

VITAMIN A AND THE NERVOUS SYSTEM

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Abstract - Vitamin A is essential for the early development and normal functioning of the brain throughout life. A deficiency of vitamin A is one of the leading causes of morbidity and mortality in developing countries, and subclinical deficiency is probably present worldwide. The main active molecule in vitamin A is retinoic acid, which is involved in vision, the immune system, skin health, olfaction and cognition (learning, memory, spatial functions, olfaction, etc.) through processes of neuroplasticity and neurogenesis. Vitamin A is involved in the regulation of about one-sixth of the human genome. It has non-genomic actions in protein translation and paracrine actions. Retinal vitamin A aldehyde is crucial for day and night vision. The best-known manifestation of hypovitaminosis A is night blindness but in more severe cases, it causes blindness. In the hypothalamus, vitamin A, with information from the retina, acts in circadian and seasonal regulation. Increased retinoic acid levels in the blood are associated with increased risk of depression, and lower levels have been connected with Alzheimer's disease, Parkinson's disease, cerebral ischemia, autistic spectrum disorders and schizophrenia. Higher doses and longer periods of treatment pose the threat of hypervitaminosis A. Vitamin A and its analogs are a promising new class of therapeutic agents in a wide spectrum of disorders, albeit with a narrow therapeutic window.

Key words: cognition; vitamin A; retinoic acid; neurodegeneration; neurogenesis

INTRODUCTION

Optimal levels of vitamin A are important from the embryonic stage to the end of life. A lack of micronutrients is of the utmost importance and the World Health Organization (WHO, 2002) found deficiencies of iron, zinc and vitamin A in the top ten leading causes of death in developing countries. Vitamin

A is a generic term for several related unsaturated molecules, retinoids, primarily involved in early development and growth, proper functioning of the immune system, vision, reproduction, skin health and in central nervous system for neuroplasticity, neurogenesis and other important processes. (Benton, 2010; Tanumihardjo, 2011). The most important forms of retinoids are retinol, which is an alco-

hol, retinal, which is an aldehyde, and retinoic acid (RA), the active form. Carotenoids, the best known being beta-carotene, are called provitamin A and can be converted to retinol by the body (Food and Nutrition Board, 2001).

We will focus on the importance of vitamin A in brain function and vision. Both nervous system and eyes are of ectodermal origin and share many similarities. Vitamin A has important signaling functions in the human brain and needs subtle balance for optimal functioning.

Metabolism

In intestinal resorptive cells, retinol is esterified to long-chain fatty acids and forms retinyl esters packaged in chylomicrons (Berry and Noy, 2012). Under normal conditions, 90% of the body's vitamin A is stored in the liver as retinyl ester. The liver releases retinol, which becomes attached in the blood to a complex of retinol-binding protein (RBP) and transthyretin (TTR). Vitamin A is transported into the cells by a membrane protein stimulated by retinoic acid 6 (STRA6) or by passive diffusion (Napoli, 2011). Retinol is oxidized in cells to retinal, and then to RA by retinaldehyde dehydrogenases (RALDH1/2/3) (Napoli, 2011; Shearer et al., 2012). Vitamin A acts in the organism mainly via its metabolite all-trans-retinoic acid (atRA) within a narrow concentration range (Napoli, 2011). Vitamin A and RA act as a pro-hormone-hormone pair. Vitamin A itself is not active. There are genomic and non-genomic actions of RA. Retinoic acid activates gene transcription via RA receptors (RARs) α , β , and γ and retinoid X receptors (RXR α , β , and γ). Retinoic acid controls a sixth of the human genome (Luo et al., 2009). Non-genomic actions are regulation of kinases and protein translation, as well as diffusing out of the cell to activate neighboring cells in a paracrine way (Shearer et al., 2012).

Vitamin A and vision

Vitamin A is necessary for vision as it converts light into neural signals in the retina. Retinol is delivered

to the eye via blood circulation and it builds up in pigmented epithelial cells. It is converted to retinal form, which combines with opsin and forms rhodopsin in rods and iodopsin in cones, molecules with the function of absorbing light involved in low-light vision (rods) and color vision (cones) (Wolf, 2001). Under the impact of light, the 11-*cis*-retinal is isomerized to the all-trans form. The all-trans retinal then separates from the opsin in a process named photobleaching. A nervous signal is transmitted down the optic nerve under the induction by isomerization. The all-trans form is afterwards recycled again to the 11-*cis*-retinal form, and in a smaller quantity to all-trans-retinol as a depot in the epithelial cells of the retina. The other functions of vitamin A in vision are the differentiation and functioning of the conjunctival membrane and cornea (Ross, 2010). It also connects perception of light with circadian and seasonal regulation in the hypothalamus depending on the duration of daylight. Vitamin A deficiency leads to night blindness and potentially complete blindness.

Vitamin A in development

Retinoic acid has the properties of a hormone and acts as a growth factor for epithelial and other cells, especially in the eye and brain during development (Tanumihardjo, 2011). In the adult brain, the retinoic acid signaling mechanism becomes more regional with different functions. Vitamin A deficiency impedes growth, induces infertility and retinal degeneration. Stem cells require retinoids for normal differentiation into erythrocytes and for iron mobilization into developing erythrocytes for incorporation into hemoglobin. Around one-third of children aged 0-5 years are vitamin-A deficient; of these around 670 000 pass away worldwide and up to 500 000 lose their sight (World Health Organization, 2009; Black et al., 2008). Increased maternal consumption of vitamin A and some other retinoids during pregnancy is associated with birth defects, such as malformation of the eye, skull, lungs and heart (Solomons, 2006). Optimal vitamin A supplementation should be done cautiously as hypovitaminosis and hypervitaminosis are divided by a narrow margin.

Vitamin A deficiency

The most useful method of vitamin A body status assessment is measurement of the plasma retinol level, but it does not show the liver vitamin depot. Vitamin A deficiency is defined as plasma retinol concentration lower than 0.70 $\mu\text{mol/L}$, with concentrations of 0.70-1.05 $\mu\text{mol/L}$ being marginal (Food and Nutrition Board,).

Primary vitamin A deficiency is the consequence of inadequate food intake of provitamins/ carotenoids from vegetables and retinoids from animal sources, as well as early weaning from breast milk. Secondary vitamin A deficiency is the result of chronic malabsorption of lipids, chronic diarrhea, insufficient bile production and release, smoking, inappropriate alcohol consumption and ageing. Usually the first sign of vitamin A deficiency is poor sight, especially at night, called night blindness, and further on xerophthalmia. Eventually keratomalacia occurs with the destruction of the cornea and complete blindness (Roncone, 2006). Vitamin A deficiency decreases immunology defense both of humoral and cell-mediated immunity, with increased morbidity and mortality from infectious diseases (Food and Nutrition Board, 2001). Another area of interest is the connection between vitamin A status and macular degeneration, a major cause of vision failure in elderly people, but research results are not conclusive.

Vitamin A and brain function

Vitamin A plays an important role in maintaining higher function in the central nervous system (Ono, Yamada, 2012). It has been shown that RA is important in cognitive activities (Luo et al., 2009). Hippocampal long-term potentiation (LTP) and long-term depression (LTD), essential for memory formation in the hippocampus, are dependent on vitamin A (McCaffery et al., 2006). Vitamin A is also necessary for plasticity, neurogenesis and circadian rhythm mechanisms in the hippocampus (Shearer et al., 2012). Another important process is synaptic scaling, a plasticity phenomenon in which

neurons adjust the strength of their synaptic networks according to external stimuli, which is dependent on RA (Poza, Goda, 2010). Human supplementation with RA results in better learning, memory, and possibly executive functions (Ergun et al., 2012).

Another area of vitamin A function is the olfactory system, which critically depends on neuronal plasticity (Rawson, LaMantia, 2006). Vitamin A is essential for both development and function of the olfactory system.

Recent studies have revealed the essential role of RA in the hypothalamus, more so in the arcuate nucleus, which regulates feeding and energy balance, and the ependymal layer that mediates transduction of extrahypothalamic signals (Shearer et al., 2012). Energy balance and reproduction change with the seasons (photoperiodic changes dependent on the length of the daytime). In the hypothalamus, RA may be one of the triggers for seasonal weight control. The circadian cycle is also RA-dependent and it can be connected to the role of RA in vision via the perception of daylight length. It is very probable that neurogenesis occurs in adult hypothalamus (crucial for energy balance regulation), as stem cells producing functional neurons are found in this structure, and that RA signaling controls this process (Shearer et al., 2012). Neurogenesis occurred in the ependymal layer and the arcuate nucleus.

Affective disorders

Retinoic acid is connected with affective disorders through retinoic acid receptor (RAR – member of the steroid/thyroid receptor family) control of corticotropin-releasing hormone (CRH) gene expression and activity of hypothalamic-pituitary-adrenal (HPA) axis (Chen et al., 2009). RAR α increases CRH gene expression. In the paraventricular nucleus of patients with affective disorders, the density of RAR α -immunoreactive neurons and CRH-RAR α double-staining neurons is significantly increased (Chen et al., 2009).

Dementia

Lower plasma and cerebrospinal fluid concentrations of vitamin A and beta-carotene have been found in Alzheimer's disease (AD) patients (Ono, Yamada, 2012). Even more importantly, there is some evidence that these vitamins slow the progression of AD. It is hypothesized that the degradation of RA signaling might influence the initiation and development of AD. Supplementation with RA improves learning and spatial functions (Ormerod et al., 2011). APP/PS1 transgenic mice treated with tretinoin, the acid form of vitamin A, also known as all-trans retinoic acid or atRA, display a substantial decrease in brain amyloid-beta deposition, tau phosphorylation and decreased activation of microglia and astrocytes (Ding et al., 2008). According to the aforementioned data, RA can be a promising prophylactic and therapeutic agent in AD.

Parkinson's disease

Retinoic acid is active in the dopaminergic system of substantia nigra. A protective effect of RA on nigrostriatal neurons in an animal model of Parkinson's disease was recently shown (Yin et al., 2012). Different protective actions of RA dopaminergic neurotoxins have been demonstrated *in vitro*.

Cerebral ischemia

In many experiments, the neuroprotective effect of RA against cerebral ischemia in rats was documented (Yin et al., 2012). In the experimental model of ischemia, RA inhibited H₂O₂-induced apoptosis in mesangial cells and improved survival during anoxia/glucose deprivation.

Autistic spectrum disorders

Fragile X syndrome results from mutations in the FMR1 gene. The RA and fragile X mental retardation protein (FMRP) are both involved in the regulation of brain plasticity (Soden, Chen, 2010). The known importance of RA in fetal development can be a possible explanation for at least some of the neu-

rodevelopmental disturbances in autism. Oxytocin is released in the brain via the CD38 transmembrane protein and is essential for social behavior, and it is linked to autism spectrum disorders (Shearer et al., 2012). Individuals with autism spectrum disorders have lower plasma levels of oxytocin than unaffected persons. There are genetic links between CD38 and autism (Riebold et al., 2011). *In vitro* studies found that RA could induce CD38 expression and consequently increase oxytocin release, which is of potential therapeutic importance (Shearer et al., 2012).

Schizophrenia

Retinoic acid regulates GABAergic interneurons of the cortex, olfactory bulb and amygdala, and dopaminergic neurons of the substantia nigra (Shearer et al., 2012). As RA regulates many genes, some of them are also candidate genes involved in schizophrenia. Recently the retinoic acid induced 1 (RAI1) gene has been associated with severity and response to treatment in schizophrenia (Toulouse et al., 2003).

Recommended daily intake and therapeutical dose

The Recommended Dietary Allowance (RDA) for vitamin A is 900 mcg/day (3 000 units) for adult men and 700 mcg/day (2 300 units) for adult women (Sarubin, Thomson, 2007). Vitamin A is safe for most people in oral amounts less than 10 000 IU per day, as higher doses may lead to hypervitaminosis. Vitamin A is utilized for improving vision, treating macular degeneration, glaucoma, cataracts, skin conditions and infections.

Tamibarotene (Am80) is a synthetic retinoid acting as a RAR agonist, a potential drug for Alzheimer's disease (AD). This molecule controls multiple genes involved in some way in AD. In animal models, it showed promising properties of lowering the deposition of insoluble amyloid-beta, reducing secretion of proinflammatory cytokines and chemokines, improving brain vascularization and increasing the cortical acetylcholine, reducing anxiety and improving sleep (Fukasawa et al., 2012).

Mega doses of vitamin A are now used in the therapy of cancer, HIV, and for dermatological purposes (Vivat-Hannah, Zusi, 2005). Chronic vitamin A therapy should not exceed 3 000-4 000 IU daily because of liver toxicity (Nolleveaux et al., 2006).

Hypervitaminosis A

Acute vitamin A toxicity occurs when adults ingest more than 100 times the RDA and children more than 20 times the RDA over a period of hours or a few days (Penniston, Tanumihardjo, 2006). Chronic toxicity occurs in subjects ingesting high doses of vitamin A for months or years.

Excessive or prolonged usage of vitamin A supplementation can cause many central nervous system problems such as irritability, anxiety, depression, cyclothymia, lethargy, insomnia, hypersomnolence, headache, sometimes even psychosis (Bremner et al., 2012). In people living within the Arctic Circle, the pibloktoq syndrome (depression, explosive outbursts etc.) is thought to be the result of eating the internal organs of polar animals, known to have high vitamin A content (Bremner et al., 2012).

CONCLUSION

A growing body of evidence testifies to the important role of vitamin A in eye and brain functions. It is a necessary factor in brain and eye development and their adequate functioning in adults. Vitamin A regulates one-sixth of the brain genome, but also has extragenomic roles. Retinoids are involved in day and night vision, circadian and seasonal regulation, immunity, olfaction, hypothalamic and cognitive functions, among others. An delicate balance of retinoids has to be kept for optimal function. There is only a narrow margin between deficiency and hypervitaminosis, probably the narrowest among various supplements. Higher levels can cause birth defects, depression, anxiety, irritability, insomnia, headache and even psychosis. Hypovitaminosis A is among the ten leading causes of mortality and morbidity worldwide, especially in developing countries, but in developed countries it is mostly subclinically expressed. Vitamin

A has a potential role in treating Alzheimer's disease, autism spectrum disorders, Parkinson's disease, cerebral ischemia, schizophrenia, as it is crucial in synaptic plasticity, neurogenesis in both in the developing brain and in adults. Clinicians should be aware of the importance of vitamin A and incorporate this knowledge in their everyday practice.

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