European Journal of Pharmacology ■ (■■■■) ■■■–■■■

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmacology

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

Review

Trafficking in neurons: Searching for new targets for Alzheimer's disease future therapies

Q1 Stefano Musardo [a,b,1], Claudia Saraceno [a,b,1], Silvia Pelucchi [a,b], Elena Marcello [a,b,*]

Q2 [a] Università degli Studi di Milano, Dipartimento di Scienze Farmacologiche e Biomolecolari, via Balzaretti 9, 20133 Milano, Italy
[b] Università degli Studi di Milano, Centre of Excellence on Neurodegenerative Diseases, via Balzaretti 9, 20133 Milano, Italy

ARTICLE INFO

Article history:
Accepted 11 July 2013

Keywords:
Alzheimer's disease
Amyloid β
Amyloid precursor protein
Secretase

ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia and no cure is available at the moment. As the disease progresses, patients become increasingly dependent, needing constant supervision and care. Prevention or delay of AD onset is among the most urgent moral, social, economic and scientific imperatives in industrialized countries. A better understanding of the pathogenic mechanisms leading to the disease and the consequent identification of new pharmacological targets are now a need. One of the most prominent molecular events occurring in AD patients' brains is the deposition of a peptide named amyloid-β (Aβ). Aβ derives from the concerted action of β-secretase, which mediates the amyloid precursor protein (APP) shedding at Aβ N-terminus, and γ-secretase, responsible for APP C-terminal stub cleavage. The production of Aβ can be prevented by the cleavage of ADAM10 on APP. In regard of AD pathogenesis, it is notable that neurons are the cell type affected in AD and that APP and the secretases are all integral transmembrane proteins, and so they are dynamically sorted in neurons. Therefore, neuronal sorting mechanisms responsible for APP and the secretases colocalization in the same membranous compartment play important roles in the regulation of Aβ production. In light of these considerations, this review provides an overview on the actual knowledge of the trafficking mechanisms involved in the regulation of APP and secretases localization, paying particular attention to the specific neuronal setting.

Contents

* Corresponding author at: Università degli Studi di Milano, Dipartimento di Scienze Farmacologiche e Biomolecolari, via Balzaretti 9, 20133 Milano, Italy. Tel.: +39 02 50318314.
E-mail address: elena.marcello@unimi.it (E. Marcello).
[1] These authors contributed equally to this work.

0014-2999/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ejphar.2013.07.019

1. Introduction

Alzheimer's disease (AD) is the largest unmet medical need in neurology, even though it is placing a considerable and increasing burden on patients, caregivers and society, as more people live long enough to become affected. Current drugs improve symptoms, but do not have profound disease-modifying effects.

AD is a progressive neurodegenerative disorder characterized by impairment of memory and cognitive function. Initially mild cognitive impairment and deficits in short-term and spatial memory appear, but the symptoms become more severe with disease progression, eventually culminating in loss of executive function.

The underlying neuropathology includes extracellular deposition of amyloid-β peptide (Aβ), intraneuronal accumulation of aberrant forms of hyperphosphorylated tau (Glenner and Wong, 1984) as well as synapse dysfunction and neuronal loss (Selkoe, 2001a). Genetic and cell biological studies led to the amyloid hypothesis, which posits that Aβ plays a pivotal role in AD pathogenesis (Hardy and Selkoe, 2002). Therefore, the basic biochemical formula for Aβ production was established in minute details to determine the etiology of the disease. The Aβ domain is located within the type I transmembrane amyloid precursor protein (APP) at the junction between the intraluminal and transmembrane domains. Two enzymatic steps liberate Aβ from APP. In the first, "β-cleavage" step, β-site APP-cleaving enzyme (BACE-1) (Vassar et al., 1999), cleaves APP at or near the N-terminus of the Aβ peptide; then, in the second, or "γ-cleavage" step, the membrane-bound C-terminal APP fragment (CTF) generated by BACE-1 goes on to be cleaved by the γ-secretase, a multimeric complex thought to be made up of an essential quartet of transmembrane proteins—presenilin 1 (or 2), nicastrin, anterior pharynx-defective phenotype 1 (APH-1) and PS-enhancer 2 (PEN-2) (Edbauer et al., 2003) (Fig. 1). Alternatively, APP can be subjected to the proteolytic cleavage by α-secretase, which occurs within the sequence of Aβ, thus precluding the formation of the amyloidogenic fragments. α-Secretase gives rise to the secretion of the neuroprotective sAPPα fragment and to a C-terminal stub that is then cleaved by γ-secretase (Fig. 1). Two recent studies finally demonstrated that the constitutively cleaving α-secretase activity is selectively mediated by a disintegrin and metalloproteinase 10 (ADAM10) (Jorissen et al., 2010; Kuhn et al., 2010), a member of the ADAM family, which are the key components in protein ectodomain shedding.

We must not forget that neurons are the cell type affected in AD, thus representing the setting where AD pathogenesis takes place and the most reliable cellular model. Colombo et al. (2012) have demonstrated the importance of studying APP processing in neurons: they showed that the inverse coupling of the endogenous α- and β-secretase cleavages depends on the cellular model, highlighting differences between cell lines and neuronal cultures.

Furthermore, it has been shown that in neurons the mechanisms regulating synaptic functioning can affect amyloid cascade and, conversely, amyloid production can influence neuronal activity. Indeed, Aβ oligomers have been described as the earliest effectors to negatively affect postsynaptic structure and plasticity of the excitatory glutamatergic synapse (Walsh et al., 2002). On the other hand, a variety of evidence suggests that Aβ levels and metabolism may be modulated in some way by the neuronal activity determining the levels of extracellular Aβ (Kamenetz et al., 2003).

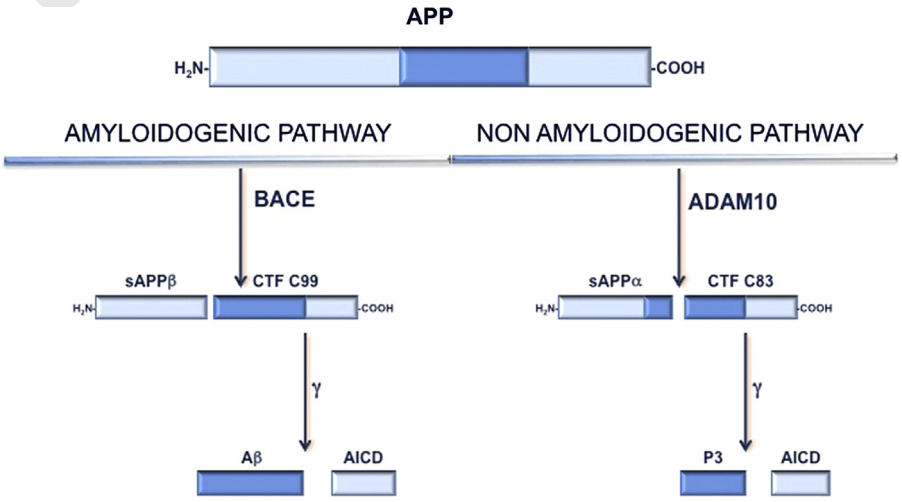

Fig. 1. Schematic representation of APP metabolism. APP is sequentially cleaved by β-secretase (BACE-1), which mediates the APP shedding at Aβ N-terminus, and γ-secretase, responsible for APP C-terminal stub cleavage; alternatively APP can be subjected to the proteolytic cleavage by α-secretase (ADAM10), which prevents Aβ production, giving rise to the secretion of the sAPPα fragment and to a C-terminal stub, then cleaved by the γ-secretase.