Prostaglandin E_2 and D_2 but Not MSH Stimulate the Proliferation of Pigment Cells in the Pinnal Epidermis of the DBA/2 Mouse

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Epidermal melanocytes proliferate following a variety of physical stimuli, for example, mechanical injury to the skin or exposure to UV radiation. We suggest that some transducer in the epidermis converts the physical modality into a biochemical signal which is responsible for initiation of mitosis. Melanocyte stimulating hormone, both α and β variants, administered parenterally for periods up to 4 weeks do not alter the number of melanocytes per mm^2 in several strains of neonatal or adult mice. Ultraviolet B and arachidonic acid both stimulate proliferation of pigment cells. Indomethacin which inhibits cyclooxygenase and the formation of prostaglandins (PGs) blocks the proliferation induced by both agents. We tested a wide variety of PGs. We observed that PGD_2 applied daily to the skin of a mouse causes a small increase in melanocyte density (cells/mm^2). PGE_2 in similar doses applied topically caused a large increase. PGE_2 caused an increase in the uptake of tritiated thymidine by dopa-positive dendritic cells. This indicates that PGE_2 stimulated some melanocytes to proliferate. Histologic studies indicate that PGE_2 also enhances melanogenesis. PGE_2 is synthesized in the skin and affects keratinocytes and Langerhans cells as well as pigment cells. We postulate that it is one compound that can modulate the interaction of these 3 main cells of the epidermis. *J Invest Dermatol 86:433–437, 1986*

Pigment cells have a highly specialized function, specifically to make the pigment melanin. Despite their highly differentiated condition, they can proliferate spontaneously [1] or in response to a variety of stimuli. Physical agents like mechanical trauma [2] or exposure of skin to electromagnetic radiation such as ultraviolet type B (UVB, 290–320 nm) [3–5] or psoralens and UVA (PUVA) (320–400 nm) [4,6] stimulate the proliferation of pigment cells in vivo. In vitro and in vivo UVB cause damage to pigment cells [7] and PUVA can retard pigment cell growth and proliferation [4,8–10]. This effect is not surprising since electromagnetic radiation causes the formation of thymine dimers within and between the double strands of DNA and within RNA. For the cell to function normally, the damaged DNA normally is repaired (unscheduled DNA synthesis) [11]. All cells, including melanocytes, are susceptible to injury by UV radiation [4–11]. It is surprising that pigment cells proliferate in vivo in response to these different physical stimuli. We suggest that some transducer within the skin converts the electromagnetic radiation or mechanical stimulus into a biochemical signal for proliferation.

In previous reports we have demonstrated that monobenzyl ether of hydroquinone (MBEH) [12,13] and arachidonic acid (AA) [12,13] both stimulate the proliferation of pigment cells. MBEH is a known melanocytotoxin. However, it is not a simple specific toxin for epidermal pigment cells and its effects on the skin are complex. We postulated and have shown in preliminary experiments that MBEH activates the oxidation of AA to a variety of products, predominantly PGE_2, thromboxane B (TXB), and prostaglandin (PG) D_2 (Nordlund, unpublished). Applications of long chain fatty acids like AA and linolenic acid to murine skin also stimulate proliferation of epidermal pigment cells [13]. This effect is partially blocked by indomethacin (IM) [12,13], an observation which suggests that some product from the oxidation of AA is involved.

We have completed a series of experiments to confirm that PGs may be involved in stimulating pigment cell proliferation and to determine which specific PGs are the active agonists.

MATERIALS AND METHODS

Animals All mice were purchased from Jackson Laboratory, Bar Harbor, Maine. For most experiments, 6-week-old DBA/2 mice were used. For some experiments, neonatal and adult C57BR/Cd and adult C3H/HE strains also were used. All mice were maintained in the animal facilities at the University Medical Center and had free access to Purina mouse chow and water for most but not all experiments.

Indomethacin: For some experiments mice were given IM to determine whether it blocked UVB (290–320 nm)-induced proliferation of melanocytes [3–5]. Mice normally consumed 3–4 g of chow per day. For some experiments food was limited to 2 g of Purina chow per mouse per day. Indomethacin (Merck, Sharp & Dohme Pharmaceuticals, New Jersey) was dissolved in ethanol and then dissolved into the nuggets of chow. The chow was

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Abbreviations:
AA: arachidonic acid
CTA_2: synthetic analog of thromboxane A_2
IM: indomethacin
MBEH: monobenzone; monobenzyl ether of hydroquinone
MSH: melanocyte stimulating hormone
PBS: phosphate-buffered saline
PG: prostaglandin
PUVA: psoralen plus UVA
TXB: thromboxane B
DMSO: dimethyl sulfoxide

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mixed carefully so it contained IM 0.3 mg/2 g food. The animals consumed daily all food in each cage. Mice weighed 20–25 g and received 12–15 mg of IM per kg of body weight 5 days per week. The maximum sublethal oral dose of IM seems to be about 0.3 mg per mouse per day (approximately 12–15 mg/kg). Over the weekends, the animals had free access to untreated chow and water.

UV Radiation: Mice were exposed to a bank of 4 FS-40 fluorescent (Sylvania Company) UV lamps. The lamps emitted negligible quantities of UVC. Seventy-five percent of the energy was UVB and 25% UVA. Fluence was measured with Spectroline DM-265N, DM-300N, and DM-360N meters (Spectronics Corp., Westbury, New York) recalibrated by the manufacturer every 6 months. For these experiments the fluence was 900 $\mu W/cm^2/s$. Animals were exposed for 5 min (270 mJ/cm^2) 5 days per week. The ears were excised from ether-killed mice on days 7 and 14. The epidermis was obtained and stained by the dopa technique as previously published [12,13] and described briefly below.

Prostaglandin Topical Application Mice were treated with one of various PGs (E_1, E_2, $F_{2\alpha}$, D_2, I_2) obtained from Sigma Chemical Company, St. Louis, Missouri. Other mice were treated with a synthetic carbocyclic thromboxane, CTA_2 (Biomol Laboratories, Philadelphia, Pennsylvania) or with TXB. The synthetic CTA_2 has a biologic activity similar to TXA_2.

Groups of 5 mice were treated on the dorsal surface of both ears with applications of 0.1 μg, 1 μg, or 10 μg of one PG dissolved in 20 μl of dimethyl sulfoxide (DMSO): H_2O (1:1). For some experiments PGE_2 was diluted in 95% ethanol. Control animals were treated with ethanol or DMSO to determine the effects of diluent. Some mice were untreated. Solutions were applied for periods of 5–21 days.

Melanocyte Stimulating Hormones Alpha and beta melanocyte stimulating hormone (MSH) were obtained from Dr. Saul Lande, Department of Dermatology, Yale University. Crude porcine ACTH (100 IU/mg) was purchased from Sigma Chemical Company. Bovine β-lipotrophin (Cohn fraction IV) was purchased from ICN Nutritional Biochemicals, Cleveland, Ohio.

Tissue Procurement and Staining The ears were surgically excised from mice sacrificed with ether euthanasia. One ear was fixed in 10% buffered formalin. The tissue was cut into 5-μm sections and prepared for routine hematoxylin/eosin and Fontana Masson staining.

The remaining ear was mechanically split into dorsal and ventral halves. The dorsal surface was incubated at 37°C for 2 h in 0.025 M EDTA at pH 7.2. The epidermis was peeled away from the dermis and incubated at 37°C for 3–4 h in a freshly prepared solution of buffered dopa (*dl*-3,4-dihydroxyphenylalanine, Sigma Chemical Company) as previously published [12,13]. The tissue was dehydrated, cleared, and mounted in Permount for viewing through a Leitz-20 microscope. An ocular grid was inserted into the eyepiece. The number of dopa-positive dendritic cells per mm^2 in 5 standardized sites of each ear was counted. At least 5 mice were used in each group.

Uptake of Tritiated Thymidine An increase in numerical density of dopa-positive cells might be due to activation of the enzyme tyrosinase in dopa-negative cells or by proliferation. To determine whether some cells were undergoing division, the treated tissues were exposed to tritiated thymidine ([^{3}H]dThd). The epidermal/dermal sheets were pulse labeled with 20 μCi/ml of [^{3}H]dThd, 2 Ci/mol (New England Nuclear, Boston, Massachusetts) at 37°C for 2 h in F-10 media pH 7.4 (Gibco, Grand Island, New York) as previously described [13]. The sections were washed in phosphate-buffered saline (PBS) and fixed in 10% buffered formalin and stained by the dopa oxidase technique. The tissue was frozen, vertical sections were cut and placed on slides. The slides were dipped in nuclear track emulsion (Eastman Kodak Company, Rochester, New York) and incubated in absolute darkness for 7 days. The slides were washed in PBS and counterstained with hematoxylin/eosin. The number of labeled dopa-positive cells/mm of basal epidermis was determined by counting with a micrometer in the eyepiece.

Table I. Effect of Indomethacin on UVB-Induced Proliferation of Murine Pinnal Epidermal Melanocytes

	Dopa-Positive Cells/mm^2 (± SE)	
	Day 5	Day 10
UVB[a]	399 ± 28	661 ± 50
	$p < 0.01$	$p < 0.001$
UVB + IM	275 ± 18	415 ± 35
	NS	$p = 0.01$
Untreated	238 ± 19	306 ± 17
		NS
IM only	ND	317 ± 22

[a]UVB (290–320 nm) fluence 900 $\mu W/cm^2$; dose 270 mJ/cm^2.
Abbreviations: IM = oral indomethacin 0.3 mg/mouse/day
ND = not done
NS = not significant ($p > 0.05$)

Statistical Analysis Differences between experimental and control groups were determined by using Student's *t*-test. The data were considered significant when the p value was <0.05.

RESULTS

Indomethacin and UVB Mice receiving IM mixed in limited quantities (2 g/mouse/day) of Purina chow were exposed to UVB. Other mice not receiving IM were exposed to UV radiation and had restricted food intake (2 g/mouse/day). Another control group of mice was given limited food with IM; a fourth group had restricted food intake only. The latter 2 controls were not exposed to UVB. We observed that the number of dopa-positive cells was not affected by limitation of food (untreated, Table I) or by limited food and IM (IM only, Table I).

The number of dopa-positive cells per mm^2 in the epidermis from mice exposed to UVB (UVB, Table I) increased from a baseline mean of 238 cells/mm^2 to 399 cells/mm^2 after 1 week and 661 cells/mm^2 after 2 weeks. Mice receiving IM and exposed to UVB radiation had a much lower increase in the number of melanocytes from 238 to 275 dopa-positive cells/mm^2 after 1 week and to 415/mm^2 after 2 weeks (UVB and IM, Table I). IM by statistical analysis significantly decreased the increment of dopa-positive cells induced by UVB. The results are consistent with the hypothesis that at least in part PGs stimulate melanocyte proliferation and/or melanogenesis.

Prostaglandin $F_{2\alpha}$, Thromboxanes, Prostacyclin The ears of groups of 5 mice were treated for 7, 14, or 21 days with one of the following compounds: $PGF_{2\alpha}$, TXB, prostacyclin, or CTA_2. To each ear 20 μl of DMSO:H_2O containing 0.1, 1.0, or 10.0 μg of reagent was applied. The number of dopa-positive cells was determined on days 7, 14, and 21. We found that these derivatives of AA oxidation, in the amounts applied, had insignificant effects on the population density of the epidermal pigment cells. Examination of the treated ears embedded in paraffin and stained by hematoxylin/eosin revealed no evidence of inflammatory infiltrate or any pathologic alterations of the epidermis or dermis.

Effects of PGD_2 on Epidermal Pigment Cells PGD_2 was dissolved in DMSO:H_2O (1:1). Groups of 5 DBA/2 mice were treated by applications of 20 μl solution containing 0.1, 1.0, or 10 μg of PGD_2. No effects on the epidermal pigment cells were noted with the 2 lower quantities (0.1 or 1.0 μg). However, in 3 separate experiments we observed that applications of 10 μg of PGD_2 produced an average of 31% increase (range 14–47%) in melanocytes per mm^2 on day 14. This increment by statistical analysis (Student's *t*-test) was significant at a $p < 0.05$ level. The

Table II. Effects of PGE_2 on Melanocytes/mm^2 in Pinnal Epidermis Treated for 14 Days

Experiment	Dose/Day	Control	Mean No. of Pigment Cells/ mm^2 Treated	Increase (% variance)
1	10 μg	225	408[a]	81
2	10 μg	138	255[a]	85
3	10 μg	176	216[b]	23
	25 μg		223[b]	27
	50 μg		295[a]	68

[a]Treated vs control, $p < 0.01$.
[b]Treated vs control (t-test), $p < 0.05$.

data suggest PGD_2 has a small stimulatory effect on epidermal pigment cells.

Effects of PGE_1 and PGE_2 on Epidermal Pigment Cells PGE_1 was applied to the pinnal epidermis for 7–14 days. On day 7, no change was observed in the number of dopa-positive cells. On day 14, the number of epidermal pigment cells increased from a baseline of 237/mm^2 to 290 (1.0 μg PGE_1; 22% increase) and 278 (10 μg PGE_1, 17% increase).

PGE_2 at 0.1 μg and 1.0 μg had little effect on the population of pigment cells. At doses of 10 μg per ear or greater applied 5 days per week over a period of 14 days, the pigment cells exhibited a marked increase in numerical density (Table II). At day 7 there was little or no change in number. However, by day 14, the numbers increased substantially (Fig 1*A,B*). At day 21, further increases were not noted. The largest increase from 3 different experiments was an 80% increment in the number of dopa-positive cells. Although there was some variation from experiment to experiment, PGE_2 was a consistent and potent stimulant of pigment cells.

Tritiated Thymidine Labeling Studies We wished to determine whether the PGE_2 was activating the tyrosinase enzyme in dopa-negative melanocytes or inducing proliferation of pigment cells. Ears of mice were treated for 5 or 10 days with 10 μg of PGE_2. The tissues were pulse labeled in [^{3}H]dThd for 2 h. The tissue was processed as described. The number of labeled, dopa-positive cells per mm of basal cells, was determined. Tissues treated with diluent had an average of 1.2 (±0.2) dopa-positive labeled cells per mm of basal cells. In contrast, PGE_2-treated animals exhibited a 13% increase (1.35 ± 0.2) labeled cells per mm of basal cells on day 5 and again on day 10. The difference was small but consistent on day 5 and day 10 in 2 separate experiments. Although the increment was observed in all experiments, the difference was not significant by statistical analysis ($p > 0.05$).

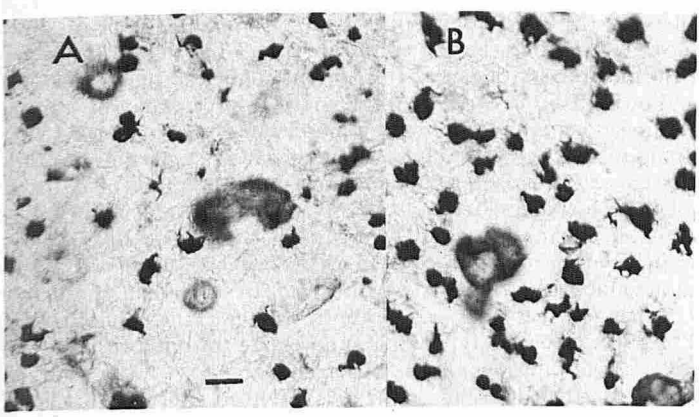

Figure 1. *A*, Photomicrograph of a sheet of pinnal epidermis from a diluent-treated DBA/2 mouse. Dopa stain. *Bar* = 10 μm. *B*, Photomicrograph of a sheet of pinnal epidermis treated for 10 days with 10 μg PGE_2. There is a significant increase in the number of dopa-positive cells.

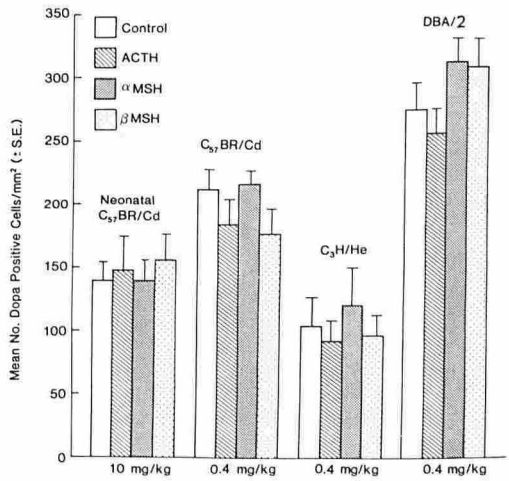

Figure 2. Effect of MSH and ACTH on epidermal dopa-positive cells from DBA/2 mice. Treatment, 21 days. Adrenocorticotrophic hormone (*ACTH*), α-MSH, and β-MSH did not alter the number of dopa-positive cells.

Melanocyte Stimulating Hormones MSH would seem to be the normal hormonal stimulant for proliferation of epidermal pigment cells [14]. To test this possibility, we injected neonatal and adult mice with α-MSH, β-MSH, ACTH, and β-lipotrophin (0.4 mg/mouse/day) for periods of 4 weeks. Mice of several strains were used. We observed that these amounts of peptide hormones did not change the number of epidermal pigment cells (Fig 2).

To determine whether the quantities of MSH in preliminary experiments were insufficient to induce proliferation, we injected groups of 5 DBA/2 mice with doses of MSH varying from 1 mg/kg up to a maximum of 40 mg/kg 5 days a week for periods up to 3 weeks. As positive controls we treated other mice with exposures to UVB or PUVA, or sensitized them to the cutaneous

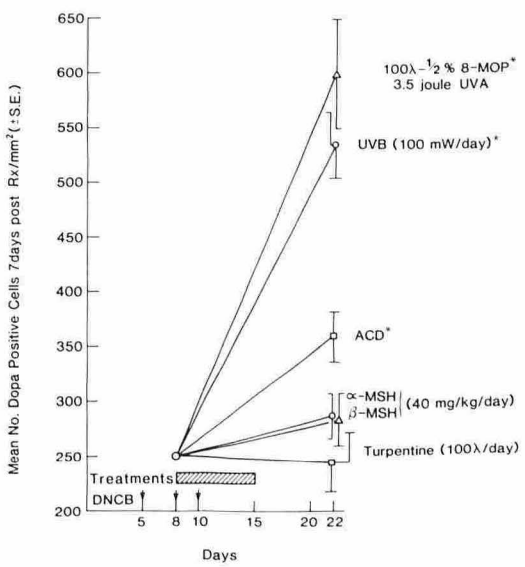

Figure 3. The number of dopa-positive cells increases significantly following exposure to UVB or PUVA ($p < 0.001$). α-MSH and β-MSH had no effects on melanocyte population. Allergic contact dermatitis (*ACD*) induced with dinitrochlorobenzene, but not the irritant turpentine, increased the number of melanocytes per mm^2. *DNCB*, dinitrochlorobenzene.

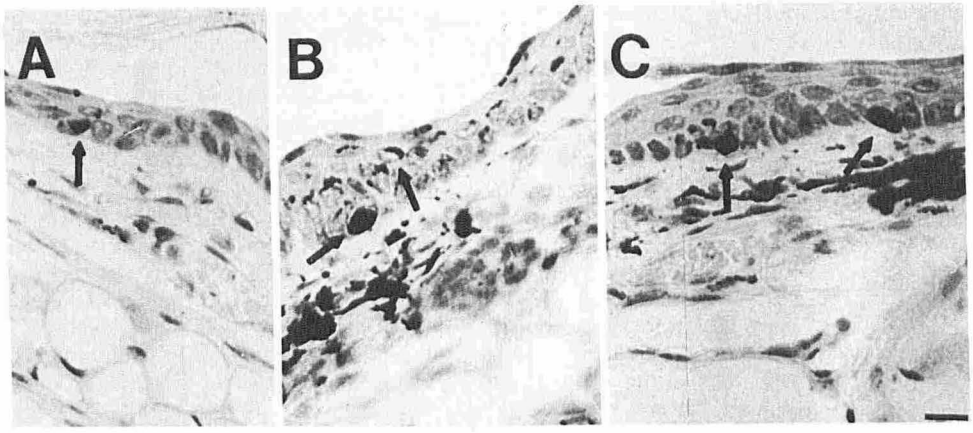

Figure 4. Photomicrograph of diluent-treated murine pinnal epidermis stained with the Fontana-Masson silver technique for melanin. Small amounts of melanin are visible (*arrows*). *B and C,* Epidermis from PGE_2-treated animals. There is a marked increase in the quantity of melanin both in the epidermis and dermis. There is no evidence of neutrophilic or mononuclear infiltrate in the dermis or damage to the dermis or epidermis. Magnification the same in *A–C, bar* = 10 μm.

allergen dinitrofluorobenzene (DNFB). Although the MSH had no effect on the melanocyte populations, the UVB, PUVA, and allergic contact dermatitis each caused a significant increase in the population densities of these cells (Fig 3). We concluded that these peptides are not effective stimulators of melanocyte proliferation in mice.

Effects of Prostaglandins on Melanogenesis Tissues treated with the different PGs were processed for histologic examination and stained with hematoxylin/eosin or the Fontana Masson silver stain for melanin. The amount of melanin was evaluated by one observer (JJN) from coded slides. Only PGE_2 showed a moderate to heavy increase in epidermal melanin (Fig 4). PGE_2 seems to accelerate melanogenesis.

DISCUSSION

Melanocytes are highly differentiated cells but are capable of proliferating in response to mechanical injuries or exposures of the skin to UVB and PUVA. Some biochemical process activated by trauma must be responsible for the proliferation of melanocytes in the skin following injury. UVB produces significant injury to the DNA of all cells, including melanocytes. Covalent photoadducts must be excised and repaired if the cells are to proliferate [15,16]. Similarly, PUVA produces damage to pigment cells. It is difficult to conceive of how these physical modalities can cause pigment cells to proliferate. It seems likely that there are transducers within the skin that convert these physical stimuli into biochemical signals.

Injury, UVB, PUVA, and allergic contact dermatitis can activate the oxidation of AA to PGs by cyclooxygenase. That a product of AA oxidation by cyclooxygenase is responsible for activation and/or proliferation of epidermal pigment cells is confirmed by results of experiments reported here. AA itself is an excellent stimulus for proliferation of pigment cells [13]. It is unknown whether AA itself produces proliferation or is converted to an active metabolite. Like phorbol esters and epidermal growth factor, AA can activate protein kinase C which may be involved in cell growth. That IM partially blocks the activities of AA [13] suggests that some of the effects of AA are produced by PGs. Murine epidermis treated with MBEH or AA synthesizes PGE_2, PGD_2, and TXB as measured by thin-layer chromatography and reverse-phase high-performance liquid chromotography (unpublished).

Our data confirm that one prostaglandin, PGE_2, can stimulate proliferation of pigment cells [17]. That PGE_2 can do this when applied to the skin does not prove that it is the biologically relevant regulator for melanocyte proliferation. That it was effective in quantities as small as 10 μg per ear and the proliferation exhibited a dose-response relationship is consistent with the hypothesis that PGE_2 is one regulator of pigment cell proliferation. PGD_2 was a less potent stimulant than PGE_2. No studies were done to determine whether it increased [^{3}H]dThd uptake.

The 13% increment in uptake of [^{3}H]dThd induced by PGE_2 was small. However, it was a consistent increase found in 2 separate experiments after both 5 days and 10 days of treatment. Although the increment was not significant by statistical analysis, the 13% increased uptake of [^{3}H]dThd represents an increment in DNA synthesis measurable during the short 2-h pulse labeling. It would seem unlikely that pigment cells which seen normally to divide sluggishly would exhibit a much greater uptake of [^{3}H]dThd within a 2-h period. Although the melanocyte population is not altered on day 7, the cells probably enter into mitosis shortly after applications of the PGE_2 were initiated. If the turnover rate is slow, a large change in the population density would not become evident until the second week. PGE_2 increased the number of dopa-positive cells by as much as 80%. It is unlikely that half the melanocytes in the skin are dopa-negative. The most likely explanation for the increase in the number of dopa-positive melanocytes is the proliferation of cells. The 2-h pulse time was chosen to minimize the possibility that the uptake of [^{3}H]dThd represented unscheduled DNA synthesis.

The importance of PGE_2 is a biologically relevant regulator of proliferation is emphasized by the lack of response of melanocytes to other PGs. This point is emphasized by the lack of response to α-MSH and β-MSH even when administered in massive doses (40 mg/kg body weight). Our observation that MSH had no effect on melanocyte proliferation in vivo is consistent with the observation of other investigators [18]. MSH does stimulate proliferation of Cloudman melanoma cells in culture [1]. Possibly the different responses represent a difference between benign and malignant cells. On the other hand, MSH may not be the most important regulator of melanocyte function in vivo [19].

PGE_2 is a common constituent found in the inflammatory exudate of skin exposed to UVB radiation or inflamed by contact allergens. In these studies, histologic examination of tissues indicate PGs did not induce an inflammatory reaction in the skin, i.e., an infiltrate of neutrophils or mononuclear cells. Tanning and postinflammatory hyperpigmentation in part may be caused by melanocyte proliferation and accelerated melanogenesis (Fig 4) modulated by PGE_2. PGE_2 has other biologic activities [14,20]. It seems to increase proliferation of epidermal pigment cells. It increases formation of tonofilaments and keratohyalin in keratinocytes. In identical quantities (10 μg/ear), it blocks the processing/presenting function of Langerhans cells in skin sensitized to dinitrofluorobenzene.* These different effects on the epidermal cells suggest that PGE_2 is an important intercellular signal which can activate one cell type while suppressing the other response to a variety of injurious or noxious agents.

Finally, that PGE_2 and possibly PGD_2 can affect pigment cell growth and/or function suggests that these or similar agents might

*Nordlund, Collins, Rheins, submitted for publication.

be used to treat patients with a variety of hypopigmentary disorders if the compounds are administered in appropriate forms and proper solvents.

REFERENCES

1. Halaban R, Lerner AB: Dual effect of melanocyte stimulating hormone on the growth of cultured melanoma cells. Exp Cell Res 108:111–118, 1977
2. Giacometti L, Montagna W: The healing of skin wounds in primates. II. The proliferation of epidermal cell melanocytes. J Invest Dermatol 50:273–275, 1968
3. Sato T, Kawada A: Mitotic activity of hairless mouse epidermal melanocytes: its role in the increase of melanocytes during ultraviolet radiation. J Invest Dermatol 58:392–395, 1972
4. Nordlund JJ, Ackles AE, Traynor, FF: The proliferative and toxic effects of ultraviolet light and inflammation on epidermal pigment cells. J Invest Dermatol 77:361–368, 1981
5. Rosdahl IK: Local and systemic effects on the epidermal melanocyte population in UV-irradiated mouse skin. J Invest Dermatol 73:306–309, 1979
6. Blog FB, Szabo G: The effects of psoralen and UVA (PUVA) and epidermal melanocytes of the tail in C57BL mice. J Invest Dermatol 73:533–537, 1979
7. Mitchell RE: The effect of prolonged solar radiation on melanocytes of the human epidermis. J Invest Dermatol 41:199–212, 1963
8. Varga JM, Wiesehahn G, Bartholomew JC, Hearst JE: Dose-related effects of psoralen and ultraviolet light on the cell cycle of murine melanoma cells. Cancer Res 42:2223–2226, 1982
9. Cohen SR, Burkholder DE, Barga JM, Carter M, Bartholomew JC: Cell cycle analysis of cultured mammalian cells after exposure to 4,5′,8-trimethylpsoralen and long-wave ultraviolet light. J Invest Dermatol 67:261–264, 1976
10. London DA, Carter M, Condit ES: Effect of pigment on photomediated production of thymine dimers in cultured melanoma cells. J Invest Dermatol 70:21–24, 1978
11. Moreno G, Vinzens F, Prunieras M: UV-induced unscheduled DNA synthesis in guinea pig skin melanocytes isolated in culture. J Invest Dermatol 70:21–24, 1978
12. Nordlund JJ: Chemical agents which mimic the effects of ultraviolet radiation on the epidermis: a possible role of oxidation of arachidonic acid in expression of surface markers on epidermal cells, The Effect of Ultraviolet Radiation on the Immune System. Edited by JA Parrish. Albuquerque, NM, Johnson & Johnson, 1983, pp 161–180
13. Nordlund JJ, Ackles AE: Melanocytotoxins and fatty acids which stimulate proliferation of melanocytes in murine pinnal epidermis: a possible role for arachidonic acid metabolism in regulation of melanocyte growth, Biological, Molecular and Clinical Aspects of Pigmentation, Pigment Cell 1985. Edited by J Bagnara, SN Klaus, E Paul, M Schartel. Univ of Tokyo Press, Tokyo, 1985, pp 501–513
14. Lowe NJ, Stoughton RB: Effects of topical prostaglandin E$_2$ analogue on normal hairless mouse epidermal DNA synthesis. J Invest Dermatol 68:134–137, 1977
15. Song PS, Ou C: Labeling of nucleic acids with psoralens. Ann NY Acad Sci 346:355–367, 1980
16. Carter DM, McMacken MdeLV, Condit ES: Defense of cutaneous cells against UV irradiation. I. Photomediated binding of trimethyl psoralen to DNA of melanoma cells in culture. J Invest Dermatol 60:270–273, 1973
17. Sauk JJ, White JG, Witkop CJ: The action of prostaglandins, precursor, and prostaglandin endoperoxide on melanocyte-keratinocytes during anagen stage of human pigmented and albino hair. Pigment Cell 3:244–253, 1976
18. Hirobe T, Takechi T: Induction of melanogenesis in the epidermal melanoblast of newborn mouse skin by MSH. J Embryol Exp Morphol 37:79–90, 1977
19. Nordlund JJ: The pigmentary system: new interpretations of old data. Jpn J Dermatol 12:9–20, 1985
20. Lupulescu AP: Cytologic and metabolic effects of prostaglandins on rat skin. J Invest Dermatol 68:138–145, 1977