Amino Acids (2002) 23: 103

Amino
Acids

Chapter III

Mechanisms and treatment of L-DOPA-induced dyskinesias – Introduction

W. Danysz

Although the introduction of L-DOPA to the therapy of Parkinson's disease (PD) was probably one of the most spectacular breakthroughs in the development of CNS targeting drugs, subsequent experience showed substantial pitfalls. The major one is the development of dyskinesia connected with the chronic L-DOPA use. Current believe is, that any plastic, long lasting changes in the brain involve a similar set of basic mechanisms. Bearing this in mind, this symposium was designed to give an overview from different perspectives.

Angela Cenci (Lund) presented a new model of L-DOPA-induced dyskinesia in rats with unilateral substantia nigra pars compacta (SNc) system lesion. It seems, that this model offers a best simulation of dyskinesia out of models available in rodents. She then demonstrated a comprehensive summary of her work in the last several years dealing with seeking for the molecular mechanism responsible for the expression of dyskinesia. In this respect, in particular prodynorphine gene and FosB seem to play a major role.

Trevor Archer working with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) treated mice demonstrated that many NMDA (N-methyl-D-aspartate) receptor antagonist reverse tolerance to the locomotor stimulant effects of L-DOPA seen after chronic treatment. However, only some of NMDA receptor antagonists did so without producing side effects.

Justin Oh (Bethesda) overviewed the concept promoted by Thomas Chase group based on the idea that NMDA receptors play a major role in the development of L-DOPA-induced motor complications. In short, pulsatile activation of dopamine D-1 (and D-2) receptors leads to phosphorylation of NMDA receptors in the output striatal neurons resulting in their hypersensitivity. Using both rat model of wearing off (shortening of action) and MPTP treated primates they showed that NMDA receptor antagonists, in particular these acting at NR2B containing subunits produce good antidyskinestic effect. Moreover, data of Oh suggest that CREB and cdk5 may contribute to the expression of the levodopa-induced motor response alterations.

Leo Varhagen-Metman overviewed a clinical features of L-DOPA-induced dyskinesia illustrating it with videos followed by classifications of motor complications produced by L-DOPA. He also presented results of clinical trials with NMDA receptor antagonists such as dextromethorphan and amantadine showing very encouraging results, particularly with the later agent.

To sum up, this symposium demonstrated that we are starting to understand the driving forces of the L-DOPA-induced dyskinesia or more widely motor complications. Some of these findings resulted already in therapeutic applications such as use of amantadine, while other will probably find therapeutic use in future such as targeting genes expression. Anyway, bringing together scientists working on the same topic was a big success resulting in providing of the audience with a lot of valid ideas and information and allowed to exchange their view points.

Authors' address: W. Danysz, Merz Pharmaceuticals, Eckenheimer Landstrasse 100, D-60318 Frankfurt/Main, Germany,
E-mail: wojclch.danysz@merz.de