

Original Article

Prophylactic effect of all-trans retinoic acid in an amyloid-beta rat model of Alzheimer's disease

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Abstract

Introduction: Retinoid signaling has been argued to have favorable effects on Alzheimer's disease (AD). We studied the role of chronic intracerebroventricular (ICV) injection of all-trans retinoic acid (ATRA) on the amyloid-beta (A β) model of AD.

Methods: Adult male rats weighing 260-330 g were divided into 12 groups of 8 each. Six groups of rats received ATRA (3nM, 30nM, 3 μ M, 0.3mM, 30mM/rat; ICV) or DMSO 1% (2 μ l/rat; ICV), bilaterally and in a chronic manner (6 times, twice a week). Forty eight hours following the last injection, memory performance was assessed using a passive avoidance paradigm. One group received A β (10 μ g/rat; ICV), bilaterally. The control group received DMSO 1% (2 μ l/rat; ICV). Twenty days later memory performance was assessed. Three groups of rats received A β (10 μ g/rat; ICV) and then ATRA (3nM or 30nM/rat; ICV) or DMSO 1%, chronically (6 times, twice a week). Another group received DMSO 1% (2 μ l/rat; ICV) and then, DMSO 1%, chronically (6 times, twice a week).

Results: ATRA at doses 0.3mM and 30mM/rat impaired memory retrieval by decreasing step-through latency (STL) and increasing time spent in the dark compartment (TDC), significantly. However, moderate doses (3nM and 30nM/rat) did not change memory performance. ATRA (30nM/rat) increased STL and decreased TDC and NST in the A β -treated rats, significantly compared to the group received A β -DMSO 1%.

Conclusion: The results propose a potential prophylactic effect of ATRA in the ICV A β model of AD and indicate the prominence of retinoic acid signaling as a target for AD prevention.

Keywords:

All-trans retinoic acid;
Alzheimer's disease;
Amyloid- β ;
Rat

Received: 6 Aug 2016

Accepted: 16 Nov 2016

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disease which is the most common cause of dementia in later life (Goodman and Pardee, 2003) with no effective treatment (Krstic and Knuesel, 2013). Both genetic risk factors (Cacabelos, 2002)

and environmental influences involve in the pathogenesis of AD (Goodman and Pardee, 2003). However, the underlying molecular mechanisms are poorly understood (Hardy and Selkoe, 2002).

All-trans retinoic acid (ATRA) is an active metabolite of vitamin A and is synthesized by retinol in cortex, amygdala, hypothalamus, hippocampus, striatum and associated brain regions (Obulesu et al., 2011).

ATRA modulates neurogenesis, neuronal survival and aids to maintain neuronal plasticity and cognitive functioning in later life (Olson and Mello, 2010). It acts via specific retinoic acid receptors (RARs) and retinoid X receptors (RXRs), each with three subtypes: α , β and γ (Olson and Mello, 2010). During aging there is a decline in retinoid signaling in the brain. It was reported that the brain and hippocampal levels of retinoid receptors and the expression of specific associated target genes were restored to adult levels in aged mice after acute administration of ATRA (150 $\mu\text{g/kg}$, sc). ATRA was also confirmed to lessen the age-related deficit in the CA_1 long-term potentiation efficacy of aged mice *in vivo*. Moreover, ATRA was found to lessen completely the performance deficit of aged mice to the control level in a two-stage spatial discrimination paradigm (Etchamendy et al., 2001). Recent studies have shown a relationship between retinoid signaling and the pathophysiology of the AD. It was reported that AD patients have low serum and plasma concentrations of vitamin A and β -carotene (Zaman et al., 1992; Jimenez-Jimenez et al., 1999; Bourdel-Marchasson et al., 2001). In people aged 65 and older, higher beta-carotene plasma level was associated with better memory performance (Perrig et al., 1997). Moreover, the transport and function of retinoic acid was shown to be defective in the AD brain (Goodman and Pardee, 2003). On the other hand, vitamin A deficiency resulted in amyloid-beta ($\text{A}\beta$) accumulation in rats (Corcoran et al., 2004) and produced a severe deficit in spatial learning and memory, which was linked to hippocampal hypofunctioning (Hernandez-Pinto et al., 2006).

Due to these reports, some studies have argued that retinoid signaling might have beneficial effects in AD (Connor and Sidell, 1997; Goodman and Pardee, 2003; Ono et al., 2004; Ding et al., 2008; Lee et al., 2009; Shudo et al., 2009; Obulesu et al., 2011; Lerner et al., 2012; Ono and Yamada, 2012; Sodhi and Singh, 2013; Sodhi and Singh, 2014). For example, Sodhi and Singh (2013) reported that ATRA treatment significantly attenuated streptozotocin-induced memory deficits.

AD has two main neuropathological hallmarks, the accumulation of $\text{A}\beta$ in extracellular plaques and the presence of intracellular neurofibrillary tangles (Serrano-Pozo et al., 2011). $\text{A}\beta$ -peptide is crucial to the pathogenesis of AD (Walsh and Selkoe, 2007).

Intracerebroventricular (ICV) injection of $\text{A}\beta$ molecules leads to the accumulation of $\text{A}\beta$ plaques in the brain tissue, oxidative stress and neurotoxicity which results in impairment of memory characteristic of the AD (Butterfield, 2002). It has been used as an animal model of AD. The step-through passive avoidance task is a learning paradigm that has been widely used to study the involvement of various treatments in learning and memory (Beheshti and Shahrokhi, 2015).

Although recent studies have proposed a beneficial role for retinoid signaling in AD, there are rare pharmacological reports assessing the effect of retinoids in animal models of AD (Ding et al., 2008; Kawahara et al., 2014). Meanwhile, these studies have assessed the therapeutic effect of retinoids and the probable protective effects of retinoids remains to be further clarified. Here, we have investigated the potential prophylactic effect of chronic ICV injections of ATRA in the $\text{A}\beta$ model of AD.

Materials and methods

Chemicals

Ketamine and xylazine were purchased from Alfasan (Netherland). ATRA and $\text{A}\beta$ (1-42) were purchased from Sigma (USA) and dissolved in DMSO 1%. ATRA solution was freshly prepared. Monomeric $\text{A}\beta$ solution was kept in -20°C .

Subjects

Adult male Wistar rats (260–330 g) were obtained from the breeding colony of Department of Biology, University of Isfahan. Rats were housed four per cage in a temperature ($24\pm 1^\circ\text{C}$) controlled room that was maintained on a 12:12 light cycle (light on at 07:00 am). Rats had unrestricted access to food and water in their home cage. After the surgery for cannula implantation, rats were housed individually in standard cages. All experiments were executed in accordance with the guide for the care and use of laboratory animals (USA National Institute of Health publication No. 80-23, revised 1996) and were approved by the graduate studies committee of the Department of Biology, University of Isfahan.

Surgical procedures

Rats were anesthetized with a mixture of ketamine (100 mg/kg, ip) and xylazine (10 mg/kg, ip) and were

bilaterally implanted with guide cannula (22-gauge) aimed at site 1mm dorsal to the lateral ventricles (anterior-posterior: -0.9mm from bregma, midline: ± 1.4 mm from midline, and dorsal-ventral: -2.5mm from dura) according to the atlas of Paxinos and Watson (2007). One screw was inserted into the skull and cannulas were fixed to it with dental cement. The cannulas were closed with stainless steel stylets smeared with mineral oil to prevent clogging with blood.

Microinjection procedure

Intracerebroventricular injections were made via guide cannula with injection needles (27-gauge) that were connected by polyethylene tubing (PE20, Stoelting) to a 2 μ l Hamilton microsyringe. The injections (2 μ l total volume) were delivered over 4 min bilaterally (1 μ l each side), and the injection needles (extending 1mm from the end of the guide cannula) were left in place an additional minute before they were slowly withdrawn.

Passive avoidance task (PAT)

The step-through passive avoidance paradigm was performed to evaluate memory performance, as previously described (Beheshti et al., 2014). Briefly, each rat was placed in the white compartment of the PAT apparatus facing the sliding door. After 5s the door was raised. When the animal stepped into the dark compartment with all four paws, the door was closed and the rat remained there for 20s. Then the animal was removed to be placed in a temporary cage. 30min later, the rat was again placed in the white compartment for 5s, then the door was raised to let the animal enter the dark compartment and following entrance, the door was closed, but this time a controlled electrical shock of 0.3 mA lasting for 1s was delivered. After 20s, the rat was placed into the temporary cage. Two min later, the same testing procedure was repeated. When the rat remained in the white compartment for a 2-min time period, the training was terminated. On the second day, a retrieval test was performed to evaluate long-term memory. Each animal was placed in the white start compartment for 20s, then the door was raised and the step-through latency (STL), the number of step-through into the dark compartment (NST) and the time spent in the dark compartment (TDC), were recorded up to 600s.

Experiment 1

Eight rats were used in each experimental group. In this experiment the effect of chronic ICV injection of different doses of ATRA was assessed on memory performance. Six groups of animals received ATRA (3nM, 30nM, 3 μ M, 0.3mM, 30mM /rat; ICV) or DMSO 1% (2 μ l/4min; ICV), 6 times (twice a week). Forty eight hours after the last injection, memory retrieval was assessed.

Experiment 2

In this experiment the effect of ICV injection of A β was evaluated on memory performance in rats. One group of animals received A β (10 μ g/rat), bilaterally. The dose of A β was selected according to previous reports (Doost Mohammadpour et al., 2015). The control group received DMSO 1%. Twenty days following the injection, memory retrieval was assessed.

Experiment 3

In this experiment the effect of ATRA was assessed on memory performance in A β treated rats. Three groups of animals received A β (10 μ g/rat; ICV), bilaterally. Two of these groups, received ATRA (3 or 30nM/rat; ICV), bilaterally and the third group received DMSO 1% (2 μ l/rat; ICV), 6 times (twice a week). One group of animals received a single regimen of DMSO 1% (2 μ l/rat; ICV) and then, DMSO 1% (2 μ l/rat; ICV) 6 times (twice a week). In these groups, the first injection of ATRA or DMSO 1% were done immediately after injection of A β . Forty eight hours following the last injection, memory performance was assessed.

Statistical analysis

One way ANOVA followed by Tukey-Kramer multiple comparison post-hoc test or Un-paired t-test were performed using Graph Pad Prism version 5.04 for Windows, Graph Pad Software. In all experiments, differences were considered statistically significant at the level of $P < 0.05$. The data are presented as mean \pm SEM

Results

Verification of cannulas placements

After completion of the experiments, each animal was euthanized with an overdose of chloroform. The

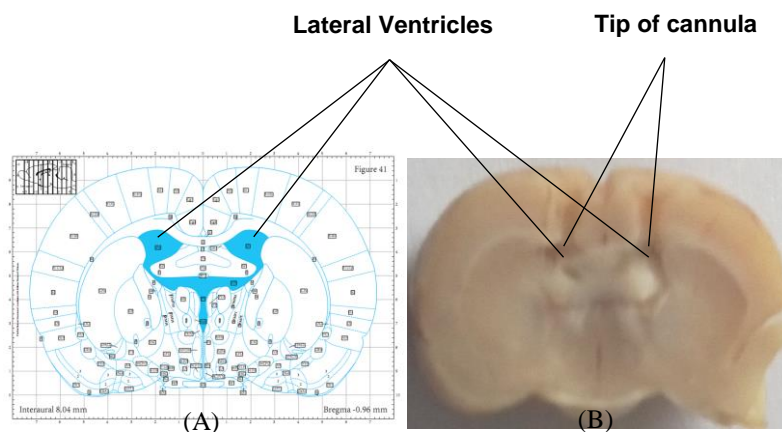


Fig.1. Coronal brain section of the rat brain at -0.96 mm from bregma. (A) Schematic drawing of the coronal section according to the atlas of Paxinos and Watson (2007). (B) Representative coronal brain section showing the position of the lateral ventricles and the tip of the implanted cannulas.

brains were removed and fixed in a 10% formalin solution 5 days before sectioning. Sections were examined to determine the location of the cannulas aimed for the lateral ventricles (Fig. 1). The cannula placements were verified using the atlas of Paxinos and Watson (2007). Data from the animals with the injection sites located outside the lateral ventricles were not included in the results.

The effect of ATRA on memory retrieval

In the passive avoidance task, the decrease in STL and the increase in TDC or NST indicate loss of memory. One way ANOVA indicated significant main effect of STL following chronic ICV injections of ATRA [$F(5, 47) = 5.18$; $P = 0.002$]. Post-hoc comparison showed that ATRA (0.3mM and 30mM/rat) significantly decreased STL as compared to control group (Fig. 2A; $P < 0.05$ and $P < 0.01$, respectively). Data analysis of this experiment also showed main effect of TDC [$F(5, 47) = 7.61$; $P = 0.0001$]. Post-hoc comparison showed that ATRA (0.3mM and 30mM/rat) significantly increased TDC as compared to control group (Fig. 2B); $P < 0.001$ and $P < 0.01$, respectively). One-way ANOVA showed that chronic ICV injection of ATRA (3nM, 30nM, 3μM, 0.3mM, 30mM /rat) did not show a significant effect on NST compared with control group [$F(5, 47) = 2.26$; $P = 0.08$; Fig. 2C].

The effect of Aβ on memory retrieval

Intracerebroventricular injection of Aβ impaired memory retrieval by decreasing STL and increasing NST and TDC, significantly compared with the control

group ($P < 0.05$; data not shown).

The effect of ATRA on memory retrieval in rats treated with Aβ

One way ANOVA indicated a significant main effect of STL following chronic ICV injections of ATRA in the Aβ treated rats [$F(3, 31) = 5.21$; $P = 0.005$]. Post-hoc comparison showed that ATRA (30nM/rat) significantly increased STL as compared to the group received Aβ-DMSO 1% (Fig. 3A; $P < 0.05$). Data analysis of this experiment also showed main effects of TDC [$F(3, 31) = 4.30$; $P = 0.01$] and NST [$F(3, 31) = 4.74$; $P = 0.009$]. Post-hoc comparisons showed that ATRA (30nM/rat) significantly decreased TDC and NST in the Aβ treated rats as compared to the group received Aβ-DMSO 1% (Fig. 3B and C); $P < 0.05$, respectively). One way ANOVA indicated that in the Aβ treated rats, ATRA (3nM/rat) did not have any significant effect on STL, TDC or NST ($P > 0.05$).

Discussion

Involvement of retinoic acid (RA) in memory is complex in that either too much or too little RA can result in similar deficits in learning behaviors (Olson and Mello, 2010). Rats deprived of vitamin A at an early age showed cognitive decline that improved once regular diet was resumed (Cocco et al., 2002; Bonnet et al., 2008). Also, RAR-β deficiency in mice eliminated hippocampal CA₁ long-term potentiation (LTP) and long-term depression (LTD). It also resulted in substantial performance deficits in spatial learning and memory tasks (Chiang et al., 1998). On

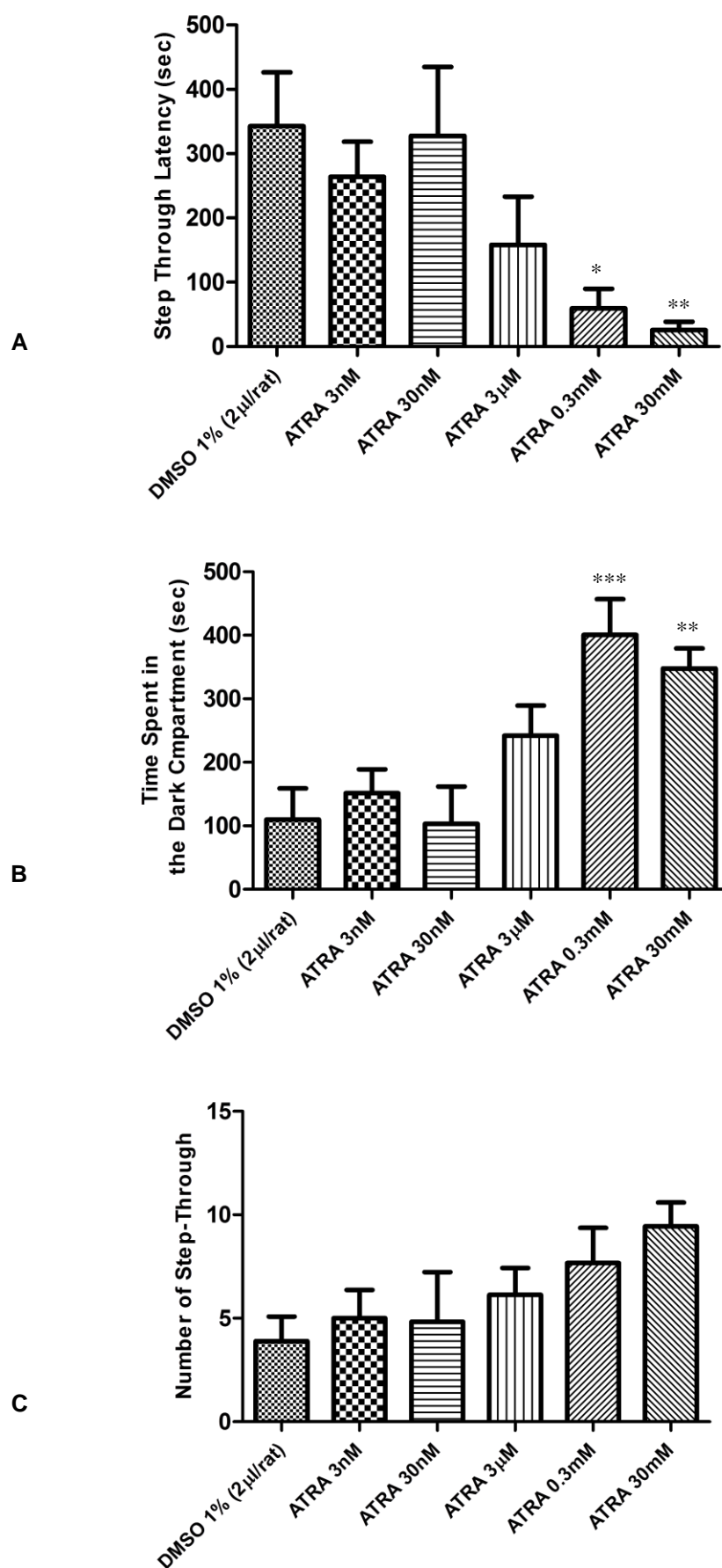


Fig.2. The effect of ICV injection of ATRA on (A) STL (B) TDC and (C) NST. Data are shown as mean±SEM(n=8). * $P<0.05$, ** $P<0.01$, *** $P<0.001$ as compared with the DMSO vehicle group.

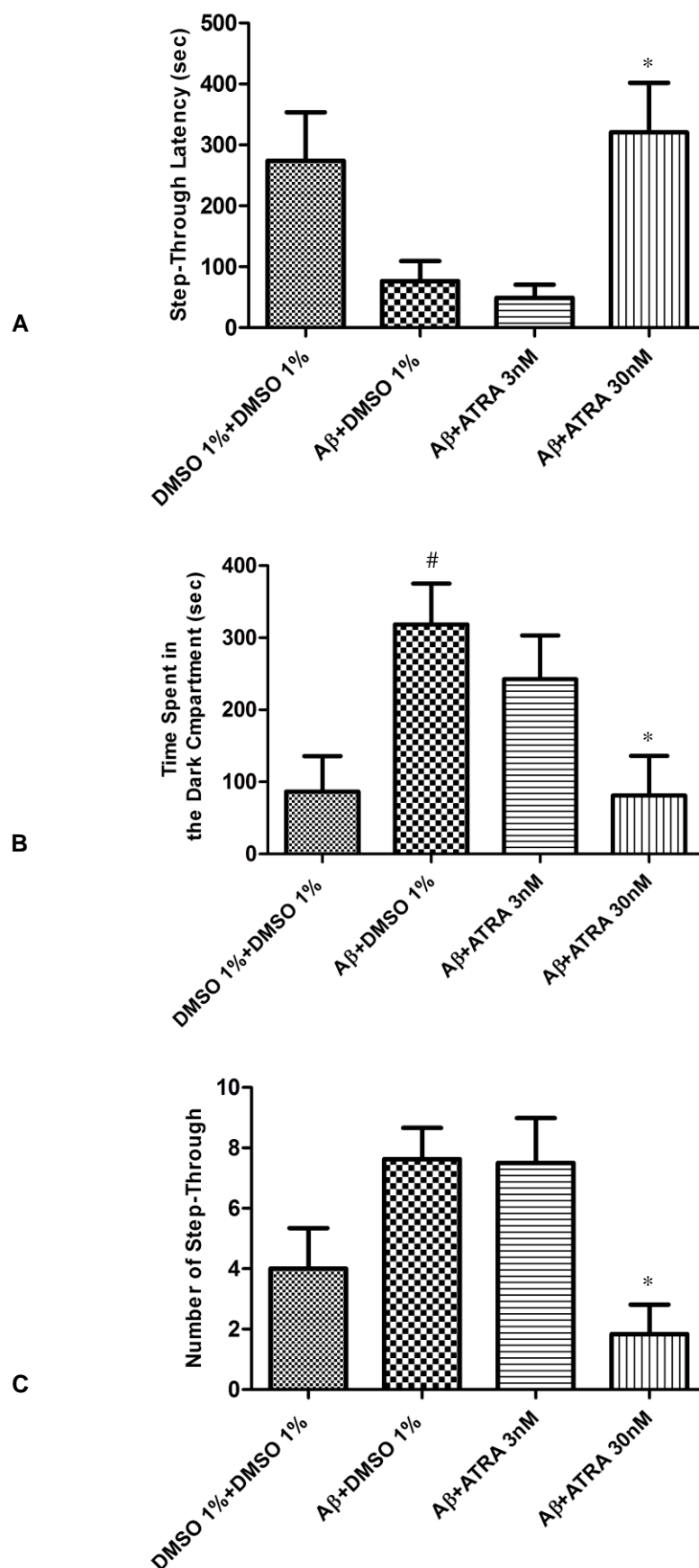


Fig.3. The effect of ICV injection of ATRA on (A) STL, (B) TDC and (C) NST in A β -treated rats. Data are shown as mean \pm SEM(n=8). * P <0.05 as compared with the A β -DMSO group, #: as compared with DMSO-DMSO group.

the other hand, high doses of 13-cis retinoic acid isomer resulted in cognitive deficits and reduced cell proliferation in the hippocampus and the proliferative regions of the ventricle in adult mice (Crandall et al., 2004). Accordingly, RA needs to be used within a narrow concentration range. In order to find an appropriate dose of the drug (the dose that would not impair memory), we evaluated the effect of chronic ICV injections of different doses of ATRA on memory retrieval, using a passive avoidance task. The results indicated that chronic ICV injections of ATRA at doses 0.3mM and 30mM/rat impaired memory retrieval. However, moderate doses of ATRA (3 and 30nM/rat) did not have a deleterious effect on memory retrieval. Hence, we used these doses to evaluate the effect of retinoid signaling in the rat brain on prevention of AD induced by A β .

The reason(s) for the impairing effects of RA on memory are not well known. One proposed mechanism is based on the influence of RA on hippocampal LTP and LTD. It is believed that chronic injection of RA (as in our study) may interfere with the normal role of RA, which has been proposed to support synaptic effectiveness (Misner et al., 2001), resulting in a decline in LTP and LTD. Vitamin A and retinoids have also been called redox-active molecules, exerting either antioxidant at low concentration or pro-oxidant effects by increasing its concentration (Roehrs et al., 2009; Pravkin et al., 2013). Therefore, by increasing the dose of the drug an oxidative response might occur in the brain, which is known to impair memory.

Our results indicated that ICV injections of A β (1-42) impaired memory retrieval in rats, which is in agreement with previous reports (Butterfield, 2002; Doost Mohammadpour et al., 2015). The main outcome of this study was that chronic administration of ATRA prevented the impairing effects of A β on memory performance in a dose-dependent manner. Retinoic acid have some rapid and non-genomic effects, beside its prolonged genomic effects. For example, external application of ATRA, reversibly reduced the amplitude of gap junctional conductance in a dose-dependent manner (Zhang and McMahon, 2000). Also, rapid reduction of gap junctional conductance was shown to be involved in the anticonvulsant effect of ATRA (Sayyah et al., 2007). As we aimed to evaluate the effects of chronic administration of ATRA on memory performance, we

assessed memory retrieval 48 hours after the last injection to avoid the impact of rapid non-genomic effects of the drug.

A large body of evidence indicate that retinoids have the potential to remove A β deposition. Reduction of A β 40/42 levels is mainly achieved by modulation of secretases, explicitly by the induction of α -secretase activity, by inhibition of β -secretases and/or γ -secretases, or by a combination of both. Koryakina et al., (2009) confirmed that ATRA regulates all secretases at the levels of transcription, expression and activation. It was reported that RA treatment of the cells resulted in a significant inhibition of γ -secretase-mediated processing of the amyloid precursor protein C-terminal fragment, APP-C99. RA-elicited signaling was found to significantly increase accumulation of APP-C99 and decrease production of secreted A β -40 (Kapoor et al., 2013).

It was indicated that agonists of the RAR α , but not RAR β or γ , lowered levels of intracellular and extracellular A β , specifically A β -42. RAR α agonists were also neuroprotective, as they prevented A β -induced neuronal cell death in cortical cultures. (Jarvis et al., 2010). RA protected hippocampal neurons from apoptosis induced by the A β peptide (Sahin et al., 2005). Vitamin A and beta-carotene were shown to inhibit formation of fibrillar A β (fA β) from fresh A β , as well as their extension. Moreover, they dose-dependently destabilized preformed fA β s (Ono et al., 2004).

Ding et al., reported a robust decrease in brain A β deposition and tau phosphorylation in the APP/PS1 transgenic mice (a model of AD, in which mice overexpress genes for A β and presenilin 1) treated intraperitoneally for 8 weeks with ATRA (20mg/kg, three times weekly). The ATRA-treated APP/PS1 mice also showed decreased activation of microglia and astrocytes, attenuated neuronal degeneration and improved spatial learning and memory (Ding et al., 2008).

It was reported that co-administration of a retinoic acid receptor α,β agonist (Am80, 0.5 mg/kg) and a specific retinoid X receptor pan agonist (HX630, 5 mg/kg) for 17 days significantly improved memory deficits in an AD model, 8.5-month-old A β protein precursor 23 (A β PP23) mice in the Morris water maze, whereas administration of either agent alone produced no effect. Moreover, only co-administration significantly reduced the level of insoluble A β peptide

in the brain. It was concluded that effective memory improvement via reduction of insoluble A β peptide in 8.5-month-old A β PP23 mice requires co-activation of RAR α,β and RXRs (Kawahara et al., 2014). Intracerebral injection of acetretin, a synthetic retinoid, enhanced APP_s/APP_s_b ratio of 40% in cortical tissue samples of APP/PS1–21 double transgenic mice and resulted in reduction of A β -42 by 50% and A β -40 by 25% in mice (Tippmann et al., 2009).

Recently, it was reported that miR-138 increased in AD models, including N2a/APP and HEK293/tau cell lines. Overexpression of miR-138 activated glycogen synthase kinase-3 β (GSK-3 β) and increased tau phosphorylation in HEK293/tau cells. Furthermore, RAR α was shown to be a direct target of miR-138, and supplement of RAR α substantially suppressed GSK-3 β activity and reduced tau phosphorylation induced by miR-138. It was concluded that miR-138 promotes tau phosphorylation by targeting the RAR α /GSK-3 β pathway (Wang et al., 2015).

In addition to the effects of retinoid signaling on A β , an interesting recent study reported that RAR α signaling was down-regulated by A β , which inhibited the synthesis of the endogenous ligand, RA. On the other hand, RAR α signaling promoted A β clearance by increasing insulin degrading enzyme and neprilysin activity in microglia and neurons. Moreover, RAR α signaling prevented tau phosphorylation (Goncalves et al., 2013).

Based on these observations, we hypothesize that the major effect of ATRA on prevention of A β -induced AD in rats might be due to its effect on preventing accumulation of A β plaques or tau phosphorylation in the brain, which needs further investigations. As the function of retinoic acid is defective in the AD brain (Goodman and Pardee, 2003) and vitamin A deficiency results in A β accumulation in rats (Corcoran et al., 2004), considering the central role of A β in the pathogenesis of AD (Hardy, 1997), it seems that retinoid signaling might have a crucial impact on the pathophysiology of AD. Taken together, our results propose ATRA as an effective therapeutic agent for the prevention of AD.

Conclusion

In conclusion, the results of the present study indicate potential prophylactic effects of ATRA in the ICV A β

model of AD. Our findings provide an important role of ATRA in AD pathology and add to accumulating data showing the prominence of RA signaling as a target for AD prevention. However, before we can propose RA supplementation for the individuals who have a high risk for AD, careful preclinical studies are required.

Acknowledgments

This work was supported by grant number 19907/93 from the Vice-chancellorships for Research and Technology, University of Isfahan.

Conflict of interest

The authors declare that there is no conflict of interest.

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