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Effects of micronutrient supplements on u.v.-induced skin damage

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Development of an orally-administered systemic agent that could reduce the effects of u.v. exposure on skin could potentially have a major effect on the incidence of skin cancers and photo-ageing. A number of micronutrients have been suggested to have metabolic properties that could induce this protection, and our data indicate that *n*-3 polyunsaturated fatty acids are particularly effective in this role. The mechanisms of action of *n*-3 polyunsaturated fatty acids appear to depend on their anti-inflammatory properties, acting to reduce the u.v.-induced release of cytokines and other mediators from a variety of skin cell types.

Polyunsaturated fatty acids: Anti-inflammatory: Antioxidant: Cytokines

Exposure of skin to u.v. radiation can result in both acute and long-term adverse effects on the skin. The acute effects include burning, photosensitivity and immunological alterations, and the longer-term effects can include photo-ageing and carcinogenesis (Taylor *et al.* 1990). The importance of these processes has been heightened by depletion of ozone in the atmosphere, leading to increased exposure of human subjects to u.v. radiation. (Frederick, 1993).

The mechanisms of u.v. radiation-induced inflammation are incompletely understood, but include increased production of prostaglandins and cytokines (Kupper *et al.* 1987). In addition, there is increasing evidence that exposure of cutaneous tissue to u.v. radiation leads to generation of free radical intermediates and reactive oxygen species (Black *et al.* 1978), potentially leading to peroxidation of membrane lipids and oxidative damage to DNA and proteins (Dixit *et al.* 1983; Punnonen *et al.* 1991).

Development of an effective systemic agent to reduce acute and chronic damage to skin due to u.v. radiation exposure could have important effects in reducing the increasing problems of premature photo-ageing of skin and skin cancers. There has been considerable interest in this area, particularly related to whether supplementation with nutritional antioxidants may influence the deleterious effects of u.v. radiation on skin (Nachbar & Korting, 1995), but efficacy has not been firmly established.

Our group has undertaken a series of *in vivo* and *in vitro* studies designed to examine the potential of supplementation with either *n-3* polyunsaturated fatty acids or common nutritional antioxidants to reduce the effects of u.v. radiation on skin cells. We reasoned that *n-3* fatty acids could act in an anti-inflammatory manner to reduce the generation of prostaglandins and other inflammatory mediators by skin cells following u.v. exposure, while antioxidants were predicted to reduce effects of reactive oxygen species in damaging key components of the skin or inducing changes in gene expression regulating cell proliferation (Fig. 1).

Polyunsaturated fatty acids

Following some studies that indicated a potential role for fish oils in reduction of erythemal sensitivity to u.v. in hairless mice (Orengo *et al.* 1989), Orengo *et al.* (1992) reported preliminary data indicating that fish oil supplements reduced u.v. sensitivity in human subjects. In order to examine the potential efficacy of this approach, we examined the effect of supplementation with 10 g fish oil (containing 1·8 g eicosapentaenoic acid (20 : 5*n*-3) and 1·2 g docosahexaenoic acid (22 : 6*n*-3), daily for 3 or 6 months in control subjects (Rhodes *et al.* 1994). Their erythemal responsiveness to u.v.B radiation was assessed at monthly intervals and at 10 weeks following cessation of supplements. In addition, paired biopsies of the epidermis were taken before and after 3 months of supplements. The dietary fish oil supplements increased the resistance of the skin to u.v.B-induced erythema, with more than doubling of a quantitative measure of sensitivity, the minimal erythemal dose. This response was associated with incorporation of *n*-3 polyunsaturated fatty acids into skin lipids, with pronounced increases in 20:5*n*-3 and 22:6*n*-3 contents.

Rhodes *et al.* (1994) speculated on the potential mechanisms by which this protection had occurred, suggesting that

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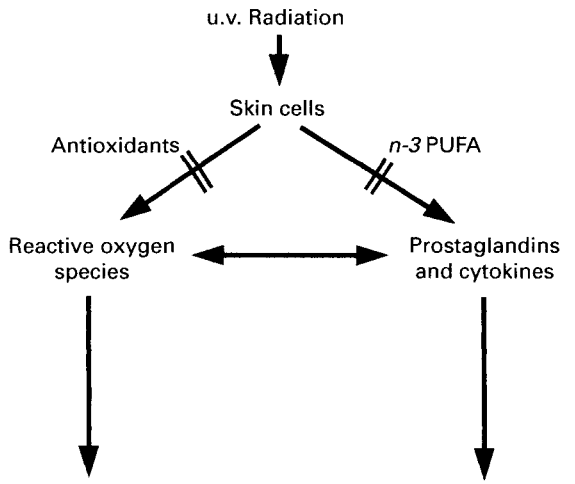

Fig. 1. Schematic diagram to illustrate the potential complementary roles of *n*-3 polyunsaturated fatty acids (PUFA) and antioxidants in reducing u.v. radiation-induced skin damage.

a reduction in prostaglandin production, immune function or free radical production may be involved. In further work Rhodes *et al.* (1995) demonstrated a reduction in u.v. B-generated prostaglandin E_2 levels in the skin of fish oil-supplemented subjects, providing support for this potential mechanism of action. They also provided data in support of the use of these supplements in a light-sensitive disorder, polymorphic light eruption. An action of 20:5*n*-3 and/or 22:6*n*-3 to reduce u.v.-induced release of prostaglandin E_2 or other inflammatory mediators is also supported by our recent data from keratinocyte and fibroblast culture studies (A Storey, L Rhodes and MJ Jackson, unpublished results).

Nutritional antioxidants

u.v. Irradiation of skin is associated with generation of a number of free radicals and reactive oxygen species, and some previous data indicate that antioxidants may play a protective role against u.v.-induced skin damage (De Rios *et al.* 1978; Hanada *et al.* 1991). Rhodes *et al.* (1994) suggested that one potential mechanism for the protective effect of fish oils was that the increased cellular content of oxidisable *n*-3 polyunsaturated fatty acids provides an oxidisable buffer protecting more vital structures against free radical damage. Such a mechanism had been proposed previously for the protective effect of fish oils against erythrocyte lipid peroxidation (van den Berg *et al.* 1991). No direct data for this possibility was provided, although epidermal lipid peroxidation was increased by the u.v. exposure.

As a preliminary to potential supplementation studies *in vivo*, we examined the effect of common nutritional antioxidants on u.v.-induced damage to skin fibroblasts (Jones *et al.* 1999). u.v. Radiation was found to induce a substantial oxidative stress in fibroblasts, resulting in increased release of superoxide anions and an increase in lipid peroxidation. Sub-lethal doses of u.v. radiation were also found to induce adaptive responses in the fibroblast antioxidant defences, with a transient rise in catalase and superoxide dismutase activities followed by a slower, larger, rise in cellular glutathione content. Supplementation of the fibroblasts with the antioxidants, Trolox (a water-soluble analogue of α-tocopherol), ascorbic acid or β-carotene (all compounds obtained from Sigma, Poole, Dorset, UK), had differential effects on these responses (Jones *et al.* 1999). Trolox supplementation reduced the u.v. radiation-induced cellular oxidative stress and adaptive response in a predictable manner, whereas both ascorbate and β-carotene had less predictable effects. Both ascorbic acid and β-carotene increased the u.v. radiation-induced release of superoxide from the fibroblasts, but only at low doses were the adaptive responses in catalase and superoxide dismutase activities reduced.

These *in vitro* data appear to be generally supported by our recent unpublished studies *in vivo* (F McArdle, L Rhodes, P Friedmann and MJ Jackson, unpublished results), that show a reduction in u.v.-induced skin lipid peroxidation by vitamin E supplements. However, such changes were not associated with a reduction in erythemal sensitivity to u.v. in contrast to previously published data (De Rios *et al.* 1978).

Conclusions

Our data firmly support a role for supplementation with *n*-3 polyunsaturated fatty acids as a systemic approach to reduction of u.v. sensitivity in man. The mechanisms involved appear to primarily involve a reduction in u.v.-induced release of inflammatory mediators from skin cells. In contrast, little firm evidence for a beneficial role of supplementation with antioxidant nutrients has been obtained.

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