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Evaluation of blood-brain barrier transport and CNS drug metabolism in diseased and control brain after intravenous L-DOPA in a unilateral rat model of Parkinson's disease

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Changes in blood-brain barrier (BBB) functionality have been implicated in Parkinson's disease. This study aimed to investigate BBB transport of L-DOPA transport in conjunction with its intra-brain conversion, in both control and diseased cerebral hemispheres in the unilateral rat rotenone model of Parkinson's disease. In Lewis rats, at 14 days after unilateral infusion of rotenone into the medial forebrain bundle, L-DOPA was administered intravenously (10, 25 or 50 mg/kg). Serial blood samples and brain striatal microdialysates were analyzed for L-DOPA and the dopamine metabolites DOPAC and HVA. *Ex vivo* brain tissue was analyzed for changes in tyrosine hydroxylase staining as a biomarker for Parkinson's disease severity. Data were analyzed by population pharmacokinetic analysis (NONMEM) to compare BBB transport of L-DOPA in conjunction with the conversion of L-DOPA into DOPAC and HVA, in control and diseased cerebral hemisphere. Plasma pharmacokinetics of L-DOPA could be described by a 3-compartmental model. In rotenone responders (71%), no difference in L-DOPA BBB transport was found between diseased and control cerebral hemisphere. However, in the diseased compared with the control side, basal microdialysate levels of DOPAC and HVA were substantially lower, whereas following L-DOPA administration their elimination rates were higher. Parkinson's disease-like pathology indicated by a huge reduction of tyrosine hydroxylase as well as by substantially reduced levels and higher elimination rates of DOPAC and HVA, does not result in changes in BBB transport of L-DOPA. Taking the results of this study and that of previous ones, it can be concluded that changes in BBB functionality are not a specific characteristic of Parkinson's disease and cannot account for the decreased benefit of L-DOPA at later stages of Parkinson's disease.

Biography

Elizabeth C M de Lange has obtained her PhD from Leiden University in 1993 and was tenured in 2004. She is the Head of the Translational Pharmacology Group at Leiden Academic Center for Drug Research (LACDR). She has published more than 100 papers and book chapters and is a Member of the Editorial Board of *FBCNS*, co-founded and co-chaired several of the international symposia on microdialysis in drug R&D. She is an AAPS Fellow since 2013.

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