

ABSTRACT

Jandovská, Kateřina: Synthesis of ceramide and dihydroceramide analogues and evaluation of their effects on the skin barrier properties.

Ceramides belong to sphingolipids, their molecule is formed by a sphingoid base and long fatty acid. They are known not just as important second messengers playing a significant role in cell differentiation, proliferation and apoptosis, but also as essential part of functional skin barrier. Although these molecules are studied intensively, the exact effect of their structure on barrier function of the skin is poorly understood. The aim of my work was to study the effect of acyl chain length and stereochemistry on C3 of dihydroceramides (ceramides with single bond on C4) on the permeability of model membranes simulating the skin barrier. I have synthesized 3 ceramides with short acyl chain of 4 carbons (derived from dihydrosphingosine (dS), *L-threo*-dihydrosphingosine (L-dS) and *L-threo*-sphingosine (L-S)), and prepared model membranes of stratum corneum (SC) containing dihydroceramides with C2, C4, C6, C8 and C24 acyl chain length and stereoisomers of C4-ceramides and C4-dihydroceramides as well. I have evaluated their electrical impedance and permeability for two model drugs. The effects of the prepared ceramides on the model membrane permeability were evaluated in Franz diffusion cells using two model drugs – theophylline (TH) and indomethacin (IND). Donor samples contained suspension of theophylline (5%) or indomethacin (2%) in 60% propylene glycol. The amount of the model drugs in the acceptor phase samples was determined by HPLC. The evaluation of the effect of prepared ceramide analogues on model membrane permeability simulating skin showed that ceramides and dihydroceramides have similar properties, but the relationship between acyl chain length on membrane permeability had different character than in ceramides. The lowest values of impedance were measured for dihydroceramides with 2-carbon acyl chain. Maximum increase in permeability was achieved in the membrane containing the analogue with 2-carbon acyl chain for TH and with 4-carbon acyl chain for IND. The behaviour of *L-threo*-isomers was surprising. While *L-threo*-isomer of ceramide displayed the highest impedance, *L-threo*-isomer of dihydroceramide showed the lowest one. The results of this work showed some similar and some different features of ceramides and dihydroceramides and pointed out the impact of C3 configuration. Other structure-activity relationships in the ceramide molecule require further investigation.