

COMPARISON BETWEEN SKIN AND LIVER METABOLISM OF [4, ¹⁴C]-TESTOSTERONE IN HUMAN AND MINIPIG

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BACKGROUND

Skin metabolism is recognized as an important consideration in evaluating the exposure of topically applied pharmaceutical products. Minipigs are considered one of the main nonrodent animal species used in toxicology studies. In addition, minipig skin is considered a good predictor of cutaneous local tolerance in humans. However, little has been published on the metabolism of drugs in the skin of minipig. The objective of this work was to compare the metabolism of [4, ¹⁴C]-Testosterone (as a reference molecule) in ex vivo human and minipig skin and liver.

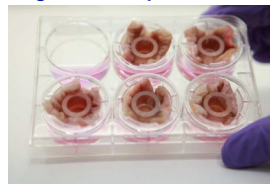
METHODS

Freshly excised full-thickness skin samples from human (1 man and 1 woman) and minipig (2 males and 1 female) were treated with [4, ¹⁴C]-Testosterone (14-28 µg/cm²; 2.5-5 µCi/cm²) for 16 hours. Skin samples were placed in cell diffusion (Figures 1 & 2) maintained between 32°C and 37°C. High performance liquid chromatography with radioactive detection was used to assess metabolism of [4, ¹⁴C]-Testosterone in epidermis, dermis as well as receptor fluid. In addition, metabolism of [4, ¹⁴C]-Testosterone was evaluated in human and minipig liver microsomes and hepatocytes.

Figure 1 Flow-through diffusion cell

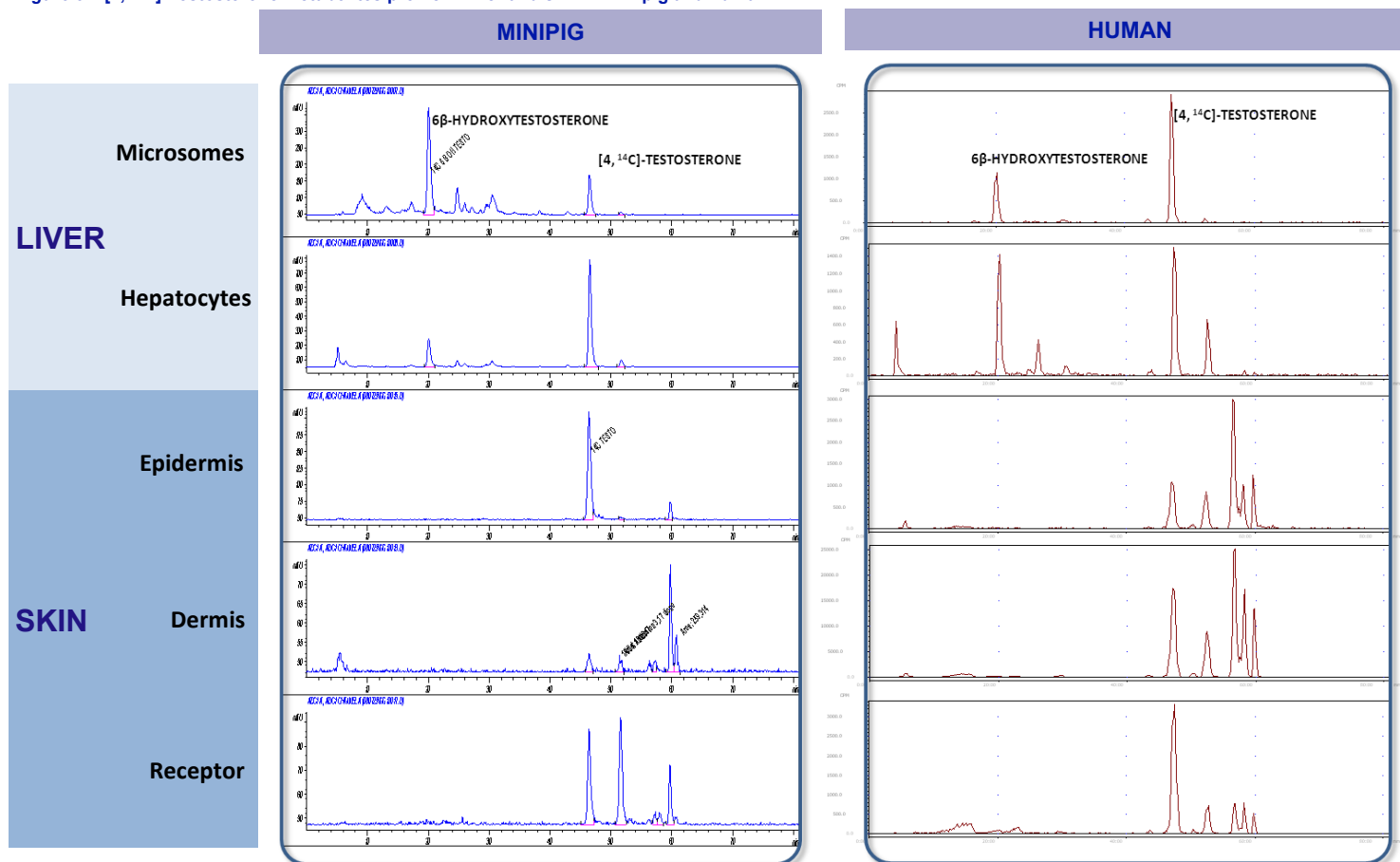


Figure 2 6-well Transwell organoculture plate



RESULTS

Figure 3 [4, ¹⁴C]-Testosterone metabolites profile in liver and skin in minipig and human



DISCUSSION

The results showed that both human and minipig freshly excised skins were able to efficiently metabolize [4, ¹⁴C]-Testosterone (Figure 3). Metabolite profiles of [4, ¹⁴C]-Testosterone were qualitatively similar in both minipig and human skin and liver. However, comparison between skin and liver showed that metabolite profiles of [4, ¹⁴C]-Testosterone were different in both species. The main metabolites of [4, ¹⁴C]-Testosterone in the skin resulted from reduction reactions whereas the main metabolites in liver resulted from oxidation reactions in both humans and minipigs.

CONCLUSION

In vitro metabolite profiles of [4, ¹⁴C]-Testosterone are similar in human and minipig in both skin and liver. Therefore, this confirms the use of minipig as a good alternative to the dog or monkey as the non-rodent species in topical toxicology studies.