-synaptic events and their contribution to dyskinesia as well as the role of the dopamine D1 receptor and the direct pathway, the potential adaptations of intracellular signaling cascades and patterns of gene expression changes will be extensively discussed in this issue by Iravani and Jenner (2011). Their differential occurrence under continuous or pulsatile dopaminergic treatment is highlighted in the contribution of Grünblatt et al. (2011, this issue). Amongst potential pharmacological treatments, only the weak *N*-methyl-D-aspartate (NMDA) antagonist amantadine has been proven to be clinically successful (Wolf et al. 2010). Its potential successor MRZ-8676, a novel negative allosteric modulator of subtype 5 metabotropic glutamate receptors (mGluR5) still awaits clinical confirmation (Dekundy et al. 2011, this issue). NMDA antagonists, AMPA antagonists or allosteric modulators, NR1A/2B antagonists, serotonin 5-HT_{1A} and/or 5-HT_{1B} agonists, 5-HT_{2a} antagonists, noradrenaline $\alpha 1$ antagonists, $\alpha 2$ agonists or antagonists, adenosine A_{2A} antagonists, cannabinoid antagonists or agonists, opioid antagonists or agonists, or histamine H_3 antagonists, to name just some, have been found to be active in experimental models of dyskinesia (summarized by Iravani and Jenner 2011, this issue) but did not find successful application in clinical practice yet. Some experimental observations on novel treatment opportunities are exemplified in detail by the papers of Dekundy et al. (2011, this issue); Gerlach et al. (2011a, b, this issue) (the reader is referred to the references listed in these papers). However, it still is a matter of discussion why the experimental findings hardly

M. Gerlach
Laboratory for Clinical Neurobiology,
Department of Child and Adolescent Psychiatry,
Psychosomatics and Psychotherapy, University of Würzburg,
Füchsleinstrasse 15, 97080 Würzburg, Germany

P. Riederer
Laboratory for Clinical Neurochemistry,
Department of Psychiatry, Psychosomatics and Psychotherapy,
National Parkinson Foundation Centers of Excellence
for Neurodegenerative Diseases Research,
University of Würzburg, Füchsleinstrasse 15,
97080 Würzburg, Germany

D. Scheller (✉)
Department Pharmacology of Parkinson's Disease
and Movement Disorders, CNS Research UCB Pharma S.A,
Chemin Du Foriest, 1420 Braine l'Alleud, Belgium
e-mail: dieter.scheller@ucb.com

translate into clinical application (Jenner et al. 2011, this issue). So far, the pharmacological observations suggest a rather complex contribution of the various transmitter systems and it is difficult to identify the predominant targets.

In addition to the already mentioned contributors to dyskinesia, the kinetics of L-Dopa administration has also been considered as a causative factor for the induction and/or expression of dyskinesia (Chase 1998): repetitive L-Dopa administration is supposed to mediate a pulsatile stimulation of dopamine receptors thus deteriorating the tonic phase of dopaminergic activity. Consequently, efforts were undertaken to achieve more sustained L-Dopa-derived dopamine levels by adding catechol-O-methyl transferase (COMT) or monoamine oxidase, type B (MAO-B) inhibitors to the treatment regimen. Indeed, continuous intravenous infusion of apomorphine avoided the occurrence of motor complications. Recently, an introduodenal infusion of L-Dopa (Duodopa) and a transdermal administration of rotigotine (Neupro®) has been developed which also lead to a more sustained dopamine or stable dopamine agonist level accompanied by a marked reduction of dyskinesia (Boroojerdi et al. 2010). The concept of continuous dopaminergic delivery is extensively discussed by Jenner et al. (2011, this issue) and has been proven to be clinically successful. Although it can avoid the adverse affects of a pulsatile drug delivery on basal ganglia function, it can reduce but cannot completely prevent the occurrence of dyskinesia. Furthermore, although being an improved therapeutic strategy, the continuous drug delivery seemingly does not avoid the priming for dyskinesia. Understanding the underlying principles, therefore, remains a scientific challenge. Addressing also the question why dyskinesia does not occur in a large population of Parkinson's disease patients, hardly any information is currently available although it could contribute to the learning process.

References

Boroojerdi B, Wolff HM, Braun M, Scheller DK (2010) Rotigotine transdermal patch for the treatment of Parkinson's disease and restless legs syndrome. Drugs Today (Barc) 46(7):483–505

Chase TN (1998) The significance of continuous dopaminergic stimulation in the treatment of Parkinson's disease. Drugs 55(S1):1–9

Dekundy A, Gravius A, Hechenberger M, Pietraszek M, Nagel J, Tober C, van der Elst M, Mela F, Parsons CG, Danysz W (2011). Pharmacological characterization of MRZ-8676, a novel negative allosteric modulator of subtype 5 metabotropic glutamate receptors (mGluR5): focus on L-DOPA-induced dyskinesia. J Neural Transm 118(12). doi:10.1007/s00702-010-0526-0

Gerlach M, Bartoszyk GD, Riederer P, Dean O, van den Buuse M (2011a) Role of dopamine D_3 receptors and serotonin 5-HT_{1A} receptors in levodopa-induced dyskinesias and effects of sarizotan in the 6-hydroxydopamine-lesioned rat model of Parkinson's disease. J Neural Transm 118(12). doi:10.1007/s00702-010-0571-8

Gerlach M, Beck J, Riederer P, van den Buuse M (2011b) Flibanserin attenuates L-DOPA-sensitized contraversive circling in the unilaterally 6-hydroxydopamine-lesioned rat model of Parkinson's disease. J Neural Transm 118(12). doi:10.1007/s00702-010-0570-9

Grünblatt E, Schmidt WJ, Scheller DKA, Riederer P, Gerlach M (2011) Transcriptional alterations under continuous or pulsatile dopaminergic treatment in dyskinetic rats. J Neural Transm 118(12). doi: 10.1007/s00702-010-0552-y

Iravani MM, Jenner P (2011) Mechanisms underlying the onset and expression of levodopa induced dyskinesia and their pharmacological manipulation. J Neural Transm 118(12). doi:10.1007/s00702-011-0698-2

Jankovic JJ (2005) Motor fluctuations and dyskinesias in Parkinson's disease: Clinical manifestations. Mov Disord 20(Suppl 11):S11–S16

Jenner P, McCreary AC, Scheller DKA (2011) Continuous drug delivery in early and late stage Parkinson's disease as a strategy for avoiding dyskinesia induction and expression. J Neural Transm 118(12). doi:10.1007/s00702-011-0703-9

Müller T, Russ H (2006) Levodopa, motor fluctuations and dyskinesia in Parkinson's disease. Expert Opin Pharmacol 7:1715–1730

Wolf E, Sepppi K, Katzenschlager R et al (2010) Long-term antidyskinetic efficacy of amantadine in Parkinson's disease. Mov Disord 25:1357–1363