Impaired Local Immune System in Vitamin A Deficiency

Vitmain A is an essential nutrient for all vertebrates. Apart from its well characterized function in vision, vitamin A has diverse functions in the body including differentiation and proliferation of epithelial cells.[1-4] In its absence, a multitude of physiological and biochemical changes take place, leading ultimately to death if the deficiency is sufficiently severe or prolonged. In addition to its role as an essential nutrient at physiological concentrations, large doses of vitamin A may also be of therapeutic value, particularly as an anticarcinogenic agent.[1,2,5] This activity may be associated at least partly with the well known adjuvant effects of large doses of vitamin A. Another possibility lies in the apparent ability of large doses of vitamin A and some of its analogues to reverse the pre-neoplastic transformation of certain epithelial tissues. Despite such early phenotypic changes under conditions of both hypo- and hyper- vitaminosis A, the cellular and molecular mechanisms of action of vitamin A remain an open and highly controversial issue. The presence of different active forms of vitamin A (including retinol, retinal and retinoic acid) in various mammalian tissues also raises the possibility that it has multiple modes of action. Certainly no single function can presently explain the postulated widespread roles of vitamin A, including regulation of nuclear events and gene expression, modification of cell-surface properties and even involvement in electron transfer. Of these various theories, a modulation of glycoprotein synthesis in vitamin A deficiency[6,7] which might in turn influence the cell surface properties of, for instance, lymphocytes is presently of some interest as it might explain at least partly the close association between immunocompetence and vitamin A nutriture.

Although it is generally accepted that vitamin A is essential for the growth and survival of all vertebrates, an earlier study[8] involving germ-free animals suggested that if all stresses were removed, animals might well survive without vitamin A. If demands were imposed on the body such as rapid growth or tissue regeneration, it was postulated that the animals would require vitamin A to survive. Although this interesting but technically demanding study has never been repeated using more recent analytical techniques to verify the vitamin A-free status of the animals or diets, this conclusion is nonetheless consistent with observations in experimental animals and epidemiological data in humans showing that vitamin A deficiency is associated with increased susceptibility to and severity of infection by virtually all types of micro-organisms.[9] Due to its diverse functions in the body, vitamin A might reasonably be expected to be involved in both non-specific and specific host defense mechanisms. Relatively little, however, is currently known about the effect of vitamin A deficiency on specific immune mechanisms, particularly in humans. Data, moreover, are usually complicated by concurrent deficiencies of other dietary components, inanition or superimposed infection. Nevertheless, several groups of investigators have reported atrophy of the thymus and various lymphoid organs in vitamin A deficiency.[10] The surface properties of lymphocytes of vitamin A deficient rats are also thought to be different from those of normal controls.[11] These vitamin A deficient rats are also lymphopenic. Also, both peripheral blood and splenic mononuclear cells from these animals respond poorly to stimulation by phytohaemagglutinin.[12-14] Such animals also have deranged humoral immune response to stimulation by dinitrophenylated bovine gamma globulin (DNP-BGG).[15,16]

It was demonstrated several years ago that children with compound protein-calorie malnutriton had impaired local immune systems, as indicated by depressed secretory IgA (SIgA) levels in nasopharyngeal washings.[17] Further analysis of the data led to the impression that this defect was more severe in those patients with concomitant vitamin A deficiency, thus suggesting that vitamin A deficiency might be causally associated with an impaired local immune system.[18] To test

this hypothesis, experiments were conducted using rats rendered vitamin A deficient by a novel technique[19] enabling the induction of deficiency with minimal secondary inanition. Furthermore, the time of onset could be precisely determined. Taking advantage of this system, it was shown that a single uncomplicated deficiency of vitamin A impaired the local immune response; both the intestinal IgA levels and the response of these animals to stimulation by DNP-BGG were significantly lower than those of control animals.[20] Additional, albeit indirect, evidence in consonance with this finding was the observation that these vitamin A deficient rats were prone to bacteremia caused by invasion of the normal intestinal flora.[21] Analysis of the literature also leaves one with the impression that vitamin A deficient animals and man are particularly susceptible to infections that occur at the body surfaces.[9]

Although the precise mechanism of action of vitamin A on the local immune system is not known, there are many possibilities, including a generalized defect in the differentiation and proliferation of lymphocytes, aberrant migration of lymphocytes to the mucosal sites, and impaired synthesis of the secretory component. Lymphopenia and alteration of the lymphocyte subpopulation noted in vitamin A deficient rats[12,14] as well as the underdevelopment of various lymphoid tissues[10,22] may be accounted for by a differential susceptibility of these cells to vitamin A depletion. Defective migration of lymphocytes to mucosal sites might conceivably affect local defense not only by reducing IgA antibody levels but also by decreasing the cellular killing capacity of mucosal lymphocyte subpopulations. It was also observed that there are fewer IgA secreting plasma cells and intra-epithelial lymphocytes in the intestine of malnourished subjects than in healthy controls.[23,24] Subsequently Pierce and his colleagues[25] reported that the localization of thoracic duct lymphocytes into intestinal tissues is reduced in protein deficient rats. Recently McDermott and his coworkers[26] extended these observations and showed by a passive cell transfer that there is reduced migration of lymphocytes from vitamin A deficient rats to mucosal sites in normal animals. While the mechanism for such a defect has yet to be elucidated, it is not unreasonable to link it, at least partly, to altered glycoproteins on the membrane of these lymphocytes as previously reported by Mark and his associates.[11] On the other hand, Takagi and Nakano[27] recently presented evidence suggesting that altered lymphocyte migration in cases of vitamin A depletion may be the result of a derangement in the integrity of lymphocyte-trapping mechanisms in some lymphoid organs and not of a change in the nature of the lymphocytes *per se*.

In addition to the above possibility, defective synthesis of the secretory component (SC) of secretory antibodies would have a direct influence on depressed local immunity of vitamin A deficient subjects. The secretory component is a glycoprotein synthesized by mucosal epithelial cells[28,29] and possibly also by goblet cells,[30] both in the crypts and villi. Such a defect is not unexpected as Rojanapo *et al*[7] have recently demonstrated that mucoproteins produced by the intestine of vitamin A deficient rats are biochemically distinct from those of normal controls. It has also been shown recently that the *de novo* synthesis of SIgA is reduced in vitamin A deficient rats.[31] This observation suggests that the SC-mediated transport of IgA may be impaired in the intestine of vitamin A deficient animals. In consonance with this suggestion we have also shown recently that the hepatocyte transport of IgA from blood to bile in these deficient animals is impaired,[31,32] a process which has been demonstrated in rodents to be SC-mediated.[33] Depressed transport of IgA in vitamin A deficient animals was not due to reduced levels of circulating IgA as the serum IgA levels in both deficient and control animals were indistinguishable.[20] In seems unlikely that the interference in the transport of IgA was due to improper conjugation of the SC synethesized by these animals.[20] Rather, a reduced immunofluorescence staining for SC in the intestinal epithelial cells of deficient rats[20] supports the earlier postulation[18] that the synthesis of SC is directly affected.

Therefore, based on evidence currently available it seems reasonable to conclude that impaired local immune response and inadequate mucosal immunity in vitamin A deficiency may be due to several factors. Those so far implicated include depressed proliferation and terminal differentiation of IgA bearing lymphocytes, abnormal migration of these lymphocytes to various mucosal sites, reduced synthesis of secretory component by epithelial cells and inadequate T cell function. Once organisms have penetrated this first line of defense, they would also have a better chance of establishing themselves within the host since bacterial clearance and phagocytosis together with serum opsonic activity in these animals is known to be impaired.[34-36] The data discussed in this communication raise a number of questions that warrant further investigation.

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