ELSEVIER

Cell Calcium 38 (2005) 427–437

cell calcium

www.elsevier.com/locate/ceca

Calcium dysregulation in Alzheimer's disease: Recent advances gained from genetically modified animals

Ian F. Smith, Kim N. Green, Frank M. LaFerla *

Department of Neurobiology and Behavior, University of California, 1109 Gillespie Neuroscience Building, Irvine CA 92697-4545, USA

Received 20 June 2005; accepted 28 June 2005

Abstract

Alzheimer's disease is a progressive and irreversible neurodegenerative disorder that leads to cognitive, memory and behavioural impairments. Two decades of research have implicated disturbances of intracellular calcium homeostasis as playing a proximal pathological role in the neurodegeneration associated with Alzheimer's disease. A large preponderance of evidence has been gained from the use of a diverse range of cell lines. Whilst useful in understanding the principal mechanism of neurotoxicity associated with Alzheimer's disease, technical differences, such as cell type or even the form of amyloid-beta used often underlie conflicting results. In this review, we discuss recent contributions that transgenic technology has brought to this field. For example, the triple transgenic mouse model of Alzheimer's disease has implicated intraneuronal accumulation of the amyloid-beta peptide as an initiating factor in synaptic dysfunction and behavioural deficits. Importantly, this synaptic dysfunction occurs prior to cell loss or extracellular amyloid plaque accumulation. The cause of synaptic dysfunction is unknown but it is likely that amyloid-beta and its ability to disrupt intracellular calcium homeostasis plays a key role in this process.

Keywords: Alzheimer's disease; Calcium dysregulation; Presenilin; Amyloid; Alzheimer's; Transgenic

1. Introduction

Alzheimer's disease (AD) is the most common form of age-related dementia in the elderly. Unfortunately, as the average age of our population continues to increase, there is also a concomitant rise in the number of people afflicted with this debilitating disorder. Currently, it is estimated that one in 10 persons over 65, and more than a third of all people over 80 have AD. According to United Nations population projections, it is estimated that 370 million people will be older than 80 years by 2050 [1]. The aging of the world's population, therefore, will potentially pose an immense social and economic burden on future societies as this susceptible cohort continues to rapidly expand. Thus, a better understanding of the molecular events underlying AD will no doubt prove invaluable for combating this affliction.

Alois Alzheimer first described the pathological hallmarks of this disorder in 1906, observing strange alterations of the neurofibrils and foci, which were built up by a "peculiar substance" [2]. Our understanding of the molecular signatures of these hallmark lesions have been refined since his initial description. We now appreciate that neuritic and diffuse senile plaques are composed primarily of a small peptide called β-amyloid (Aβ), whereas the intracellular neurofibrillary tangles are composed of aggregates of hyperphosphorylated tau protein. The neuritic (or senile) plaques are dense deposits of Aβ around which dystrophic neuronal cell processes are observed. Plaques are generally noted within various parts of the brain but are especially abundant within the cerebral cortex, hippocampus and amygdala [3]. It is the gradual build-up of Aβ that is generally believed to account for the onset of this form of dementia [4]. Strong support

* Corresponding author. Tel.: +1 949 824 1232; fax: +1 949 824 7356.
E-mail address: laferla@uci.edu (F.M. LaFerla).

0143-4160/$ – see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ceca.2005.06.021

for this hypothesis comes from human genetic data although recent advances in transgenic models have also provided critical corroborating evidence [5–7]. The preponderance of evidence supports a role for Aβ as the initial trigger of this disease in a process known as the amyloid cascade hypothesis. However, even though Aβ may trigger all forms of this disease, it should not preclude investigating and understanding other molecular and cellular aspects of AD even if they lie downstream of Aβ. In this regard calcium dysregulation, for example, represents a critical molecular defect that potentially can be attenuated with appropriate therapies. Moreover, it is interesting to note that Aβ and tau can both be influenced by calcium dysregulation, and alternatively the accumulation of these lesions can perturb calcium regulation. The point of this article is not to exhaustively review the entire body of literature concerned with calcium and AD but to focus on recent data generated using in vivo models. Here, we discuss advances in understanding the role of calcium dysregulation in AD with particular emphasis on the contribution of genetically modified animals. For a more comprehensive review we refer the reader to a recent review [8].

2. APP processing

Before we describe the evidence for calcium dysregulation in AD, it is critical to understand the process by which Aβ is generated and the influence that mutations have on the processing of amyloid precursor protein (APP). Aβ is generated by the sequential cleavage of APP, a type I integral membrane protein anchored to the plasma membrane and internal membranes of the ER, Golgi and trans-Golgi apparatus. Aβ is generated in very small quantities in normal healthy individuals and does not typically build up to very high levels [9]. However, in individuals afflicted with AD, differential processing of APP or the failure to degrade Aβ leads to its excessive accumulation.

Endoproteolysis of APP is achieved by the sequential cleavage by groups of enzymes or enzyme complexes termed α-, β-, and γ-secretases. For α-secretase there are currently two members of the ADAM family (a disintegrin and metalloproteinase-family) of proteases, ADAM-10, and ADAM-17, the latter of which is also referred to as tumour necrosis factor α converting enzyme (or TACE), that have been suggested as likely candidiates [10,11]. Several groups

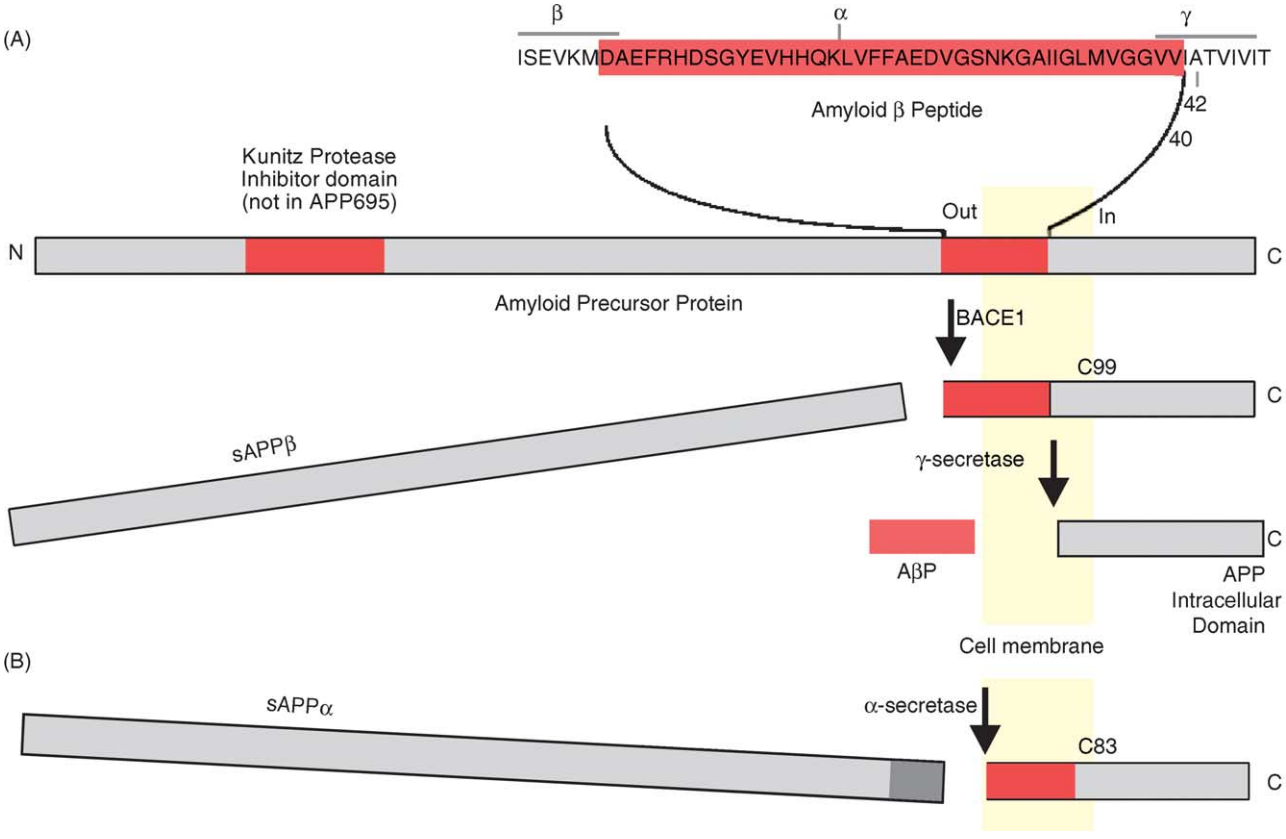

Fig. 1. Proteolytic processing of the amyloid precursor protein (APP). (A) Amyloidogenic processing of APP leads to the liberation of the 4 kDa Aβ peptide. For this to occur, APP must first be cleaved by BACE which releases a large ectodomain called sAPPβ whereas the remaining 99 amino acid carboxy terminal (C99) is retained within the membrane. Subsequent cleavage of C99 by the γ-secretase complex leads to the liberation of the Aβ peptide. (B) Non-amyloidogenic processing of APP precludes Aβ formation. Enzymatic cleavage of APP by α-secretase cleaves APP within the Aβ region of APP and thus precludes its formation. α-secretase cleavage liberates a large ectodomain called sAPPα, which is released into the extracellular space, whereas an 83 amino acid stub, C83, is retained within the membrane and can be further processed by γ-secretase (not shown). The vast majority of APP is processed in the non-amyloidogenic pathway.