Neurobiology of Aging 35 (2014) 2701–2712

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Therapeutic benefits of a component of coffee in a rat model of Alzheimer's disease

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ARTICLE INFO

Article history:
Received 4 March 2014
Received in revised form 29 May 2014
Accepted 10 June 2014
Available online 17 June 2014

Keywords:
Protein phosphatase-2A
Tau
Aβ
Hyperphosphorylation of tau
Rat model of sporadic Alzheimer's disease
Coffee
Eicosanoyl-5-hydroxytryptamide
Cognitive impairment
Methylation of protein phosphatase-2A
Adenoassociated virus vector serotype 1
Inhibitor-2 of protein phosphatase-2A
SET

ABSTRACT

A minor component of coffee unrelated to caffeine, eicosanoyl-5-hydroxytryptamide (EHT), provides protection in a rat model for Alzheimer's disease (AD). In this model, viral expression of the phosphoprotein phosphatase 2A (PP2A) endogenous inhibitor, the I_2^{PP2A}, or SET protein in the brains of rats leads to several characteristic features of AD including cognitive impairment, tau hyperphosphorylation, and elevated levels of cytoplasmic amyloid-β protein. Dietary supplementation with EHT for 6–12 months resulted in substantial amelioration of all these defects. The beneficial effects of EHT could be associated with its ability to increase PP2A activity by inhibiting the demethylation of its catalytic subunit PP2Ac. These findings raise the possibility that EHT may make a substantial contribution to the apparent neuroprotective benefits associated with coffee consumption as evidenced by numerous epidemiologic studies indicating that coffee drinkers have substantially lowered risk of developing AD.

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1. Introduction

Alzheimer 's disease (AD), the major cause of dementia in middle and old age, is characterized by neurodegeneration that is associated with neurofibrillary tangles and neuritic plaques. A current major goal in medicine is the development of disease-modifying therapeutic drugs for AD. The microtubule-associated tau protein is abnormally hyperphosphorylated in AD where it is the principle component of neurofibrillary tangles (Bancher et al., 1989; Grundke-Iqbal et al., 1986a, 1986b). Similarly, the amyloid-β (Aβ) polypeptide, is the principle component of neuritic plaques (Masters et al., 1985; Wong et al., 1985). Evidence suggests that tangle and plaque precursors, the nonfibril forms of abnormally hyperphosphorylated tau and soluble oligomers of Aβ, are the major cytotoxic species in AD (Alonso et al., 1994, 2010; Grundke-Iqbal et al., 1989; Iqbal et al., 1986; Klein, 2002; Kopke et al., 1993; Santacruz et al., 2005). As much as 40% of the abnormally hyperphosphorylated tau is cytosolic in AD brains (Kopke et al., 1993), and intraneuronal Aβ accumulation precedes plaque deposition (Bancher et al., 1989; Cataldo et al., 2004; Grundke-Iqbal et al., 1989; Mori et al., 2002) and is correlated with neuronal cell death in AD transgenic mouse models (Espana et al., 2010; Gandy et al., 2010; Oddo et al., 2003).

Phosphoprotein phosphatase 2A (PP2A) accounts for ~70% of the total phospho-tau phosphatase activity in healthy human brain (Bennecib et al., 2000; Gong et al., 1993, 1995, 2000; Liu et al., 2005) and also functions to dephosphorylate the Aβ precursor protein (APP) so as to reduce the formation of the Aβ (Sontag et al., 2007). In

This article is dedicated to Dr Inge Grundke-Iqbal who supervised most of the immunohistochemical and biochemical studies before she passed away on September 22, 2012. GB-I and JB contributed equally to this study.

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0197-4580/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2014.06.012

AD, PP2A activity is curtailed so that levels of hyperphosphorylated tau and Aβ increase, leading to neurodegeneration and dementia (Gong et al., 1993). Two cellular inhibitor proteins, I_1^{PP2A} and I_2^{PP2A}, regulate the activity of PP2A (Li et al., 1995, 1996). I_2^{PP2A} or SET inhibits PP2A activity toward hyperphosphorylated tau (Tsujio et al., 2005). I_2^{PP2A} is a 277 amino acid–long nuclear protein that is overexpressed and selectively cleaved at N175 into N-terminal (I_{2NTF}) and C-terminal (I_{2CTF}) fragments, which are translocated from the neuronal nucleus to the cytoplasm in affected areas of the AD brain (Tanimukai et al., 2005). Both I_{2NTF} and I_{2CTF} bind to PP2A catalytic subunit (PP2Ac) and inhibit its phosphatase activity toward hyperphosphorylated tau (Arnaud et al., 2011). Transduction of brains of new born rat pups with adenoassociated virus 1 vector (AAV1) encoding I_{2NTF} and I_{2CTF} inhibit PP2A activity and cause abnormal hyperphosphorylation and aggregation of tau and accumulation of intraneuronal Aβ in 13-month-old animals (Bolognin et al., 2012). These protein hallmarks of AD are associated with cognitive defects in memory and learning.

From these results, it seems likely that a therapeutic agent that acts to maintain healthy levels of PP2A might provide a disease-modifying approach for the treatment of AD. A number of different PP2A-activating compounds and mechanisms have been identified (Voronkov et al., 2011). An in vitro screen was conducted for natural products that support PP2A activity toward phospho-tau, and a suitable activity was identified in coffee extracts. The active agent was purified to homogeneity and identified as eicosanoyl-5-hydroxytryptamide (EHT). Synthetic EHT exhibited the same ability to support PP2A activity as EHT isolated from coffee. Dietary supplementation with synthetic EHT exhibited neuroprotective efficacies in mouse models for Parkinson's disease (Lee et al., 2011, 2013). Here, we report the beneficial effects of chronic dietary supplementation with EHT on PP2A activity, abnormal tau hyperphosphorylation, accumulation of intraneuronal Aβ, and cognitive performance in a rat model for AD.

2. Materials and methods

2.1. Study design

AAV1 was used to express the I_2^{PP2A} N- and C-terminal fragments (I_2-N/C) in rat brain to replicate the cleavage of I_2^{PP2A} found previously in AD brains (Tanimukai et al., 2005). AAV1-I_2-N/C–infected rats that express the predicted I_2-N/C fragments, are cognitively impaired, show hyperphosphorylation and aggregation of tau, and accumulate intraneuronal Aβ (Bolognin et al., 2012). As described previously (Bolognin et al., 2012), on the day of birth (postnatal day = 0.05), Wistar rat pups were transfected by injecting 2 μL containing 4×10^9 AAV1 genomic equivalents encoding I_2-N/C or, as a control, green fluorescent protein (GFP) into each lateral ventricle of the brain (Fig. 1). Successful transfection of rat brains with I_2-N/C was confirmed by reverse-transcription polymerase chain reaction (RT-PCR). At 21 days of age, the pups were weaned and 15 female AAV1-I_2-N/C and 15 female AAV1-GFP rats were put on 0.1% (wt/wt) EHT formulated diet (Research Diets; New Brunswick, NJ, USA). As controls, 15 female AAV1-I_2-N/C and 15 female AAV1-GFP pups were put on similar diets lacking EHT. The rats were housed and bred according to the United States Public Health Service Policy on Human Care and Use of Laboratory animals with 2–3 animals per cage, a 12:12 h light-dark cycle, and ad libitum access to food and water. Studies on animals were carried out according to the protocols approved by the Animal Welfare Committee of the New York State Institute for Basic Research. Rats were subjected to behavioral tests at 6 months of age. Seven animals from each group were perfused after behavioral tests, and the remaining 8 animals from each group were perfused after a second set of behavioral tests at 12 months while they were still on EHT or vehicle diet. Animals were anesthetized with sodium pentobarbital (125 mg/kg) and then sacrificed by transcardial perfusion with 0.1 M phosphate-buffered saline. The left hemispheres were dissected into hippocampus, cerebral cortex,

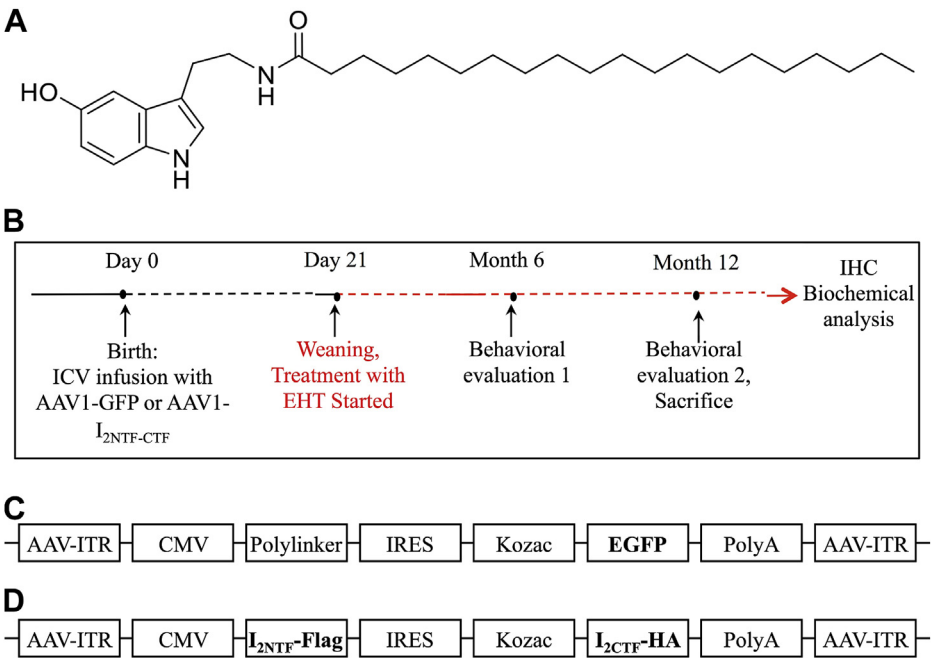

Fig. 1. Eicosanoyl-5-hydroxytryptamide (EHT) structure and experimental design and I_2^{PP2A} N- and C-terminal fragments (I_2-N/C) transduction in adult rat brains. (A) EHT chemical structure. (B) Schematic representation of the study. (C) Rat pups were injected intracerebroventricularly with adenoassociated virus (AAV) on the day of birth. (D) Linear maps of the AAV plasmids (based on pTRUF12) containing (C) green fluorescent protein (GFP) or (D) I_{2NTF} and I_{2CTF} genes inserted between the inverted terminal repeats (ITRs). CMV, cytomegalovirus promoter; IRES, internal ribosomal entry site from poliovirus. After weaning on day 21, GFP and I_2-N/C animals were put on either standard rat chow or chow containing 0.1% EHT for up to 1 year.

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