Neuroscience Letters 621 (2016) 15–21

Contents lists available at ScienceDirect

Neuroscience Letters

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

Research paper

LXR activation protects hippocampal microvasculature in very old triple transgenic mouse model of Alzheimer's disease

Adrián G. Sandoval-Hernández[a,1], Alejandro Restrepo[a,1], Gloria P. Cardona-Gómez[b], Gonzalo Arboleda[a,*]

[a] Grupos de Neurociencias y Muerte Celular, Instituto de Genética y Facultad de Medicina, Universidad Nacional de Colombia, Colombia
[b] Area de Neurobiología Celular y Molecular, Grupo de Neurociencias de Antioquia, Calle 70, No. 52–21, Medellín, Universidad de Antioquia, Colombia

HIGHLIGHTS

- GW3965 reduced GFAP expression in the hippocampi of 3xTg-AD mice.
- GW3965 partially restores LRP1 levels in neurons of 3xTg-AD.
- GW3965 restores microvasculature length of 3xTg-AD mice.
- GW3965 decreased Aβ deposition in blood vessels of 3xTg-AD mice.

ARTICLE INFO

Article history:
Received 1 December 2015
Received in revised form 30 March 2016
Accepted 4 April 2016
Available online 4 April 2016

Keywords:
GW3965
Alzheimer's disease
Neurovascular endothelium
Neuroinflammation
Liver x receptors

ABSTRACT

The vascular hypothesis of Alzheimer's disease postulates that disruption of the brain microvasculature is important for the accumulation of amyloid beta and increased neuroinflammation. Liver X Receptor agonist, GW3965, has been demonstrated to successfully modulate neuroinflammation and lipid metabolism in murine models of AD. This is partially due to increased expression of ApoE levels and increased mobility of endothelial progenitor cells. This paper analyzes changes in the neurovascular unit and in astrocytes and microglia markers following oral administration of GW3965 in a very old triple transgenic AD mice (3xTg-AD mice). We found that astrogliosis, but not activation of microglia, decreased in very old (24 months) 3xTg-AD mice treated with GW965. In addition, GW3965 increased LRP1 levels in neuron-like cells and partially restored microvascular morphology by decreasing tortuosity and increasing length as shown by Lectin immunostaining. Interestingly, these changes were associated with decreased Aβ in blood vessels. In conclusion, short-term treatment of 3xTg-AD mice with GW3965 restored microvascular architecture which may be important in the cognitive improvement previously shown.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia [1]. The hippocampus is the first brain region affected in human AD. [2] It is now recognized that most cases of AD have alterations in vasculature, in particular of small-vessels [3], which leads to blood-brain barrier (BBB) damage that contributes to pathogenesis and progression of AD. Under normal conditions, the BBB contributes to the regulation of brain amyloid beta (Aβ) levels by mediating its transport from brain parenchyma to the blood stream for degradation [4]. BBB integrity prevents the filtration of toxic substances such as TNFα that interfere with proper synaptic communication and further exacerbates BBB damage [5].

Aβ transport through the BBB is mainly regulated by interaction with two proteins: apolipoprotein E (ApoE) and low-density lipoprotein related protein 1 (LRP1). ApoE, a natural ligand for LRP1, has been extensively described as the main risk factor for AD [3,6]. LRP1 is expressed in endothelial cells and is required for the integrity and normal functioning of the BBB, in part by controlling proinflammatory pathways (CypA–Nf-κB–MMP9) through direct interaction with APOE [7]. It is suggested that increased expression

Abbreviations: AD, Alzheimer's disease; BBB, blood brain barrier; Aβ, Amyloid beta; LRP1, low-density lipoprotein related protein 1; LXR, liver X receptor; GFAP, glial fibrillary acidic protein; Iba1, ionized calcium-binding adapter molecule 1.

* Corresponding author at: Departamento de Patología, Facultad de Medicina, Universidad Nacional de Colombia, Bogotá, Colombia.
E-mail addresses: gharboledab@unal.edu.co, garboled@hotmail.com (G. Arboleda).

[1] These authors contributed equally to this study.

http://dx.doi.org/10.1016/j.neulet.2016.04.007
0304-3940/

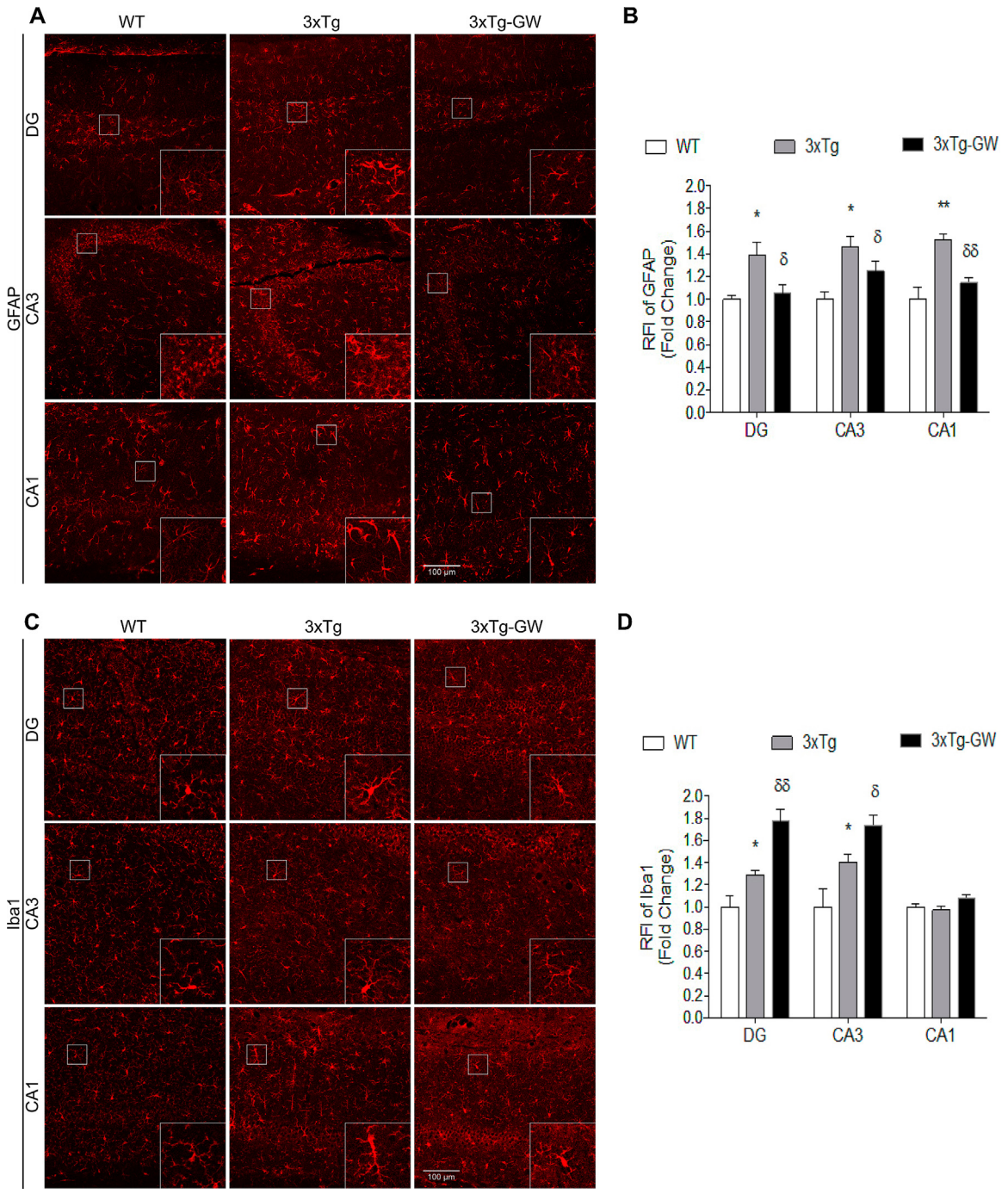

Fig. 1. Short-term treatment with GW3965 reduces GFAP staining in the hippocampus. (A) Immunohistochemistry for GFAP in the Dentate Gyrus (DG), CA3 and CA1 regions of the hippocampus. Images are representative of 3 mice per group. (B) Quantification of the intensity of fluorescence. $^{*}p < 0.05$ and $^{**}p < 0.01$ for WT. δ $p < 0.05$ and δδ $p < 0.01$ for untreated mice. (C) Immunohistochemistry for Iba1 in DG, CA3 and CA1 regions. Images are representative of 3 mice per group. D) Quantification of fluorescence intensity. $^{*}p < 0.05$ for WT; δ $p < 0.05$ and δδ $p < 0.01$ for untreated mice.

of ApoE and LRP1 might accelerate clearance of Aβ species in mice [8].

Activation of Liver X Receptor (LXR) improves cognition in murine models of AD [9]. It increases the expression of ApoE and ABCA1 associated with decrease in Aβ load [10], attenuates neuroinflammation [11], and protects against the detrimental effect of Aβ-oligomers on LTP [12]. In murine models of vascular endothelial damage, LXR agonists (GW3965 or T0901317) promote proliferation and migration of endothelial progenitor cells inducing reendothelialization [13].

This paper analyzes the role of the LXR agonist GW3965 in reversion of BBB changes and astrogliosis in very old 3xTg-AD mice (24 months old) [14,15]. Our results suggest that the hippocampus of treated 3xTg-AD mice increases lectin staining of endothelial cells and that this is associated with increased length of microvasculature, decreased deposition of perivascular Aβ, and decreased GFAP staining. These changes in microvasculature may contribute to the cognitive improvement observed [9].