EFFECT OF UV-IRRADIATION ON DERMAL PHARMACOKINETICS OF KETOPROFEN AND ITS PHOTOPRODUCTS IN GUINEA PIGS

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[Purpose] Topical administration of NSAIDs is widely used for analgesic and antipyretic. However, contact skin sensitivity and photosensitivity by the UV exposure have been reported in topical application of ketoprofen (KP). Causal relation between these adverse drug reactions and the formation of photoproducts of KP (KP-PPs) has been pointed out, but concentration-time profiles of KP and KP-PPs in the skin are not well clarified. The aim of this study is to investigate dermal pharmacokinetics of unbound KP and KP-PPs in the skin using microdialysis (MD).

[Methods] Ventral side of the body of female Hartley guinea pig was shaved followed by the tape-stripping. A piece of Mohrus® Tape (2.5 cm x 2.5 cm) (Hisamitsu Pharmaceutical Co.) was applied to the skin. Dermal Lipo-MD* (CMA20, 10 mm) using 10% Intralipos as the dialysate (1 μL/min) was performed to monitor KP and KP-PPs concentrations in the skin under the UV-irradiation (10 J/cm²) or non-irradiation condition. The amounts of KP and 2 major KP-PPs, i.e., 3-(1-hydroxy)ethylbenzophenone (KP-OH) and 3-acetylbenzophenone (Ac-KP), were determined by LC-MS.

[Result] Lipo-MD enabled the determination of KP in the skin. Although KP was determined in both the UV-irradiated and non-irradiated conditions, facilitated elimination of KP was observed in the UV-irradiated condition. Neither of KP-PPs was determined in the non-irradiation skin, but both KP-PPs were detected in the UV-irradiated skin.


Improvement of Intestinal Absorption by Peptide-Derivation of Nonabsorbable Drug via Peptide Transporter PEPT1

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The purpose of the present study was to improve the absorption of poorly absorbable drugs by utilization of intestinal uptake transporter PEPT1. In our previous study, we reported that improvement of intestinal absorption of peptide-mimetics via PEPT1 is possible by modification of amino acid-like drugs to peptide derivation, and by optimization of the PEPT1 activity through coadministration of a proton-releasing polymer that supplies the driving force for PEPT1. In the present study, we examined the effectiveness of peptide derivation of non-amino acid like drugs to be absorbed by PEPT1. In the present study, we used rebamipide as the poorly absorbable model drug. We synthesized several peptide-derivatives of rebamipide and examined the inhibitory effect of them on the uptake of [³H]gly-sar, a typical substrate of PEPT1, by PEPT1-expressed HeLa cells. As the results, some of the rebamipide derivatives exhibited inhibitory effect on PEPT1-mediated transport of gly-sar. Then, the uptake of rebamipide derivatives was evaluated by PEPT1-expressed HeLa cells. The rebamipide derivative, Reb-Ser-Gly, showed higher uptake by PEPT1 expressed cells than by mock-transfected cells. Furthermore the permeability of Reb-Ser-Gly across Caco-2 cells was decreased in the presence of PEPT1 substrates, such as Gly-Sar, cefadroxil and cefixime. These results suggested that Ser-Gly dipeptide modification is useful to improve the absorption of the poorly absorbable compounds via the intestinal transporter PEPT1.