Synopsis of Original Research Paper

# Development of Theoritical Design for Skin Penetration Enhancement of Drugs

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Effectiveness of prodrug-enhancer combination for enhancement of skin penetration of drugs is proposed and confirmed in this study. Based on a skin diffusion model, we hypothesized that skin permeation of drug could be the most effectively enhanced by derivatizing into a prodrug with the optimal lipophilicity for the enhancer, when its action mechanism is elucidated in the same model. Employing acyclovir as a model drug, the hypothesis was proved by synthesizing seven types of its prodrugs and evaluating their in vitro permeation in rat skin, pretreated with 1-geranylazacycloheptan-2-one (GACH), a penetration enhancer. Among seven prodrugs, those with higher lipophilicities (propionate, butyrate, valerate, and hexanoate isovalerate, pivarate prodrugs) showed larger enhancement in their skin penetration than those of hydrophilic ones (acetate and acyclovir), when administrated in combination of GACH. In this approach, prodrugs applied topically were metabolized through the skin, since skin was metabolically active tissues. We have proposed that a two-layer skin diffusion model with polar and nonpolar route in the stratum corneum, which included metabolic process in the viable epidermis and dermis, could comprehensively account for skin permeation of acyclovir prodrugs. Concerning the effect of GACH, the estimated partition parameters of prodrugs in the nonpolar route increased with an increase in pretreatment dose of GACH, but their diffusivities were little affected being in good agreement with the theoretical prediction. In addition, GACH was significantly decreased the enzymatic hydrolysis rate constants of all prodrugs in the skin. These experiments have been studied with an in vitro condition, and a goal of in vitro studies is the prediction of in vivo absorption behavior. We previously demonstrated quantitative in vitro/in vivo differences in skin penetration in terms of diffusion and partition parameters. However it has not been established these differences concerning metabolic process. So we demonstrated to quantitate in vitro/in vivo differences in skin penetration and bioconversion of acyclovir prodrugs. In order to confirm the possibility of this combination approach with an in vivo condition, penetration profiles was evaluated by a deconvolution method which enabled to estimate first-pass metabolism. Next we analyzed in vivo skin urinary excretion profile based on a diffusion/bioconversion model, and diffusion, partition and metabolic parameters were compared between in vitro and in vivo condition.

In conclusion, skin permeation of prodrugs applied with an enhancer can be predicted and optimized based on a model analysis. This combined approach would be applicable to a wide range of drugs, since extreme alteration of physicochemical properties of drugs is not necessary as is the case of single prodrug application.