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2. **Title**

   Risk Evaluation of Smoking Metabolites and Clarification of Its Mechanism Using 3D-keratunicyte Culture System

3. **Period**

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4. **Summary**

Smoking is a risk factor for the development of early skin wrinkles, psoriasis, and palmoplantar pustulosis. Transepidermal water loss is also high in smokers. Smokers also experience reduced wound healing and delayed Transepidermal water loss value recovery. Here, we focused on nicotine as a factor that affects tight junction (TJ) structure. It is known that nicotine stimulation depending on nicotine-like acetylcholine receptor (nAChR) affects skin barrier formation. However, there have been no studies focusing on the nAChR effect on skin TJ function. We used an in vitro skin model to examine the nicotine effects on TJ protein expression and function in keratinocytes.

In this study, we show that nicotine causes decreased TJ function at concentrations close to those found in human blood during smoking. Nicotine also caused localized changes in its component proteins and decreased their expression, leading to TJ destruction. To account for the effects of chronic tobacco smoking, 0.3 μM nicotine was administered over 2–4 days. In a three-dimensional human skin culture model, nicotine altered the continuous structure of TJs between cell membrane. This was due to nicotine decreasing the expression of zonula occludens-1 (ZO-1), which binds to the membrane on the cytoplasmic side of TJs, and by altering the localization of the TJ constituent protein occludin. In normal human epidermal keratinocyte, the nicotine-induced reduction in ZO-1 protein levels was mediated by the α7 nAChR in groups treated with the agonist PNU282987 and pre-treated with the antagonist α-bungarotoxin.

In conclusion, we showed that long-term exposure to nicotine causes a reduction in TJ structure and function. This mechanism may involve the mediation of nicotine by α7 nAChRs on the surface of keratinocytes. These results suggest that smoking is a risk factor for the breakdown of the skin barrier function, and may serve as a warning of the adverse effects of smoking on skin condition. This should lead to the elucidation and treatment of skin diseases caused by smoking.