RESEARCH PAPER | Medical Science | Volume : 6 | Issue : 2 | FEBRUARY 2016 | ISSN - 2249-555X

Possible Blood – Brain--Barrier and Blood – CSF--Barrier for Vitamin A

KEYWORDS: Vitamin A, Brain, CSF

DR. SALIL KUMAR MANDAL

DEPARTMENT OF PHYSIOLOGY KPC MEDICAL COLLEGE & HOSPITAL 1F, Raja S.C. Mullick Road, Kolkata – 700032, India

ABSTRACT *Vitamin A is essential for the vision and for the development of the body including the brain as some Scientist suggested. Normally in albino rats and in human being the serum level in resting condition is 44.83 IU/ 100ml and 91.00 I.U/ 100ml respectively. After oral administration in rats this level is increased by threefold in the serum. In liver also this level is increased many fold after an oral dose . But no vitamin A was detected in rat brain before and after oral dose . In the human being CSF (cerebro spinal fluid) was investigated for vitamin A but no vitamin A was detected. From these experiments it can be concluded that possibly there is blood – brain and blood—CSF- barrier for vitamin A*

McCollum and Kennedy in 1916 classified growth factors into two – one is fat and other is soluble. Later the fat soluble one was renamed as vitamin A by Drummond in 1920(1,2). Vitamins are, by definition, substances that cannot be synthesized by mammalians but are required in small amounts to support normal metabolism (3,4). Since vitamins are not synthesized by the brains they must be obtained from the blood. Thus specific transport systems are present in the blood – brain barrier for most of the vitamins (5). Vitamin A is one of the names of a group of fat- soluble vitamins known as retinoids, including retinol, retinal, retinylester and retinoic acid(6,7). Plasma retinol concentration lower than 0.70 micromoles /L (or 20micrograms /dL) reflects vitamins A inadequacy in a population. According to the World Health Organization, 190 million preschool children and 19.1 million pregnant woman around the world have a serum retinol below 0.70 micromoles/L(7,8).Deficiency or excess of vitamin A in the mother's diet during pregnancy have been shown to cause malformations of the fetal brain and hydrocephal (Millen *et al.*1954)(6).

Howell and Thompson (1967) reported that there was obstruction to CSF circulation in vitamin A deficient chickens and also reported lower IQ in vitamin A deficient children(7). When newborn rats were deprived of vitamin A, it resulted in a defect of myelination without gross destruction or deformity of brain structure (Clausen 1969)(8). When mothers were deprived of vitamin A early in pregnancy, their surviving offspring exhibited gross deformities of the visual system(9). Corey and Hayes (1972) reported that, in most species studied, deficiency of vitamin A brought about a rise in cerebrospinal fluid pressure (10) . Blood- brain barrier (BBB) is the separation of circulating blood from brain extracellular fluid in the central nervous system (CNS). It consists of tight junctions around the capillaries that do not exist in normal circulation, Blood-CSF barrier in formed by epithelial cells of the coroid plexus. P-glycoprotein is found to play a great role to prevent the drugs entry in the CNS (11).

Blood-brain barrier is composed of high density cells preventing passage of substances from the blood much more than endothelial cells in Capillaries elsewhere in the body. The astrocytes around the endothelial cells of the BBB provide support to the these cells . Some areas of the human brain are without these barrier, eg circum veribucular or say roof of the third and fourthly ventricles , capillaries of the pineal glands etc.(11) Reports stating necessity of vitamin A for the development of brain and other tissues are described by several scientists(12,13) but the report of the presence of this vitamin in brain or CSF is rare. ***Animal experiments:*** Twelve animals (male albino rats) weighting 50-60grams were taken and kept in laboratory condition for 15 days . They were divided into two group (group A –control & group B experimental) containing 6 animals in each group. They were given standard laboray diet and water at labitum. On the 16th day in the laboratory each experimental animals were given 5000 I.U. of retinol in 0.5ml coconut oil. After 24 hours all the animals (control & experimental) were sacrificed and blood , liver and brain were collected and vitamin A was estimated in each sample collected by the methods described earlier (14) after homogenezization. Vitamin A standard was prepared with retinol purchased from sigma chemical.

Human experiments :

Samples of CSF were collected from the Biochemistry laboratory of our Hospital and vitamin A was measured in 10 samples by the methods described earlier (14). Serum vitamin A was also investigated in these subjects.

Some results are given in the table – I & table – II

Table – I: Level of vitamin A in different tissues of rats before and after oral administration (n = 6) (I.U±SE)

Tissues	Control	Experimental	P-level
Blood(per 100 ml)	44.83±1.58	114.00±3.34	P<0.001
Liver (per 100ml)	6.42±0.54	63.28±2.35	P<0.001
Brain (per gram)	ND	ND	

Table – II : Vitamin A in serum and CSF in human (n = 10)

Serum	(I.U. / 100ml ±SE)
	90.8 ± 5.4
CSF	--- N.D. (not detected)

Vitamin A was investigated in the Human CSF in ten samples and no vitamin A could be have been defected. In the present experiments vitamin A was not detected in the

Volume : 6 | Issue : 2 | FEBRUARY 2016 | ISSN - 2249-555X

brain neither before - nor after oral administration of vitamin A . In the human beings there was high level of vitamin A in normal individual but no vitamin A was defected in the Cerebrospinal fluid. Earlier reports show that vitamin A deficiency causes different neurological problems as seen like in coordination level degeneration, by docepralus etc (15). From this present work it seems that the blood brain barrier and a blood CSF barrier prevents vitamin A . Possibly brain development and function are not dependent on vitamin A. Brain development is dependent upon NGF (nerve growth factor) and other growth factors(16). Retinoic acid, regulates gene expression throughout the body, and many components of the signaling system through which it acts, are also present in the brain. An understanding of the role of retinoids in normal brain function may provide clues to the long – standing question of whether abnormalities in retinoic acid signaling contribute to the pathogenesis of some brain diseases with uncertain etiologies that involve both genetic and environmental factors. Retinoic acid (RA) plays a crucial role in the brain during embryogenesis. Because radial glial cells supply the brain with RA during the developmental cascade and associate closely with the developing vasculature it is hypothesized that RA is important for the induction of BBB epithermal cells properties in brain (17). It is presumed that RA helped the induction of the BBB during human and mouse brain development . Recent work has suggested that retinoic acid may influence the adult brain; animal studies indicated that the administration of isotretinoin is associated with alterations in behavior as well as inhibition of neurogenesis in the hippocampus. (16) Besides oral administration of RA, it was found both in serum and brain.

More RA was found in white mater than gray mater (17, 18, 19). From these observations it can be concluded that retinoic acid passes blood – brain – barrier but vitamin A cannot enter the CSF brain subset Mammals cannot synthesize vitamin A, so they must extract it from their diet in the from of carotenoids (from plants) and retinyl esters (from animal products). These dietary components are stored as retinyl esters in the liver and in several extrahepatic sites, including the lungs, bone marrow , and the kidneys (5). Transport of retinoids from these storage sites to the target cells is performed under retinol form, which is released into the bloodstream and circulates bound to retinol – binding protein. Retinol is taken up by target cells, then enters the cytoplasm, and is metabolized into retinaldehyde and then into *all – trans* retinoic acid (RA) (5). The adult brain possesses all the machinery to metabolize and produce RA from retinol supplied by the blood. In the brain, the highest levels of RA were observed in the striatal region, which strongly expressed RAR β,one of the RAR isoforms. The hippocampus is a region highly involved in neuronal processes such as synaptic plasticity, long term depression, and long term potentiation, which are all strongly affected by changes in vitamin A availability (12). Previous studies have shown the presence of retinoid – specific receptors in the hippocampus and have demonstrated that vitamin A deficiency produces a severe deficit in spatial learning and memory, which are linked to proper hippocampal hypofunctioning (13). Several reports are available showing vitamin A is essential for the brain development (12,13,18,19). RA is also can do almost the same function in the brain . But report of the presence of vitamin A in brain is rarely found. But retinoic acid is found to be present in different parts of brain in different experimental condition (20, 21, 22,23). From these observations including the present findings it can be presumed that vitamin A is converted in different tissues including the endothelium of the blood vessels of brain into Retinoic acid which ultimately is responsible for the anatomical and metabolic changes in central nervous system.

REFERENCE Pitt GAJ Vitamin A in Diplock A.T.edrs Fat – Soluble vitamins , Heinemann, London 1985,pp – 1 –75 Drummond J C and Coward K H Research on the Fat – soluble Accessory Substance. III : Technique for soluble A. Biochem J. October 1920 ; 14(5) : 661 – 664. Johnson EJ, Russell RM. Beta – Carotene. In: Coates PM, Betz JM, Blackman MR, et al., eds. Encyclopedia of Dietary Supplements. 2nd ed. London and New York : Information Healthcare; 2010: 115-20. Ross CA. Vitamin A. In : Coates PM, Betz JM, Blackman MR, et al., eds. Encyclopedia of Dietary Supplements.2nd . London and New York : Information Healthcare ; 2010:778 –91. Siegel GI; Albers RW; Bardy S.T.; Price DL Basic Neurolochemistry 7th ed. Academic press, London 2006 . MILLEN JW, WOOLLAM DHM, LAMMING GE: Congenital hydrocephalus due to experimental hypovitaminosis A. Lancet 1954 267: 679 – 683. HOWELL JM, THOMPSON JN: Leisions associated with the development of ataxia in vitamin A deficient in chicks. Br J Nutr1967 21: 741 – 750. CLAUSEN J: The effect of vitamin A deficiency on mylination in the central nervous system of the rat. Eur J Biochem 1969 7: 575 – 582. Warkany J : Congenital malformation . Year book publisher Chicago. 1971. COREY JE, HAYES KC: Cerebrospinal fluid pressure, growth and hematology in relation to retinol status of the rat in acute vitamin A deficiency. J Nutr 1972 102; 1585 – 1593.11. Begley, D.J., and Brightman , M.W. Structureal and functional aspects of the blood – brain barrier. prog . Drug Res., 2003, 61: 39 – 78.T. Ramakrishna., Vitamins and Brain Development Physiol. Res. 1999 48: 175- 18 SHARMA HS, MISRA UK: Maternal vitamin A restriction alters biochemical development of the brain in rats. Experientia 1990 46: 208 -2011. Bayfield RF and cole ER colorimetric estimation of vitamin A with trichloroacetic acid. Methods Enzymology 1980;67;189- 195. C.Wiesmann and A. M. de Vos Nerve growth factor : structure and function , CMLS Cell. Mol. Life Sci. 2001, 58 : 748-759. Elizabeth A. Werner and Hector F. Deluca : Retinoic acid is detected at relatively high levels in the CNS of adult rats. Am J Physiol Endocrinol Metab 2002, 282: E672-E678. INDIAN JOURANAL OF APPLIED RESEARCH iElizabeth A. Werner and Hector F. Deluca : Retinoic acid is detected at relatively high levels in the CNS of adult rats. Am J Physiol Endocrinol Metab 2002, 282: E672-E678. Patricia L. Martinez – Morales, Ruth Diez del Corral, Isabel Olivera – Martinez , Alejandra C. Quiroga, Raman M. Das, Julio A. Barbas, Kate G. Storey, and Aixa V. Morales FGF and retinoic acid activity gradients control the timing of neural crest cell emigration in the trunk. JCB Home 2011: 194 (3): 489. Crandall J.E, Goodman T and Mc Cattery : Retinoic acid influences neuronal migration from ganglionic eminence to the cerebral cortex. J. Neurochem. 2011,119(4) 723 – 730. Mizee Mr, Wooldrik D, Lakeman KA, Van het Hof B, Drexhage JA, Geerts D, Bugiani M, Aronica E, Mebius RE, Prat A, De, Vries HE, Reijerkerk A. Retinoic acid induces blood – brain barrier development. J Neurosci. 2013 Jan 23; 33(4): 1660-71. Bremner JD, Mc Caffery P. The neurobiology of retinoic acid in affective disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2008 32(2): 315-31. Francois Le Doze, Daniele Debruyne, Francoise Albessard, Louisa Barre and Gilles Louis Defer Pharmacokinetics of All- trans Retinoic Acid ,13 – cis Retinoic Acid, and Fenretinide in Plasma and Brain of Rat. 2000 28 (2) 205 –208. Kalin JR, Milton E, Starling, Hill DL Disposition of all – trans – retinoic acid in mice following oral doses . Drug Metab Dispos 1981, 9: 196 – 201. Wang C - C , Campbell S, Furner RL, Hill DL Disposition of all – trans – and 13 - cis – retinoic acids and N – hydroxyethylretinamide in mice after intravenous Administration. Drug Metab Dispos 1980, 8:8 – 11.