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Enhancement of topical delivery of drugs via direct penetration by reducing blood flow rate in skin

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Abstract

The purpose of this work was to investigate the effect of blood flow in the skin on the direct penetration of topically applied drugs into the muscular layer, and to show that the skin blood flow could also be one of the important factors determining the direct penetration of drugs to the muscular layer. In vivo percutaneous absorption study was performed for antipyrine, salicylic acid or diclofenac by using rats with tape-stripped skin. Phenylephrine, which is well known to reduce the local blood flow by vasoconstrictor action, was topically applied to decrease the local blood flow in the skin. The concentrations of drugs in viable skin and muscle, and the local blood flow in the skin under the applied and the contralateral sites were determined to evaluate the effect of the local blood flow on the delivery of topically applied drugs into the muscular layer. Dose dependency for the effect of phenylephrine was, first of all, investigated for antipyrine in the range from 0.4 to 10 μmol. The distribution of antipyrine into the viable skin and muscular layer 2 h after topical application significantly increased, but the effect of phenylephrine was saturated around 2 μmol and the dose-dependent profiles for both tissues were almost superimposed. On the other hand, the fraction dose absorbed, plasma concentration and concentrations in viable skin and muscular layer under the contralateral site showed the decreasing tendency and the saturation of the effect around 2 μmol. To confirm the effect of phenylephrine on the local blood flow in the skin, the skin blood flow was measured 2 h after topical application of 2 μmol phenylephrine, and the significant decrease in the blood flow was recognized. In vivo percutaneous absorption studies were performed for salicylic acid and diclofenac, too. Extensive enhancement of penetration into the viable skin and muscular layer was observed for both drugs, although total absorption from the donor cell showed the decreasing tendency. In conclusion, direct penetration of drugs applied topically is enhanced by reducing the local blood flow in the skin, which would be a possible approach to improve the local delivery of drugs applied topically.

Keywords: Direct penetration; Skin blood flow; Local therapeutics; Transdermal absorption; Topical application

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1. Introduction

Transdermal delivery system for the local therapeutics would be expected to avoid the systemic absorption and to make the substantial penetration into deeper tissues, such as muscle, of topically applied drugs as much as possible. As a main barrier against transdermal absorption, the stratum corneum, could be overcome by a lot of promising physical and/or chemical approaches (Barry, 2001; Higaki et al., 2003), the regulation of intradermal disposition of drugs after the passage across the stratum corneum would be the next issue to be pursued to develop the efficient transdermal delivery system. However, there is still controversy regarding with the mechanisms by which topically applied drugs are distributed into deeper tissues, i.e. "direct penetration" or "re-distribution from blood flow after systemic absorption". Diclofenac (Radermacher et al., 1991) and felbinac (Dawson et al., 1988) were reported to distribute into deeper tissues mainly from systemic blood supply. On the other hand, the substantial direct penetration was shown for estradiol, progesterone (Marty et al., 1989), salicylic acid (Singh and Roberts, 1993; Cross et al., 1997) and piroxicam (M-Riviere et al., 1993). In the previous studies, we performed the in vivo transdermal absorption studies using rats with tape-stripped skin for seven different drugs including diclofenac, felbinac and salicylic acid, and clearly showed that these topically applied drugs are substantially distributed into muscular layer via direct penetration (Nakayama et al., 1999; Higaki et al., 2002). The pharmacokinetic analysis based on the six-compartment model with contralateral tissues explicitly indicated that the contribution of direct penetration to the deeper tissue distribution of drugs applied topically is dependent on drugs, and that the balance in the contribution between direct penetration and blood supply is time-dependently changed (Nakayama et al., 1999; Higaki et al., 2002). Furthermore, we showed that the unbound fraction of drugs in the viable skin is possibly one of the most important factors to regulate the direct penetration of drugs into the muscular layer (Higaki et al., 2002). Blood flow in the skin, particularly the dermis, must also be an important factor, because the blood vessels in the dermis are supposed to absorb and dilute most compounds passing the epidermis, keeping a "sink" condition and thus promoting the percutaneous absorption (Barry, 2002). However, at the same time, this means that blood flow in the dermis prevents drugs from directly penetrating into deeper tissues by removing them to the systemic circulation. It was also suggested that topical penetration of drugs could be dependent on the distribution of the local cutaneous vasculature (McNeill et al., 1992; M-Riviere et al., 1993). In the present study, therefore, we investigated the effect of the skin blood flow on the penetration of drugs into the muscular layer after their topical application, by reducing the skin blood flow rate with topical application of phenylephrine, α_1-agonist, in rats with stripped skin.

2. Materials and methods

2.1. Materials

Diclofenac sodium, aminopyrine and L-phenylephrine hydrochloride were purchased from Sigma Chemical Co. (St. Louis, MO). Antipyrine and salicylic acid were obtained from Ishizu Pharmaceutical Co. (Osaka, Japan). Flufenamic acid and *o*-anisic acid were obtained from Sankyo (Tokyo) and Tokyo Chemical Industry Co. (Tokyo), respectively. All other reagents were of the highest grade commercially available.

2.2. Animals

Male Wistar rats (Japan SLC, Hamamatsu, Japan), maintained at 25 °C and 55% of humidity, were allowed free access to standard laboratory chow (Clea Japan, Tokyo) and water prior to the experiments. Rats weighing 230–270 g were randomly assigned to each experimental group. Our investigations were performed after approval by our local ethical committee at Okayama University and in accordance with "Principles of Laboratory Animal Care (NIH publication #85-23)".

2.3. In vivo transdermal absorption study

Abdominal hair was removed by using 7% thioglycolic acid gel 2 days before performing the absorption study and the stratum corneum was stripped with adhesive tape about twenty times under urethane anesthesia just before starting the absorption study. Under urethane anesthesia, 2 ml of a model drug solution