Brain Research Bulletin 103 (2014) 18–28

Contents lists available at ScienceDirect

Brain Research Bulletin

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

Review

The dendritic hypothesis for Alzheimer's disease pathophysiology

J. Nicholas Cochran, Alicia M. Hall, Erik D. Roberson*

Center for Neurodegeneration and Experimental Therapeutics, Departments of Neurology and Neurobiology, University of Alabama at Birmingham, Birmingham, AL 35294, United States

ARTICLE INFO

Article history:
Received 6 July 2013
Received in revised form
28 November 2013
Accepted 2 December 2013
Available online 12 December 2013

Keywords:
Postsynaptic
Spine
Amyloid
Tau
Fyn
Calcium

ABSTRACT

Converging evidence indicates that processes occurring in and around neuronal dendrites are central to the pathogenesis of Alzheimer's disease. These data support the concept of a "dendritic hypothesis" of AD, closely related to the existing synaptic hypothesis. Here we detail dendritic neuropathology in the disease and examine how Aβ, tau, and AD genetic risk factors affect dendritic structure and function. Finally, we consider potential mechanisms by which these key drivers could affect dendritic integrity and disease progression. These dendritic mechanisms serve as a framework for therapeutic target identification and for efforts to develop disease-modifying therapeutics for Alzheimer's disease.

This article is part of a special issue Dendrites and Disease.

© 2013 Elsevier Inc. All rights reserved.

Contents

1. Introduction

Alzheimer's disease (AD) affects about five million Americans, and prevalence is rising (Alzheimer's Association, 2010). Current treatments provide only modest benefit against clinical worsening (Geldmacher et al., 2003; Hellweg et al., 2012), so there is considerable interest in identifying new treatments for AD. Extensive investigation of AD neuropathology revealed to Heiko Braak and colleagues that "the outcome of the Alzheimer's disease-related pathological process in general is not primarily determined by massive neuronal loss but, rather, is the result of enormous numbers of surviving nerve cells with limited functionality" (Braak and Del Tredici, 2012). Much of this neuronal dysfunction arises at the synapse. The "synaptic hypothesis" of AD is based on pioneering work by Robert Terry (Terry et al., 1991) and was formulated

* Corresponding author. Tel.: +1 205 996 9486; fax: +1 205 996 9436.
E-mail address: eroberson@uab.edu (E.D. Roberson).

0361-9230/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.brainresbull.2013.12.004

in several excellent and influential reviews (Selkoe, 2002; Tanzi, 2005). Intensive investigation of the synaptic mechanisms underlying AD over the last several years has revealed that many of the key changes in AD and AD models occur on the postsynaptic side of the synapse, in the dendrite. Furthermore, extrasynaptic signaling in dendrites also plays an important role in AD models (Bordji et al., 2010; Li et al., 2011a). As reviewed in other articles in this special issue, we have only recently learned how great a role dendrites play in neuronal signaling and how frequently they are involved in disease. Thus, it is opportune to consider a closely related cousin of the synaptic hypothesis of AD, namely the "dendritic hypothesis" of AD.

Here we provide the results of a systematic review of the literature on the role of dendrites in AD. We searched PubMed for "dendrit* alzheimer*", which returned 1178 results. We reviewed each of these abstracts, and the full text when available, and grouped the publications into categories that are reflected in the organization of the review. In order to narrow our review to the literature most relevant to disease, we focused on pathways that have been validated in human tissue and have been investigated mechanistically in models of AD. Furthermore, we chose to cite excellent reviews for conciseness where possible.

We first summarize the dendritic neuropathological abnormalities seen in human subjects with AD. Next, we examine how Aβ, tau, and AD genetic risk factors affect dendritic structure and function. Finally, we consider potential mechanisms by which these key drivers could intersect to affect dendritic integrity and disease progression. This "dendritic hypothesis" serves as a framework for therapeutic target identification and for ongoing efforts to develop disease-modifying therapeutics for AD.

2. Dendritic pathologies are hallmarks of AD

Before delving into the causative mechanisms and key proteins involved in dendritic pathophysiology in AD, we begin with a brief review of the human neuropathology data. Dendritic abnormalities in AD are widespread and occur in the early stages of the disease. Generally, dendritic abnormalities in AD fall into the following categories: (1) dystrophic neurites, (2) reduction of dendritic complexity, and (3) loss of dendritic spines.

2.1. Dystrophic neurites

Dystrophic neurites were observed in some of the first descriptions of AD pathology (Fischer, 1907; Simchowicz, 1911) (Fig. 1A and D). Dystrophic neurites are misshapen neuritic processes that are immunoreactive with antibodies against abnormal tau, and can arise from either axons or dendrites (Su et al., 1993). Although they sometimes appear as bulbous dilations on silver stains, upon quantitative analysis dendritic dystrophic neurites have normal width but increased curvature compared to normal dendrites, which are fairly straight (Knowles et al., 1999). Dendritic dystrophic neurites are present both in and around amyloid plaques (plaque-associated neuritic dystrophy) and apart from plaques (neuropil threads or neuritic threads). Neuritic threads may originate from aberrant dendritic sprouting (Ihara, 1988).

Two points are important to emphasize regarding dystrophic neurites. First, computational modeling predicts that these changes in dendritic morphology would significantly alter dendritic signal integration and spike timing (Knowles et al., 1999; Le et al., 2001). Second, neuritic dystrophy around plaques is reversible with immunotherapy targeting amyloid-β (Aβ) in a mouse model of AD (Brendza et al., 2005). Indeed, many of the dendritic abnormalities that we will discuss appear to be reversible, an important consideration as therapeutic targets for AD are considered.

Table 1
Factors affecting susceptibility of regions in the hippocampal circuit to reduced dendritic complexity. See Anderton et al. (1998) for details.

	Entorhinal cortex	Dentate gyrus	CA3	CA1	Subiculum
Cell death	√			√	
Afferent loss		√			√
NFT propensity	√			√	√
↓ Dendritic complexity		√		√	√

2.2. Reduced dendritic complexity

The second major dendritic abnormality seen in AD is reduced dendritic complexity (Fig. 1B and E; reviewed in Anderton et al. (1998)). Reduced dendritic complexity is prominent in dentate granule cells (de Ruiter and Uylings, 1987; Flood et al., 1987a) and in pyramidal neurons in hippocampal area CA1 and subiculum (Flood, 1991; Hanks and Flood, 1991). Of note, there is no reduction of dendritic complexity in CA3 neurons (Flood et al., 1987b). Two factors probably contribute to this selective vulnerability: afferent supply and propensity to form neurofibrillary tangles (NFTs) (Table 1; ref (Anderton et al., 1998)). Anderton et al. (1998) propose that reduced dendritic complexity in dentate granule cells is driven by loss of afferents caused by widespread loss of entorhinal cortex neurons in AD (Braak et al., 1993; Gomez-Isla et al., 1996). Dentate granule cells are relatively spared from cell death in AD (West et al., 1994), which explains the sparing of dendritic complexity of CA3 neurons, since dentate granule cells provide their primary afferent supply. However, CA3 pyramidal neurons are also resistant to neuronal death in AD, which would predict sparing of most afferents onto CA1 pyramidal neurons. Thus, another factor is necessary to explain the widespread reduction of dendritic complexity in area CA1, which Anderton et al. propose is due to the high propensity of CA1 neurons to form NFTs. Finally, loss of dendritic complexity in subicular pyramidal cells is likely a result of both the loss of afferents from CA1 and NFT propensity (Anderton et al., 1998).

The association between NFT propensity and dendritic complexity is consistent with the hypothesis that somatodendritic accumulation of tau plays a key role in AD pathogenesis (see Section 4). But do NFTs directly cause dendritic pathology or are they simply a marker of a more toxic process? A study comparing several measures of dendritic complexity in tangle-bearing vs. non-tangle neurons in the same AD patients showed that dendritic trees were >50% larger in tangle-bearing neurons than in non-tangle bearing neurons (Gertz et al., 1987). This is somewhat counter-intuitive unless the toxic species is soluble tau, not NFTs, and the NFTs sequester soluble tau and thus provide some degree of protection. *In vivo* imaging supports this idea, showing that NFTs form in neurons in response to toxic events and tangle-bearing neurons are long-lived relative to neurons that do not form tangles (de Calignon et al., 2010). A similar observation was made in neurons expressing mutant huntingtin; neurons that form huntingtin inclusion bodies are actually protected and soluble huntingtin appears to be toxic (Arrasate et al., 2004). A recent review summarized the evidence for and against toxicity of various forms of tau with the same conclusion: a soluble form of tau is likely the most toxic (Cowan and Mudher, 2013). This has been corroborated by a recent report specifically implicating oligomeric forms of tau as toxic (Blair et al., 2013). Therefore, therapeutic strategies should be focused on pathways involving soluble forms of tau.

2.3. Spine loss

A marked loss of dendritic spines is the final major dendritic abnormality in AD patients (Fig. 1C and F). Specifically, widespread spine loss is seen in pyramidal neurons in both the cortex and

Download English Version:

https://daneshyari.com/en/article/4318833

Download Persian Version:

https://daneshyari.com/article/4318833

Daneshyari.com