The mechanism of solar erythema

Synopsis
Solar erythema is induced by UVB. Even when mild, it is associated with epidermal alterations, the most typical being sunburn cells formation. Usually preceded by a thermal erythema, the delayed solar erythema involves the release of histamine followed by prostaglandins, but the biochemical changes are not different from those seen in non-specific inflammatory processes. The probable UV targets are some amino-acids in membrane proteins, melanin and DNA. The latter mostly include pyrimidine dimer formation. Free radical initiation might be the primary event inside both the cell membranes with subsequent lipid alteration, and the nucleus inducing sunburn cells formation. Free radical scavengers may prevent such alterations to some extent. Any solar erythema is associated with a temporary impairment of the skin immune barrier. Delayed adverse effects include enhancement of premature skin ageing, higher risk of epithelial skin cancer and malignant melanoma. The practical conclusion is that sunburns must be avoided and that careful skin protection is mandatory for fair skinned people.

Riassunto
L'eritema solare è provocato dagli UVB. Anche quando tale eritema si manifesta in forma leggera è associato ad alterazioni epidermiche quali la formazione di celluline attiniche che è quella più comune.
L'eritema solare ritardato, generalmente preceduto da un eritema termico, comporta la liberazione di istamine seguite da prostaglandine ma i cambiamenti biochimici non si differenziano molto da quelli che si riscontrano nei normali processi infiammatori. I probabili bersagli degli UV sono alcuni amino-acidi delle membrane protetiche della melanina e del DNA. Quest'ultimo, comprende principalmente la formazione di dimeri di pirimidina. L'avvio del radicale libero potrebbe essere il primo evento che si verifica sia entro le membrane cellulari, con conseguente alterazione lipoidea, che nel nucleo che provoca la formazione di celluline attiniche.
I radicali liberi che assorbono le impurità possono in un certo qual modo prevenire tali alterazioni. Tutti gli eritemi solari sono associati ad un indebolimento temporaneo della barriera immunitaria della pelle. Effetti ritardati negativi sono: una tendenza maggiore allo invecchiamento della pelle, rischi più alti di cancro della cute epiteliale e di melanoma maligno. La conclusione pratica è che le scottature dovute al sole devono essere evitate ed inoltre, un'accurata protezione della pelle è di rigo­re per le persone di carnagione chiara.
Résumé
L'érythème solaire est provoqué par les UVB. Même lorsque il se manifeste dans une forme légère il est associé à des altérations épidermiques telles que la formation de cellules actiniques (c'est l'altération la plus commune). L'érythème solaire rétardé suit généralement un érythème termique et comporte la libération d'histamines et ensuite de prostaglandines; les modifications biochimiques ressemblent aux conséquences des processus inflammatoires normaux. Les cibles les plus probable des UV sont des aminoacides et les membranes protéiniques de la mélanine et du DNA qui comprend principalement la formation des dimères de pyrimidine. Dans les membranes cellulaires et dans le nucleus qui provoque la formation des cellules artiniques l'amorçage du radical libre pourrait être la première manifestation. Les brûlures solaires sont associées à un affaiblissement de la résistance immunitaire de la peau. Les effets retardés négatifs sont: tendance accrue au vieillissement de la peau, risques majeurs de cancer et de mélanome malin. Donc, les brûlures doivent être évitées et, en outre, les personnes qui ont un teint délicat doivent absolument se protéger.

Resumen
El eritema solar es causado por os rayos UVB. Aún cuando es blando, está relacionado con alteraciones de la epidermis, la más típica de las que es la formación de células quemadas. Usualmente precedido por un eritema térmico, el eritema solar comporta la emisión de histaminas y de prostaglandinas, pero los cambios bioquímicos no son diferentes de los que se han observado en comunes procesos inflamatorios. El probable objetivo de los rayos UV son algunos aminoácidos, proteinas, melanina y ADN. En este caso se añade la formación de dimeros primidinos. La iniciación de los radicales libres podría ser la causa primaria al interior de las membranas celulares con la consecuente alteración lipídica e la inducción por parte del nucleo de la formación de células quemadas. El levantamiento de los radicales libres puede, en parte, prevenir estas alteraciones. Cada eritema solar se asocia con un provisional impedimento de la barrera inmunológica. Entre los efectos negativos se señalan el precoz envejecimiento de la piel, mayor riesgos de cancer epitelial y de melanoma maligno. La conclusión práctica es que hay que evitar las quemaduras solares y que la cuidadosa protección de la piel es fundamental para los que la tienen delicada.

Synopse

Introduction

Almost every caucasian has experienced a solar erythema in his (her) lifespan and noticed the unpleasant burning sensation enhanced by any mild contact, even with the sheets in one’s bed. The further skin shedding period is also remembered as a disgraciously although painless event. Much is known today about the tissular, cellular, molecular events which take place inside the skin during solar erythema, but this is not sufficient to fully understand its mechanism. Nevertheless present scientific data, mostly from the last decade, allow to get an interesting insight into the subject and useful information for practical purpose.

Time Course of Solar Erythema

Immediate Erythema

After a few minutes of sun exposure in summertime, the skin feels warmer, while a light redness appears. This type of erythema is caused by infrared (IR) radiations, beyond a threshold dose of about 25 mJ/cm² (31), and lasts as long as the irradiation is maintained. Essentially it is a thermal effect with neither histologically nor electron-microscopically visible lesions but only capillary congestion. Biochemically it has been shown that elevating the skin surface temperature from 30 to 38°C by IR radiation increased the level of free arachidonic acid and prostaglandins E₂, D₂, F₂α, and 6 oxo PGF₁α (17). As most IR rays are absorbed by water, any cloud or wet atmosphere strongly reduces skin heating by the sun, with subsequent subsiding of thermal erythema. But other wavelengths of the solar spectrum, namely ultraviolet (UV) light, are not absorbed by water and consequently can pass through the clouds when these are not too dense (otherwise they would be attenuated by scattering) and cause another and more serious type of erythema if no attention is paid for.

Delayed Erythema

As far as sunburn and eventually suntan are concerned, they are related to what is called delayed solar erythema, a redness which arises only a few hours after irradiation. The very start depends on the intensity of sunlight (23) and sensitivity
of the skin, but the timelapse is usually 6 to 8 hours; the erythema peaks between 12 and 24 h and fades away by the 3rd to the 5th day in normally tanning skins. In people unable to tan, the redness may last more than a week. This delayed solar erythema will be dealt with later in the paper.

**Action Spectrum**

UV rays have been shown to be responsible for the delayed solar erythema. While the sun emits a wide range of radiations, only the wavelengths beyond 290 nm, reach the earth surface thanks to the atmospheric ozone layer which absorbs shorter ones. Using high intensity UV sources and monochromators it has been possible to give the skin the same amount of energy at successive narrow wavelength bands of light and plot the erythemal response against wavelengths, thereby obtaining the actinic erythema action spectrum. The curve has a maximum from 290 to 300 nm then sharply falls down to almost zero at 320 nm. Accordingly only this small part of solar light is efficient; it exactly corresponds to the definition of UVB given by the «Commission Internationale de l'Eclairage». The smallest amount of UVB energy able to elicit erythema (Minimum Erythema Dose) lies about 18 mJ/cm² in Caucasian skin. The 320-400 nm wavelengths, called UVA, also can elicit an erythema but they are 1000 times less potent. On the other hand it was found that the degree of UVB erythema was linearly related to the logarithm of dose at 297 nm, 300 nm, 303 nm and 313 nm. Obviously under normal conditions of sun exposure, only UVB are responsible for the solar erythema. Thus the first and major aim of sunscreens is to absorb this range of radiations and thereby reduce the amount which reaches the skin surface.

**Morphological Events**

Conventional histological and ultrastructural methods provide an easy way to investigate the tissue and cell changes associated with delayed solar erythema. Even when the sample is taken from a minimally red area, i.e. induced by a Minimum Erythema Dose, clear-cut damages are seen. Together with cellular oedema in the epidermis and vascular congestion in the superficial dermis, some epidermal cells stain deeply eosinophilic and have a shrunken nucleus. They are called «sunburn cells». It has been shown that their number increases as the amount of UV energy received by the skin raises. Under the electron-microscope, sunburn cells were shown to result from membrane-bound condensation of tonofilament bundles, pyknosis and further fragmentation of the nucleus, vacuolisation of cytoplasm with loss of organelles. Ultimately they appear as filamentous bodies which eventually are shed in the dermis and transformed into amyloid substance, a phenomenon called apoptosis (a Greek derived term which etymologically means «dropping off»). Such dead cells are the hallmark of an acute toxic effect of sunlight on epidermis. Accordingly a first statement can be drawn: any solar erythema is an actual burn, a «sunburn», even if the naked eye does not notice any real damage. In the case of a severe erythema, other types of tissue damage are seen involving the dermis, such as endothelial cell swelling, extravasation of red blood cells, perivascular cell infiltrates of lymphocytes but also of PMN cells. The latter may undergo necrosis and show «nuclear dust».
Biochemical changes

As previously seen, the late solar erythema is associated with a rise in skin and sometimes body temperature, suggesting it might be an inflammatory process due to the release of pro-inflammatory substances. Recent works have confirmed this view, through assessment of such mediators in the succion blister fluid on human skin or dermal perfusions. Histamine levels rise in the erythematous area by the 4th hour (i.e. the onset of erythema), but has returned to normal level by 24h, when erythema is still peaking (9, 14). Type I antihistamines, while lowering actinic erythema in guinea pig, have no effect in man (22). During the same period skin serotonin level decreases (14). Arachidonic acid also starts to rise in the skin together with the onset of erythema. Prostaglandins PGFα, PGD2, PGE2 are found only later, 24h up to 48h following exposure, whereas erythema has a much longer duration (32). Kinins might be also involved through the release of activators by damaged lysosomes (7). All these biochemical events are by no way, different from those induced by heat and resemble those found in the immediate solar erythema but with a much higher intensity. They belong to a non specific inflammation. The major involvement of prostaglandins is in accordance with the partially suppressive effect of indomethacin on UV delayed erythema in man (10). But it only can explain the starting phase. The protracted later phase, from the third day onward, is supposed to be related to the diffusion of (a) unknown mediator(s) as suggested by the spreading of the erythema beyond the irradiated area (8, 35).

The UV Targets

In the above paragraph only the effector limb of solar erythema has been examined, namely that which takes place after or during cell damage. Let us move upstream and consider what occurs before cell damage. Obviously the UV target must lie inside the epidermis as more than 90% of UVB are absorbed par this layer (6, 37). Among the main candidates are some aminoacids (tryptophan, tyrosine), urocanic acid (a derivate from histidine), DNA and, of course, melanin. Experimentally, wavelengths with the maximum activity in terms of producing erythema and sunburn cells are located in UVC, between 260 and 290 nm suggesting that either proteins and/or nucleic acids may be the primary radiation absorber (5). Tyrosine absorbs UV up to 295 nm, Tryptophan up to 315 nm, Urocanic acid up to 325 nm. They all belong to the protein moieties of epidermal cells. As a consequence of UV absorption et subsequent rise in energy level, biochemical reactions might the generated inside cell membranes or lysosomal membranes (4, 15), initiating the biochemical inflammatory cascade leading to erythema. The absorption spectrum of melanin is continuous and monotonously decreasing from 290 to 400 nm (6, 37). There is clinical, histological, and experimental evidence that it is a potent protector against UVB, perhaps the best one. But we still poorly understand how it works. Surprisingly after UVB irradiation a skin deprived of melanin produces less sunburn cells that a lightly pigmented skin, and after melanin ingestion «in vitro» macrophages get much more sensitized to UV induced lysis. Consequently melanin might be both a screen and a photosensitizer (16). DNA absorbs UV rays up to 320 mm, i.e.
in the exact range of UVB. Repeated or intense skin exposure in humans can induce permanent damages, such as base losses or alterations, mostly through the formation of pyrimidine dimers. These lead to errors in DNA replication (e.g. sister chromatid exchanges) and even single strand breaks. These changes may last for the lifetime and be transmissible to daughter cells, mostly if repair mechanisms are congenitally deficient or have become exhausted by repeated actinic insults. It has been shown that cells in S phase are prone to become sun-burn cells probably through a higher sensitivity to UVB induced pyrimidine dimer formation. Recent data lend support to a dual target for sun damage: cell membrane proteins for producing erythema, DNA for inducing sunburn cells.

**What happens in UVB Target Molecules?**

UV radiation is capable of reducing the oxygen molecule (dioxygen) into so-called oxygen-intermediates, or reactive species of oxygen, such as superoxide anion $^\cdot \text{O}_2^-$ and hydroxyl radical $^\cdot \text{OH}$. These products have one unpaired electron in an outer orbital giving them a very powerful aptitude to react, especially with molecules having a double bond in their structure, like unsaturated lipids. Reactive oxygen species are produced through UVB dose radiation dependently, in human skin, where they might damage the cell membranes and initiate the prostaglandin cascade. They also are involved in sulphydryl oxidation with resultant formation of disulphide bonds, and accordingly might contribute to the formation of sunburn cells.

These mechanisms have been substantiated by the protection afforded by free-radical scavengers against sunburn cell production in UVB irradiated biopsy samples of guinea-pig skin in *vitro*. The same protection was found in mouse skin *in vivo* by intravenous injection of superoxide-dismutase. In Xeroderma Pigmentosum, a human disease characterized by an increased sensitivity to UVB with overproduction of actinic skin cancers, a strong increase in skin hydrogen peroxide content was found together with reduced catalase activity. Moreover, these changes were found parallel to the clinical severity and photosensitivity. In two patients, catalase given topically for 3 months reduced both clinical and biochemical abnormalities. More recently, it was found that catalase topically applied could decrease the intensity and duration of UVB erythema in normal people.

**Delayed Adverse Effects of Solar Erythema**

Sun exposure is vital for the human species but overexposure, as visually assessed by the occurrence of an erythema, is potentially harmful, even for the lifetime, although no visible sequellae are left at the moment except in case of severe blistering sunburn.

**Impairment of the Immune System**

Any UV irradiation strong enough to cause a light redness, alters the immunological barrier function of the skin. This is morphologically assessed by the loss of Langerhans cells, a type of skin specific macrophage permanently located among the epidermal cells, close to the limit of the living organism. Their function is to phagocyte and analyse any isolated particle or molecule, and if found alien, to present it to the T lymphocytes, also permanently seated inside the epidermis, with a label indicating it should be reco
gnized and rejected by the entire body immune system. Accordingly the disappearance of Langerhans cells after solar erythema is followed by a period of immune tolerance. But after a couple of days the Langerhans cells would re-appear and the immune barrier be restored.

An ordinary suntanning exposure (e.g. One hour per day for two weeks) is followed by a decrease in blood helper T lymphocytes and increase in suppressor T lymphocytes, together with a reduction in natural killer cell activity against malignant melanoma target cells (11, 12). These side-effects are dose dependent and also occur after non erythemogenic doses of radiation (20). On the other hand during a heavy solar exposure a small amount of UVB and a much larger amount of UVA penetrate the superficial dermis where lymphocytes are circulating inside blood vessels. These cells once irradiated may undergo similar changes as those found in epidermal cells, especially DNA alterations. The latter, irrespective of impairment of immune function may involve a potential danger of future malignancies.

**Actinic Skin Cancer**

Any solar erythema may contribute to increase the cumulative amount of UV rays received by the skin for years and consequently favour premature ageing both at the epidermal and dermal sides, and the occurrence of epithelial skin cancers such as basal cell epitheliomas or spindle cell carcinomas and of melanocytic melanomas (Hutchinson’s lentigo maligna).

The action spectra for biological events linked to skin cancer, such as cell lethality, mutagenesis and pyrimidine dimer formation, lies in UVB range and fit quite closely the erythema action spectrum (28). Experimentally actinic carcinomas are easily produced in animals. In humans there is a close relationship between the incidence of cancer and the low amount of melanin in the skin on one hand, and the cumulated amount of sunlight received by a given area on the other hand (34). Furthermore, diseases associated with a greater UV sensitivity display an abnormally high incidence of such skin cancers, and those people with acinic skin cancer have an abnormally persistent UVB erythema (1, 18, 33).

Other hazard are closely linked to the past personal history of sunburn(s) and their severity. Naevocytic lentigos can occur on previously heavily sunburned areas. But the main risk is the initiation of naevocytic melanomas, which is far more distressing that any of the above quoted ones.

Epidemiological studies, mostly made in Australia (24) and in Israel (13), have shown that the prevalence of the disease, which mainly occurs during the 3rd decade, is highest in people of fair complexion having spent their childhood in low latitude countries. The prevalence is lower but still abnormally elevated in people with the same complexion who arrived in the same climates later in life. Also significantly related with the prevalence of malignant melanoma is the personal history of sunburn(s) in childhood (21).

**Conclusions and Practical Considerations**

While a certain amount of sun exposure is good for caucasian’s both mental and physical health, any effort should be made to prevent the occurrence of a late solar erythema. The statement is especially valid for children in relation to the risk.
of malignant melanoma later in life, as seen above. Melanin pigmentation affords a natural and often effective protection. But in fair skinned people it is often scanty in usually non exposed areas. Consequently the first yearly sun exposures should be progressive. That may be facilitated by repeated application of sunscreens of appropriate absorbancy for UVB. Red skin people and those who never tan represent the population at higher risk. They should avoid long sun exposure. If they are obliged to do so, they should seek protection through repeated application of very potent sunscreens. As melanin is a good protector even if induced by UVA plus photosensitizers like psoralens, a PUVA treatment prior to the period of exposure may be sought from a dermatologist. Topical ointments containing both UVB filters and enhancers of UVA pigmentation may be also of value (29). Nevertheless it should be born in mind that UVA, although non erythemogenic nor carcinogenic under natural solar exposure, can induce the same hazards as do UVB if they are enhanced by photosensitizers like psoralens. Consequently their use should be of the shortest possible duration.
REFERENCES

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