Synopsis of Original Research Paper

Development of transdermal penetration enhancer by regulating epidermal tight junction barriers

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The tight junction (TJ) is responsible for the epithelial barrier function of the skin. A TJ is composed of membrane proteins such as claudins, occludin, and ZO-1. It has previously been thought that only the stratum corneum is responsible for skin barrier function; however, knock-out mouse analysis has shown that claudin-1 is essential for skin barrier function. Furthermore, other TJ components including claudin-4 and occludin also contribute to the skin TJ-barrier. Homoharringtonine (HHT) is an alkaloid derived from the evergreen tree Cephalotaxus harringtonia. HHT reduces intestinal epithelial barrier function by inducing a change in the expression and localization of TJ components. However, the effect of HHT on the skin TJ barrier remains unclear. In the present study, we investigated HHT's influence on the skin TJ barrier and the compound's potential to enhance transdermal absorption. HHT decreased transepithelial membrane electrical resistance (TEER) values and enhanced the paracellular flux of FD-4 in NHEK cells in a dose-dependent manner. The protein expression of TJ components such as claudin-1, claudin-4, and occludin was decreased by HHT in NHEK cells. HTT also reduced the expression of TJ components that are important for construction of the skin TJ barrier, including claudin-1, claudin-4, and occludin. Examination of the transdermal absorption-promoting activity of HHT *in vivo* showed that the amount of FD-4 absorbed over 24 h of treatment was increased by HHT in a dose-dependent manner. A time-course of FD-4 absorption indicated that HHT increased the amount of FD-4 absorbed starting after about 6 h of treatment. Analysis using model dextrans showed that compounds with molecular weights of up to 10,000 were absorbed. These findings indicated that HHT acts on the epidermal TJ barrier and may serve as a novel transdermal absorption-promoting agent that permits the passage of high-molecular-weight drugs such as biopharmaceuticals.