

New insights in contact allergy and drug delivery

A study of formulation effects and hapten targets in skin using two-photon fluorescence microscopy

CARL SIMONSSON



GÖTEBORGS UNIVERSITET

Institutionen för kemi
Naturvetenskapliga fakulteten
Göteborgs Universitet
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Abstract

The skin is a remarkable barrier, protecting us from invasion of e.g. harmful microorganisms and UV-radiation. However, the skin is not adapted to resist repeated exposure to the multitude of xenobiotics introduced into modern society. Some of these chemicals are skin sensitizers, and exposure can lead to the development of contact allergy. Contact allergy has significant social and economic consequences, both for the individual and for society. It is therefore important to prevent sensitization. The skin also constitutes a potential route for administration of drugs, and much effort is put into the development of cutaneous and transdermal drug delivery systems.

The work of this thesis aims to improve the understanding of processes related to the interactions between the skin and topically applied compounds, i.e. drugs and skin sensitizers. Specifically, two-photon microscopy has been used to study the cutaneous absorption and distribution of model drugs and a series of model skin sensitizers. Improved cutaneous absorption was demonstrated using formulations composed of lipid cubic phases. The work also showed elevated sensitization potency of haptens depending on delivery vehicles. Putative mechanistic explanations for the observed effects have been proposed. Specifically, phthalates were shown to increase the sensitization potency of isothiocyanates. The phthalate-induced effect could be linked to a PSU-targeted delivery of the haptens into the skin. It could also be shown that vehicles alter hapten reactivity to *stratum corneum* proteins leading to variations in sensitization potency. Moreover, hapten protein targets in skin have been identified using caged fluorescent model haptens. Specifically, basal cell keratinocytes and the keratins were identified as specific hapten targets in the skin.

In conclusion, the work presented in this thesis contributes to the general understanding of the mechanisms involved in the cutaneous absorption of topically applied drugs and skin sensitizers. It also demonstrates the capabilities of using TPM when investigating the interactions between the skin and xenobiotics.

Keywords: allergic contact dermatitis, bromobimane, confocal microscopy, contact allergy, cubic phases, cutaneous absorption, dermatochemistry, ethosomes, FITC, hair-follicle, hapten, isothiocyanate, lipid vesicles, local lymph node assay, nano, percutaneous absorption, pilosebaceous unit, RBITC, two-photon microscopy, vehicle effects.

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