01D10-4

DIRECT DELIVERY OF STEROID TO THE TRACHEA BY TOPICAL APPLICATION

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Inhaled steroid is recommended as the first-line therapy for the chronic asthma. Side effects such as oral ulcer and inadequate delivery of steroids to the inflammatory sites decreased the therapeutic effects. We have evaluated direct delivery of drugs into the subcutaneous and muscular tissues by the topical application. We then evaluated direct delivery of topical steroid to the trachea. A fluorescent compounds, rodamin B (M.W.; 443.56, clogP; 2.13) and a steroid, prednisolone sodium succinate (M.W.; 482.50, clogP; -1.02) were selected as model compounds. Their aqueous solutions or white petrolatum ointments were applied on the full-thickness or stripped neck skin in hairless rats. Rodamin B was successfully delivered to viable cutaneous tissues, submandibular gland, sternohyoid muscle and trachea through stripped skin as well as full-thickness skin. On the other hand, little skin permeation was observed for prednisolone succinate through both skins. Next, we applied iontophoresis to increase the skin permeation of prednisolone succinate, resulting in successful skin permeation of the steroid.

The present results suggest that topical steroid therapy with iontophoresis may be applied as an alternative for inhaled steroid in chronic asthma patients who have inadequate therapeutic effects by inhaled steroid and/or severe side effects such as oral ulcer.

01D10-5

CONTRIBUTION OF SPLENIC MARGINAL ZONE B (MZ-B) CELLS ON REVERSE DOSE DEPENDENCY OF THE ABC PHENOMENON

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PEG is considered as non-immunogenic material, and surface modification with PEG can improve pharmacokinetics of nanocarriers. However, we have reported that PEGylated liposomes (PL) lose their long circulating properties when they are injected secondary with certain interval (the accelerated blood clearance (ABC) phenomenon). We have elucidated that anti-PEG IgM, secreted in response to first dose of PL, is responsible for this phenomenon. We further have found that such accelerated clearance is caused when first dose is low, while it is not caused by high dose. It is suggested that production of anti-PEG IgM is affected by first dose level. In this study, therefore, we investigated the effect of first dose level on the production of anti-PEG IgM and also on each splenic B cell population which is considered as producer of anti-PEG IgM.

First, we measured anti-PEG IgM in serum and spleen cell culture from the rat received PL with two dose level (0.001 or 5 μmol/kg). Anti-PEG IgM was detected in both serum and spleen cell culture from low dose rat, but not from high dose rat. This suggests that high dose gives some suppressive effects on spleen cells. In order to identify the susceptible cell against first dose level, we investigate the uptake of secondary injected PL by each spleen cell population after first injection. In comparison to high dose rat, the uptake of secondary injected PL by IgM⁺high B cell, mainly MZ-B cell, significantly increased in low dose rat. On the other hand, the uptake of PL by IgM⁻negative cell and IgM⁻low cell didn't change. These results may indicate that splenic MZ-B cell involve in reverse dose dependency of the ABC phenomenon.