Invited commentary

Vitamin A: not for vision only

It would probably be 'bringing coals to Newcastle' to stress the common knowledge that vitamin A (retinol) is involved in vision. In contrast, the other functions of this micronutrient taking place in tissues other than the eye are still only sporadically appreciated. These are essential in various phases of animal as well as human development starting with reproduction, fetal and postnatal development, and in adult life as well. Experimental findings of these non-visual functions of retinol and its derivatives, retinoids, in the last decade have been astonishing. The reason this progress remains to be appreciated, for instance by physicians, lies in the fact that even the topic of xerophthalmia, a well-known sign of vitamin A deficiency, has been rather scarce, and in some instances not at all covered according to the latest survey of medical textbooks (McLaren, 1998). In the epidemiology of vitamin A deficiency, positive effects of supplementation on vision using retinyl palmitate, the compound of choice due to its superior stability to retinol, are well documented (Sommer & West, 1996). In contrast to night blindness which is relatively easy to diagnose, lesions caused in organs other than the eye surprisingly have been considered only recently.

Little attention was paid to classic findings that more organs than the eye are influenced by vitamin A. The diagnosis of xerophthalmia caused by lack of retinol in the eyes is much easier to ascertain than the recognition of other effects of retinol deficiency, occurring well before manifestation of night blindness which by itself does not lead to death.

The organs first affected when experimental animals are fed on retinol-deficient diets are those of the oral cavity, trachea and bronchopulmonary tree. Other effects follow, ending with lesions in the eye (Wolbach & Howe, 1925). Histology of these organs of vitamin A-deficient animals has shown that the epithelial lining undergoes profound changes. Originally present, mucociliary cells disappear and are replaced by a keratinized layer. Such change to mucociliary cells normally serving in the lungs as a 'barrier' to the deleterious attack for instance of bacteria or carcinogenic insult renders the animal, as well as humans, sensitive to pulmonary infections and even to cancer. In addition, loss of specialized epithelial cells called type 11 cells which under normal conditions produce surfactants, a group of lipoproteins responsible for lowering surface tension, causes collapse of the lungs which is followed by death. In other words, in the bronchopulmonary system, deprivation of retinol leads to activation of genes coding for some keratins. In other organs like testes, deprivation of vitamin A leads to the loss of seminiferous tubules with no keratinization. Thus vitamin A has tissue-specific effects.

The deleterious effects of dietary vitamin A deprivation in the lungs and epithelia in other organs are fully reversible. Supplementation of vitamin A in the diet brings the morphology of the bronchopulmonary tree back to normal (Wolbach & Howe, 1933).

Mechanistic analysis of the phenomenon of the reversibility of vitamin A action in the whole animal suggests that retinol or some of its metabolites such as retinoic acid, the product of retinol oxidation, influences the 'cell memory' which is encoded in specific sequences of DNA. Such mechanisms would be reminiscent of that of steroid hormones. Indeed it has been shown that refeeding of vitamin A deficient animals with retinol or retinoic acid leads to a rather quick repression or activation of the synthesis of some gene products (Omori & Chytil, 1982). Later, more direct evidence that mechanism of action involves the cell nucleus was generated by the discovery of nuclear retinoic acid receptors, proteins which bind specifically to retinoic acid and its stereoisomers and not retinol (Chambon, 1996). Thus, retinoic acid which is formed *in vivo* in small quantities binds to the nuclear retinoic acid receptors which in turn find specific sequences on DNA called retinoic acid response elements. These sequences are different from those which interact with steroid hormones receptors including vitamin D. The consequences of the contact of the retinoic acid receptor with DNA are in the transcription of specific gene products which are activated or repressed by a mechanism and is currently under intensive study. Unlike the steroid hormone receptors, the nuclear retinoic acid receptors are expressed in multiple forms. The occurrence of such diversity indicates that vitamin A, probably through its metabolite retinoic acid, performs its action in tissues which contain the nuclear receptors. Retinoic acid in the whole animal as well as in cells in culture works faster than retinol, which suggests that retinol first has to be converted to retinoic acid which appears to be the 'active' form of vitamin A. Nuclear retinoic acid receptors act as homo- or heterodimers. For instance, steroid hormone receptors are part of the heterodimers. If such complexes established in experiments with transfected cells exist in the whole animal, then there would be an explanation of how various factors work in concert during embryogenesis and development, for example. In addition, the fetal and adult lungs contain nuclear retinoic acid receptor indicating that in this organ retinoic acid works on the transcription. This does not mean that this presently fashionable mechanism is the only action involving retinoids.

Enough evidence has been accumulated that retinoids, specifically retinoic acid, are factors intimately involved in the perinatal lung development (Chytil, 1996). Thus, supplementation of retinyl palmitate to children when xerophthalmia has been diagnosed should provide not only this vitamin to the eye, but also to the developing lungs which suffer

from respiratory problems, the main cause of morbidity and mortality in these children (Sommer & West, 1996). The prevalent idea that no vitamin A deficiency exists in developed countries should be modified as it has been firmly established that premature babies are vitamin A-deficient and that supplementation with retinyl palmitate improves their pulmonary status (Chytil, 1996).

The very potent effects of retinoic acid on the lungs have been recently demonstrated experimentally. It was reported that retinoic acid administered to neonatal rats causes significant elevation of the number of pulmonary alveoli (Massaro & Massaro, 1996). These results and the more recent findings showing that administration of this compound to adult rats treated with elastase to induce pulmonary emphysema can alleviate the deleterious effects of the elastase treatment, stresses the idea that retinoic acid should be considered for treatment of epithelial lesions (Massaro & Massaro, 1997).

Various forms of supplementation are used: fortification of specific food components like sugar; oral application, used successfully in alleviating night blindness; and intravenous or intramuscular administration, used in experimental animals or in hospital settings.

The paper by Biesalski and colleagues in this issue introduces for the first time delivery of retinyl palmitate by inhalation of an aerosol (Biesalski *et al*. 1999). Although this method cannot deliver all of the vitamin A inhaled to the lungs since part of it is swallowed, it offers a unique mode to deliver this vitamin to the lungs directly. Furthermore, this type of delivery gives an opportunity to deliver retinoic acid directly to the lungs by bypassing thereby the necessity of *in vivo* oxidation of retinol to retinoic acid which may be a critical limiting factor in some pulmonary lesions. Thus retinoic acid may be more effective than retinyl palmitate.

Frank Chytil
Department of Biochemistry
Vanderbilt University School of Medicine
Nashville, TN 37232
USA

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