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Topical Irradiation of UVA to The Eye Induces Immunosuppression in The Mice via Nitric-Oxise Dependent Neuronal Pathways

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It has been well documented that dermal irradiation by ultraviolet A (UVA) locally decreases the number of Langerhans cells and suppresses contact hypersensitivity of the skin. We found that topical irradiation of UVA to the eye systemically decreased the number of Langerhans cells (LC) in the dorsalskin and lymph nodes and elicited lymphocyte apoptosis in the latter tissues but not in the thymus. Optic nerve resection, but not ciliary ganglionectomy, eliminated the UVA-induced decrease in dermal Langerhans cells by a mechanism that was partially inhibited by hypophysectomy. The immunosuppressive effect of UVA was not observed in knockout mice lacking inducible-type of nitric oxide synthase (iNOS). These results suggested that topical irradiation of UVA to the eye induced immunosuppression via NO-dependet neuronal pathways.

Key words : UVA, immunosuppression, Langerhans cell, lymphocytes, apoptosis, iNOS

INTRODUCTION

Irradiation by ultraviolet ray (UV) causes a wide variety of events in the skin including sunburn and cancer (1,2). Irradiation of mice by UVA also decreases the number of Langerhans cells (LC) and results in the suppression of contact hypersensitivity. We previously reported that UVB irradiation of not only the skin but also the eye causes immunosuppression in the mice (3). However, the mechanisms of immunosuppression by topical UVA irradiation to the eye remains unknown. The present work describes the mechanism of immunosuppression by topical UVA irradiation to the eye.

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MATERIALS AND METHODS

Animal experiments. Specific pathogen-free, 8-week-old male DBA/2 Crj mice, hypophysectomized DBA/2 mice, and iNOS-knockout C57/B6j ($iNOS^{-/-}$) mice were used for experiments. Ciliary ganglionectomy and optic nerve resection were performed bilaterally as described previously (4,5). Under light ether anesthesia, either the eye or the ear was topically exposed to UVA at a dose of 110 kJ/m^2. Skin samples from the ear and dorsal trunk were dissected and incubated in phosphate buffered saline containing 20 mM EDTA. After incubation, the epidermis

was separated from the dermis using fine forceps under a light microscopy. Lymph nodes and the thymus were removed, embedded in tissu-Teck OCT compound and stored at –80°C.

Analysis of LC and CD45R. The epidermal sheets and frozen sections of lymph nodes and the thymus were subjected to immunohistochemistry for LC and CD45R.

Analysis of apoptosis. Apoptosis of lymphosytes in the thymus and lymph nodes were determined by terminal deoxynucleotidyl-transferase-mediated dUTP nick-end labeling staing using a Takara Apoptosis Detection Kit.

RESULTS AND DISCUSSION

Topical UVA irradiation of either the eye or the ear significantly decreased the number of LC in the epidermal sheets and lymph nodes a similar extent. Furthermore, UVA irradiation the eye induced apoptosis of CD45R-positive B cells in lymph nodes.

We also examined the effect of UVA irradiation in animals that had been subjected to either ciliary ganglionectomy or the optic nerve denervation. Optic nerve denervation, but not ciliary ganglionectomy, prevented the UVA-induced suppression of dermal LC.

Because hypophysectomy partially inhibited the suppressing effects of optic UVA irradiation (~60%), the UVA-induced immunosuppression might be mediated through hypothalamic and non-hypothalamic neuronal pathways.

The immunosuppressive effects of topical UVA irradiation to the eye were not observed in iNOS knockout mice.

These observations suggest that a signal evoked by UVA irradiation in the retina is transmitted to the hypothalano-pituitary pathway and non-hypothalamic neuronal pathway, thereby down-regulating LC and inducing B cell apoptosis in lymph nodes. Physiological significance of immunosuppression induced by topical UVA-irradiation to the eye was discussed with respect to dermal defense mechanism.

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