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All-Trans-Retinoic Acid as a Novel Therapeutic Strategy for Alzheimer's Disease

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Abstract

Retinoic acid, an essential factor derived from vitamin A, has been shown to have a variety of functions including roles as an antioxidant and in cellular differentiation. Since oxidative stress and de-differentiation of neurons appear to be common pathological elements of a number of neurodegenerative disorders, we speculated that retinoic acid may offer therapeutic promise. In this vein, recently compelling evidence indicates a role of retinoic acid in cognitive activities and anti-amyloidogenic properties. Here, we review the actions of retinoic acid that indicate that retinoic acid may have therapeutic properties ideally served for the treatment of neurodegenerative diseases such as Alzheimer's disease.

Keywords

Alzheimer's disease; cell cycle; oxidative stress; retinoic acid; therapeutics

Retinoic acid (RA) is a metabolic product of vitamin A (retinol), and since animals cannot synthesize vitamin A, they must take it from their diet. Retinol taken up by cells enters the cytoplasm, where it is metabolized to all-trans RA [1]. RA exists in several stereoisomeric forms including predominantly all-trans retinoic acid (ATRA), 13-cis RA and less-stable isomers such as 9-cis RA. 13-cis RA has more-favourable pharmacokinetic properties than ATRA or 9-cis RA, with higher peak plasma concentrations and a significantly longer half-life. However, continuous treatment with low dose of 13-cis RA failed to provide a clinical benefit in neuroblastoma patients [2]. ATRA is a lipophilic molecule, thus it can diffuse easily through the cellular membrane. However, 13-cis RA shows low penetration efficiency compared to ATRA. Less 13-cis RA is taken up by brain cells than ATR which is speculated to be due to their configurations [3]. Current understanding of RA as signaling molecules suggests that ATRA is the main biologically-active form. 13-cis RA markedly isomerizes to ATRA in neuroblastoma cells, therefore, the favourable pharmacokinetics of 13-cis RA may play a role in allowing it to act as a reservoir for continuing isomerization to ATRA [4].

RA mediates its effects by binding to nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs) [5] and, thereafter, modulates a large number of essential biological processes including proliferation, differentiation, and apoptosis [6,7]. Each receptor has three subtypes (alpha, beta, and gamma), and each subtype has different isoforms. Many of the therapeutic effects of RA, including cancer chemoprevention and treatment of dermatologic disorders, are mediated through RAR β . In humans, five isoforms of this gene have been described [3]. Specific isoforms of RAR β exert distinct and sometimes opposing functions by altering patterns of target gene induction. Functional isoforms that activate distinct cassettes of target genes with differing biologic consequences include RAR β 1' and RAR β 2 [8]. Dominant negative isoforms of this gene that inhibit target gene activation include RAR β 4 and RAR β 5 [9,10]. RAR β 1 is poorly understood although it may function as an oncogene in certain cancers [11]. Chromatin modifying drugs have been shown to trigger isoform-specific changes in the RAR β gene [10].

The molecular mechanism by which RA mediates cellular differentiation and growth suppression in neural cells remains unknown. However, RA-induced release of arachidonic acid and its metabolites may play an important role in cell proliferation, differentiation, and apoptosis [12].

Alzheimer's disease (AD) is the most common form of neurodegenerative disease associated with dementia in the elderly [13]. A growing body of evidence suggests that free radical formation during oxidative stress is an early event in AD pathogenesis [14]. Therefore, the development of novel interventions which can target early changes such as oxidative stress has been the focus of anti-AD therapeutics [15-17]. Vitamin A has been suggested to reduce the oxidative stress associated with AD [18,19]. Studies in AD patients show that serum concentrations of vitamins A, C, E and β -carotene were significantly reduced in patients than in controls [20-24]. Epidemiologic studies show that dietary intake of natural or synthetic products with a putative antioxidant effect, such as vitamin E, reduces the risk of AD [25,26].

Vitamin A has been traditionally considered as antioxidant compounds by acting as chain breaking antioxidant [27]. Using an *in vitro* peroxidation system, antioxidant activities of retinoids have been ranked as retinol > retinal > retinyl palmitate > retinoic acid [28]. However, vitamin A and retinoids have been called redox-active molecules, exerting either antioxidant at low concentration or pro-oxidant effects by increasing vitamin concentration depending mainly on its concentration [29,30].

RA exerts their antiapoptotic and antioxidant activity by regulating gene expression through its nuclear receptors. In human neuroblastoma cells, ATRA induce expression of manganese superoxide dismutase (MnSOD2) gene, mitochondrial-localized antioxidant enzyme [31]. Ahlemeyer and Kriegelstein reported that RA protects embryonic neurons from oxidative damage and apoptosis by inhibiting of glutathione depletion [32]. RA, at 10 nM, reduced staurosporin-induced oxidative stress and apoptosis by preventing the decrease in the levels of Cu,Zn-superoxide dismutase (SOD-1) and Mn-superoxide dismutase (SOD-2) in primary hippocampal cultures [33] and facilitating nerve growth factor-induced protection in chick embryonic neurons [34]. These effects of RA protect neurons by reducing mitochondrial oxidative damage, which is an important pathological factor of AD [35]. RA, by binding the retinoic acid receptor, stimulates phospholipase A2 (PLA2), which generates arachidonic acid and its metabolites in the nucleus. Under normal conditions, these metabolites are known to control fundamental processes, including neurite outgrowth, neurotransmitter release and long-term potentiation. However, excessive production of arachidonic acid metabolites under pathological situations results in oxidative stress, inflammation, and neurodegeneration [36-39]. Of note, the activities of PLA2 have been shown to be altered in

the early stages of AD [40] and, in this vein, the anti-inflammatory activity of RA may be important [41,42]. Based on the fact that the neuro-inflammation is one of the factors involved in AD pathogenesis, ATRA may also play an inhibitory effect on AD pathology. Abnormal retinoid metabolism may be involved in the downstream transcriptional regulation of PLA2-mediated signal transduction in AD [12]. Studies using primary neurons treated with 9-cis RA showed increases in ATP-binding cassette transporter A1 (ABCA1) expression, which is a major regulator of peripheral cholesterol efflux and increased apoA-I-mediated cholesterol efflux consequently decreasing cellular cholesterol content [43]. Ligands alone, or in combination with apoA-I, caused a substantial reduction in the stability of amyloid- β protein precursor (A β PP) C-terminal fragments and decreased A β production [44].

Components of the retinoid metabolic pathway have been identified in adult brain tissues, suggesting that ATRA can be synthesized in discrete regions of the adult brain including the cortex, amygdala, hypothalamus, hippocampus, striatum and associated brain regions [45]. A number of neuronal specific genes contain recognition sequences for the retinoid receptor proteins and can be directly regulated by retinoids [46]. There is also evidence to suggest that processes involved in the synthesis, transport, or function of retinoid are potential targets for the treatment of AD [46,47].

Because of the recognition that ATRA halts the cell cycle and induces apoptosis, RA can act as a proapoptotic agent in neoplastic and developing cells [48,49]. Such activity has been leveraged in a variety of preclinical and clinical models, and clinical trials with ATRA have been documented in a variety of conditions. For example, Guo and colleagues [50] found that ATRA arrests the cell cycle at the G0/G1 stage and induces apoptosis in a pancreatic tumor cell line. ATRA has also been used, to a limited extent, in the treatment of malignant gliomas [51]. Such anti-mitotic actions may be useful in the treatment of AD where the ectopic re-entry of neurons [52,53] that precipitates pathological changes including tau phosphorylation, cell death, and DNA replication [54-56] is evidence of a de-differentiated phenotype. Indeed, cyclin B, one of the cell cycle proteins aberrantly expressed in the brains of AD patients [57,58], has been shown to be involved in the phosphorylation of tau and A β PP processing [59-62]. Overexpression of cyclin B1 in primary neuron triggers neuronal apoptosis [63,64]. As a well known anti-mitotic and differentiation-inducing agent, ATRA may play a role in inhibiting A β PP processing and tau hyperphosphorylation through suppressing the cell cycle proteins.

With respect to the involvement of RA in the depositions of A β , the expression of some of AD-related genes are under the control of RA in the brain including β -secretase enzyme (BACE) [65], and A β PP [66-69]. Furthermore, presenilin 1 (PS1) and presenilin 2 (PS2), which have been shown to be involved in the generation of A β , are also regulated by RA [70]. In fact, it has recently been shown that ATRA regulates the levels of A β peptides by increasing α -secretase expression and activity. In addition, ATRA treatment alters the localization of BACE1 and PS1 to impair A β PP cleavage [71]. In accordance with this, Vitamin A deficiency results in the down-regulation of components of the amyloid pathway, A β PP695, the β -secretase enzyme (BACE), and the membrane bound carboxy terminal fragment (A β PP-CTF). The levels of each of these proteins were improved or restored by the subsequent administration of RA [72]. Long-term deprivation of vitamin A showed an accumulation of A β peptide in cerebral vessels that accompanied decreases in the expression level of RAR α , CHAT, loss of hippocampal long-term potentiation (LTP), and memory deficit, all of which are hallmarks of AD [73-75]. Those effects are reversed by the administration of RA [75]. An accumulation of A β peptide in a long-term deprivation animal model is speculated to come from the rise in γ -secretase activity and/or degeneration of cholinergic neurons [46,49]

While the role of A β is still debatable [76-78], it is clear that A β and BACE are redox sensitive [79-81]. In accordance with the finding from animal models of AD, studies in patients with AD also have shown decrease in RAR α density and down-regulation of retinaldehyde dehydrogenase 2 (RALDH2) [73,82]. Although the exact mechanism is unknown, vitamin A and β -carotene dose-dependently inhibit the formation and destabilize preformed fibrillar A β [83], suggesting that impaired RA signaling might be a consequence of neurodegeneration in the onset of AD in humans. In a recent study, the effect of ATRA treatment on the neurodegenerative pathology and memory deficits of an A β PP and PS1 double-transgenic AD mouse model were examined [84]. ATRA administration to A β PP/PS1 double-transgenic mice effectively reduced A β accumulation and tau hyperphosphorylation. Moreover, ATRA significantly attenuated glial activation and neuronal loss in the brain and improved spatial learning and memory deficits. These findings support the therapeutic potential of ATRA in AD pathogenesis.

There are multiple links between RA signaling and AD [46]. While 19q13.1 (APOE) is clearly the major loci [85], chromosomes 10q23 and 12q13 are also frequently associated with late onset Alzheimer disease (LOAD) [86-88]. The genes that encode RAR γ and several retinol dehydrogenases are located at 12q13, together with a large number of genes that have been implicated in AD pathology. 10q23 is another region, where retinol-binding protein 4 (RBP4) which has been found in amyloid plaques and two retinoic acid-inactivating enzymes, CYP26A1 and CYP26C1, are clustered [46,89]. These findings indicate genetic interactions between RA signaling pathways and AD pathways. At the molecular level, RA has been shown to control the expression of genes involved in early onset AD, including MAPT, A β PP, PS, BACE, ADAM10, and APOE [65,82,90-94]. Additionally, A β PP-CTF, the product of the β -secretase action, has been found to repress RA gene expression [95]. Insulin degrading enzyme (IDE) contains a RARA response element in its promoter and the transcription of IDE is regulated by RA [96]. These findings suggest ATRA may play a role in the direct regulation of A β PP cleavage through the regulation of multiple enzymes involved in synthesis, production, and degradation pathways. Such a coordinated response is likely not coincidental.

Based on the fact that the loss of CHAT-expressing neurons is characteristic of AD and A β peptides down-regulate this enzyme [97], the effects of RA in inducing CHAT expression are also likely important [98,99]. Furthermore, RA overcomes the reduction in CHAT that is caused by A β peptides [100]. Beside CHAT, RA induces the expression of human inducible nitric oxide synthase (iNOS) gene through binding of RAR α /RXR α [101]. Since nitric oxide (NO) plays a major role as a retrograde signaling molecule in LTP, RA could act as a neuroprotective agent in AD by restoring CHAT and NO level.

In conclusion, RA appears to act on a wide variety of pathways and mechanisms that are affected in AD. Given recent clinical trial failures of targeted therapy, as well as uncertainty about which of these pathways to actually target in the first place, the promiscuity of RA may offer distinct advantages for a treatment regimen for AD.

Expert Commentary

The pathogenesis of AD is frequently described as multifactorial and such a notion would be consistent with the relatively modest benefits from targeted therapeutics [102]. We propose that treating the disease from multiple angles may prove more efficacious. While polypharmacy is one option, vitamin A/ATRA may offer a similar strategy in a single entity. With anti-apoptotic, antioxidant, pro-differentiative, A β -lowering, and acetylcholine activation activities, ATRA may be a potent therapeutic option in AD.

Five-year view

RA may have therapeutic properties ideally served for the treatment of neurodegenerative diseases such as AD. We expect a line of clinical trials to emerge in the near future, which will be designed to better understand the efficacy of the above mentioned mechanisms. Dosage and safety monitoring will be a challenge to focus on first.

Key issues

1. AD is the most common form of neurodegenerative disease associated with dementia in the elderly. Free radical damage from oxidative stress is an early event in AD pathogenesis. Attention should be focused on developing therapeutics which can target early changes such as oxidative stress in AD.
2. Vitamin A and RA are chain breaking antioxidants and could be useful to reduce the oxidative stress associated with AD.
3. ATRA significantly attenuates glial activation and neuronal loss in the brain and restored spatial learning and memory deficits in a mouse model of AD, supporting the therapeutic potential of ATRA in modulating AD pathogenesis.
4. The anti-mitotic actions of ATRA may be useful in the treatment of AD where the ectopic re-entry of neurons in the cell cycle, which precipitates pathological changes (tau phosphorylation, cell death, and DNA replication), is an obligate feature.
5. Impairments in RA signaling might be a consequence of neurodegeneration in the onset of AD in humans. Therefore, since vitamin A and β -carotene dose-dependently inhibit the formation of A β , ATRA may be a potent element in the treatment of AD pathology.
6. RA exerts its anti-apoptotic and antioxidant activity by regulating gene expression through its nuclear receptors and has been shown to control the expression of genes involved in early onset AD (MAPT, A β PP, PS, BACE, ADAM10, and APOE) which further supports its potential therapeutic value for AD.

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