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Transthyretin: A key gene involved in the maintenance of memory capacities during aging

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Abstract

Aging is often associated with decline of memory function. Aged animals, like humans, can naturally develop memory impairments and thus represent a useful model to investigate genes involved in long-term memory formation that are differentially expressed between aged memory-impaired (AI) and aged memory-unimpaired (AU) animals following stimulation in a spatial memory task. We found that alterations in hippocampal gene expression of transthyretin (TTR), calcineurin, and NAD(P)H dehydrogenase quinone 2 (NQO2) were associated with memory deficits in aged animals. Decreased TTR gene expression could be attributed at least partially to diminish activity of C/EBP immediate-early gene cascade initiated by CREB since protein levels of C/EBP, a transcription factor regulating both TTR and NQO2 expression, was decreased in AI animals. Memory deficits were also found during aging in mice lacking TTR, a retinol transporter known to prevent amyloid-β aggregation and plaque formation as seen in Alzheimer's disease. Treatment with retinoic acid reversed cognitive deficits in these knock-out mice as well as in aged rats. Our study provides genetic, behavioural and molecular evidence that TTR is involved in the maintenance of normal cognitive processes during aging by acting on the retinoid signalling pathway.
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1. Introduction

Brain aging is a complex process accompanied by molecular modifications that may lead to memory impairments related to disorders ranging from the benign senescent forgetfulness to the memory loss that characterizes Alzheimer's disease (AD) (Mattson and Magnus, 2006). Stable forms of long-term plasticity require the induction of a cascade of genes to produce and maintain structural changes associated with memory formation (Kandel, 2001). Despite progress that has been made in elucidating molecular mechanisms underlying memory formation (Silva, 2003), little is known about molecular events most relevant to memory deficits during brain aging. Global alteration of basal gene expression during the course of aging was recently evaluated in humans (Lu et al., 2004) and animals (Blalock et al., 2003; Verbitsky et al., 2004). However, a genome wide study investigating genes differentially expressed between aged memory-impaired (AI) and aged memory-unimpaired (AU) animals following a behavioural stimulation has yet to be performed.

High-density microarray represents a powerful tool to investigate hippocampal gene expression profiles in aged animals. Aged rats are a well-established natural model to study age-related memory deficits. The performances of aged rats in the reference memory version of the Morris water maze (MWM) task has been used routinely to characterize AI and AU rats when compared to young adult rats (Frick et al., 1995; Gage et al., 1989; Rowe et al., 1998; Stemmelin et al., 2000). Decreased spatial memory ability of aged rats was correlated to defective long-term potentiation (LTP) in the

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hippocampus (Bach et al., 1999; Barnes and McNaughton, 1985; Tombaugh et al., 2002). The hippocampus, a structure vulnerable in the course of aging (Driscoll and Sutherland, 2005), is essential for the formation and retrieval of spatial memory (Hollup et al., 2001) and is necessary for consolidation or long-term storage (Riedel et al., 1999).

Studies in various behavioural paradigms (Bourtchouladze et al., 1998; Igaz et al., 2002) have suggested that long-term memory formation depends on two distinct temporal periods requiring gene expression and protein synthesis: shortly and several hours after training. Many immediate-early genes associated with the first phase have already been identified (Lanahan and Worley, 1998) but downstream genes expressed during the second time period have been studied to a lesser extent, especially in the context of aging.

This study combines behavioural, genetic and molecular approaches to investigate possible mechanisms underlying age-related memory deficits. First, we characterized individual memory capacities of young adult and aged animals at behavioural level with the MWM task. Using a microarray approach, we identified several known and novel downstream hippocampal genes related to age-associated memory deficits following stimulation in a spatial memory task. We then focused on genes differentially expressed between AI and AU rats and carried out a functional analysis using knock-out mice lacking transthyretin (TTR), one of the most markedly affected genes between the two groups. A role of TTR, in association with retinol-binding protein, is to transport retinol (vitamin A) from liver storage to target tissues where it can be metabolized into retinoic acid (RA) in response to physiological needs (Monaco, 2000). Some evidence thus far has suggested a role for perturbed RA pathway in age-related memory impairments (Chiang et al., 1998; Cocco et al., 2002; Etchamendy et al., 2001; Misner et al., 2001). However, the function of the retinol transporter TTR in mnemonic processing during aging has yet to be investigated. Our study identified genes altered between AI and AU animals, and provides evidence that TTR is a critical component of the retinoid pathway for the maintenance of memory capacities during aging.

2. Methods

2.1. Animals

Aged (A) and young adult (Y) male Long-Evans rats were purchased from Charles River Laboratories (St-Constant, QC, Canada). The animals were left undisturbed for a minimum of 2 months in our facility and behavioural testing of A and Y animals was started at the age of 24- and 7 months, respectively. Aging animals were monitored on a weekly basis by a veterinarian for weight loss, obesity, abscesses, cataracts, sebaceous cysts, tumours, malocclusions. Seventy-four healthiest rats were used in this study. Animals were housed in groups of two per cage and maintained on a 12 h light/dark cycle with *ad libitum* access to food and water. Wild-type (WT; $n = 12$) and TTR$^{-/-}$ ($n = 18$) mice (F2 generation maintained on a mixed C57BL/6 × 129S background) were purchased from The Jackson Laboratory (Bar Harbor, ME).

2.2. Drug administration

Retinoic acid (Sigma, St. Louis, MO) was dissolved in a vehicle solution containing polyethyleneglycol, NaCl (0.9%), and ethanol mixed in a proportion of 70:20:10 by volume. Daily administration of RA (150 μg/kg, sc) to 7 months old TTR$^{-/-}$ and WT mice as well as aged and young rats commenced 4 days prior to behavioural testing and continued until the end of testing in the MWM. An equal volume of vehicle solution was similarly administered to control animals. The treatment duration, time of injection (18:00 h), dose and route of administration used here have previously been shown to reverse age-related memory deficits in mice (Etchamendy et al., 2001). We used the same treatment in rats since the previous study was based on results showing differential gene expression of retinoic acid nuclear receptor in the brain of young, adult and aged rats (Enderlin et al., 1997a,b) suggesting similar drug pharmacokinetics in these two species.

2.3. Morris water maze task

Animals were required to find, in a 1.4 m diameter pool, a submerged platform (14 cm in diameter) located 1 cm below the surface of water (24 °C), rendered opaque by the addition of skim milk powder. Animals were pseudo-randomly started from a different position at each trial and used distal visuo-spatial cues to find the hidden-platform that remained in the centre of the same quadrant throughout all training days (Morris, 1984). Animals were given three trials of 90 s per day with a 45 min inter-trial interval over five consecutive days. If the platform was not located within 90 s, animals were guided to it and remained there for 10 s before removal. One probe trial of 60 s was given 24 h after the acquisition phase on day 5 to a subset of six AI, AU, and Y rats or immediately after the end of the training to WT and TTR$^{-/-}$ mice to evaluate the number of times the animals crossed the previous location of the platform, time spent in the target quadrant, swimming speed, and swim pattern. The AI, AU, and Y rats chosen randomly for the probe trial were not the same as those used for microarray analysis since both the probe and hidden-platform trials are hippocampus-dependent and may interfere with gene expression. After each trial, animals were immediately placed under heat lamps to dry and prevent hypothermia. Five aged rats with a swimming speed lower then 16 cm/s on training days 3–5 were considered to have locomotor deficits and were eliminated from the study. Aged animals ($n = 26$) falling between 0.5 and 2.0 standard deviations of the performance of Y rats were not used in any further tests. The

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