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Suppression of an Established Immune Response by UVA: A Critical Role for Mast Cells

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Abstract

Exposing experimental animals or human volunteers to UVA II (320–340 nm) radiation after immunization suppresses immunologic memory and the elicitation of delayed-in-time hypersensitivity reactions. Previous studies indicated that the mechanisms underlying UVA-induced immune suppression are similar to those described for UVB-induced immune suppression, i.e., transferred by T regulatory cells, overcome by repairing DNA damage, or neutralizing interleukin-10 activity, or by injecting recombinant interleukin-12. Here we continued our examination of the mechanisms involved in UVA II induced suppression. Antibodies to *cis*-urocanic acid blocked UVA-induced immune suppression. Treating UVA-irradiated mice with histamine receptor antagonists, calcitonin gene related peptide receptor antagonists or platelet activating receptor antagonists blocked immune suppression in UVA-irradiated mice. In light of the fact that *cis*-urocanic acid and calcitonin gene related peptide target mast cells, which can then release platelet activating factor and histamine, we measured UVA-induced immune suppression in mast cell deficient mice. No immune suppression was noted in UVA-irradiated mast cell deficient mice. These findings indicate that exposure to UVA II activates many of the same immune regulatory factors activated by UVB to induce immune suppression. Moreover, they indicate that mast cells play a critical role in UVA-induced suppression of secondary immune reactions.

INTRODUCTION

Exposure to ultraviolet (UV) radiation is responsible for a number of adverse health effects. The UV wavelengths in sunlight are the primary cause of non-melanoma skin cancer (1) and undoubtedly play a role in inducing melanoma (2). In addition to its carcinogenic properties, UV exposure is also immunosuppressive (3), and UV-induced immune suppression has been identified as a major risk factor for skin cancer induction (4). Moreover, acute UV exposure of both experimental animals and human volunteers suppresses cell-mediated immune reactions; such as contact and delayed type hypersensitivity (5–8).

A great majority of studies investigating photocarcinogenesis and photoimmunology employ sunlamps emitting primarily UVB (290 to 320 nm) radiation, even though approximately 95% of the solar UV radiation that reaches the biosphere is contained in the UVA (320 to 400 nm) region of the solar spectrum. Exposure to UVA radiation can be harmful. UVA exposure causes premature ageing of the skin (9) and very high rates of exposure have been associated with skin cancer induction in mice (10). The exact role of UVA in activating immune suppression

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has been an area full of controversy (11). Current information indicates that UVAII radiation (320 to 340 nm) suppresses secondary immune reactions (12) and immunologic memory (13). On the other hand, data generated by Reeve and colleagues (14) and latter confirmed by others (15), indicates that pre-exposure to UVAI radiation (340 to 400 nm) will block the immunosuppressive effects of subsequent exposure to UVB radiation. Thus, depending upon the sequence of events and wavelengths involved, UVA radiation can have disparate effects on the immune response.

Determining the role of UVA radiation in immune suppression has broad implications beyond its obvious interest to photobiologists. Until very recently most commercial sunscreens provided little to no protection against UVA radiation because of the perception that UVA was not as harmful as UVB. The realization that complete protection against immune suppression results only when broad spectrum sunscreens, protecting across both the UVB and the UVA region of the solar spectrum has changed the perception that UVA is not immunosuppressive (16–18). In addition, the observations that UVA exposure suppresses immunological memory suggest that excess sunlight exposure may have the potential to depress immune protection afforded by prior vaccination. These findings indicate that studies designed to determine the mechanism by which UVA radiation suppresses the immune response are important.

Previously, we reported that although the photobiological mechanisms that are involved in suppressing secondary immune reactions differ greatly from the photobiological mechanisms that suppress the induction of primary immune reactions (UVA II vs. UVB) the immunological mechanism are similar. We noted that pyrimidine dimers are found in the skin of UVA-irradiated mice, and repairing dimer formation blocks immune suppression. Antigen specific T regulatory cells were found in the spleens of UVA-irradiated mice. Cytokines are involved in transmitting the immune suppressive signal from the skin to the immune system. No suppression was noted in UVA-irradiated, anti-interleukin (IL)-10 injected mice. Similarly, treating UVA-irradiated mice with recombinant IL-12 blocked immune suppression (19).

Here we continued our examination of the mechanisms leading to UVA-induced immune suppression. Antibodies to *cis*-urocanic acid blocked UVA-induced immune suppression. Treating UVA-irradiated mice with histamine receptor antagonists, calcitonin gene related peptide receptor antagonists or platelet activating receptor antagonists blocked immune suppression in UVA-irradiated mice. Because *cis*-urocanic acid and calcitonin gene related peptide target mast cells, which can then release platelet activating factor and histamine, we measured UVA-induced immune suppression in mast cell deficient mice. No immune suppression was noted in UVA-irradiated mast cell deficient mice.

MATERIALS AND METHODS

Animals

Specific pathogen-free C3H/HeNNCr (MTV-) and C57BL/6NCr mice were obtained from the National Cancer Institute Frederick Cancer Research Facility Animal Production Area (Frederick, MD). Breeding pairs of mast cell deficient mice ($Kit^{w\text{-}sh}/Kit^{w\text{-}sh}$), backcrossed onto the C57BL/6 background were obtained from The Jackson Laboratories (Bar Harbor, ME). The animals were maintained in facilities approved by the Association for Assessment and Accreditation of Laboratory Animal Care International, in accordance with current regulations and standards of the National Institutes of Health. All animal procedures were reviewed and approved by MD Anderson Cancer Center Animal Care and Use Committee. Within each experiments all the mice were age and sex matched. The mice were generally 8–10 weeks old at the start of each experiment.

Antibodies and Reagents

Calcitonin gene related peptide antagonist ($CGRP_{8–37}$), cyproheptadine, cimetidine and mouse IgG were purchased from Sigma-Aldrich (St Louis, MO). PCA 4248 and trans-2,5-bis (3,4,5-trimethoxyphenyl)-1,3-dioxolone (hereafter referred to as dioxolone) were purchased from Biomol (Plymouth Meeting, PA). Dr Mary Norval, University of Edinburgh, provided us with the monoclonal anti-*cis*-UCA antibody (20).

Radiation Source

A 1000W xenon UV solar simulator, equipped with a Schott WG-335 atmospheric attenuation filter (3 mm thick), a visible/infrared band pass blocking filter (Schott UG-11; 1 mm thick) and a dichroic mirror (Oriel, Stratford, CT) was used to provide UVA radiation, devoid of UVB. The intensity and spectral output of this light source were measured with an Optronics model OL 754 scanning spectrophotometer interfaced to a laptop computer (Optronics Laboratories, Orlando, FL), and has been published previously (12). During irradiation of the shaved dorsal skin, the mice were held individually in a specially constructed Plexiglas container with a quartz glass top. Spectrophotometric readings were taken through the quartz glass top. During the irradiation period (15 to 20 min in duration), the mice were conscious and had full range of movement.

Suppression of the elicitation of DTH by solar simulated UV radiation

The design of the experiment is outlined in Figure 1. On day 0, mice were immunized by the subcutaneous injection of 10^7 formalin-fixed *Candida albicans* into each flank. Nine days later the mice were exposed to 80 kJ/m^2 of UVA radiation. The next day the mice were sedated, the thickness of each hind footpad was measured with an engineer's micrometer (Mitutoya, Tokyo, Japan), and the mice were challenged by injecting, 50 μl of Candida antigen (Alerchek Inc, Portland, ME) into each hind footpad. Eighteen to 24 h later, the thickness of each footpad was re-measured and the mean footpad swelling for each mouse was calculated (Δ left footpad thickness + Δ right footpad thickness ÷ 2). Generally there were 5 mice per group; the mean footpad swelling ± the standard error of the mean was calculated for each group. The background footpad swelling (negative control in each experiment) was determined in a group of mice that were not immunized but were challenged. The positive control in each experiment was determined by measuring the immune response in mice that were immunized and challenged, but were not exposed to UVA radiation. Subtracting the background response from the response found in each experimental group yielded the specific footpad swelling response. Percent immune suppression was determined by the following formula: % immune suppression = (1−[specific footpad swelling of the UV-irradiated mice ÷ specific footpad swelling of the positive control] × 100. Statistical differences between each group was determined by use of a one way analysis of variance followed by the Dunn's multiple comparison test (Prism, GraphPad Software, San Diego CA). Probabilities less than 0.05 were considered significant. Each experiment was repeated independently 2 to 3 times.

RESULTS

Is *cis*-UCA involved in UVA induced immune suppression?

Because others have shown that *trans*-UCA can be converted to the *cis*-isomer by wavelengths in the UVA region of the solar spectrum (21), we first wanted to determine if *cis*-UCA contributes to UVA-induced immune suppression. UVA-irradiated mice were injected with a monoclonal antibody to *cis*-UCA or control IgG, and the effect this treatment had on DTH was measured (Figure 2). The DTH response in mice that were exposed to 80 kJ/m^2 of UVA and injected with 1, 5, or 20 μg of control IgG was significantly suppressed ($p < 0.05$ vs. the positive control). Treating the UVA-irradiated mice with 1 or 5 μg of anti-*cis*-UCA antibody did not

reverse immune suppression. When the mice were injected with 20 μg of anti-*cis*-UCA monoclonal antibody the immune suppression was reversed, in that the DTH reaction generated in these mice was not significantly different ($p > 0.05$) from the positive control. These data indicate that neutralizing *cis*-UCA reverses UVA-induced immune suppression.

Is Calcitonin Gene Related Peptide involved in UVA induced immune suppression?

Others have demonstrated that calcitonin gene related peptide, which is released by cutaneous nerves can play a role in UV-induced immune suppression, in part by the induction of IL-10 (22). Because our previous data implicated IL-10 in UVA-induced immune suppression (19), we asked if calcitonin gene related peptide plays a role. The mice were immunized with *C albicans* and treated with UVA 9 days post irradiation as described above. Some animals received the calcitonin gene related peptide antagonist ($GCRP_{8–37}$) one h prior to UVA treatment. Others were injected with GCRP $_{8–37,}$ but were not treated with UVA. The data from this experiment (Figure 3) indicates that injecting $GCRP_{8–37}$ by itself did not affect the DTH reaction, as the mice that received GCRP $_{8–37}$ without UVA generated a DTH reaction that was indistinguishable from the positive control. As expected, exposing the mice to 80 kJ/m^2 of UVA radiation caused a significant decrease in the DTH reaction (67% immune suppression; $p < 0.05$ vs. the positive control). Injecting GCRP $_{8–37}$, into UVA-irradiated mice, at all doses tested, reversed the immune suppression. The DTH response generated in UVA-irradiated, CGRP $_{8–37}$-injected mice was not significantly different from the positive control. These data indicate that blocking CGRP activity blocks UVA-induced immune suppression.

Reversal of UVA-induced immune suppression by histamine receptor antagonists

The role of histamine in UV-induced immune suppression is well recognized (23). Therefore, we decided to determine if histamine plays a role in UVA-induced immune suppression by using two well-known histamine receptor antagonists, cyproheptadine (H_1 receptor antagonist) and cimetidine (H_2 receptor antagonist) (Figure 4). The mice were immunized with *C albicans* and treated with UVA 9 days post irradiation as described above. Some animals received the 100 μg of cimetidine or 300 μg of cyproheptadine one h prior to UVA treatment. Others were injected with cimetidine or cyproheptadine, but were not treated with UVA. The doses of cimetidine and cyproheptadine used here were chosen from the literature (23). Similar to what was reported earlier when contact hypersensitivity was used as the immunological endpoint (23), injecting cimetidine or cyproheptadine into non-UV-irradiated mice did not effect the DTH reaction ($p > 0.05$ vs. the positive control). UVA-treatment significantly suppressed the DTH reaction (72% immune suppression, $p < 0.01$ vs. the positive control). Treating the mice with cimetidine or cyproheptadine prior to irradiation totally reversed UVA-induced immune suppression, as there was no significant difference between the DTH reaction generated in these mice and the positive control. These data indicate that blocking histamine from binding to either the H_1 or the H_2 receptor prevented UVA-induced immune suppression.

Does blocking platelet activating factor (PAF) receptor binding block UVA-induced immune suppression?

Previously we demonstrated that blocking the binding of PAF to its receptor blocked UVB-induced immune suppression (24,25). Also, interfering with PAF receptor binding blocks the immune suppression when another dermal immunotoxin, jet fuel, was used (26). Based on these findings, we decided to test the hypothesis that blocking PAF receptor binding will block UVA-induced immune suppression. Nine days after immunization and one h before UVA exposure, the mice were injected with PAF receptor antagonists. The mice received either 500 nmol of PCA-4248, or 500 nmol of dioxolone. The doses of two PAF receptor antagonists used were chosen from the literature (24,26). The effect that this treatment had on UVA-induced immune suppression is shown in Figure 5. Exposure to UVA radiation, one day prior to

antigenic challenge induced significant immune suppression (80% immune suppression, $p < 0.01$ vs. the positive control). When the mice were injected with either of the PAF receptor antagonists prior to UVA-irradiation, no immune suppression was noted, as the DTH reaction in these mice was not significantly different from that found in the positive control ($P > 0.05$). Because we previously noted that injecting the PAF receptor antagonists into non-irradiated mice 9 days after immunization had no effect on the elicitation of DTH (26), this control was not run here in order to reduce the numbers of mice needed for this study.

A critical role for mast cells in UVA-induced immune suppression

It is interesting to note that many of the factors that are involved in UVA-induced immune suppression either target, or are produced by mast cells. Mast cells respond to *cis*-UCA (27) and CGRP (28). Mast cell express histamine and PAF receptors on their surface, and they can secrete cytokines such as IL-10 in response to activation (29). Therefore, we decided to examine the role of mast cells in UVA-induced immune suppression. We essentially repeated the experiment described in Figure 1 with one modification. One arm of the experiment employed wild-type C57Bl/6 mice, and the other arm of the experiment employed mast cell deficient mice ($Kit^{W\text{-}sh/W\text{-}sh}$), which have been backcrossed onto the C57Bl/6 background. The results from this experiment are found in Figure 6. As demonstrated above, exposing *C albicans* immunized C57Bl/6 mice to 80 kJ/m^2 of UVA radiation suppressed the elicitation of DTH (86% immune suppression; $p < 0.01$ vs. the positive control). Treating mast cell-deficient mice with an equal dose of UVA radiation did not suppress the elicitation of DTH ($p > 0.05$, UVA-irradiated mast cell−/− mice vs. non-irradiated mast cell−/− positive control). These data indicate that UVA-induced immune suppression is mast cell dependent.

DISCUSSION

Besides being of interest to photobiologists, we believe that studying the mechanism underlying UVA-induced suppression of established immune reactions has implications beyond photobiology. The most successful public health campaign of the 20^{th} century was the widespread use of vaccination to reduce the morbidity and mortality due to infectious disease. Our previous data (12,19), and those published by Halliday and colleagues (16,17) and Moyal and co-workers (13,18) clearly indicate that UVA radiation can suppress immunological memory, suggesting that sunlight exposure has the potential to suppress immunologic protection afforded by previous vaccination. With these findings in mind, and in light of the fact UVA radiation comprises greater than 95% of the UV radiation found in ambient sunlight, experiments designed to determine the mechanisms by which UVA radiation suppresses established immune reactions have merit. The data reported here agree with our initial report on the mechanisms involved. Although the basic photobiological mechanisms differ (12), the immunological mechanisms are remarkably similar. We report here that *cis*-UCA, histamine receptor binding, PAF receptor binding and CGRP receptor binding are all required for UVA-induced immune suppression. We were surprised by the close agreement between our results and those reported previously documenting immune suppression by UVB (30). The only small difference we noted was the requirement for more anti-*cis*-UCA monoclonal antibody to block UVA induced immune suppression. Previously we noted that 5 μg of anti-*cis*-UCA monoclonal antibody was sufficient to block UVB-induced immune suppression (31), here we needed to use at least 20 μg to overcome UVA-induced immune suppression. The reason why more anti-*cis*-UCA antibody was required to reverse UVA II-induced immune suppression remains unknown, but perhaps it reflects the fact that in these studies we measured the effect of UV radiation on the elicitation of an immune response and in previous experiments the effect of UVB on the induction of immunity were examined. The doses of $CGRP_{8–37}$, cimetidine, cyproheptadine and the PAF receptor antagonists used here to abrogate UVA-induced immune suppression were identical to those that successfully used in the past to block UVB-induced

immune suppression. It is of interest to note that one of the strongest inducers of PAF is reactive oxygen species (32). Because UVA is a well-recognized generator of reactive oxygen species, it is entirely possible that UVA-induced reactive oxygen is activating PAF production in this system.

In a previous study we reported that we could suppress secondary immune reactions with UVB/UVA radiation (290 to 400 nm), and with UVA II (320 to 340 nm), but not UVA I (340 to 400 nm) (12). The fact that the immunological mechanisms involved in suppressing established immune reactions by UVA (19) and those involved in suppressing the induction of an immune response with UVB are the same (30), suggests that from an immunological point of view the skin immune system does not distinguish between UVB and UVA II. Alternatively, the results generated here and in our previous reports (12,19) may simply reflect that fact that UVAII exposure represents the "tail-end " of the UVB spectrum. Action spectra showing isomerization of *cis*-UCA by UVAII (21,33) and immune suppression by narrow band 320 nm light (34) would support this concept.

Our data document a critical role for mast cells in UVA-induced immune suppression. These findings add to the growing appreciation of a role for mast cells in regulating adaptive immune reactions. Conventional wisdom suggests that mast cells primarily serve as effector cells in IgE-mediated allergic inflammation, in part through the release of preformed mediators stored in the cell's cytoplasmic granules. However, immunologists now realize that mast cells regulate the adaptive immune response, in part though regulated release of cytokines and soluble factors (35). Important contributions for appreciating the role of mast cells in regulating adaptive immune reactions came from studies in photobiology. For example, Hart and colleagues failed to induce immune suppression in UV-irradiated mast cell deficient mice. Moreover, when mast cell deficient mice were reconstituted by injecting wild-type bone marrow-derived mast cells into the dermis (so called "mast cell knock-in mice"), immune suppression was restored (36). Our findings expand on these observations by showing that mast cells are also involved in the UVA-induced suppression of the elicitation of DTH. Whether this observation contributes to skin cancer induction is not known. It is important to note that increased mast cell prevalence has been associated with susceptibility to melanoma and basal cell carcinoma in humans (37, 38). Because of the well-known role of mast cells in mediating UVB-induced immune suppression, and in light of the fact that UVB-induced immune suppression is a risk factor for skin cancer development, it has generally been accepted that mast cells and the immunosuppressive products released by them are contributing to cancer development via immune suppression. Our data suggest that UVA may play also play role in this process through its effects on mast cells.

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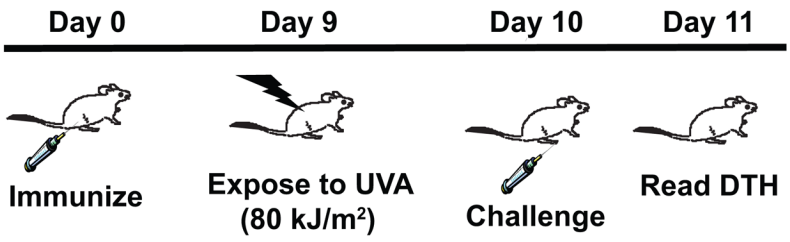

Figure 1.
Suppressing the elicitation of DTH with UVA radiation. Mice were immunized on day 0 and then exposed to an immunosuppressive dose of UVA radiation 9 days later. On day 10 they were challenged with antigen, and DTH was measured 18 to 24 h later.

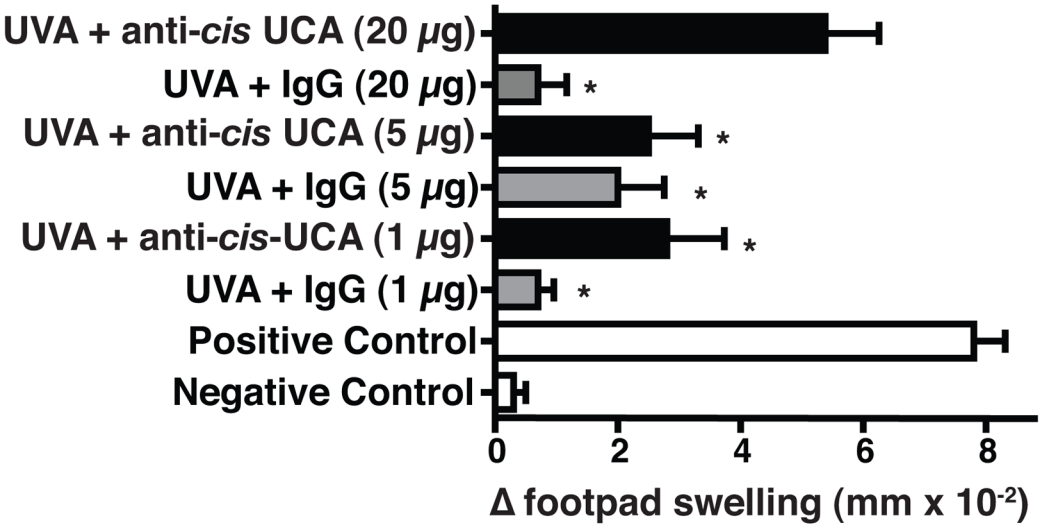

Figure 2.

Monoclonal anti-*cis*-UCA antibody blocks UVA-induced immune suppression. One h prior to UVA exposure, the mice received an intraperitoneal injection of anti-*cis*-UCA (black bars) or control IgG (grey bars). The data are expressed as mean Δ footpad swelling ± the standard error of the mean. * indicates a statistically significant difference ($p < 0.05$) from the positive control.

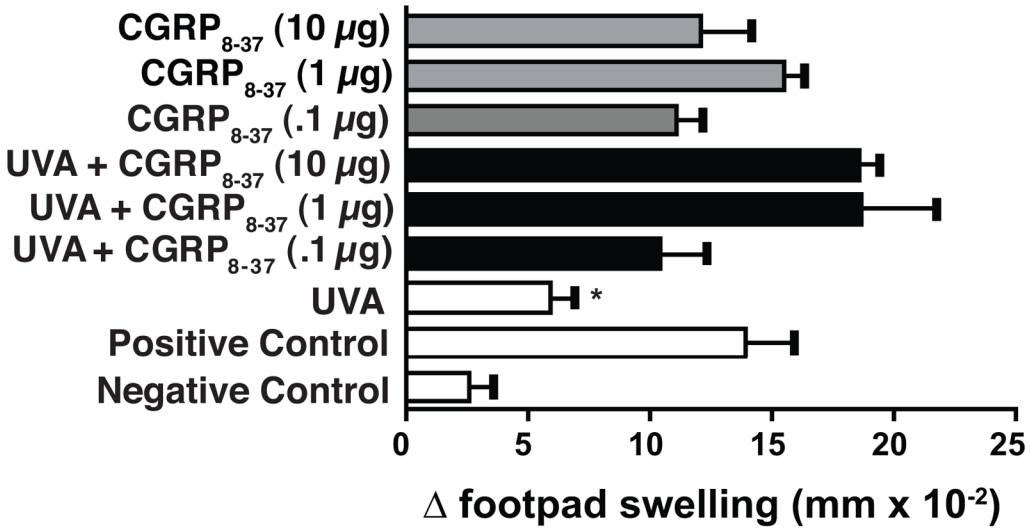

Figure 3.

Injecting calcitonin gene related peptide antagonists into UVA-irradiated mice blocks immune suppression. One h prior to UVA exposure, the mice received an intraperitoneal injection of CGRP $_{8–37}$ (black bars). Control groups were injected with CGRP $_{8–37}$ but not exposed to UVA (grey bars). The data are expressed as mean Δ footpad swelling ± the standard error of the mean. * indicates a statistically significant difference ($p < 0.05$) from the positive control.

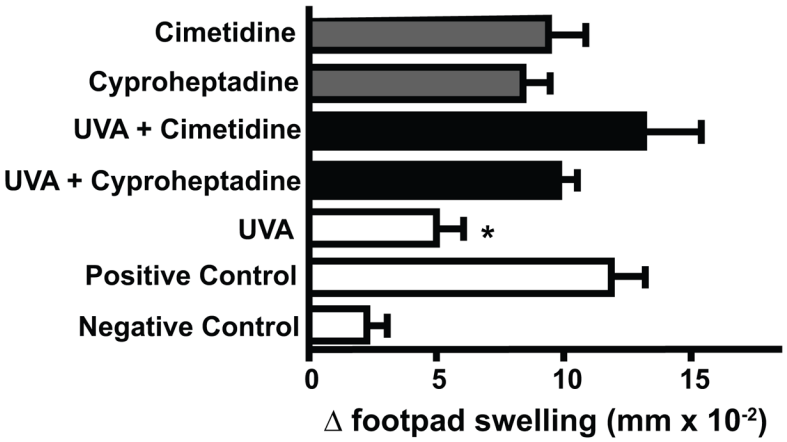

Figure 4.

Treating UVA-irradiated mice with histamine receptor antagonists blocks UVA-induced immune suppression. One h prior to UVA exposure, the mice received an intraperitoneal injection of 100 μg of cimetidine or 300 μg of cyproheptadine (black bars). Control groups were injected with cimetidine or cyproheptadine but not exposed to UVA (grey bars). The data are expressed as mean Δ footpad swelling ± the standard error of the mean. * indicates a statistically significant difference ($p < 0.01$) from the positive control.

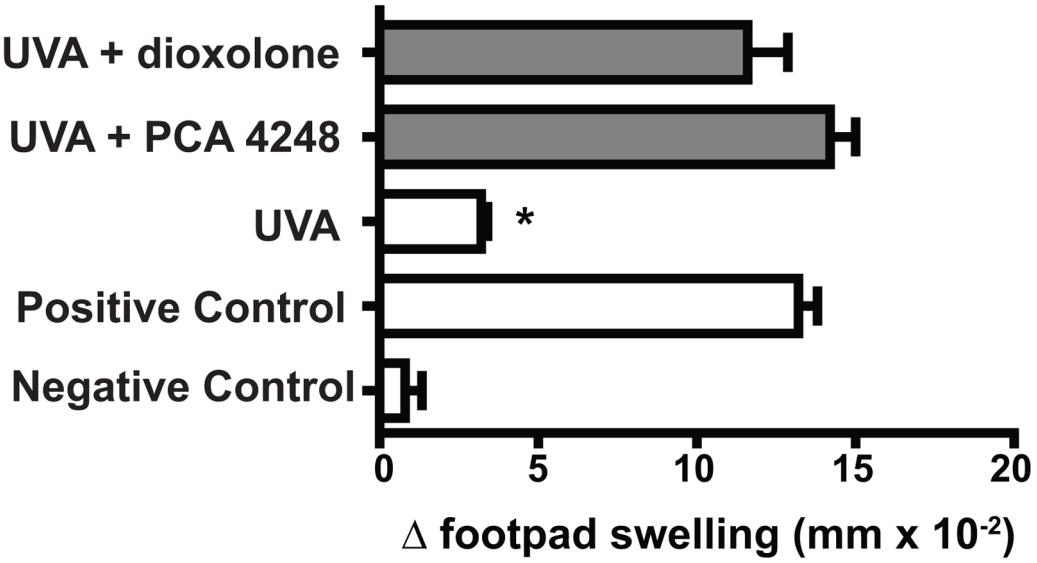

Figure 5.
PAF receptor antagonists block UVA-induced immune suppression. One h prior to UVA exposure, the mice received an intraperitoneal injection of 500 pmol of PAC 4248 or dioxolone. The data are expressed as mean Δ footpad swelling ± the standard error of the mean. * indicates a statistically significant difference ($p < 0.01$) from the positive control.

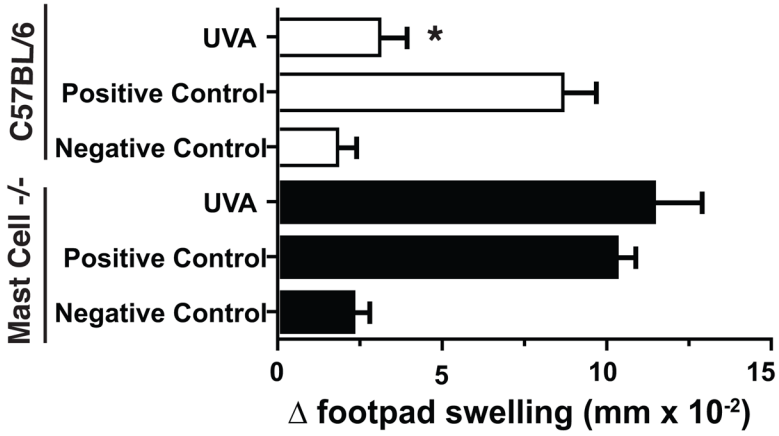

Figure 6.

Exposing mast cell-deficient mice to UVA fails to suppress the elicitation of DTH. C57Bl/6 (black bars) and mast cell-deficient mice (open bars) were immunized with antigen on day 0 and then exposed to 80 kJ/m^2 of UVA on day 9. The mice were challenged on day 10 and DTH was measured on day 11. The data are expressed as mean Δ footpad swelling ± the standard error of the mean. * indicates a statistically significant difference ($p < 0.01$) from the positive control.