CYTOCHROME P450 2E1 – RELEVANCE FOR CENTRAL DOPAMINE NEUROTRANSMISSION AND PARKINSON'S DISEASE

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin
vid Göteborgs universistet kommer att offentligen försvaras i föreläsningssalen, LNC,
Medicinaregatan 13A, Göteborg torsdagen den 11 september 2008 kl 9.00

av

Haydeh Niazi Shahabi

Fakultetsopponent: Professor Giovanni Corsini
Department of Neuroscience, University of Pisa, Pisa, Italy

Avhandlingen baseras på följande arbeten:

I. **Niazi Shahabi H.**, Bergquist F. and Nissbrandt H. An investigation of dopaminergic metabolites in the striatum and in the substantia nigra in vivo utilising radiolabelled L-DOPA and high performance liquid chromatography: A new approach in the search for transmitter metabolites. *Neuroscience 120: 425-433, 2003*

II. **Niazi Shahabi H.**, Andersson D. R. and Nissbrandt H. Cytochrome P450 2E1 in the substantia nigra: Relevance for dopaminergic neurotransmission and free radical production. *Synapse 62:379-388, 2008*

III. **Niazi Shahabi H.**, Westberg L., Melke J., Håkansson A., Carmine Belin A., Sydow O., Olson L., Holmberg B., and Nissbrandt H. Cytochrome P450 2E1 gene polymorphisms/haplotypes and Parkinson's disease in a Swedish population. *Submitted, 2008*

IV. **Niazi Shahabi H.**, Melke J., Nordborg C., Kjellström C. and Nissbrandt H. Expression of alternatively spliced cytochrome P450 2E1 in the putamen and the caudate nucleus of human brain. *Manuscript, 2008*

UNIVERSITY OF GOTHENBURG

Abstract

CYTOCHROME P450 2E1 – RELEVANCE FOR CENTRAL DOPAMINE NEUROTRANSMISSION AND PARKINSON'S DISEASE

Introduction: The enzyme cytochrome P450 2E1 (CYP2E1) has been found in dopamine (DA) containing brain regions that are of relevance for Parkinson's disease (PD), and is known to generate reactive oxygen species (ROS), toxic molecules that have been implicated in the degeneration of DA neurones. In addition, previous investigations have indicated that inhibition of CYP2E1 increases extracellular DA in the substantia nigra, a nucleus which degenerates in PD. It is therefore of interest to elucidate a possible involvement of CYP2E1 in DA metabolism/neurotransmission and participation in producing ROS. Furthermore, CYP2E1 gene polymorphisms have been reported, variations which could influence susceptibility to PD. Thus, an inspection of polymorphic variants in a population of PD patients as compared to controls was conducted. ***Methods and observations:*** By injection of the radioactive DA precursor L-DOPA to rats in vivo, major catecholamines and their metabolites could be separated and quantitatively examined for radioactivity utilizing a liquid chromatography system. Inhibition of CYP2E1 induced significant changes in the radioactivity pattern. Moreover, the increase in extracellular DA in the substantia nigra, measured by in vivo microdialysis in rats, induced by CYP2E1 inhibition was unaltered following pharmacological inhibition of DA neurone firing and the DA transporter. Tetrodotoxin or reserpine treatment conversely abolished this effect. In addition, an increase in ROS production in the substantia nigra was observed during the presence of an exogenous CYP2E1 substrate (isoflurane). Investigation of polymorphic forms of CYP2E1 was carried out via a tag-single nucleotide polymorphism approach, obtaining Haplotype block data. An association between a C/G polymorphism at intron 7 of this gene and PD was found. Furthermore, extraction of genomic CYP2E1 RNA from putamen/caudate nucleus of five individuals revealed two alternatively spliced variants. ***Conclusions:*** The results support the notion that CYP2E1 is located near or in the same compartment as stored DA in the substantia nigra, possibly modulating DA neurotransmission and generation of ROS. Furthermore, inspection of polymorphic forms of CYP2E1 revealed a possible association of this enzyme with PD. Finally, we show that both intra- and inter-nuclei alternatively spliced variants of CYP2E1 exist in brain parts that are of relevance for PD pathophysiology.

Keywords: cytochrome P450 2E1, dopamine, substantia nigra, polymorphism, alternative splicing.

ISBN 978-91-628-7542-8 Göteborg 2008