Neurobiology of Aging 39 (2016) 90–98

Contents lists available at ScienceDirect

Neurobiology of Aging

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

Partial BACE1 reduction in a Down syndrome mouse model blocks Alzheimer-related endosomal anomalies and cholinergic neurodegeneration: role of APP-CTF

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ARTICLE INFO

Article history:
Received 13 July 2015
Received in revised form 17 November 2015
Accepted 23 November 2015
Available online 2 December 2015

Keywords:
Trisomic mice
BACE1
APP-βCTF
Alzheimer's disease
Endosomes
Basal forebrain cholinergic neurons

ABSTRACT

β-amyloid precursor protein (APP) and amyloid beta peptide (Aβ) are strongly implicated in Alzheimer's disease (AD) pathogenesis, although recent evidence has linked APP-βCTF generated by BACE1 (β-APP cleaving enzyme 1) to the development of endocytic abnormalities and cholinergic neurodegeneration in early AD. We show that partial BACE1 genetic reduction prevents these AD-related pathological features in the Ts2 mouse model of Down syndrome. Partially reducing BACE1 by deleting one BACE1 allele blocked development of age-related endosome enlargement in the medial septal nucleus, cerebral cortex, and hippocampus and loss of choline acetyltransferase (ChAT)-positive medial septal nucleus neurons. BACE1 reduction normalized APP-βCTF elevation but did not alter Aβ40 and Aβ42 peptide levels in brain, supporting a critical role in vivo for APP-βCTF in the development of these abnormalities. Although ameliorative effects of BACE1 inhibition on β-amyloidosis and synaptic proteins levels have been previously noted in AD mouse models, our results highlight the additional potential value of BACE1 modulation in therapeutic targeting of endocytic dysfunction and cholinergic neurodegeneration in Down syndrome and AD.

1. Introduction

Endosomes are sites of highly active APP processing, and genes that influence endocytosis are over-represented as Alzheimer's disease (AD) risk factors (Israel et al., 2012; Nixon, 2013). Moreover, abnormalities of neuronal endocytosis, characterized by swelling of rab5-positive early endosomes and upregulated expression of rab5 and other endocytosis-related genes, are the earliest disease-specific response of neurons in AD so far reported (Cataldo et al., 1997). In Down syndrome (DS, Trisomy 21), a cause of early-onset AD has been linked to an extra copy of APP, and these changes appear progressively, beginning before birth (Cataldo et al., 2000). Similar endosomal changes in fibroblasts derived from DS individuals and in neurons of the Ts65Dn mouse model of DS have been shown to represent the pathologic acceleration of endocytosis rate (Cataldo et al., 2008), which is dependent on APP triplication, rab5 activation (Cataldo et al., 2003), and possibly additional triplicated genes on human chromosome 21 (HSA21) (Cossec et al., 2012). Aberrant signaling from abnormal endosomes (Laifenfeld et al., 2007; Salehi et al., 2006) disrupts neurotrophin signaling leading to degenerative changes in cholinergic neurons in DS and AD mouse models (Choi et al., 2013; Salehi et al., 2006). In DS fibroblasts and neuronal APP models of AD, rab5-mediated endosomal dysfunction is driven by an elevated level of APP-βCTF, the product of APP cleavage by β-site APP-cleaving enzyme 1 (BACE1) (Jiang et al., 2010; Choi et al., 2013). APP-βCTF elevation is found in both AD and DS human brains (Kim et al., 2015; Pera et al., 2013).

We dedicate this work to the memory of Dr Anne Cataldo, our colleague and friend, who was a pioneer in describing neuronal endosomal pathology in the brain of Alzheimer's disease and Down syndrome patients. Dr Anne Cataldo passed away on April 13, 2009.

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0197-4580/$ – see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2015.11.013

APP-βCTF has also been shown recently to pathologically activate rab5 by recruiting APPL1 (adaptor protein containing pleckstrin homology domain, phosphotyrosine binding (PTB) domain, and leucine zipper motif), an adaptor protein unrelated to APP, to early endosomes where it binds both APP-βCTF and GTP-rab5 and stabilizes this activated GTP form of rab5 on the endosome. Pathologic rab5 activation enlarges endosomes, which slows their axonal transport in an APPL1-dependent manner (Kim et al., 2015). These findings and others (Choi et al., 2013; Salehi et al., 2006) have increasingly implicated APP-βCTF in the pathogenesis of AD and DS, but so far there is no in vivo validation. Partial BACE1 reduction in a model without β-amyloid deposition enabled the possibility of

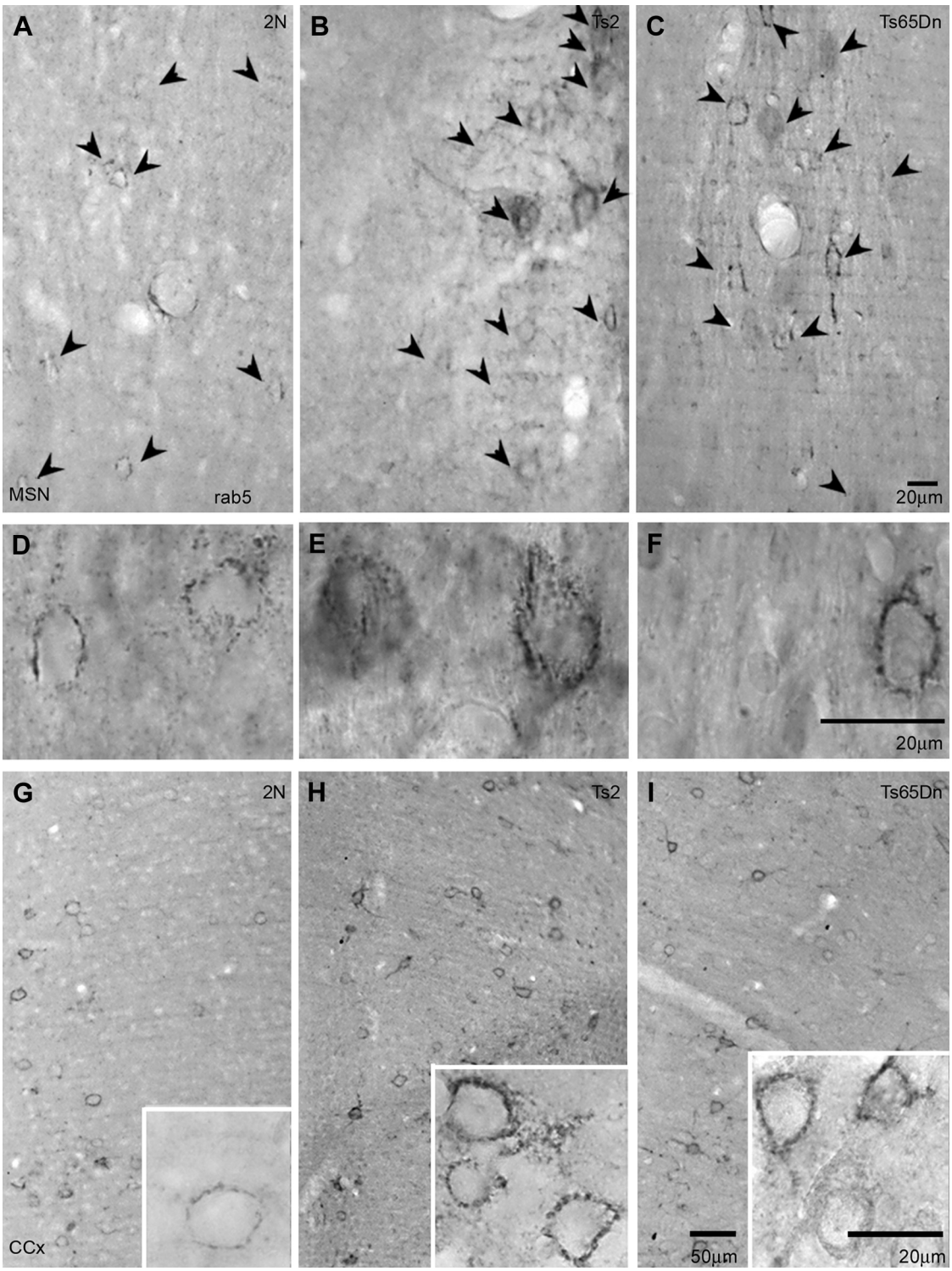

Fig. 1. Ts2 mice display endosomal abnormalities similar to Ts65Dn mice. Representative neurons labeled with anti-rab5 (arrow heads) antibody in the MSN (A–F) and cingulate cortex (G–I) of 9-month old 2N (A, D, G), Ts2 (B, E, H) and Ts65 (C, F, I) mice. rab5-positive early endosomes are enlarged in Ts2 mice (E, H inset) compared to 2N (D, G inset) and resemble those seen in Ts65Dn mice (F, I inset).