ABSTRACT

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmacology & Toxicology

Student: **Nikol Vykoukalová**

Supervisor: **prof. PharmDr. František Štaud, Ph.D.**

Title of diploma thesis: **Prediction of tacrine-BQCA derivatives across blood-brain-barrier**

This master thesis deals with the determination of permeability prediction for tacrine BQCA derivatives, potential drugs for Alzheimer´s disease, through the blood-brain barrier (BBB) using the method of parallel artificial membrane penetration (PAMPA). We attempted to predict the central bioavailability by the permeability coefficient, to study the relationship between the solubility of the compounds and their log P (or Log D) and the subsequent significance of these data for the prediction of their passage through the blood-brain-barrier. A solution of 1% Pluronic F-127 in PBS was used to solubilize compounds and to ensure the constant concentration during the measurement. The assay was performed so that the solutions of compounds were applied to the donor part of microtiter plate (so-called sandwich arrangement), the bottom compartment was covered by a solution of a polar brain lipid isolated from pig brain (PBL), which serves as a membrane simulating the phospholipid membrane of the brain capillary endothelium. The solution of the substance was allowed to diffuse into the acceptor part of the system from which it was then sampled at specific time intervals and measured on a spectrophotometer. The results were then correlated to commonly used drugs with known passage through the BBB and to the physical-chemical properties. The results obtained from measurements in a 1% F-127 solution were extrapolated to the results in PBS using a set of standard drugs evaluated in both solvents. Based on these data, we conclude that most of the tested substances showed the extent of permeability in PBS represented by the value between 2-4 x 10^{-6} cm.s^{-1}, suggesting limited penetration through the BBB. Only two tested agents reported a value sufficient to permeate through the BBB. We also demonstrate the fact that passive transport is not always dependent only on the lipophilicity but another parameters such as the molecular weight of each substance, the degree of ionization or concentration gradient can play a crucial role. Likewise, the effectiveness of Pluronic F-127 as the solvent is not strictly dependent on the lipophilicity of the tested compounds.

Keywords: Alzheimer´s disease, tacrine, PAMPA, blood-brain-barrier