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# The neurotoxic effects of vitamin A and retinoids

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**ABSTRACT**

Vitamin A (retinol) and its congeners – the retinoids – participate in a panoply of biological events, as for instance cell differentiation, proliferation, survival, and death, necessary to maintain tissue homeostasis. Furthermore, such molecules may be applied as therapeutic agents in the case of some diseases, including dermatological disturbances, immunodeficiency, and cancer (mainly leukemia). In spite of this, there is a growing body of evidences showing that vitamin A doses exceeding the nutritional requirements may lead to negative consequences, including bioenergetics state dysfunction, redox impairment, altered cellular signaling, and cell death or proliferation, depending on the cell type. Neurotoxicity has long been demonstrated as a possible side effect of inadvertent consumption, or even under medical recommendation of vitamin A and retinoids at moderate to high doses. However, the exact mechanism by which such molecules exert a neurotoxic role is not clear yet. In this review, recent data are discussed regarding the molecular findings associated with the vitamin A-related neurotoxicity.

**Key words:** mitochondrial dysfunction, neurotoxicity, oxidative stress, retinoids, vitamin A.

## INTRODUCTION

Increased access to vitamin A through fortified foods and supplements is an important strategy to avoid deficiency of such fat-soluble vitamin to humans. However, it is necessary to monitor the impact of such practice on human health due to the potential risk of several deleterious effects classically induced by vitamin A, retinoids, and carotenoids, which are vitamin A precursors from vegetal diet (Snodgrass 1992, Napoli 1999, 2012, Myhre et al. 2003). In addition to its origin from diet, vitamin A is utilized therapeutically in cases of dermatological disturbances, immunodeficiency, weight gain of preterm infants, and leukemia (Tsunati et al. 1990, Ross 2002). It was previously reported that vitamin A doses ranging from 150,000 to 300,000 IU/kg.day$^{-1}$ or more were being utilized in the treatment of leukemic children of different ages (Fenaux et al. 2001). Also, vitamin A at doses that exceed 8500 IU/kg.day$^{-1}$ were administered to very-low-weight-preterm infants during weight gain therapy (Mactier and Weaver 2005). It was previously reported the utilization of vitamin A supplementation at 100,000 to 200,000 IU to treat children in attempt to prevent mortality in Guinea-Bissau (Fisker et al. 2014). Then, vitamin A may be obtained from both diet and as a supplementation with clinical use or even inadvertently.

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Some authors discuss that it is rare to observe toxicity resulting from excessive vitamin A intake (Allen and Haskell 2002). However, the most common parameters that are analyzed in cases of vitamin A intoxication include observation of acute signs and symptoms, among which are nausea, vomiting, diarrhea, headache, bulging of the fontanelle in infants (as a result of increased intracranial pressure), and fever, to cite a few (Allen and Haskell 2002, Lam et al. 2006). Disturbances related to nervous functions also appear on the list of side effects resulting from excessive vitamin A intake, as for instance confusion, irritability, anxiety, depression, and suicide ideation (Snodgrass 1992). However, such central effects are more commonly observed after chronic vitamin A exposition. On the other hand, acute behavioral impairment was reported in individuals that experienced high vitamin A concentrations due to consumption of bear liver. Such altered behavior was called "polar hysteria" and was compared to schizophrenia (Rodahl and Moore 1943, Restak 1972). Additionally, acute vitamin A intoxication may lead to blurred vision and decreased muscular coordination (Olson 1993).

Some aspects of vitamin A intoxication may be easily assessed, as for example, through analyses of liver and renal function (Penniston and Tanumihardjo 2006). However, with the exception of morphological observations or the consequent behavior resulting from pain (as occurs during headache), it is very difficult to affirm that the acute vitamin A exposition will not lead to sequels that may negatively affect the neuronal function later. Gender, age, and nutritional quality, among other factors, influence the degree of intoxication of almost all existing toxicants (or xenobiotics). Therefore, caution must be taken when concluding that previous vitamin A intake at higher than normal concentrations not induce posterior dysfunction mainly when analyzing neuronal environment, since neurons did not divide during adulthood (with exception to some hippocampal areas and other regions) and its loss would lead to irreversible alterations of brain function (Aimone et al. 2014).

In this review, the effects of vitamin A on neuronal cells will be described and discussed to show that vitamin A – and its derivatives, the retinoids – may exert long-term effects on brain areas that either facilitate (indirect effect) or induce (direct effect) central malfunction.

## VITAMIN A AND RETINOIDS: A BRIEF OVERVIEW

Vitamin A (retinol – a hydrocarbon chain-containing isoprenoid with a hydroxyl group at one end of the molecule) may be obtained from both vegetal (provitamin A) and animal (preformed) diet (Olson 1993, Napoli 1999, 2012). β-carotene is a main source of vitamin A in vegetables, and retinol esters occurs in animals (Castenmiller and West 1998, von Lintig 2012, Van Loo-Bouwman et al. 2014). After digestion, retinol and retinoids must bind to proteins to be soluble in aqueous solutions such as blood and cytosol (Noy 2000, Napoli 2012). The cellular metabolism of retinol is as follows: retinol is converted to retinal (an aldehyde) or to retinoic acid (a carboxylic acid) through oxidation of the hydroxyl group (Olson 1993). Furthermore, retinol may be esterified by lecithin retinol acyl transferase (LRAT) or acyl-Coa acyl transferase (ARAT) leading to the formation of palmitate retinol, as well as other chemical forms, as for instance retinol oleate, retinol linoleate, and more (Sauvant et al. 2003). Retinoic acids (mainly all-*trans*-retinoic acid and 9-*cis*-retinoic acid) exert its effects by binding to receptors that act as nuclear factors when translocate to nucleus (Napoli 1996). However, an increasing body of evidence shows that retinol and retinoids may trigger specific signals through non-genomic events (Piskunov et al. 2014, Rochette-Egly 2015).

Vitamin A plays important roles during both mammalian development and adulthood through maintenance of several tissue functions, including the central nervous system as a whole (Olson 1993, Tanumihardjo 2004, Tafti and Ghyselinck 2007).

This vitamin and its derivatives participate in the regulation of cell proliferation, differentiation, survival, and death (by triggering apoptosis), leading to the formation of the normal shape of the embryo, organogenesis, and tissue physiology, for example (Das et al. 2014). Furthermore, some biological processes including, for example, vision, structure and function of skin and bones, immune defenses, and neuronal activity will depend on regular access to vitamin A during the entire human life (Olson 1993, Napoli 1996, Huang et al. 2014).

The main site of vitamin A storage in mammals is the liver, but it is also possible to find vitamin esters in adipose tissue (Napoli 1996, Van Loo-Bouwman et al. 2014). Vitamin A content in the liver of adult humans is about 100 µg/g (Furr et al. 1989). It was suggested that a concentration of vitamin A of roughly 300 µg/g in the liver reveals intoxication (Olson 1993).

## THE BIOLOGY OF VITAMIN A IN THE CENTRAL NERVOUS SYSTEM

After hydrolysis of retinol esters, retinol binds to retinol binding proteins (RBP) and is transported through circulation. In the target organ, a membrane receptor with high affinity for retinol mediates its uptake (Kawaguchi et al. 2007). All-*trans*-retinoic acid is produced from retinol by retinol dehydrogenase (generating retinal) and retinaldehyde dehydrogenase (producing retinoic acid) (Napoli 1996). The synthesis of all-*trans*-retinoic acid occurs in several brain areas of mammals, including cerebrum, cerebellum, meninges, basal ganglia, and hippocampus (Lane and Bailey 2005). Interestingly, it was demonstrated that retinal dehydrogenase enzyme expression occurs in blood vessels of all brain areas (Thompson Haskell et al. 2002). Recently, it was published that astrocytes may participate in the maintenance of the homeostasis of retinoids levels in brain by regulating its synthesis (Shearer et al. 2012a). Moreover, retinoid binding proteins were detected throughout the entire brain (Lane and Bailey 2005). Cellular retinol binding proteins (CRBP-I and II) and cellular retinoic acid binding proteins (CRABP-I and II) solubilize retinoids in the cytoplasm and avoid non-specific interactions and even oxidation of such molecules (Napoli 1996, 1999, 2012, Folli et al. 2001). The binding of retinoic acids to cellular retinoic acid binding protein (CRABP) forms a complex that it is thought to migrates to the nucleus and induce different effects through interacting with nuclear receptors to retinoic acid (RAR and RXR) (Lane and Bailey 2005, Shearer et al. 2012b). Brain contains RAR and RXR and its functions are better observed during development. During adulthood, these nuclear receptors are still found in neuronal cells, but show a specific pattern of localization (Tafti and Ghyselinck 2007). It was reported that RAR binds with all-*trans*-retinoic acid and with 9-*cis*-retinoic acid (with lower affinity for the later) and RXR binds with 9-*cis*-retinoic acid (Napoli 1996, Lane and Bailey 2005). There is a myriad of genes that contain response elements to retinoids in adult mammalian brain, as previously reviewed (Lane and Bailey 2005). Then, retinoids are metabolized in brain areas and exert its effects in nervous and glial cells specifically throughout all life.

However, even being a biological target of vitamin A and its derivatives, the ability of vitamin A to induce serious effects that may compromise neuronal function has been described. Such effects include impaired bioenergetic parameters related to mitochondrial function, oxidative and nitrosative stress, alterations of dopamine signaling, and behavioral disturbances, to cite some examples.

## MOLECULAR EVIDENCES OF VITAMIN A-RELATED NEUROTOXICITY

Even though vitamin A and its derivatives are essential during both development and maintenance of central nervous system activity, there is a considerable body of evidences showing that vitamin A concentrations exceeding that which is required for normal function of cells lead

to deleterious effects including disruption of the redox environment, mitochondrial dysfunction, and induction of cell death, as discussed below (Napoli 1999, Myhre et al. 2003, Lane and Bailey 2005).

All-*trans*-retinoic acid, a retinoid originated from retinol, is able to induce oxidative stress in cultured Sertoli cells (Conte da Frota et al. 2006), but not in PC12 cell line (Gelain and Moreira 2008), which is derived from pheochromocytoma of rat adrenal medulla (which is, in turn, originated from the neural crest) and produces dopamine and norepinephrine. In PC12 cell line treated with retinol, increased rates of reactive oxygen species production through a real-time 2′,7′-dichlorohydrofluorescein diacetate (DCFH-DA) assay designed for live cells were observed (Wang and Joseph 1999). Also, decreased viability was reported in PC12 cells treated with retinol. DCFH-DA serves as a probe to detection of hydrogen peroxide, hydroxyl, and peroxyl radicals (LeBel et al. 1992). Then, retinol, but not all-*trans* retinoic acid may alter redox environment of such catecholamine producing cells, possibly leading to loss of viability by a mechanism that may be associated to its ability to act as a pro-oxidant. However, it remains to be determined whether the loss of cell viability is really related to the pro-oxidant effect of retinol in that cell system. Recently, it was demonstrated that all-*trans* retinoic acid modulates gene expression through a redox mechanism during SH-SY5Y cell line differentiation, since the effects seen were blocked by an antioxidant that is analogue to α-tocopherol (de Bittencourt Pasquali et al. in press). However, it was not analyzed in that work whether retinoic acid altered redox environment parameters, as for instance by inducting oxidative damage or increasing the rates of reactive species.

Vitamin A is necessary for both development and maintenance of the nigrostriatal axis (*substantia nigra* and *striatum*), which regulates dopamine signaling in brain. However, as mentioned above, such vitamin and its derivatives may cause oxidative impairment of such brain areas by increasing reactive oxidative species. Actually, it was reported that vitamin A supplementation (in the form of retinol palmitate) at doses commonly utilized clinically (1,000 to 9,000 IU/kg.day$^{-1}$ for 3, 7, or 28 days) induced some redox disturbances in the nigrostriatal axis of adult male rats. Increased lipid peroxidation, protein carbonylation, and oxidation of protein thiol groups were observed in the *substantia nigra* and *striatum* of vitamin A-treated rats (De Oliveira et al. 2007a, 2008). Moreover, vitamin A modulated antioxidant enzyme activity, as observed with superoxide dismutase (SOD) and, in some cases, with catalase (CAT), but not with glutathione peroxidase (GPx). It is interesting to note that, in that experimental model, retinol palmitate supplementation induced an increase in SOD enzyme activity, but did not affect either CAT or GPx enzyme activity or even decreased CAT enzyme activity. Therefore, vitamin A is favoring an increase in $H_2O_2$ production that may lead to hydroxyl radical (OH) formation through Fenton reaction (Halliwell 2006), since SOD converts $O_2^{-\bullet}$ to $H_2O_2$, but this reactive specie probably accumulates due to decreased or unaltered CAT and unaltered GPx enzyme activities. Regarding the toxic effects of $O_2^{-\bullet}$, it was shown that $O_2^{-\bullet}$ is able to inhibit CAT enzyme activity directly (Kono and Fridovich 1982). Thus, it may be a mechanism by which vitamin A modulates CAT enzyme activity *in vivo*. Interestingly, vitamin A supplementation for 28 days decreased rat exploration of and locomotion in an open field arena (De Oliveira et al. 2007a, 2008). However, it was not analyzed whether such behavioral abnormalities were associated with impaired redox status observed in the brain areas that participate in movement control.

More recently, De Oliveira et al. (2012a) demonstrated that vitamin A supplementation at 500 to 2,500 IU/kg.day$^{-1}$ induced mitochondrial dysfunction and increased β-amyloid$_{1–40}$ peptide and tumor necrosis factor-alpha (TNF-α) contents in *substantia nigra* and *striatum* of adult rats. Additionally, increased monoamine oxidase (MAO) enzyme activity was observed in that

experimental model. Mitochondrial dysfunction was found by assessing mitochondrial electron transfer chain activity. Decreased complex I-III, complex II, succinate dehydrogenase (SDH), complex II-III, and complex IV enzyme activity was reported, which may lead not only to decreased rates of ATP production, but may favor electron leakage from that system, which may lead to $O_2^{-\bullet}$ formation (Halliwell 2006). In addition, it was seen increased Mn-SOD (manganese SOD – the mitochondrial SOD) enzyme activity, as well as MAO enzyme activity was observed increased. These two enzymes differ in location (Mn-SOD is a mitochondrial matrix enzyme, and MAO is located at the outer mitochondrial membrane), but both produce $H_2O_2$ during the reaction of dismutation of $O_2^{-\bullet}$ and degradation of dopamine, respectively (Halliwell 2006, Edmondson 2014). Then, mitochondria seem to be a potential source of $H_2O_2$ in the case of increased vitamin A intake as a supplement. Interestingly, vitamin A supplementation also induced a decrease in the immunocontent of D2 receptor (D2R) in both *substantia nigra* and *striatum* (De Oliveira et al. 2012a). Low levels of D2R may cause an increase of dopamine release from catecholaminergic neurons, which may lead to exceeding dopamine levels in both extracellular and intracellular environments of post-synaptic neurons (Lotharius and Brundin 2002, Jorg et al. 2014). Dopamine is very reactive under physiologic pH, giving rise to semi-quinones that may react with thiol groups in protein and affect its structure and function (Graham 1978, Maker et al. 1981, Lotharius and Brundin 2002). In fact, increased concentration of oxidized protein thiol groups was observed in that experimental model. However, it remains to be investigated whether a causative link between such effects really exists. Carta et al. (2006) demonstrated that vitamin A deficiency impaired locomotion and striatal cholinergic function in rats. Even though vitamin A is necessary to modulate signaling pathways associated to dopamine and other neurotransmitters (Lane and Bailey 2005), excessive vitamin A intake may trigger several neuronal dysfunctions that may be originated from its pro-oxidant ability, for example.

It is interesting the fact that vitamin A supplementation also increased glutathione-S transferase (GST) enzyme activity in several rat brain areas (De Oliveira et al. 2009f, 2011a, 2012a, c). GST conjugates reduced glutathione (GSH) with apolar xenobiotics in order to increase its solubility in aqueous solution, rendering its excretion easy after biotransformation (Sheehan et al. 2001). However, by increasing GST enzyme activity during vitamin A metabolism, such enzyme consumes greater amounts of GSH. GSH is the major non-enzymatic antioxidant inside cells and organelles such as mitochondria (Halliwell 2006). Thereby, vitamin A affects neuronal redox status not by directly inducing the production of $O_2^{-\bullet}$, for example, but also through increasing the consumption and consequent excretion of GSH, weakening the antioxidant power of cells.

Sub acute vitamin A supplementation also increased both 3-nitrotyrosine (total and mitochondrial) and α-synuclein contents in the rat *substantia nigra* and *striatum* (De Oliveira et al. 2012a). Increased 3-nitrotyrosine levels may result from high rates of $O_2^{-\bullet}$ and $NO^{\bullet}$ production (Squadrito and Pryor 1998, Radi 2013). Indeed, it was demonstrated that vitamin A intake increased mitochondrial $O_2^{-\bullet}$ production in different rat tissues including brain (De Oliveira and Moreira 2007, 2008, De Oliveira et al. 2009a, b, c, d, e, f, 2011a, 2012b). The protein α-synuclein may be a target of 3-nitrotyrosine, as previously demonstrated (Giasson et al. 2000, Souza et al. 2000). Aggregated α-synuclein may lead to proteasome inhibition, a step towards accumulation of protein aggregates inside cells (Snyder et al. 2003). Nagl et al. (2009) published the mechanism by which all-*trans*-retinoic acid induced the expression of neuronal nitric oxide synthase (nNOS) in TGW-nu-I, a neuroblastoma cell line. They found that all-*trans*-retinoic acid induced nNOS expression through activation of the phosphatidylinositol 3-kinase (PI3K)/Akt

signaling pathway and the orphan nuclear receptor DAX1 (NR0B1). All-*trans*-retinoic acid, among other retinoids, as for example, 9-*cis*-retinoic acid, are originated from vitamin A intake *in vivo* (Napoli 1996, 1999, 2012), and increased access to retinoids may lead to an increased expression of nNOS and augmented rates of NO production, which favors increased production of peroxynitrite ($ONOO^-$), a reactive specie that give rise to nitryl cation ($NO_2^+$), nitrogen diozide radical ($^{\bullet}NO_2$), and hydroxyl radical ($^{\bullet}OH$) through a reaction called homolytic fission (Radi 2013, Carballal et al. 2014). In spite of this evidences, the effects of vitamin A supplementation on NOS enzyme activity and expression in the mammalian brain remain to be investigated.

Even though NO may play an important role in the neurotoxicity elicited by vitamin A, the co-treatment with NG-nitro-L-arginine methyl ester (L-NAME) did not affect either mitochondrial dysfunction or other redox-related parameters in the experimental model of vitamin A supplementation at clinical doses (1,000 – 9,000 IU/kg.day$^{-1}$ for 28 days) (De Oliveira et al. 2012c). Furthermore, L-NAME co-treatment did not prevent behavioral disturbances induced by vitamin A. Taken together, these data suggest that the neurotoxicity of vitamin A is not dependent on the formation of $NO^1$, $ONOO^-$, and/or 3-nitrotyrosine. However, the experimental model utilized has some limitations, since only one dose of L-NAME was tested. For a better conclusion, two or even three concentrations of L-NAME should be applied.

In cerebral cortex and cerebellum, retinol palmitate supplementation at clinical doses (1,000 to 9,000 IU/kg.day$^{-1}$) for 3, 7, or 28 days induced oxidative stress and mitochondrial dysfunction, as assessed through quantification of lipid peroxidation, protein carbonylation, and oxidation of protein thiol groups (De Oliveira and Moreira 2007). Similar results were obtained *in vitro* by exposing isolated rat liver mitochondria to retinol. It was observed that 20-40 μM retinol increased $O_2^{-\bullet}$ production and lipid peroxidation levels (Klamt et al. 2005). It has been reported that higher than normal mitochondrial lipid peroxidation levels may lead to cytochrome c release through oxidation of cardiolipin (Hüttemann et al. 2011). In the cytoplasm, cytochrome c may trigger apoptosis (Green et al. 2014). However, release of cytochrome c from mitochondria is associated with increased rates of $O_2^{-\bullet}$ production due to electron leakage from the mitochondrial electron transfer chain (Halliwell 2006, Hüttemann et al. 2011). Then, $O_2^{-\bullet}$ is able to increase its own production by favoring cytochrome c release through cardiolipin oxidation. Vitamin A (retinol) alters mitochondrial function and may induce cell death by a mitochondrial dependent route, as demonstrated (Klamt et al. 2008). Vitamin A supplementation did not induce cell death in any rat brain region investigated, but increased caspase-3 enzyme activity was found in the rat cerebral cortex after sub acute treatment the vitamin (De Oliveira et al. 2010). However, it was not analyzed whether such enzyme activation participates in the mechanism of cell death in such rat brain region. It is known that 13-*cis*-retinoic acid may suppress cell survival in the hippocampus of mice (Sakai et al. 2004). Additionally, cell division may be inhibited *in vivo* by the same retinoid (Crandall et al. 2004). Indeed, such cellular impairments may be the cause of depressive behavior previously reported in mice exposed to 13-*cis*-retinoic acid (O'Reilly et al. 2006), as well as explain, at least in part, the decreased capacity in animals to learn after receiving such drug (Crandall et al. 2004). Actually, anxiety-like behavior was observed in adult rats maintained under vitamin A supplementation at pharmacological doses administered sub acutely (De Oliveira et al. 2007b). On the other hand, vitamin A deficiency impaired cognitive functions, as for instance learning and memory in different experimental models (Jiang et al. 2012, Navigatore-Fonzo et al. 2014, Hou et al. 2015).

Vitamin A supplementation also affected the levels of one of the most important neurotrophins in the mammalian brain experimentally. It was

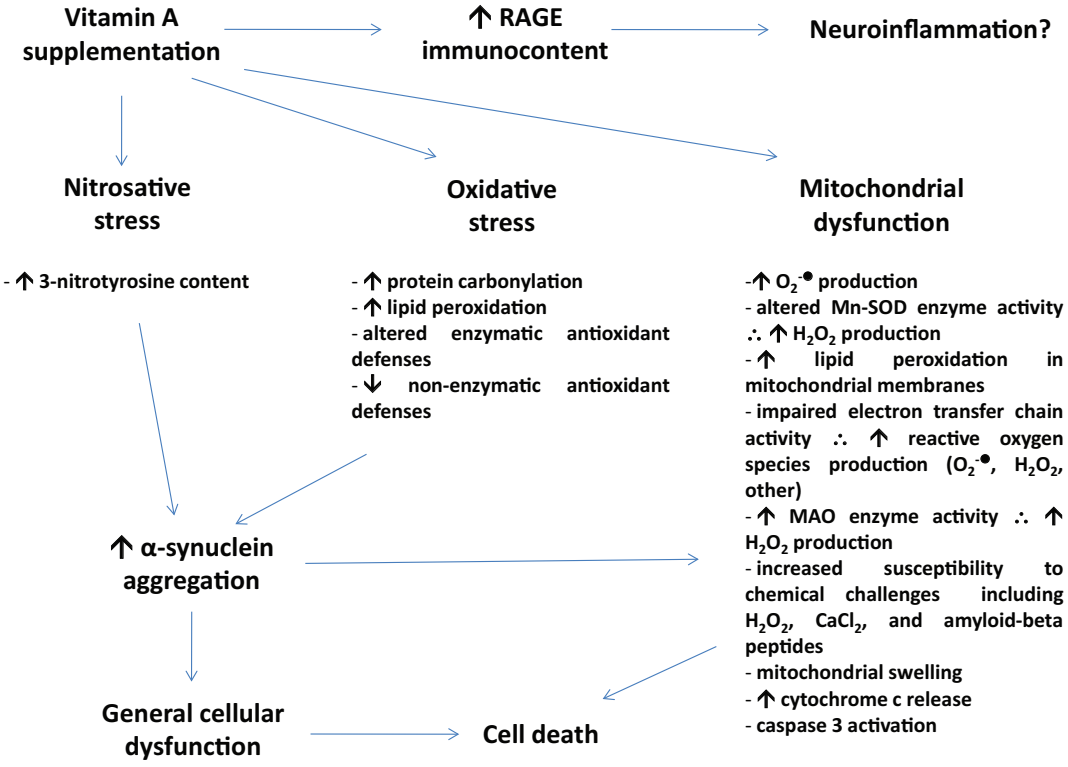


**Figure 1** - A summary of possible effects elicited by vitamin A (either retinol or retinol palmitate) on the mammalian central nervous system. It has been demonstrated that vitamin A supplementation (in the form of retinol palmitate or retinol) is able to induce an increase in the immunocontent of RAGE, which mediates neuroinflammation in some experimental models. Additionally, such supplementation may lead to altered redox environment parameters, which has been evidenced as oxidative and nitrosative stress. Moreover, vitamin A supplementation induces mitochondrial dysfunction *in vitro* and *in vivo*. Increased levels of $O_2^{-\bullet}$ may affect the function of several enzymes, including catalase (CAT) and Mn-superoxide dismutase (Mn-SOD, the mitochondrial isoform of SOD). Furthermore, $O_2^{-\bullet}$ may be a consequence of impaired electron transfer chain due to vitamin A-dependent electron leakage from that complex system. Vitamin A, which is liposoluble, may interact with mitochondrial membranes disrupting the normal flow of electrons between mitochondrial complexes, which in turn may favor abnormal electron flux. Alternatively, increased activity of this system may be due to an augmentation in the need for adenosine triphosphate (ATP) in acute phases of intoxication with vitamin A. Both Mn-SOD and monoamine oxidase (MAO) enzyme activities may lead to increased hydrogen peroxide ($H_2O_2$) production, which may diffuse from mitochondria to other organelles. Increased levels of oxidative and nitrosative stress markers may induce α-synuclein aggregation, which may interact negatively with mitochondria (please see text for details). General cell dysfunction and cell death may result if vitamin A concentration remains elevated. Other effects may be induced by vitamin A and/or retinoids on neuronal cells. This figure represents just a summary of some of them.

reported that retinol palmitate supplementation (1,000 to 9,000 IU/day$^{-1}$) for 28 days decreased brain-derived neurotrophic factor (BDNF) in the rat hippocampus (De Oliveira et al. 2011a). BDNF regulates neuronal plasticity, bioenergetics, mitochondrial biogenesis, and neuronal survival, to cite a few (Cheng et al. 2010, Agrawal et al. 2014, Marosi and Mattson 2014). Decreased BDNF may lead to limited mitochondrial biogenesis and mitochondrial dysfunction during events of neurotoxicity. By decreasing BDNF levels, vitamin A impairs not only neuronal plasticity that is necessary to the learning and memory processes, but also the ability of this organelle to produce

adequate amounts of ATP needed to counteract acute and chronic stress. In fact, it was demonstrated that vitamin A affects mitochondrial function *in vitro* and *in vivo*, as discussed above.

In another study, it was observed that vitamin A daily administrated to rats is able to increase receptor for advanced glycation endproducts (RAGE) immunocontent in rat cerebral cortex (De Oliveira et al. 2009e). This receptor is implicated in the amplification of oxidative stress by a neuroinflammation-related mechanism (Brownlee 2000, Schmidt et al. 2001, Bierhaus et al. 2005). Moreover, RAGE may play a crucial role in the onset and progression of Alzheimer's disease, as previously postulated (Sato et al. 2006). In fact, RAGE mediates the transport of β-amyloid peptides from blood to brain across the blood-brain barrier (Deane et al. 2003) and possibly plays a crucial role in the onset of Alzheimer's disease in diabetic patients. Additionally, sustained RAGE activation may trigger cell death and tissue dysfunction (Bierhaus et al. 2005). More investigations are needed to better address the role of vitamin A on inducing RAGE activation in brain.

It was recently demonstrated that retinol palmitate supplementation at 100, 200, or 500 IU/kg.day$^{-1}$ for 2 months did not induce any antioxidant effect in frontal cortex, hippocampus, *striatum*, and cerebellum of adult female rats (De Oliveira et al. 2011b). Retinol palmitate at 100 IU/kg is equivalent to 7000 IU/day for a human weighing 70-kg. Such dosage is far below the approximate 25,000 IU/day that some vitamin A supplements users ingest. Additionally, such supplementation did not decrease endoplasmic reticulum stress, as assessed through quantification of BiP/GRP78 protein level. In addition, vitamin A did not affect either TNF-α or RAGE immunocontent, showing that vitamin A may not be the best choice to prevent inflammation in such brain areas.

Interestingly, it was reported that *in vivo* retinol palmitate supplementation increased *in vitro* susceptibility of mitochondrial to different challenges. Mitochondria were isolated from *substantia nigra*, *striatum*, frontal cortex, and hippocampus and challenged with $H_2O_2$, β-amyloid peptide$_{1-40}$, and $CaCl_2$ and it was observed an increased impact of each challenge on mitochondria that were isolated from retinol palmitate-treated rats (De Oliveira et al. 2012a, b). It suggests that prior vitamin A supplementation may increase vulnerability of mitochondria to posterior chemical insult that affect mitochondrial electron transfer chain activity, for example, as demonstrated. Thus, excessive intake of vitamin A may, at least in part, facilitate neuronal abnormalities (including both redox and bioenergetics states) that may appear from other pathological event, as for instance increased rates of β-amyloid peptides production in the case of Alzheimer disease. However, the data obtained with animal research are not sufficient to conclude that vitamin A supplementation is a risk factor for neurodegenerative diseases in humans. Nonetheless, it has been demonstrated that vitamin A intake among well-nourished subjects may lead to decreased life quality and increased mortality rates (Bjelakovic et al. 2007, 2008, 2012, 2014). Recently, it was suggested that mefloquine (a drug used to prevent and treat malaria) may elicit its deleterious effects by altering the concentrations of retinoids in circulation, leading to cognitive disturbances, as for example, anxiety, depression, psychosis, and violence (Mawson 2013). The author suggests that mefloquine would be able to impair retinoid metabolism in liver, causing posterior spillage of retinoids from liver to blood at toxic concentrations. Takeda et al. (2014) did not find any association between blood levels or dietary intake of retinoids and the risk of Parkinson's disease, *i.e.* whether decreased levels of retinoids may favor PD is not known, but it did not prevent individuals from such neurodegenerative disease. In spite of this, some authors have reported that vitamin A derivatives may reduce chemotherapy-associated neuropathy in both animal model and patients under lung cancer therapy (Arrietá et al. 2011). Furthermore, retinol and retinoids possess antioxidant ability, since such effects have been

demonstrated in different experimental models. However, it is mainly an issue of dosage. Depending on retinoid concentration, but also other factors, as for instance age, gender, and some nutritional parameters, as well as exposition to environmental toxicants, retinoids may favor a pro-oxidant state and cell damage with consequent increased rates of cell death and inflammation. Some of the effects discussed here are summarized in Figure 1.

## CONCLUSIONS

Overall, even though vitamin A is an essential micronutrient to normal brain development and function, caution must be taken when administering such vitamin to individuals without any sign of deficiency and/or with history of neurodegenerative diseases in the family, for example, since central nervous system is a clear target of vitamin A-associated toxicity. The utilization of vitamin A or retinoids in the treatment of some types of cancer and dermatological disturbances is based on the fact that such molecules may trigger cell death or slow cell cycle progression, leading to decreased rates of tumor growth. However, it would be catastrophic if an individual with history of neurodegenerative disease in the family exceeds vitamin A intake through either supplement use or clinical administration, for example. More investigations are needed to clarify the mechanisms by which vitamin A and its derivatives affect neuronal function, as well as the glial network.

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## RESUMO

A vitamina A (retinol) e seus congêneres – os retinoides – participam de um vasto número de eventos biológicos, como por exemplo, diferenciação, proliferação, sobrevivência, e morte da célula necessários para manter a homeostasia tecidual. Além disso, tais moléculas podem ser aplicadas como agentes terapêuticos no caso de algumas doenças, incluindo distúrbios dermatológicos, imunodeficiência, e câncer (principalmente, leucemia). Apesar disto, há um crescente corpo de evidências mostrando que doses de vitamina A que excedem as necessidades nutricionais podem levar a consequências negativas, incluindo disfunção do estado bioenergético, prejuízo redox, sinalização celular alterada, e morte ou proliferação celulares, dependendo do tipo celular. Neurotoxicidade tem sido demonstrada há bastante tempo como um possível efeito colateral do consumo inadvertido ou mesmo sob recomendação médica de vitamina A e de retinoides em doses moderadas e altas. No entanto, o mecanismo exato pelo qual tais moléculas exercem um papel neurotóxico ainda não é claro. Nesta revisão, dados recentes em relação aos achados moleculares associados com a neurotoxicidade relacionada à vitamina A são discutidos.

**Palavras-chave:** disfunção mitocondrial, neurotoxicidade, estresse oxidativo, retinoides, vitamina A.

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