ROLE OF RETINOIDS AND ITS NEUROPROTECTIVE IMPLICATIONS FOR ALZHEIMER'S DISEASE

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Abstract

Chemically, all retinoids, organic and conventional, are linked to vitamin A. To initiate particular signalling pathways in cells, both synthetic and natural retinoids utilise specific nuclear receptors which including retinoic X acid receptors and retinoid receptors. As in the central nervous system, retinoic acid signalling is critical. In the central nervous system, particularly in the adult brain, retinoic acid signalling pathway dysfunction results in severe pathological processes. During ordinary brain function and growth, retinoids play a vital role in neural characterization,axon outgrowth, and differentitation. Alzheimer's disease is profoundly defined by the intensification of extraneuronal amyloid plaques and intra-neurofibrillary tangles with in temporal lobes, is caused by dysfunction retinoic acid signalling, which also results in , oxidative stress, neuroinflammation, neurodegeneration,and mitochondrial dysfunction. Alzheimer's disease is the primary cause of cognitive impairment and memory lapse in the elderly.Inactive cholinergic neurotransmission causes memory problems in Alzheimer's patients. In mice, decline of spatial memory and learning is linked to retinoic acid deficiency or defect. In Alzheimer's disease, retinoids prevent the formation of chemokines and neuro - inflammatory cytokines in astrocytes and microglia. Retinoic X receptor and retinoid acid receptor stimulation reduces amyloid deposition, decrease neuronal damage, and hence prevents AD pathogenesis through mice. In this review, We present an overview of retinoid biology, with a focus on potentianeuroprotective processes which could focus on the importance of such receptor proteins in Alzheimer's disease pathogenesis

Keywords: Amyloid plaques,neurodegeneration, retinoids, Oxidative stress, Neuroprotection, neuroinflammation,alzheimer's disease

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1. Introduction

Alzheimer's disease is the foremost cause of cognitive decline in humans after the years old of 65. Dementia is marked by neuronal and white matter destruction, inflammation, and oxidative damage, in addition tothe abnormal buildup of neuronal aβ plaques and visible neurofibrillary tangles through processes in the medial temporal region Tau protein and aggregated amyloid-(Aβ) peptide, including both, form neurofibrillary tangles and amyloid plaques [1-2].

Aβ peptides is a 36–43 amino acid biochemical molecule that occurs naturally. with 40 as well as 42 amino acids (Aβ40 and Aβ42) being the most commonly produced. Aβ peptides are produced β-site amyloid precursor protein dissociates enzyme 1 (BACE-1), γ-secretase, but also β-secretase, a protein involved with presenilin 1 (PS1) at the catalytic core, sequentially cleave amyloid-precursor protein (AβPP) from proteolysis [1,3,4]. Aβ40 Monomers are far common than the accumulation and serious Aβ42 peptides. Thereby, it is thought that deregulation of synthesis and clearance, resulting in the formation of complete Aβ42 peptides, was the initiating factor in AD.

Vitamin A analogues called retinoids have an impact on cell morphogenesis, differentiation, and proliferation [5]. Additionally, it has recently been found the Retinoid mechanism is critical. for controlling older brain processes such neurite development, neuronal differentiation and anteroposterior neuronal tube design. generation of neurotransmitter causes long-term activation [5]. The term retinoid refers to systemicallyVitamin A-associated substances usually involve vitamin A and also its biologically related compounds, namely carotenoids., all-trans-retinoic acid, is a breakdown product of a vitamin A which initiates nuclear receptors, RAR β, α as well as γ , and substituted derivatives, substances which stimulate retinoid X receptors (RXR β,α and γ), and that are nuclear ligands that, like RARs, are enabled by 9-cisRA (9cRA),and substances which alters a functions of ATRA through affecting biosynthesis, metabolism or certain paths working upon co-factors and carriersinstead of being compelled by RARs or RXRs ; however, some researchers use the term 'retinoids' purely only for molecules coming under category . [6]. The elements of retinoids can be facilitated upon nuclear receptor termed as retinoic X receptors (RXR) and retinoid acid receptors (RAR β,α or γ) [6]. Each receptor subtype (β,α or γ) is processed by a distinct gene with several influencers, there components of these can facilitateDifferential ligase leading to different receptor homologs. (for example,RARβ1, RARβ2, RARβ3 and RARβ4). As a result of this complexity, RARs and RXRs will construct heterodimers, and RXRs can form heterodimers with the a wide range of nuclear receptor molecules. RAR agonists activate RAR/RXR heterodimers and regulate target transcriptional regulation even in lack of RXR agonists.

RETINOID SIGNALLING IN CNS

Numerous investigations have demonstrated that Retinoids are vital elements of the elderly brain's central nervous system.. Retinoid signalling pathways is prevalent in regions of the brain associated with neuroplasticity, which include the prefrontal cortex, hippocampus, and retrosplenial regions. RAR has been found in hippocampus, cortex, and cerebellum; RAR is highlighted in spinal cord and striatum; RAR is found lower concentrations in hippocampus. [7]. RXRα was being found in hippocampus, the RXRβ in cerebellum, and the RXRγ is predominent in limbic cortex, striatum as well as in the spinal cord [8]. Those receptor expression while growth in the adult brain suggests individuals could take part in distinct brain functions. Reduction in RAR expression, memory impairment, and LTP distress, as seen in VAD rodents, are also seen in older rodents. It's also important to note that while RA may prevent these effects, co-administration of the RAR antagonist, CD3106, may enhance them . A disrupted RA signalling system may cause age-related neurodegeneration, cognition and memory impairment impairment, and the onset of some neurological diseases [9].

RETINOID SIGNALLING IN ALZHEIMER'S DISEASE

Many previous studies found a direct link between impaired RA signalling and In vivo vitamin A deficiency. In vitamin A-deficient conditions, RARα and ChAT expression were suppressed, as wasIn vitamin A-deficient conditions, Aβ peptide accumulation was noticed in rat frontal brain cortical neurons, each of which is recognised defining characteristics of Alzheimer's disease [10]. RARβ, AβPP695, BACE, and AβPP-CTF concentration of cerebral cortex or Brain had been diminished in vitamin A-deficient rodents, but their effect was restored by RA administration [11]. Numerous research involving Alzheimer's disease genetic testing had already revealed a clear relation between the genes which code for molecules associated inthe RA sensing pathway, and some of the those thought to be involved in Alzheimer's disease pathology [11]. Several previous studies [12] have also shown that retinoids can regulate AβAPP. As a result of APP alternative splicing, three significant excerpts (AβPP770, AβPP751, and AβPP695) were produced . In these, AβPP695 seems to be more important for Alzheimer's disease pathogenesis. α-, β-, and γ-secretases

proteolytically alter those three AβPP products. Retinoids can activate a neuroprotective α -secretase (ADAM10) through connection with two putative RXR reactive sites, increase in long-term action , a design process for neural plasticity associated to learning consolidation [13]. Kuroda and Satoh proved that retinoids influence the β-secretase BACE-1, that enhances the processing of a Aβ from AβPP through N-terminal cleavage [14]. By targeting AβPP-CTF, γ-secretase, that enables the transferring Aβ from AβPP through the C-terminal cleavage, was found to restrict retinoid causing neurodegeneration, leading to apoptosis [15]

Retinoids have demonstrated to aid in downregulation of ChAT transcription induced by Aβ peptides in alzheimer's disease [16]. Many previous studies confirmed retinoids' neuroprotective effects by inducing ChAT formation in a wide range of cells via RARα modulation. [17] Similarly, RALDH2 suppression of RARα damage were noticed within vitamin A flawed rats, proving such destruction of a retinoid signalling pathway may contribute in a commencement of Alzheimer's disease. [18].

Inflammation like in brain provokes neuronal damage but also synaptic functional impairment . Excessive stimulation of neuroinflammatory mediators results in the creation but also collection of β-amyloid protien and increased phosphorylation of tau protein. When these series of, chemokines or cytokines are released. Profound neuroinflammatory actions are frequently observed in a AD patients and also in animal models [19]. Based on the assumption that optimal microglial action is required for trapping functions, overactivity of such cells within the brain provokes proinflammatory reactions, oxidative stress, neuroprotective retinoid disruption, and RA signalling downregulation, and promote the degeneration of surrounding healthy neurons [18].

Aβ-stimulated signalling pathways promote plaque formation by inducing the production and assessment of inflammation cytokines (i.e, IL-1, IL-6, tumour necrosis factor-α), chemokines (i.e, C-C sequences chemokine receptor 2), small proteins, responsive nitrogen and ros, and other molecule. Alzheimer's disease subjects showed astrogliosis, microgliosis, and severe neuroinflammation [20].Retinoidsbeen demonstrated to activate RAR and RXR, altering astrocyte and microglia mechanisms and decreasing a production of proinflammatory cytokines and chemokines.

One of the most crucial objectives in treating AD was reduces neuroinflammatory response.. Preceding research has demonstrated that retinoids could really assist to prevent neuroinflammation in neurodegenerative processes [9]. Because retinoids significantly inhibit IL-6 production [21],Retinoids could help with Alzheimer's therapeutic interventions. We comprehend retinoids to constrain overexpression nitric oxide synthase expression in executed microglia through impairing nuclear factor-kappa B signaling pathway and also to inhibit lipopolysaccharide secreted or Aβ-secreted tumour necrotic lesions factor-alpha development. In an animal model of Alzheimer's disease, ATRA forbids lipopolysaccharide causing neurodegeneration, amyloidogenesis, or even cognitive problems mostly in old rats, as well as promotes neuronal stem cell proliferation thereby lowering microglia activation, giving rise through neurodevelopment in the hippocampus [22].

The functions of the RAR agonist Am80 in reducing neuroinflammation (Tamibarotene) in a lipopolysaccharide-induced neuroinflammation method in vivo were observed , and thus findings demonstrate that Am80 may facilitate a yields of brain-derived neuroprotective component, which provide neuroprotective effects in disease states.[20] Am580 inhibited inflammatory cell apoptosis in refined neuronal cells after Aβ exposure. Retinoids play a key role in impairing neuro - inflammatory reactions & encouraging phagocytes of Aβ clusters in a wide range of neurological disorders, such as Alzheimer's disease. Intensive research is currently being carried out to better determine the molecular processing activity of retinoids & carotenoids in the preventative measures of neurodegenerative in Alzheimer's disease[23].

Because they are powerful anti-oxidative and anti-inflammatory agents. retinoids and carotenoids provide neuroprotection.For the purpose of enhancing cognitive abilities, peopleappear to be efficient of inhibiting AD development across a multiple pathways, including inhibitory activity of Aβ development and also formation, inhibition of oxidative stress, and reduction of pro-inflammatory mediator efflux [23]. All of the above current studies strongly recommend that retinoids and carotenoids have powerful neuroprotective effects in Alzheimer's disease through multiple pathways. ATRA diminished neuroinflammation in rodent brain by governing the stages of Sirtuin 1, type III histone deacetylase & part of a Sirtuin range of proteins, and nuclear factor-kappa B, as shown in a latest report.

Higher levels of oxidative stress are being found in Alzheimer's disease cases and Tg2576 APP genetically modified mice, implying the oxidative stress has been one of the fundamental neurodegeneration representations of Alzheimer's disease.It has been proven that ATRA has antioxidant qualities in living person neuroblastoma cells by increasing the process of manganese superoxide dismutase (MnSOD2) gene, that is a

mitochondrial confined anti- oxidative enzyme. ATRA has arisen to demonstrated for secure cultivated neurons from staurosporine-induced oxidative stress or even cell apoptosis by limiting Cu, Zn-SOD-1, and MnSOD2 depletion. APP and Aβ have been found in numerous studies to inhibit mitochondrial exporting channels, degrade mitochondrial transit and the electron transport chain, and boost production of free radicals, all of which leads a mitochondrial damage. In Alzheimer's disease animal models, mitochondrial dysfunction leads to nerve cells necrosis & downregulation of PGC-1, NRF-1, NRF-2, and TFAM. As a result, treatment goals for Alzheimer's disease that aim oxidative stress as well as mitochondrial damage must be appealing participants. Retinoids may be able to reduce Aβ levels while also indirectly lowering mitochondrial dysfunction and oxidative stress.

NEUROPROTECTIVE IMPLICATIONS OF RETINOIDS

Dietary carotenoids are said to be necessary for the proctection of so many neurodegenerative disorders, such as Alzheimer's. Retinoids influence neurological patterning, distinctions, axonal extension, and regeneration. Retinoid deficiency impairs healthy brain formation and function, leading to the emergence of signs of neurological disorders such as Alzheimer's [8]. Retinoids, according to research, will influence the development of neuronal cell types and regrow axons after serious harm [9]. Furthermore, retinoids have participated in the control of elderly nerve cells' and neural stem cells' distinguishable states, along with adequate concentration ofactivation by retinoids in the adult brain for neural plasticity, learning, and perception [5]. Retinoids appear to be essential for improving cognitive function and regulating a number of neurological diseases that affect the brain, including Alzheimer's disease. Several retinoids, including vitamin A, will effectively prevent the formation of Aß plaques in vivo, suggesting that retinoids have potential for neuroprotective effects and, therefore, pathogenesis protection in Alzheimer's condition.

Vitamin A and several retinoids will actively prevent the development of Aβ plaques through vivo, implying that retinoids have promising clinical activities in neuroprotective effects and therefore pathogenesis protection in Alzheimer's disease [24]. The hypothesis has been suggested that RA could greatly enhance the action of acetylcholine neurotransmission in cholinergic neurons within the brain. Degradation of cholinergic neurons adds value to cognitive and memory deficiencies [25]. The cholinotrophic features of RA and also its variants suggest that they could be used to cure Alzheimer's disease. Co-activation of RARα and RARβ (with the agonist Am80 or Tamibarotene) also RXRs was required for effective treatment in a rodent model of Alzheimer's. (with the pan agonist HX630). This study discovered that giving Am80 (0.5 mg/kg) or HX630 (5 mg/kg) together in 17 days markedly increased memory impairment in AβPP23 mice, and whichever operative had a pharmacological index when used alone. These investigator made no findings of any possible adverse effects of combining RAR as well as RXR agonists.

A recent study reworked bexarotene, an RXR activator also defined as rexinoid, for a treatment of dementia in rodent models. Bexarotene was dispersed into water and given orally to Alzheimer mice at a dosage of 100 mg/kg everyday for 15 days, beginning at both 3.5 and 7.5 months after birth. Treating with bexarotene markedly raised recent memories, olfactory cross-conditioning, and neuron sustenance whereas decreasing plaque impact, astrogliosis, but also inflammatory gene regulation. Overall, bexarotene treatment decreased neuron deficit and enhanced synapse compliance markers in mice with forceful Alzheimer's disease, leading to enhanced mental function. In this revew, however, no undesirable therapies with bexarotene were reported. Bexarotene was typically utilized as specific rexinoid in anticancer therapy, anyhow its is arising like a serious contender for Alzheimer's disease human research. Bexarotene treatment at doses ranging from 300 mg/m2 a day increased triglycerides approximately to 2.5 times & resulted in hypothyroidism in further over half of the subjects. The cholesterol as well as triglyceride rates were restored after therapy was stopped, and These amounts could be medically tolerable with antilipidemic treatment while taking bexarotene. As a whole, bexarotene's site of action and related rexinoids is currently being debated though since those who cause unique undesirable side effects in individuals, which could be more severe in adult Alzheimer's disease patients that unless required to take for an extended period of time.

Disruptions through many neural pathways, particularly its cholinergic and catecholaminergic network, characterise Alzheimer's disease [26]. AD is distinguished by the breakdown of such basal forebrain contains cholinergic neurons.which project towardsAlzheimer's disease is accomplished by the damage of cholinergic neurons in the basal forebrain. which project towards the In the starting stages of dementia, cholinergic signaling pathway is impaired, and destruction of cholinergic neural activity effects in cognitive dysfunction in experimental animals [27]. RARα activation can boost ChAT and vesicular acetylcholine transmission promoter activity, where it aids in the transmission of acetylcholine is incorporated into

synaptic vesicles for synaptic discharge [28]. Acetylcholine & ChAT mRNA levels were demonstrated to be raised by retinoids [29,30].
Retinoids may be involved in neuronal cells rejuvenation, according to evidence. RARα agonists, according to Goncalves et al., enhanced the differences of a neural progenitor cells (NPCs) in to the cholinergic neurons. Am80, that converted neuroblastoma cells into neuronal cells, yielded comparable results. Retinoids have been studied in the context of spinal cord injury , with RARβ gene emergence promoting neuron development but also improving animal retrieval upon trauma. RA administration during SCI may reduce inflammatory reactions and raise the amount of subsistence elements like development of collaborative factor-β, insulin-like growth factor-2, and neurotrophins. All those results suggest that retinoids may have a role in neurodegenerative disorders such as Alzheimer's. According to reports, Thr668 phosphorylation promotes APP , β secretase cleavage and improves Aβ generation. Cyclin dependent kinase 5 is thought to be a primary kinase concerned for APP and tau phosphorylation in neural cells (CDK5). By blocking APP phosphorylation through the CDK5, ATRA therapies altered the increase through APP phosphorylation through APP/PS1 mice. Increased expression of p35 has also been linked to an increase in Aβ levels concentration in the brain, feasibly via axonal transport impairment. ATRA, according to Ding et al., diminishes Aβ amounts by controlling axonal transmission via p35 downregulation.

2. Conclusion

Retinoid sensing has previously been described as a vital procedure for evolving new treatment options for Alzheimer's disease, Parkinson's, schizophrenia, or even distress. In human trials, retinoids are being used to treat cystic acne, neuroblastoma, acute promyelocytic leukaemia, or even psoriasis. The progression of Alzheimer's aetiology is impacted by distorted retinoid signaling. Retinoids have emerged as promising pharmacological targets for Alzheimer's diseasetherapies owing to their ability to influence key disease elements such as plaque development, cholinergic distribution, ApoE & ABCA1 expression, fat substance, also the provocative surroundings in brain. As a result, approaching those certain receptor sites could be able to treat Alzheimer's disease-related cognitive dysfunction. Both organic and artificial retinoids, and there own receptor activators, are being studied to control an ongoing activities of stem cell revenue, cell plasticity, also tissue formation. Dysfunction of retinoid signalling encourages Symptoms. Because retinoids seem to be tiny particles which could freely penetrate tissues, they are important clinical participants. Limiting the doses or incorporating them between several neuroprotective therapies may help to reduce undesirable effects through non-target tissues. Because retinoids can inhibit various clinical symptoms of Alzheimer's disease, which include plaque development , neuroinflammatory reactions, and neurodegenerative disorders with in brain, they are a novel treatment approach to the prevention of the disease. To fully comprehend the known for producing of retinoids and their receptors in Alzheimer's disease, it is going to essential to investigate the strength of these receptors in vivo models.

3. References

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