Mechanisms of UV-Induced Inflammation

Luciann Lisi Hruza and Alice P. Pentland

The inflammation produced by exposure to ultraviolet (UV) light has been well documented clinically and histologically. However, the mechanisms by which mediators induce this clinical response remain poorly defined. It is clear that photochemistry occurring after UV absorption must be responsible for initiating these events. Some of these underlying mechanisms have been defined. After exposure to UV light, the formation of prostaglandins and the release of histamine are increased. In addition to an increase in the quantity of these mediators, an increase in sensitivity of irradiated tissue to agonist stimulation also occurs. This increased sensitivity may cause tissue to respond to agonist levels previously present. Phospholipase activity also increases, making more substrate available for prostaglandin formation. Oxygen radical – induced peroxidation of membrane lipids caused by irradiation may contribute to increased phospholipase activity. Oxygen-free radicals also participate in sunburn cell formation and in UV-induced decreases in Langerhans cell numbers. Several enzymatic and non-enzymatic mechanisms are present in skin for reducing these highly reactive oxygen species. *J Invest Dermatol 100.35S-41S, 1993*

Exposure of the skin to an adequate dose of 200–400 nm wavelength light produces inflammation. Because ultraviolet light – induced injury can be easily reproduced and quantified, it has often been studied as a model of inflammation [1–3]. Distinct patterns of inflammation are produced by exposure to specific wavelengths of light, probably due to different injury mechanisms. Based on these differences in the pattern of erythema, investigators generally divide the ultraviolet wavelengths into three main groups for purposes of study. The shorter wavelengths (200 to 290 nm) are called UVC or ''germicidal radiation,'' wavelengths between 290 and 320 nm are termed mid-UV or UVB radiation, and those between 320 and 400 nm are designated UVA or long-wave UV [4].

CLINICAL AND HISTOLOGIC ALTERATIONS INDUCED BY UV EXPOSURE

The physiologic response to UV light exposure has been carefully documented. Acute exposure results in erythema, heat, edema, pain, and pruritus, followed by tanning and epidermal thickening. Chronic exposure can induce skin aging and carcinogenesis [5,6]. When erythema is environmentally induced (primarily by UVB wavelengths), this reaction to light is termed sunburn.

The dose of light needed to produce erythema, and the time course of its development and color, are dependent on the wavelength of light responsible for erythema production [1,7,8]. For example, the intensity of UVC-induced erythema increases very gradually in response to increasing doses of light, producing a flat dose-response curve. Both UVB and UVA produce erythema at lower exposure doses, and erythema intensity increases sharply as a function of the exposure dose [9]. Thus, the dose-response curve for erythema production is a function of wavelength.

The wavelength of incident light also influences erythema duration. Shorter wavelengths of light produce erythema of shorter duration; UVC erythema fades within 3 h of exposure but UVA or UVB erythema may persist for days. This difference in the intensity of the inflammatory response to various wavelengths of light may be due in part to differences in their penetration of the skin. UVC wavelengths are absorbed completely by the epidermis, UVB wavelengths penetrate the epidermis and are nearly fully absorbed in the upper dermis, and UVA penetrates to the deep dermis [10].

The clinical pattern of erythema produced after UVB exposure may be biphasic (particularly in the guinea pig and the rat) with a transient immediate phase beginning in seconds and lasting only a few minutes. A prolonged delayed phase begins subsequently, which generally has its onset in 3 to 5 h, is maximal between 12 to 24 h, and fades over 72 h [11]. This time course may be manipulated by the exposure dose; small doses produce short-lived erythema, whereas larger doses produce erythema that is faster in onset, more intense, and persistent [6].

These changes differ somewhat from those observed after UVA irradiation. Erythema induced by UVA without psoralen photosensitization may produce a biphasic response depending on the dose of light administered. After exposure to 2.5 times the minimal erythema dose, erythema begins immediately, and peaks at 8 h. Erythema persists 24 to 48 h [3,12], depending on the dose of UVA. UVA radiation doses required to produce inflammation are about 1000 times greater than for UVB doses.

The histology of immediate erythema due to UVB exposure has been characterized in the guinea pig and rat [1,2] because its existence in humans is usually not clinically apparent [8]. In immediate erythema, the histologic changes are localized to the dermal vasculature; vasodilation is present in arterioles, capillaries, and venules [13]. Similar histologic changes are evident early in UVA-induced inflammation. The underlying mechanism is unknown, but may be due in part to the effects of vasoactive mediators [14].

The histology of changes occurring during the delayed phase of UV-induced erythema has been well documented. The shorter wavelengths (200 to 320 nm) result in both epidermal and dermal changes whereas more pronounced dermal injury results primarily from longer wavelengths. This pattern of inflammation correlates with the difference in the capacity of these wavelengths to penetrate the skin [10]. After exposure to three times the minimal erythema dose of UVB, some sunburn cells appear in the skin as early as 30 min. These cells are dyskeratotic keratinocytes with dark vacuolated cytoplasm and enlarged nuclei. They appear first in the lower half of the epidermis, and by 24 h after exposure are present in the upper layers of the epidermis [11]. It is hypothesized that these cells are produced

Division of Dermatology, Washington University School of Medicine, St. Louis, Missouri, USA

Reprint requests to: Dr. Alice P. Pentland, Washington University School of Medicine, 660 S. Euclid Avenue, Campus Box 8123, St. Louis, MO 63110.

Abbreviations: AA, arachidonic acid; ATPase, adenosine triphosphatase; DNA, deoxyribonucleic acid; HETE, hydroxyeicosatetraenoic acid; 6-keto-PGF, 6-keto-prostaglandin F; PG, prostaglandin; UV, ultraviolet; UVA, long-wave ultraviolet (320–400 nm); UVB, middle-wave ultraviolet (290–320 nm)

due to an inability to repair DNA damage adequately or as a result of lysosomal breakdown [15,16]. Actively cycling cells rather than differentiated cells are more likely to form sunburn cells after exposure to UVB [17].

After UVB exposure, the number of resident Langerhans cells seen on histologic examination of skin specimens stained by hematoxylin and eosin decreases by 25% within 1 h. By 24 to 72 h, only 10% of the Langerhans cell population remains [11]. Others have confirmed UVB-induced decreases in Langerhans cells in murine epidermis exposed to low-dose (0.5 MED) UVB daily for 4 d. Adenosine triphosphatase (ATPase)-positive Langerhans cells numbers decreased to 5% of control values, a decrease that did not return to normal for 8 d [18]. Increased vacuolization in melanocytes occurs by 1 h after UVB exposure and returns to baseline by 4 to 24 h. In the dermis, endothelial cell swelling is noted as early as 30 min after exposure. Swelling increases over the next 24 h, persisting for as long as 72 h after UVB. In addition, a slight perivascular lymphocytic infiltrate is evident 24 to 72 h after UVB exposure [11]. Mast cell number and granularity in papillary and reticular dermis are decreased at 1 h and appear to return to normal at 24 to 72 h post–UVB irradiation. Later, by 24 to 48 h, melanin synthesis, epidermal proliferation, and thickening of the stratum corneum occur [6].

The histologic changes associated with UVA erythema differ from UVB-induced tissue damage with respect to the greater dermal changes produced by the longer wavelengths [19]. Epidermal injury resulting from long-wave UV is characterized by spongiosis with a conspicuous absence of sunburn cells [5]. There is a dense mononuclear cell infiltrate with a few neutrophils that may extend into deep dermis. Vascular damage may be severe with endothelial swelling, extravasation of red blood cells and extravascular fibrin deposition [20]. The range of effects varies with the intensity of UV light administered; high-dose UVA irradiation results in marked dermal damage [8]. It has been suggested that UVA-induced erythema may be related to keratinocyte cytotoxicity. This hypothesis is based on a comparison of action-spectra data for erythema and cytotoxicity that is essentially superimposable [21].

LIGHT ABSORPTION BY SKIN CHROMOPHORES RESULTS IN PHOTOCHEMISTRY

UV-induced inflammation is the result of chemical reactions occurring in the skin initiated by incident light. When light falls upon the skin it may be scattered, reflected, or absorbed. Only absorbed light can produce chemical changes in light-absorbing molecules, a process termed photochemistry. When light is absorbed, the absorbing molecule is called a chromophore. The range of wavelengths of light with sufficient energy to cause a chemical change in the chromophore is termed the absorption spectrum of that chromophore, and is specific for each substance. The sum of the photochemical reactions occurring when light interacts with chromophores present in skin initiates UVR injury, which in turn results in the biochemical and immunologic perturbations that cause inflammation [6]. Because different wavelengths of light may be absorbed by different chromophores, the pattern of inflammation occurring after exposure to radiation of differing wavelengths is altered (Fig 1). The shorter wavelengths (less than 300 nm) act on nucleic acids, amino acids, urocanic acid, and melanin as the major chromophores whereas melanin is the chromophore at longer wavelengths (350–1200 nm) [22]. In addition, the amount and location of chromophores in the skin, as well as variations in epidermal thickness, determine the degree to which UVR is absorbed [6].

Details of the linkage between photochemical reactions and the biochemistry that produces a given clinical response are not defined in most cases. However, UV radiation – induced changes have been documented in a number of cellular biochemical pathways. UV absorption by nucleic acids leads to pyrimidine dimer formation [23]. UVB and UVC are effective inducers and promoters of skin cancer in mice [24], although the carcinogenic potential of UVA is not well established. In general, UV radiation enhances the production of metabolites of arachidonic acid [11,25,26], inflammatory cytokines
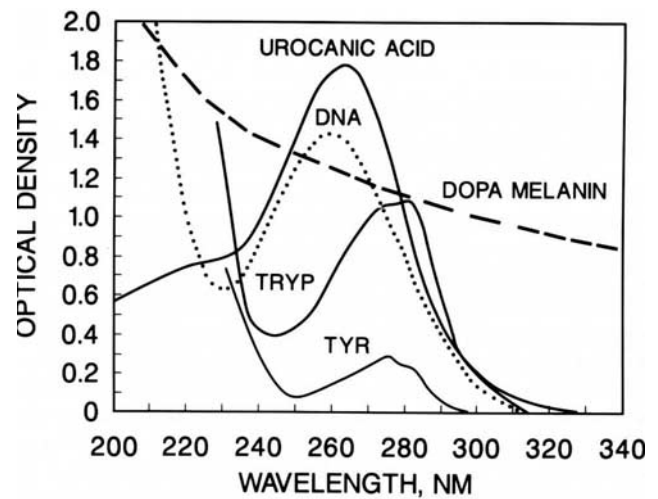

Figure 1. UV absorption spectra of major epidermal chromophores. DOPA-melanin, 1.5 mg% in H_2O; urocanic acid, 10^{-4} M in H_2O; calf thymus DNA, 10 mg% in H_2O (pH 4.5); tryptophane, 2×10^{-4} M (pH 7); tyrosine, 2×10^{-4} M (pH 7). Reproduced by permission, Dr. R. Anderson [22].

[27], adhesion molecules [28], and mast cell-derived mediators [29]. Reactive oxygen species are also generated by UVR exposure, which can result in membrane lipid peroxidation and destruction. Although the exact photochemistry is not well understood, lipid mediators, reactive oxygen radicals, effects on DNA, and immune mechanisms undoubtedly interact to produce UV-induced inflammation. This review focuses on lipid mediator generation and the mechanisms that have evolved to combat membrane oxidative damage induced by ultraviolet radiation in the skin.

PROSTAGLANDINS AS MEDIATORS OF UV INJURY

Eicosanoids, 20-carbon fatty-acid mediators synthesized from arachidonic acid present in membrane phospholipids, play a prominent role as soluble mediators of the delayed erythema response. As evidence for this, the production of tissue eicosanoids parallels the onset of erythema, and eicosanoid inhibitors decrease UVB erythema. The pattern of eicosanoid synthesis initiated by ultraviolet light depends on the wavelength and probably represents a mixture of the eicosanoid synthetic profile of the cell types present in skin [25,30]. Studies of the effects of UVB on cutaneous eicosanoid synthesis have been done on suction blister fluid exudates and on cells in culture. In both settings, eicosanoid metabolism is enhanced (Table I). Metabolites of arachidonic acid (AA) prostaglandin E_2 (PGE$_2$), PGD$_2$, PGF$_{2\alpha}$, and 12-HETE are increased in suction blister aspirates immediately following exposure to UVB (before onset of noticeable erythema) and persist for 48 h, with peak concentrations present at 18 to 24 h [11,30–32]. The quantity of PGD$_2$, a mast cell-derived prostaglandin, rises in a pattern similar to that of keratinocyte-derived PGE$_2$ and PGF$_{2\alpha}$, implying a contribution of the mast cell to UVB-induced inflammation. Prostacyclin (as measured by its metabolite 6-keto-PGF$_{Ia}$), which is likely to be derived from vascular endothelium, increases within 5 to 9 h post-irradiation and returns to baseline levels by 24 to 48 h [2,6,29]. The increase in prostaglandin and HETE formation after UVB irradiation may simply be due to increases in the release of membrane arachidonic acid, as the release of free arachidonic acid from membrane phospholipids is rate limiting in the synthesis of these compounds [33]. Studies of cultured cells support the contribution of enhanced phospholipase activity [34–36]. In human epidermal cultures, release of AA occurs in a dose-dependent fashion after UVB irradiation [35], a change that is confirmed by associated increases in glycerophosphorylcholine release derived from membrane phos-phatidycholine [25].

Evidence for a role for arachidonic acid cyclooxygenase products in UV induced erythema is supported by the reduction of erythema by selective inhibitors [37]. UVB erythema is suppressed by the cyclooxygenase inhibitors aspirin and indomethacin up to 50% during the first 24 h after injury [31,38–40]. However, erythema persisting after 24 h is not suppressible by indomethacin, and may therefore be due to other mediators. Unfortunately, interpretation of inhibitor studies to document the mechanism of UV injury is limited by difficulty validating drug efficacy in all responding cell types.

Examination of eicosanoid metabolism after UVA exposure reveals some similarities with the effects of UVB exposure. UVA, like UVB, increases the concentrations of AA, PGD_2, PGE_2, and the prostacyclin metabolic product 6-keto-$PGF_{1\alpha}$ in suction blister aspirates (Table I). The time course of mediator synthesis reaches a maximum concentration at 5 to 9 h, declines by 15 h, and returns to control levels by 24 h [29]. The increase in mediator formation observed is linearly dependent on the UVA dose. The rise of eicosanoids corresponds to the time course of observed erythema, suggesting a role for these substances in the complex inflammatory response [29]. Similar studies *in vitro* using fibroblasts corroborate an increased release of eicosanoids following UVA irradiation [41]. However, topical or intradermal indomethacin in the concentrations tested had no effect on UVA-induced erythema [42]. Inhibitor studies are inherently problematic because of the inability to demonstrate adequate drug delivery to the epidermis.

In addition to their likely role in mediating UV erythema, eicosanoids may be mediators of some of the other changes occurring in UV-irradiated tissue. PGE_2 has been shown *in vivo* to mediate the suppression of contact sensitization that occurs in irradiated skin [43]. It can also increase plasma exudation, as can LTC_4 [44]. Leuko-triene B_4 is one of the most potent chemotactic substances known, and may therefore play a role in the inflammatory cell influx that occurs [33,45]. Keratinocytes can also synthesize 12-R-HETE, a compound that could influence cellular water balance by inhibition of Na^+-K^+ ATPase in irradiated cells [46–49]. Epidermal keratino-cyte proliferation in culture is regulated by PGE_2, and may have this same effect *in vivo* [34,50]. In addition, PGE_2 released from irradiated cultures parallels their release of the epidermal cytokine IL-1 following UVB irradiation, suggesting a relationship between the synthesis of these two compounds [51]. Although progress has been made in elucidating the contribution of eicosanoids to UV-induced inflammation *in vitro,* further work is necessary to better define these processes *in vivo.*

Table I. Pattern of Metabolite Formation After UV Exposure[a]

Metabolite (ng/ml)	Control	5–9 h	25 h	48 h
UVA				
AA	2122 ± 342	3561 ± 1041	2389 ± 439	1917 ± 547
PGD_2	46 ± 10	161 ± 42	56 ± 10	31 ± 15
PGE_2	36.9 ± 12	102.3 ± 32.3	61.8 ± 16.4	24.5 ± 10.4
UVB				
AA	276.3 ± 19.5	360.2 ± 69.3	785 ± 56.8	232.9 ± 24.4
PGD_2	21.8 ± 1.3	35 ± 47	34.9 ± 6.7	34.3 ± 4.8
PGE_2	17.06 ± 0.7	28.2 ± 3.3	49.4 ± 5.2	19.2 ± 0.8
$PGF_{2\alpha}$	18.2 ± 1.1	ND	32.4 ± 2.9	ND

[a]Recoverable levels (mean $\pm$ SEM) of AA, PGD_2, PGE_2, and $PGF_{2\alpha}$ measured by gas chromatography–mass spectroscopy in suction blister exudates raised over irradiated human skin. UVA data obtained after exposure to 2.5 MED (by permission from Hawk [29]). UVB data obtained after exposure to three MED (by permission from Black [30]). ND, not done.

UV IRRADIATION ENHANCES HISTAMINE-STIMULATED PROSTAGLANDIN SYNTHESIS

Data that suggest that histamine must play a role in the erythema response have been obtained by many investigators [2,11,52,53]. Inhibitor studies have established the relationship between histamine and the erythema response in several animal models. In guinea pigs, erythema occurring up to 120 min post-irradiation is suppressible with antihistamines [2,54]. In rats, an antihistamine-suppressible component occurs during the delayed erythema phase [2]. In humans, mast cells have been shown to degranulate and release histamine 4 h after exposure to UV light [11,53]. At the same time, aspirates from suction blisters overlying irradiated skin contain elevated levels of histamine [11]. Others have documented elevations of histamine peaking 9 to 15 h after irradiation and returning to baseline by 24 h [29].

Studies using skin explants irradiated *in vitro* suggest that histamine-stimulated prostaglandin synthesis is an underlying mechanism early in the delayed phase of the human erythema response. UV-stimulated prostaglandin synthesis is inhibited by the presence of the HI antihistamines brompheniramine or pyrilamine, but is not influenced by the H2 antagonist cimetidine (Fig 2) [55]. Further studies using cultured cells reveal that increased prostaglandin synthesis is primarily due to an increase in the sensitivity and maximal response of irradiated keratinocytes (Fig 3) and fibroblasts to agonist stimulation (Fig 4). The increased response of irradiated cells to agonist stimulation is not restricted to histamine, but is also observed with bradykinin, indicating that irradiation increases sensitivity to multiple agonists. This increased sensitivity to stimulation imparted by irradiation implies that mediators may contribute to UV-induced inflammation even when the injury does not increase the quantity of the mediator in tissue [56]. Clearly, the inflammatory potential of a mediator must be assessed both by changes in its concentration as well as the capacity of the stimulated tissue to respond.

OXYGEN RADICALS CONTRIBUTE TO UV-INDUCED INFLAMMATION

One underlying mechanism for the initiation of UV-induced erythema may be the photochemical production of activated oxygen species [57–59]. Oxygen radicals are known to cause a number of disruptive cellular processes, including lipid peroxidation, cleavage of DNA, altered enzyme activity, polymerization of polysaccharides, and cell death. These products are also produced physiologically in numerous ways, including the microbicidal action of phagocytic neutrophils and autoxidation of metabolites such as hydroquinones, catecholamines, and thiols [60]. Because radical production occurs physiologically, the cell has several mechanisms for their removal. The oxygen radicals are reduced in biologic systems by electron transfer to produce water. This reduction process results in the formation of reactive intermediates including superoxide anion (O_2^-, hydrogen peroxide (H_2O_2), and the hydroxyl radical (OH^-) [59]. UVB-induced oxygen radicals are produced from photolysis of water, cysteine-containing epidermal proteins, and in the course of enzyme/substrate reactions [61,62]. It is likely that UV irradiation produces inflammation when the cellular capacity to reduce oxygen radicals is exceeded.

LIPID PEROXIDATION MAY BE AN INITIAL EVENT FOR LIPID MEDIATOR RELEASE

Lipid peroxidation induced by oxygen radicals has been linked circumstantially to increased formation of lipid mediators such as prostaglandins. Lipid peroxidation is a free-radical – induced chain reaction that occurs when superoxide anion and hydrogen peroxide form hydroxyl radicals in the presence of redox active metals such as iron [63–65]. These hydroxyl radicals then react with nearby polyunsaturated fatty acids to abstract hydrogen. Subsequent to this initiation reaction, a propagation phase occurs in which a peroxidative chain reaction spreads through the membrane, generating new radical species as the reaction
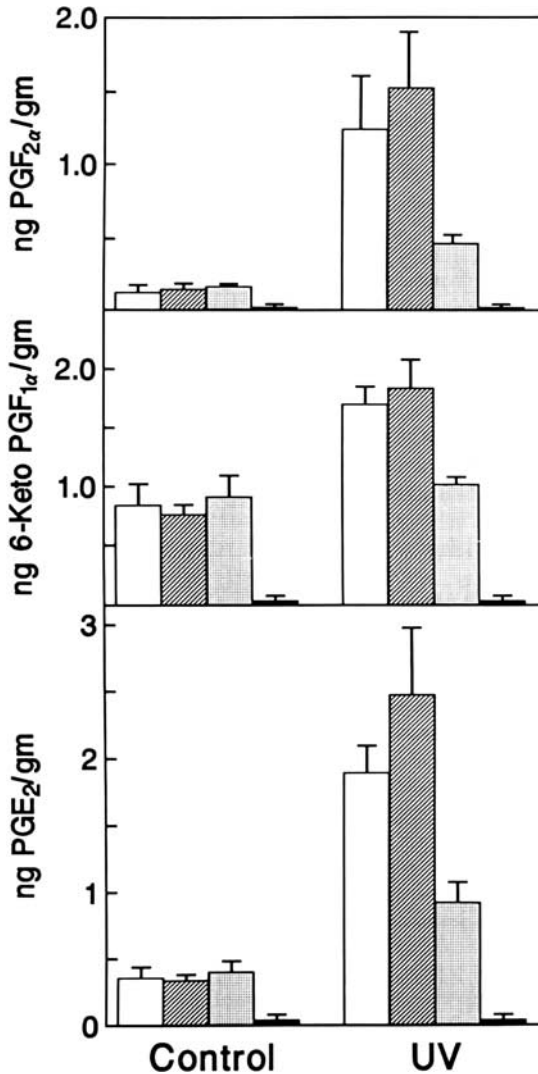
Figure 2. Brompheniramine, but not cimetidine, suppresses irradiated ex-plant prostaglandin synthesis. Control or irradiated explants were incubated with 50 μM brompheniramine (▨), 30 μM cimetidine (▨), or 1 μM indo-methacin (■) or no addition (□). The average release of prostaglandin was then determined 6 h after irradiation. Quadruplicate determinations from a representative experiment are shown. The experiment was repeated with similar results (reproduced by permission from J Clin Invest 86:566–574, 1990) [55].

Figure 3. Irradiation increases the response of epidermal cultures to bradykinin stimulation. Control (●) or irradiated (○) cultures were incubated with 1 nM to 10 μM bradykinin for 15 min, and the synthesis of PGE_2 and $PFG_{2\alpha}$/μg protein determined. The average values from three experiments ± the SEM are shown; $p \leq 0.1$, Student paired t test (reproduced by permission from Am J Physiol 261:R543–R547) [56].

proceeds. This oxygen-dependent process is enhanced by NADPH and Fe^{+++}-ADP [66]. The importance of lipid peroxidation in mediating injury is well established in several trauma injury models [63,67–69]. Peroxidation has recently been demonstrated in irradiated epidermis, together with evidence showing that the natural antioxidants ubiquinone and vitamin E are depleted, suggesting it has a role in mediating UV injury as well [70].

A possible mechanism by which lipid peroxidation may initiate inflammatory events is via activation of phospholipases. Lipid peroxidation has been shown to increase phospholipase A_2 (PLA_2) activity in rat liver microsomes and to increase phospholipase C (PLC) activity in cardiac sarcoplasmic reticulum, rat liver lysosomes, and brain [43,71]. Increased release of AA suggesting increased phospholipase activity, has been documented after UV exposure [35,36,55] although it has not yet
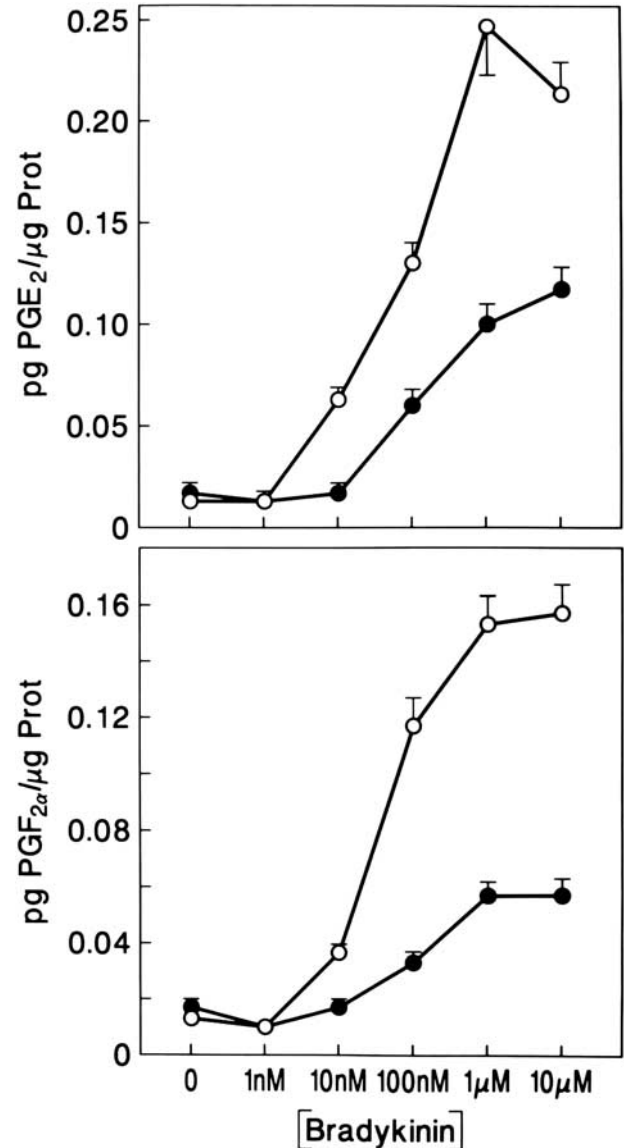
been directly linked to peroxidation of membrane lipid occurring during UV exposure. Increased activity of PLA_2 results in increased amounts of free AA (the substrate for prostaglandin formation). The immediate increase in pros-taglandin formation found after UV exposure [30] supports the hypothesis that peroxidation-induced increases in phospho-lipase activity act as an initiating mechanism. In addition, peroxidation-induced increases in the activity of PLC would result in enhanced diacylglycerol release (a co-factor for protein kinase C). Evidence to support such a mechanism has recently been obtained in UVA injury, where increased synthesis and activity of protein kinase C have been documented in UVA irradiated fibroblasts [72]. This alteration may be responsible for enhanced cellular proliferation, as well as promotion of carcinogenesis, because protein kinase C has been reported to mediate these effects in other systems [73].
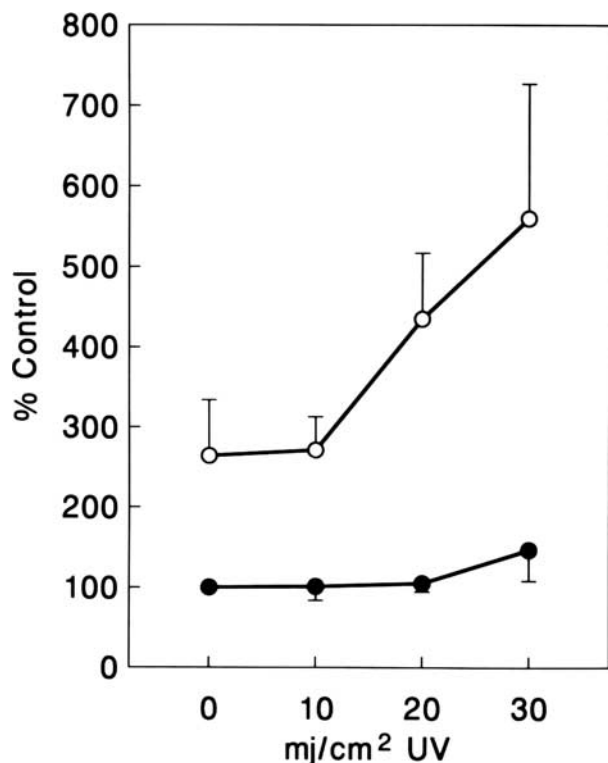
Figure 4. Irradiated fibroblasts synthesize increased quantities of prostaglandin when stimulated with bradykinin. Fibroblasts were exposed to 0–30 mJ/cm^2 UV 6 h prior to stimulation with 1 μM bradykinin (BK). Unstimulated ($\bullet$), + BK ($\circ$). This increase in synthesis is dependent on the dose of light to which the cells have been exposed, p $\leqslant$ 0.01 by Jonckeere's distribution-free test for ordered alternatives. Each *point* represents the mean ± SEM for three experiments (reproduced by permission from Am J Physiol 261:R543–R547) [56].

EPIDERMAL ANTIOXIDANTS OFFER PROTECTION FROM UV INJURY

Due to its location adjacent to the oxygen-rich extracellular environment, epidermis requires well-developed defenses against oxygen radical damage. Enzymatic mechanisms that may repair oxidation injury induced by UV include superoxide dismutase [59], catalase [74], and thioredoxin reductase [58]. There are also high concentrations of molecules, such as urocanic acid and melanin, that harmlessly absorb and scatter incident UV radiation, thereby preventing oxygen radical formation [6]. Natural antioxidants, including vitamins A, E, and C, as well as reduced glutathione, also act to prevent oxygen radical damage (Table II). Despite this, epidermis remains susceptible to damage by light-induced oxidative damage if sufficient exposure occurs, as demonstrated by the protection against photocarcinogenesis afforded by antioxidants in the diet [75,76] and the attenuation of UV damage by antioxidants [77].

Glutathione, a cysteine-containing tripeptide, is distributed throughout the cell and is an endogenous antioxidant [78]. Its many functions include oxygen radical scavenging as well as being a co-factor for the synthesis of AA metabolites such as leukotrienes and prostaglandins [79]. In tissues, glutathione is maintained in reduced form, where its reducing potential helps maintain cellular function by the reduction of oxidized tissue components such as lipid peroxides. Its reducing capacity is also used in the regeneration of cellular antioxidants such as vitamin C to their reduced state [74]. The role of glutathione in modulating UV injury has been implicated in several studies. The protective effects of glutathione have been shown in cultured human fibroblasts, and in hairless mice, where its presence was found to decrease the cytotoxic effects of UVB

Table II. Mechanisms for Defense Against Oxidative Damage[a]

Enzymatic
$2H_2O_2 \xrightarrow{\text{Catalase}} 2H_2O + O_2$
$2O_2^- + 2H^+ \xrightarrow{\text{SOD}} H_2O_2 + O_2$

Non-enzymatic
$2O_2^- + 2H^+ + 2GSH \longrightarrow GSSG + 2H_2O_2$
$2OH^- + 2GSH \longrightarrow GSSG + 2H_2O$
$O_2^* + GSH \longrightarrow GS_{OX}$

[a]SOD=superoxide dismutase; O_2^-=superoxide anion; GS$_{OX}$=cysteic acid; H_2O_2=hydrogen peroxide; GHS=reduced glutathione; OH$^-$=hydroxyl radical; GSSG=oxidized glutathione; O$_2^*$=singlet oxygen.

[80,81]. Its importance in protecting the skin from oxidant injury is also supported by the observation that ultraviolet exposure depletes glutathione [82,83].

The epidermal thioredoxin system [58] is an epidermal membrane-associated free radical scavenging system that catalyzes the reduction of oxygen radicals to peroxide ions that are then reduced to water. Although it is widely distributed in a variety of organisms and tissues, the location of the enzyme system at the outer membrane surface in human epidermis suggests it may be a first line of defense against free radical production induced by UV light [84]. One of its functions in epidermis is probably to prevent membrane lipid peroxidation and inactivation of sulfur-containing amino-acid compounds. Interestingly, activity of thioredoxin reductase is decreased 30% in vitiliginous skin, implicating free-radical damage in the pathogenesis of this disease.

Catalase is a heme protein that catalyzes the dismutation reaction of hydrogen peroxide to form water and oxygen [74]. It functions with glutathione to remove hydrogen peroxide from the cell and decreases the likelihood of the hydrogen peroxide combining with superoxide anion to form the highly reactive hydroxyl radical (Haber-Weiss reaction). Catalase is found in skin, liver, and blood cells where it is important in protecting against oxygen toxicity, and is depleted by UV exposure [74].

Superoxide dismutases are a family of metalloproteins that catalyze the removal of superoxide radicals (O_2^-) by combination with hydrogen ions (H^+) to form H_2O_2 and O_2. In human epidermis, the active site may contain both copper and zinc (CuZn-SOD); others have manganese (Mn-SOD) at their active site [85]. Superoxide dismutases are present in both mitochondria (primarily Mn-SOD) and cytosol of epidermal cells and function as an adaptive mechanism to protect the cells against the damage of oxygen-free radicals.

The importance of antioxidant systems in the protection of skin from UV injury has been studied by several investigators. Sunburn cells are a marker for UVB-induced epidermal injury and have been the histologic marker assessed in many of these studies [77]. Miyachi and colleagues found a dose-dependent decrease in the number of sunburn cells in mouse skin explants treated with antioxidants. Superoxide dismutase, catalase, and xanthine, which quenches singlet oxygen and hydrogen peroxide, all inhibit UV-induced sunburn cell formation [86]. The protective effect of superoxide dismutase was also demonstrated *in vivo* in mice by Danno and colleagues, who showed the antioxidant prevented the formation of sunburn cells [87]. This protection occurred whether the superoxide dismutase was given before or with 15 min after irradiation. However, UV-induced ear swelling (edema) was not affected by these substances, suggesting a different mechanism is responsible for this effect of UV injury.

Oxygen intermediates may also be partially responsible for the decrease in the epidermal Langerhans cell population that occurs after UV exposure [88]. In UVB-irradiated guinea pig skin, partial protection of the Langerhans cell population is achieved by intra-dermal injection of superoxide dismutase. However, erythema reduction by

indomethacin has no effect on UV-induced reduction in Langerhans cell numbers [89], indicating that discrete mechanisms for this damage exist that do not involve prostaglandin production.

In summary, although the clinical and histologic effects of ultraviolet light exposure on the skin have been documented in detail, much remains to be discovered about the mechanisms by which light interacts with skin chromophores to produce ultraviolet injury. A better understanding of these processes should improve phototherapy and the treatment of sunburn. In addition, because it is likely that perturbations of normal mechanisms result in photosensitive conditions such as lupus, understanding the mechanisms underlying ultraviolet light injury should be useful in the understanding and treatment of photosensitivity disorders.

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