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Kranz J[1], Geyer J[1]
1. *Justus-Liebig-University Giessen, Institute of Pharmacology and Toxicology*

BLOOD-BRAIN BARRIER IN AGING: INFLUENCE ON THE BRAIN PERMEATION OF THE ANTICHOLINERGIC OAB DRUG TROSPIUM CHLORIDE?

Hypothesis / aims of study

Antagonists of the acetylcholine muscarinic receptors (e.g. trospium chloride, oxybutynin, tolterodine, darifenacin) are the cornerstone of pharmacotherapy for the symptoms of overactive bladder (OAB). Potential undesirable side effects involving the central nervous system (CNS) can occur including dizziness, nervousness, sleep disorders, cognitive impairment, memory impairment, hallucination, and confusion. Occurrence of these CNS side effects is greatly dependent on the ability of the individual drug to pass the blood-brain barrier (BBB) and, therefore, to interact with CNS acetylcholine receptors. While most of the aforementioned antimuscarinic drugs are tertiary amines that are quite lipophilic and can easily penetrate into the brain, trospium chloride is a highly polar quaternary amine that exhibits low permeability across biological membranes. Moreover, recently it was shown that BBB permeability of trospium chloride is highly restricted by the drug efflux carrier P-glycoprotein (P-gp) that is encoded by the multidrug resistance (*mdr1*) gene [1]. However, it is reasonable to speculate that in elderly patients, who represent the majority of patients with OAB who are treated with antimuscarinic drugs, drug brain penetration might be increased due to histological and functional changes at the BBB implicating an increase of CNS side effects with aging. In the present study we aimed to analyse in a mouse model the expression of important components of the BBB during aging and to directly compare the brain penetration of trospium chloride in young and aged mice.

Study design, materials and methods

In order to study functional drug permeation across the BBB in aged mice, we intravenously applied trospium chloride in a dosage of 1 mg/kg to adult (6-12 months) and aged (24 months) mice and analysed the absolute drug concentrations in the brain after 2 hours. Moreover, using quantitative real-time PCR we analysed the mRNA expression levels of the BBB marker proteins mdr1 (P-gp), glut-1 (glucose carrier), occludin, and claudin-5 (tight junction proteins) in the brain of adult and aged mice.

Results

Animal housing was performed in a SPF facility and required special care for the aged mice. All of the aged mice showed typical age-related characteristics including drawn-out bonce, sparse coat, and decreased general activity. Several mice died before they reached the scheduled age of 24/25 months. *In vivo*, the absolute brain concentrations of trospium chloride did not increase in aged mice compared with adult mice (Fig. 1). By quantitative real-time PCR analysis, we detected no significant age-related differences in the mRNA expression levels of mdr1, glut-1, occludin, and claudin-5 (Fig. 2).

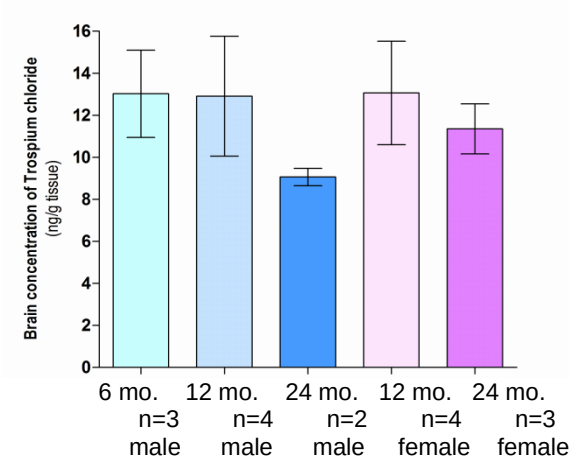

Fig.1: Brain penetration of [^{3}H]trospium chloride in aged mice. Trospium chloride concentrations in the brain were not significantly different between the groups (aged, adult, male, female).

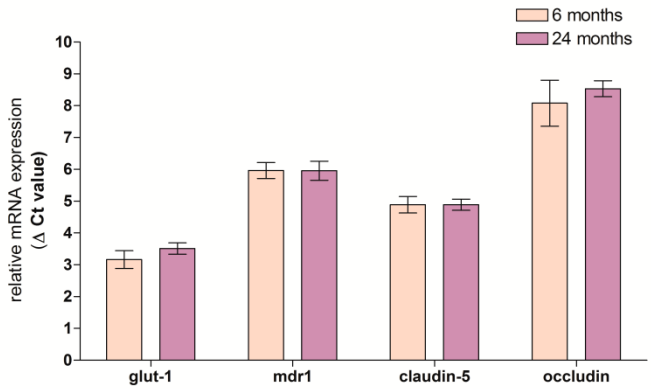

Fig. 2 : mRNA expression levels of glut-1, mdr1, claudin-5 and occludin in the brain of adult (6 months, n=8) and aged (24 months, n=7) female C57Bl6 mice analysed by quantitative real-time PCR.

Interpretation of results

Our study revealed no age-related down-regulation of mdr1, glut-1, occludin, and claudin-5 indicating that the mRNA expression of these important blood-brain barrier proteins is tightly regulated during aging. Brain permeation of trospium chloride is not increased during aging indicating tightness of the BBB in the aged mice.

Concluding message

Based on our *in vivo* data, it cannot be expected that the permeation of trospium chloride across the BBB and the occurrence of CNS side effects are increased in old patients.

References

1. Geyer et al. 2008, Drug Metabolism and Disposition, 37:1371-1374

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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**Regierungspräsidium Gießen Dezernat V 54 - Veterinärwesen (Hessian Ethical Committee)**