FEBS Letters 587 (2013) 2046–2054

journal homepage: www.FEBSLetters.org

Review

The amyloid precursor protein: A biochemical enigma in brain development, function and disease

Natalia N. Nalivaeva [a,b], Anthony J. Turner [a,*]

[a] School of Molecular and Cellular Biology, Faculty of Biological Sciences, University of Leeds, Leeds LS2 9JT, UK
[b] I.M. Sechenov Institute of Evolutionary Physiology and Biochemistry, RAS, St. Petersburg, Russia

ARTICLE INFO

Article history:
Received 22 April 2013
Revised 6 May 2013
Accepted 6 May 2013
Available online 16 May 2013

Edited by Alexander Gabibov, Vladimir Skulachev, Felix Wieland and Wilhelm Just

Keywords:
Amyloid precursor protein
APP intracellular domain (AICD)
Histone deacetylase
Hypoxia
Mediator
Neprilysin

ABSTRACT

For 20 years the amyloid cascade hypothesis of Alzheimer disease (AD) has placed the amyloid-β peptide (Aβ), formed from the amyloid precursor protein (APP), centre stage in the process of neurodegeneration. However, no new therapeutic agents have reached the clinic through exploitation of the hypothesis. The APP metabolites, including Aβ, generated by its proteolytic processing, have distinct physiological functions. In particular, the cleaved intracellular domain of APP (AICD) regulates expression of several genes, including APP itself, the β-secretase BACE-1 and the Aβ-degrading enzyme, neprilysin and this transcriptional regulation involves direct promoter binding of AICD. Of the three major splice isoforms of APP (APP_{695}, APP_{751}, APP_{770}), APP_{695} is the predominant neuronal form, from which Aβ and transcriptionally-active AICD are preferentially generated by selective processing through the amyloidogenic pathway. Despite intensive research, the normal functions of the APP isoforms remain an enigma. APP plays an important role in brain development, memory and synaptic plasticity and secreted forms of APP are neuroprotective. A fuller understanding of the physiological and pathological actions of APP and its metabolic and gene regulatory network could provide new therapeutic opportunities in neurodegeneration, including AD.

1. Introduction

Alzheimer's disease (AD) and related dementias constitute a spectrum of age-related neurodegenerative diseases leading to major cognitive and behavioural deficits. AD is a global problem affecting over 30 million people worldwide and some 10 million in Europe alone with lesser developed countries predicted to harbour 70% of dementia cases over coming decades, creating a rapidly growing epidemic. It is now just over 20 years since the amyloid cascade hypothesis was formulated to provide a framework for explaining the biochemical mechanisms underlying the neurodegenerative processes occurring in Alzheimer's disease and for the design of potential therapeutics [1]. The hypothesis places the 40–42 amino acid, amyloid β-peptide (Aβ), derived by proteolytic processing of the membrane glycoprotein amyloid precursor protein (APP), centre stage in the cell death process. Recent reappraisals of the hypothesis have, however, highlighted that Aβ-independent factors may also contribute to the disease process and that oligomeric forms of Aβ may be the principal toxic agents [2–4]. Furthermore, no new therapeutic agents have reached the clinic based on exploitation of the amyloid cascade hypothesis [5]. A variety of factors probably contribute to this, especially the limitations in the animal models currently available, which are based on the rare, familial forms of the disease, and the heterogeneity of the late-onset forms of AD. We, and others, have hence emphasised that a major unmet scientific need in the AD field is to understand completely the normal biochemistry of APP, and the physiological roles of its key metabolites, in order to clarify what is happening in the disease situation. Indeed, APP is more than just an "amyloid precursor" but is expressed ubiquitously as a type I membrane glycoprotein and has specific biochemical and pathological roles in other tissues which are generally ignored since its historic origins unsurprisingly led to a predominant focus on AD-related mechanisms. For example, APP is a primary androgen target gene that promotes prostate cancer growth and which is up-regulated also in colon and pancreatic tumours implying a general role for the protein in cell growth, differentiation and carcinogenesis [6,7].

2. APP isoforms and metabolism

APP is expressed in both neuronal cells and extra-neuronal tissues [8] and belongs to a larger evolutionarily conserved APP superfamily found in diverse organisms from nematode to man

* Corresponding author.
E-mail addresses: n.n.nalivaeva@leeds.ac.uk (N.N. Nalivaeva), a.j.turner@leeds.ac.uk (A.J. Turner).

0014-5793/$36.00
http://dx.doi.org/10.1016/j.febslet.2013.05.010

[9] which, in mammals, consists of APP itself and APP-like proteins APLP1 and APLP2 (Fig. 1). In *Drosophila melanogaster* and *C. elegans* their APP homologues have been named APPL and APL-1, respectively [10,11]. In, neuronal cells, it is anterogradely transported in vesicles by kinesin-mediated fast transport to various cell compartments including synapses [12], reviewed in [13]. There are three major isoforms of APP (APP_{695}, APP_{751}, APP_{770}) generated as a result of alternative splicing of exons 7 and 8. Compared with APP_{695}, the APP_{751} isoform contains an additional Kunitz-type protease inhibitor (KPI) domain and the 770 isoform also contains a 19-amino acid, OX-2 domain. APLP2 more closely resembles APP_{770} in domain composition whereas APLP1 is more similar to APP_{695} (Fig. 1). In brain, APP_{695} is principally neuronal and is expressed at relatively high levels compared with the other two isoforms. In human cortex the ratio of different APP isoform mRNAs is approx $APP_{770}/APP_{751}/APP_{695}$ = 1:10:20, although there are regional differences. In AD brain the various isoforms show different temporal- and disease-specific expression implying they exert distinct functional and metabolic roles [14,15]. Until recently, no clearcut functional differences have been ascribed to the different APP isoforms apart from the protease-inhibitory role of the KPI domain. However, it appears that the neuronal APP_{695} isoform is preferentially involved in regulation of gene expression [16], as detailed in Section 6.

APP isoforms were shown to be differentially expressed during brain maturation [17] and alternative splicing and processing of the APP gene was found to be regulated by various factors, including hormones, growth factors, phorbol esters and interleukins [18–20]. The regulatory region of the APP gene contains consensus sites recognised by the transcription factor, specificity protein 1 (SP1) [21]. Recently microRNAs, which represent small, non-coding RNAs interacting with target mRNA and mediating translational inhibition or transcript destabilisation, were suggested to regulate APP gene expression and to play an important role in neurodegeneration [22]. In particular miR-101 and miR-153 were shown to down-regulate expression of APP in human cell cultures suggesting their relevance to AD pathology [23,24].

APP is expressed in various organs and tissues. Northern blot analysis has demonstrated that, in rat, endogenous APP mRNA is expressed significantly more in the brain, kidney and lung compared to heart and liver. A similar APP expression pattern was also seen when the human APP transgene, driven by the ubiquitin-C promoter, was introduced to the animals aiming at producing a rat model of AD. The tissue specificity of APP expression suggests the presence of regulatory elements within the cDNA sequence of APP determining the character of its expression [25]. However,

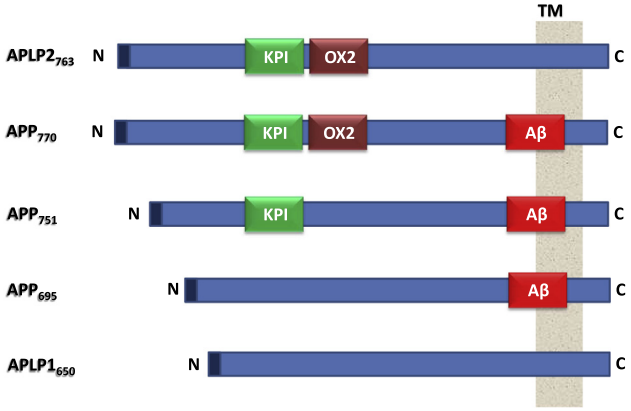

Fig. 1. Schematic representation of the proteins from the APP family and their main domains. They are all type I transmembrane glycoproteins. APLP1 and APP_{695} both lack the KPI and OX2 domains, contained in APLP2 and APP_{770} while APP_{751} has only the KPI domain.

there are some data suggesting that membrane localisation and processing of APP in neurones differ from those in peripheral cells (e.g., lymphoid cells, hepatocytes or kidney) which suggests that functioning of this transmembrane holoprotein and production of Aβ in the brain is a critical determinant of its receptor-transducer properties unique to this organ [26]. Abnormal APP metabolism in the pancreas is also linked to the pathogenesis of type 2 diabetes and strong epidemiological evidence suggest a link between diabetes and AD [27] and AD has been referred to as type 3 diabetes [28].

Despite APP from various species being characterised by a rather significant conservative amino acid sequence, rodent APP in the region of Aβ peptide differs from human by 3 amino acids (Arg^5 is substituted by Gly, Tyr^{10} by Phe and His^{13} by Arg) which makes rodent Aβ less prone to form amyloid aggregates [29]. As recently suggested, His^{13} in Aβ peptide is critical for the ability of the peptide to bind Zn which is required for initiation of fibrillogenesis [30]. Because of this difference in the Aβ peptide structure, rodent models of AD require the over-expression of human APP and/or other proteins involved in human AD pathology, which brings some limitations to the utilisation of mouse and rat models of AD for a full understanding of the pathology of this human disease. Furthermore, there is also a proteolytic processing difference between species, as the sequence differences in mouse versus human APP also protect against β-secretase processing [31].

Platelet and leukocyte APP isoforms are processed using mechanisms similar to those in neuronal cells to generate Aβ and soluble forms of APP [32]. They therefore potentially provide a peripheral model of APP biochemistry and perhaps a mirror into abnormalities in APP processing in the brain. In the transition from normal to mild cognitive impairment to AD, a small but significant shift in the ratio of platelet APP isoforms from the larger to the smaller forms has been consistently observed [33–35] and has been suggested as a possible AD biomarker. However, when utilising extra-neuronal cells as models for studying APP metabolism and its effects, interpretation of data may be influenced by the nature of the isoforms endogenously expressed in these cells.

3. APP processing

There are two divergent pathways of APP metabolism occurring naturally (Fig. 2), of which the minor (amyloidogenic) pathway involves the consecutive actions of two membrane-bound aspartic proteinases generically termed β- and γ-secretases [36,37]. This pathway generates not only Aβ but a number of other physiologically active metabolites, including the cleaved intracellular domain (AICD), which could all contribute to, or ameliorate, the pathological processes leading to AD. More than 90% of APP metabolism, however, normally involves the initial alternative cleavage of APP by a zinc metalloproteinase termed α-secretase followed again by γ-secretase. Since α-secretase cleaves APP within the Aβ peptide region, it prevents Aβ formation and activation of this pathway is hence potentially neuroprotective. Some recent data suggest that subcellular trafficking of APP to the non-amyloidogenic pathway is regulated by huntingtin associated protein-1 (HAP-1) since down-regulation of the latter in neurons results in increased production and accumulation of Aβ [38].

The γ-secretase mediated cleavage of APP C-terminal membrane-bound fragments formed after α- or β-secretase action on the holoprotein is but one example of the general phenomenon of intramembrane proteolysis [39,40] and is analogous to the cleavage of the Notch receptor in the Notch signalling pathway. The γ-secretase complex with its catalytic presenilin (PS) core functions as a promiscuous aspartic protease able to act on a diverse range of membrane protein substrates and showing flexibility in its site of cleavage of susceptible substrates. These