

ADVANCES IN VITAMIN A

TAUFIQ AHMAD MUFTI

*Department of Biochemistry,
Postgraduate Medical Institute,
Lady Reading Hospital Peshawar.*

Current research dealing with vitamin A is vigorous and diverse, with a strong impact on several fields of medicine and public health, ranging from ophthalmology and nutrition to dermatology and oncology. Retinoids may in time prove of value in other areas of medicine (such as rheumatic connective tissue disorders) as well. Future research will determine the scope and promise of these developments.¹

In Karachi, low plasma vitamin A levels were recorded and children under 15 years of age were found to be at risk.²

SYNTHESIS AND ABSORPTION

Vitamin A cannot be synthesised in the body and must, therefore, be taken in with food as either retinol and its esters or B-carotene. Many people in rich countries and most people in poor countries derive majority of their retinol from the pro-vitamin A carotenoids in plants. B-carotene is converted to retinol in intestinal mucosa. It involves two enzymes: B-carotene-15,15'-dioxygenase and retinaldehyde reductase.³

CIRCULATION

Retinol absorbed in the intestinal mucosa⁴ is esterified but unbound.⁵ It is transported via the lymphatic route in chylomicron and their remnants.⁶ The retinyl esters remain with the chylomicron remnant particles and

are removed from the circulation by the liver.^{7,8} Stellate cells store more than 90% of liver retinol in most instances.⁹

Some of the dietary B-carotene and other carotenoids are absorbed unchanged from intestine and stored in adipose tissue. Vitamin E increases the absorption of vitamin A from intestines^{10,11} where as low levels of vitamin A may be due to malabsorption.

BINDING

Vitamin A circulates in plasma mainly as retinol, associated with a transport protein. Action of vitamin A in tissues is mediated by specific intracellular binding proteins, similar to that known for steroid hormones. Two binding proteins have been described in rats¹² and human tissues¹³ called cellular retinol binding protein (CRBP) and cellular retinoic acid binding protein (CRABP), which bind retinol and retinoic acid respectively, with high affinity and specificity.^{14,15}

RBP molecules synthesised in liver, leave it as soon as they have picked up a retinol molecule from the liver stores. If retinol store is depleted RBP builds up in the liver which is characteristic of hypovitaminosis A.¹⁶ It is suggested that low levels of zinc might reduce the synthesis of RBP and thus reduce the mobilization of vitamin A from liver.¹⁷

HYPER AND HYPOVITAMINOSIS

In hyper vitaminosis A, liver retinol storage capacity is exceeded causing liver damage and allowing unbound retinol to circulate. Prolonged use of vitamin A in pharmacological dosage causes important side effects; these include fatigue, irritability, anorexia, nausea, cracked lips and dry skin with desquamation and eventually vomiting, headaches, hair loss, bone pains and hepatomegaly. A teratogenic effect could exist for exposures to high doses of vitamin A.¹⁸

Blood levels of bound retinol is not dependent on free retinol absorbed from intestine;¹⁹ rather there are some extrinsic determinants, for example, oral contraceptives²⁰, diabetes, thyroid disease²¹ and anorexia nervosa²², which elevate retinol and B-carotene levels. RBP levels were significantly higher in epidermoid carcinoma of oral cavity and oro pharynx compared to normal adjacent tissue. RBP was also found to be higher in few cases.²³ Elevated levels for both RBP and CRBP in tumour have been observed in breast^{24,25}, lung^{25,26} skin and stomach compared to adjacent tissues. RABP was also detected in 80% cases of colon, caecum and rectum tumours.²⁷

METAPLASIA

In 1920s it was discovered that deficiency of vitamin A leads to metaplastic changes in epithelia of respiratory, gastrointestinal and genito - urinary tract. The importance of vitamin A in maintaining normal histology of certain epithelia is well known. A deficiency of this vitamin induces metaplasia with marked keratinization. Dietary vitamin A inhibits this keratinization and prevents deficiency metaplasia.²⁸

IMMUNE MODULATION

It is suggested that vitamin A has a definite influence on the lymphoid organs and immune responses, therefore, its deficiency indirectly enhances the cellular growth by depressing immunity.^{29,30} Protein synthesis by membrane bound but not by free polyribosomes of intestinal mucosa of albino rat, is depressed under conditions of vitamin A deficiency. It is, therefore, involved, directly or indirectly, in protein synthesis at the translational level.³¹ Vitamin A deficiency also causes a decrease in synthesis of fucose containing glycopeptide (Fuc-glycopeptide) and a reduction in goblet cells in rat small intestine.³²

ANTI-CANCER ROLE

It is apparent that a variety of retinoids possess anticancer activity in experimental models for cancer of the breast and urinary bladder and that minor modifications of the retinoid molecule can have striking effects on organ distribution and the cancer chemopreventive activity of a compound.³³ Additive or synergistic interactions between retinoid and other modulators of carcinogenesis have been demonstrated.^{34,35,36}

It is proposed that inhibition of the function of natural antipromoters such as retinoic acid may be one mechanism of action of tumor promoters,³⁷ and agents that inhibit the synthesis of retinoic acid will in doing so enhance tumour promotion risks or act as co-carcinogens.³⁸

Retinoic acid treatment of several cell lines enhances the binding of epidermal growth factor (ECF) to its receptor, by increasing the number of ECF receptors.³⁹ It also stimulates embryonal carcinoma cell line diffe-

rentiation.⁴⁰ Vitamin A and its analogues have antitumour⁴¹ activity in suspension culture, organ culture⁴² and in animal system.⁴³ In man, their efficacy is reported in treatment of premalignant and malignant lesions.⁴⁴ In human tumour cloning system in soft agar, these retinoid analogues can occasionally decrease the number of tumour colony forming units (T-CFU), which is dose dependent for only a few tumours.⁴⁵ Complete clearing of plaques was seen in cutaneous T-cell lymphoma with 13-cis-retinoic acid⁴⁶ and regression of metastatic melanoma⁴⁷ was noted with B-all-trans-retinoic acid.

In one day old chick embryo, retinol deficiency causes failure of mesenchymal cells to proliferate and differentiate to form the early vascular system⁴⁸ and normal development can be restored by injection of appropriate amounts of various retinoids.⁴⁹ In human promyelocytic leukemia cells, retinoids can induce terminal differentiation leading to formation of morphologically mature granulocyte.⁵⁰

Adding vitamin A palmitate to the fluid used for painting the cervix of Syrian hamster, prevented the development of carcinoma of cervix and vagina.⁵¹ Retinoids effect the expression of genes or gene products involved with both differentiation and proliferation.⁵² Retinoids control the expression of many proteins, for example, keratins⁵³, collagens⁵⁴, collagenase⁵⁵, transglutaminase⁴⁸, laminin, plasminogen activator⁵⁵ and alkaline phosphatase.⁵⁴ It has also been shown that physiological levels of all-transretinoic acid suppress myc oncogene expression in HL-60 cells.⁵⁶

Increased cAMP-dependent protein kinase activity is shown in B16 melanoma cells.⁵⁷ N⁶, O²- dibutyryl-cAMP markedly potentiates the differentiating effects of retinoic acid in

F9 teratocarcinoma cells⁵⁴ and HL-60 leukemia cells.⁵⁸ Some workers have also suggested calcium and phospholipid dependent, cAMP independent protein kinase activity.⁵⁹

Despite the achievements obtained in treatment of various skin diseases and preneoplastic lesions, we are still far from the point where we can be satisfied with the practical clinical progress.⁶⁰

REFERENCES

1. Goodman D S. Vitamin A and retinoids in health and disease. *New England Journal of Medicine*, 1984; 16: 1023.
2. Ibrahim K, Yousafi M A, Hasnain S N. Plasma vitamin A and carotene levels in Karachi population. *J.P.M.A.*, 1987; 37: 117.
3. Goodman D S, Olson J A. The conversion of all-trans B-carotene into retinol. *Methods Enzymol.*, 1969; 15: 462.
4. Helgerud P, Peterson L B, Norum K R. Retinol esterification by microsomes from mucosa of human. *Jilin Invest.*, 1983; 71: 747.
5. Peto R, Doll R, Buckley J D, Sporn M B. Can dietary B-carotene materially reduce cancer rates. *Nature*, 1981; 290: 201.
6. Goodman D S, Huang H S, Shiratori T. Vit. A transport and metabolism. *J. of lipid Res.*, 1965; 6: 390.
7. Blomhoff R, Helgerud P, Dueland S, et al. Retinyl esters in liver cells. *Biochimica et Biophysica Acta*, 1984; 722: 109.
8. Blomhoff R, Helgerud P, Resmussen, et al. *Proceedings of National Academy of Sciences. USA.* 1982; 79: 7326.
9. Blomhoff R, Berg T, Norum, K R. Distribution of retinol in rat liver cells. *Br. J of Nutr.* 1988; 60: 2333.
10. Ames SR. Factors affecting absorption and transport of vitamin A. *Am J. Clin. Nutr.* 1969; 22: 934.

11. Bauernfeind JC, Newmark H, Brin M. Vitamin A and E nutrition via intramuscular or oral route. *Am. J. Clin. Nutr.* 1974; 27: 234.
12. Bashor M M, Toft D O, Chytil F. In vitro binding of retinol to rat tissue component. *Proc. Natl. Acad. Sci., USA*, 1973; 70: 3483.
13. Chytil F, Page D L, Ong D E. Presence of cRBP and cRABP in human uterus. *Intl. J. Vit. Nutr. Res.*, 1975; 45: 293.
14. Ong D E, Chytil F. Specificity of cRBP for compounds with vitamin A activity. *Nature*, 1975; 255: 74.
15. Ong D E, Chytil F. RABP in rat tissue. *J. Biol. Chem.*, 1975; 250: 6113.
16. Kanai M, Raz A, Goodman D S. Retinol binding protein. *J. Clin. Invest.*, 1968; 47: 2025.
17. Ataukorala S, Basu T K, Dickerson J W T, et al. Vitamin A, Zinc & lung cancer. *Br. J. Cancer* 1979; 40: 927.
18. Marteniz-Fris M L, Salvador J. Megadose of vitamin A and teratogenicity. *Cancer*, 1988; 1: 236.
19. Underwood B A, Siegel H, Wiesell R C, et al. Liver stores of vitamin A. *Am. J. Clin. Nutr.*, 1970; 23:1037.
20. go. *NUTR. TEV.* 1979; 37: 346.
21. Nieman C, Obbink H J K. *Vita Horm.*, 1954; 12: 69.
22. Crisp A H, StoneHill E. B-carotene leuds in diabetes and thyroid disease. A and anorecia neruosa. *Post Grad. Med. J.*, 1967; 43: 721.
23. Ong D E, Goodwin W J, Jesse R H, Griffin C. Presence of cRBP and cRABP in epidermoid carcinoma of oral cavity and oropharynx. *Cancer*, 1982; 49: 1409.
24. Huber P R, Geyer E, Kung W, Matter A, Torhorst J, Eppenberger U. RABP in human breast cancer and dysplasia. *J. Natl. Cancer, Int.*, 1978; 61: 1375.
25. Ong D E, Page D L, Chytil. RABP occurance in human tumors. *Science*, 1975; 190: 60.
26. Palan P R, Romney S L. Cellular binding proteins for vitamin A. *Cancer Res.*, 1980; 40: 4221.
27. Sani B P, Condon S M, Brockman R W, et al. RABP in experimental and human colon tumors. *Cancer*, 1980; 45: 1199.
28. Harris L J, Irmes J R M, Griffith A S. Pathogenesis of a vitaminosis A. *Lancet*, 1932; 223: 614.
29. Jurin M, Tannock I F. Influence of vitamin A on immunological responses. *Immunology*, 1972; 23: 2837.
30. Krislman S, Bhuyan U N, Talwar G P, et al. V. Effect of vitamin A and protein caloric under nutrition on immune responses. *Immunology*, 1974; 27: 383.
31. Deluca L, Little E P, Wolf G. Vitamin A and protein synthesis by rat. *J. Biol. Chem.*, 1969; 244: 701.
32. Deluca L, Schumacher M, Nelson D P. Localization of retinol dependent fucose glycopeptide in goblet cell of the rat of small intestine. *J. Biol. Chem.*, 1971; 246: 5762.
33. Moon R C, McCormick D L, Mehta R G. Inhibition of carcinogenesis by retinoids. *Cancer Res.*, 1983; 43: 2469s.
34. McCormick D L, Mehta R G, Thompson C A, et al. Enhanced inhibition of mammary carcinoma by combined treatment with 4- HRP and ovariectomy. *Cancer Res.*, 1982; 42: 508.
35. Thompson H J, Meeker L D, Becci P J. Effect of combined selenium and retinyl acetate treatment of mammary carcinogenesis. *Cancer Res.*, 1981; 41: 1413.
36. Weeks C E, Slaga T J, Hennings H, et al. Inhibition of phorhol ester induced tumor by vitamin A. *J. Natl. Cancer Inst.*, 1979; 63: 401.
37. Deluca L M. In: J. Surat (ed) *Retinoids: New trends in research and therapy.* Basel: Karger Press, 1985; pp. 66.
38. Conner M J. Oxidation of retinol to retinoic acid. *Cancer, Res.*, 1988; 48: 7038.

39. Jetten A M. Retinoids specifically enhance the number of EGF receptors. *Nature*, 1980; 284: 626.
40. Jetten A M, Jetten M E R. Possible role of RABP in embryonal carcinoma cell differentiation. *Nature*, 1979; 278: 180.
41. Ueda H, Takenawa T, Milan J C, Gesel M S, Brandes D. Inhibitory effects of retinoids on breast cancer. *Cancer*, 1980; 46: 2203.
42. Chopra D P, Wilkoff L J. Reversal by retinoids of hyperplasia in mouse prostate culture cells. *J. Natl. Cancer Inst.*, 1977; 58: 923.
43. Sporn M B, Squire R A, Brown C C, et al. 13-Cis retinoic acid: Inhibition of bladder carcinogenesis in rats. *Science*, 1977; 487.
44. Meyskens F L, Salmon S E. Inhibition of melanoma colony Res., 1979; 39: 4055.
45. Cowen J D, Von Hoff D D, Dinesman A, et al. Tumour colony forming (T-CFO) in humsn. *Cancer*, 1983; 51: 92.
46. Kessler J F, Meyskens F L Jr, Levine N, et al. Treatment of T-cell lymphoma with 13-cis retinol. *Lancet*, 1983; 1345.
47. Levine N, Meyskens F L. Topical vitamin A acid therapy for metastatic melanoma. *Lancet*, 1980; i: 224.
48. Scot K F F, Meyskens F L, Russell D H. Retinoids increase trans glutaminase activity and inhibit ornithine decarboxylase activity. *Proc. Natl. Act. Sci. USA*, 1982; 79: 4093.
49. Sporn M B Harris E D Jr. Proliferative diseases. *Am. J. Med.*, 1981; 70: 1231.
50. Breitman T R, Collins S J, Keene B R. Terminal differentiation of human promyelocytic leukemia cells in primary culture in response to retinoic acid. *Blood* 1981; 57: 1000.
51. Chu E W, Malgren R A. Vitamin A inhibitory effect on tumour induction. *Cancer Res.*, 1965; 25: 884.
52. Sporn M B, Roberts A B. The role retinoids in differentiation and carcinogenesis. *Cancer Res.*, 1983; 43: 3034.
53. Fuchs E, Green H. Regulation of terminal differentiation of cultured human keratinocytes by vitamin A. *Cell*, 1981; 25: 617.
54. Strickland S, Mahdani V. Theinduction of differentiation in teratocarcinoma stem cells by retinoic acid. *Cell*, 1978; 15: 393.
55. Brinkerhoff C E, Harris E D Jr. Modulation by retinoic acid and corticosteroids of collagenase production. *Biochem. Biophys. Acta.*, 1981; 677: 424.
56. Westin E H, Wongstaal F, Gelmann E P, Dalla favara R, Papas T S, Lautenberger J A, Eva A, Reddy E P, Tronick S R, Aoronson S A, Gallo R C. Expression of cellular homologues of retroviral oncogenes in human hemato-poietic cells. *Proc. Natl. Acad. Sci., USA*, 1982; 79: 2490.
57. Ludwig K W, Lowey B, Niles R M. Retinoic acid increase cAMP-dependent protein kinase activity in murine melanoma cells. *J. Biol. Chem.*, 1980; 255: 5999.
58. Olsson I L, Breitman T R, Gallo R C. Priming of human myeloid leukemic cell lines HL-60 and U-937 with retinoic acid. *Cancer Res.*, 1982; 42: 3928.
59. Nishizuka Y, Takai Y. Calcium and phospholipid turnover in a new recep-tor function for protein phospho-relation. *Cell proliferation*, 1981; 8: 237.
60. Bollag W. Vitamin A and retinoids: from nutrition to pharmacotherapy. *The Lancet*, 1983; i: 860.