Biochemical Pharmacology 88 (2014) 486–494

Contents lists available at ScienceDirect

Biochemical Pharmacology

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

Review - Part of the Special Issue: Alzheimer's Disease - Amyloid, Tau and Beyond

Alzheimer's disease therapeutics targeted to the control of amyloid precursor protein translation: Maintenance of brain iron homeostasis

Sanghamitra Bandyopadhyay, Jack T. Rogers *

Neurochemistry Laboratory, Department of Psychiatry-Neuroscience, Massachusetts General Hospital (East), Charlestown, MA 02129, United States

ARTICLE INFO

Article history:
Received 5 November 2013
Received in revised form 16 January 2014
Accepted 22 January 2014
Available online 7 February 2014

Keywords:
Alzheimer's disease
Amyloid precursor protein
Brain iron homeostasis

ABSTRACT

The neurotoxicity of amyloid beta (Aβ), a major cleavage product of the amyloid precursor protein (APP), is enhanced by iron, as found in the amyloid plaques of Alzheimer's disease (AD) patients. By contrast, the long-known neuroprotective activity of APP is evident after α-secretase cleavage of the precursor to release sAPPα, and depends on the iron export actions of APP itself. The latter underlie its neurotrophic and protective effects in facilitating the homeostatic actions of ferroportin mediated-iron export. Thus APP-dependent iron export may alleviate oxidative stress by minimizing labile iron thus protecting neurons from iron overload during stroke and hemorrhage. Consistent with this, altered phosphorylation of iron-regulatory protein-1 (IRP1) and its signaling processes play a critical role in modulating APP translation via the 5′ untranslated region (5′UTR) of its transcript. The APP 5′UTR region encodes a functional iron-responsive element (IRE) RNA stem loop that represents a potential target for modulating APP production. Targeted regulation of APP gene expression via the modulation of 5′UTR sequence function represents a novel approach for the potential treatment of AD since altering APP translation can be used to improve both the protective brain iron balance and provide anti-amyloid efficacy. Approved drugs including paroxetine and desferrioxamine and several novel compounds have been identified that suppress abnormal metal-promoted Aβ accumulation with a subset of these acting via APP 5′UTR-dependent mechanisms to modulate APP translation and cleavage to generate the non-toxic sAPPα.

Contents

* Corresponding author.
E-mail address: jrogers@partners.org (J.T. Rogers).

0006-2952/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bcp.2014.01.032

1. Introduction

Extracellular amyloid beta (Aβ) plaques and intraneuronal neurofibrillary tangles are the predominant histopathological hallmark lesions of Alzheimer's disease (AD), which is the most common form of dementiating disorder, predicted to affect approximately 65 million individuals by 2030 [1,2]. The "amyloid hypothesis" of AD specifies a deposition of pre-plaque Aβ in the brain as a primary factor in AD causality. Briefly, generation of Aβ is dependent on the processing of amyloid precursor protein (APP), the pivotal protein involved in AD pathology [3]. APP (predominant 695, 751, 770 amino acid isoforms in the brain) is post-translationally processed via amyloidogenic or non-amyloidogenic pathways that involve pathological and physiological functions, respectively [4].

Key factors underlying Aβ pathogenicity through dysregulated processing of APP include the switch from the non-amyloidogenic to the amyloidogenic pathway, where β-secretase (BACE) cleaves APP at the 1st or 11th residue of the Aβ peptide sequence (Fig. 1), resulting in sAPPβ and a C-terminal 99mer (C99). The γ-secretase, composed of presenilins (PS), cleaves the β-stub to generate the APP intracellular domain (AICD) and amyloidogenic Aβ40 and Aβ42 [5] that can form neurotoxic amyloid fibrils in the brain. The alternative pathway prevents formation of Aβ in the event of cleavage by an α-secretase at the 17th amino acid within 40–42 amino acid 'Aβ' to release neurotrophic sAPPα and the 83mer C terminal fragment (CTF)α [6]. CTFα is further cleaved by γ-secretase to generate the non-amyloidogenic P3 peptide and AICD, both of which are internalized and degraded.

In the present review, novel RNA-based approaches are described that have the potential to limit amyloid production and thus may represent a unique approach to AD therapy. This strategy is an alternative to current amyloid targeted drugs, that while showing promise in animal models, have repeatedly failed in clinical trials [7].

Aβ cannot always be regarded as a purely deleterious entity. Thus Aβ40 and Aβ42 were found to attenuate paralyzing brain inflammation in models of experimental autoimmune encephalomyelitis (EAE), that included models of chronic progressive disease, relapsing remitting disease, adoptive Th1 transfer, and adoptive Th17 transfer [8]. Aβ40 and Aβ42 suppressed the proliferation capacity and cytokine secretion of activated lymphocytes that penetrated and damaged the CNS during EAE, reducing inflammation in lymphoid tissues and CNS parenchyma indicating that the beneficial and pathological roles of Aβ are dependent on whether the inflammation arises from secondary lymphoid tissues or the glial-rich microenvironment surrounding senile plaques [8].

The failure of anti-amyloid therapies that target γ-secretase [9] and Aβ vaccine in clinical trials has generated considerable interest in discovering safer and more effective alternatives [10]. The work described below is focused on the development of RNA targeting approaches to block APP translation. In the present review strategies to assess the interaction of compounds with APP 5′ untranslated region (APP 5′UTR), that reduce amyloid production and may optimize brain iron balance, a result of the iron export protein actions of APP [11], are described in the context of the control of APP translation by iron-regulatory protein 1 (IRP1) [12].

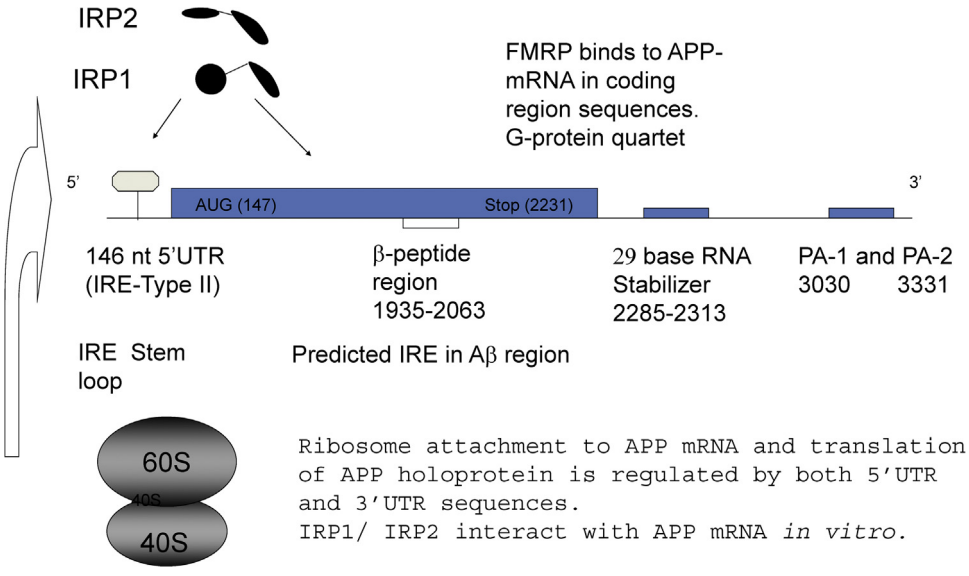

Fig. 1. RNA regulatory domains in the APP transcript. The 3 kb APP transcript is controlled at the level of message translation by the action of 5′UTR regulatory domains that are responsive to IL-1 and iron. The 3′ untranslated region is alternatively polyadenylated, and the longer APP transcript is translated more efficiently than the shorter transcript. A 29 nt RNA destabilizing element was mapped to the 3′UTR of APP mRNA. A second IRE-like RNA sequence is depicted in the Aβ domain of the APP coding region, and the Fragile X mental retardation protein (FMRP) is a cytoplasmic mRNA binding protein that binds to downstream segment of the coding region of APP mRNA at a guanine-rich, G-quartet-like sequence. IL-1 co-induces APP mRNA translation and α-secretase cleavage in the APP Aβ domain where this primary inflammatory cytokine induces the non-amyloidogenic secretion of APP(s) from astrocytes.