Abstract

Ceramides are a complex group of lipids, naturally occurring in the uppermost layer of the epidermis, in the stratum corneum (SC). They constitute a major component of extracellular matrix and they are responsible for the skin barrier properties. Diseases such as atopic dermatitis or psoriasis are associated with the decline in content and changes in the composition of ceramides, which lead to the reduction in the protective functions of the skin.

Although the importance of ceramides is known, the relationship between their structure and effect on the barrier function is not yet fully elucidated. Earlier studies indicate that the length of ceramide acyl chain affects the skin permeability. It appears that ceramides with short acyl lose the protective properties.

First, I have prepared a series of analogues of ceramides with fifteen carbon atoms chain in the sphingosine part and the acyl part of a length of 2, 4 and 6 carbons. Starting substance of the synthesis was N-protected L-serine methyl ester, which was further protected by the formation of a cyclic acetal and subjected to the reduction of the ester to aldehyde. The resulting aldehyde reacted with 1-alcynide in the presence of HMPA. The triple bond was subsequently reduced to a *trans*-double bond by lithium in ethylamine. After deprotection of the functional groups, the sphingosine analogue was acylated using succinimidyl esters of the pertinent acids to yield the target ceramides.

The effects of the prepared ceramides on the skin permeability were evaluated on pig skin in Franz diffusion cells using two model drugs – theophylline and indomethacin. Donor samples contained suspension of theophylline (5%) or indomethacin (2.5%) with the addition of ceramide (1%) in 60% propylene glycol, control samples did not contain ceramide. As the acceptor phase for the determination of drug was used phosphate buffer saline. The amount of the model drugs in the acceptor phase samples and in the skin was determined by HPLC.

The results confirmed our hypothesis that short chain ceramides decrease the barrier function of skin. Maximum increase in permeability was achieved by applying the analogue with 4-carbon acyl chain, the highest concentration of the drug in the skin was observed after the application of ceramide with 6-carbons acyl chain. Surprisingly, these ceramides containing 15-carbon sphingosine generally caused greater permeability increase than those with 12 and 18-carbon sphingosine.

The results are consistent with our hypothesis about the impact of the short chain ceramide analogues on the skin permeability. Nevertheless, the role of the sphingosine chain

length, double bond geometry and other structural features in the ceramide molecule warrants further investigation.