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EDITORIAL

The physiological functions of the β-amyloid precursor protein APP

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Introduction

The reviews and research articles compiled in this Special Issue of *Experimental Brain Research* (*EBR*) focus on the physiological functions of the amyloid precursor protein (APP) gene family in the nervous system. They look at APP from a new perspective and report data on the physiological rather than pathological functions of this protein and other members of the APP gene family. Since APP and APP family members appear to play an important role in pathways protecting or maintaining normal function, lack of APP may contribute to some of the symptoms seen in Alzheimer's disease (AD). At present, however, the evidence for such an essential role of APP in normal brain function is incomplete and much work needs to be done to fully understand its role in physiology. The need for this work has also been recognized by the Deutsche Forschungsgemeinschaft (DFG), which established the research unit FOR1332 on the "Physiological Functions of the APP Gene Family in the Central Nervous System" in 2010. Groups in this research unit as well as other groups working on APP around the globe have been asked to contribute to this Special Issue to draw the interest of the scientific community to this hot topic in the neurosciences. The positive response we have received from our colleagues to our "call for papers" has convinced us further that research into the physiological functions of APP and its family members is a topic of general interest in the field. We thank all contributors and the editors of *EBR* for their enthusiastic support in the preparation of this Special Issue.

APP and Alzheimer's disease

It is well known that proteolytic processing of APP gives rise to the β-amyloid peptide (Aβ) that is deposited in the brains of patients suffering from AD, affecting more than 25 million people worldwide. AD constitutes the most common form of late-onset dementia, and delineating the underlying pathogenic mechanisms will be crucial for the development of new therapeutic strategies. AD is pathologically characterized by a reduction in synaptic contacts, correlating with impairments in memory and higher cognitive function (DeKosky and Scheff 1990). In addition, the brains of AD patients exhibit neurofibrillary tangles mainly composed of hyperphosphoryraled τ and extracellular neuritic plaques mainly composed of Aβ aggregates. Since the molecular cloning of APP, more than 20 years ago (Kang et al. 1987; Tanzi et al. 1987; Goldgaber et al. 1987), a large body of biochemical and genetic evidence has accumulated that firmly established Aβ as a central trigger for AD pathogenesis. Despite this, the physiological role of APP and the question of whether a loss of its functions contributes to AD are still unclear. The enzymes involved in APP processing and Aβ generation (termed

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secretases) have been cloned and have since then become major therapeutic targets. However, as APP processing occurs in virtually all cells and can be regarded as part of normal cell metabolisms (Haass et al. 1992), therapeutic interference with APP processing is likely to alter physiological APP functions and may compromise APP-dependent signaling pathways. Moreover, there is a growing body of evidence suggesting that not only Aβ accumulation but also a reduction in other APP processing products, in particular the secreted APPsα ectodomain, plays a critical role in memory dysfunction associated with AD. Thus, there is an urgent need for a more detailed understanding of the functional consequences of altered levels and activity of full-length APP and its various proteolytic fragments in CNS physiology.

Proteolytic processing of APP

APP is an integral type I transmembrane protein with a single transmembrane domain, a large extracellular ectodomain and a short cytoplasmic tail (Fig. 1). Processing is initiated either by the cleavage of APP by α-secretase within the Aβ region or by cleavage by β-secretase (BACE) at the N-terminus of Aβ, leading to the secretion of large soluble ectodomains, termed APPsα and APPsβ, respectively. Subsequent processing of the C-terminal fragments (CTFα or CTFβ) by γ-secretase results in the production of Aβ, p3 and the APP intracellular domain AICD that has been proposed to act as a transcriptional regulator in a Notch-like fashion (Fig. 1). Two major obstacles complicate the analysis of APP functions: (1) as indicated, APP is subject to complex processing that generates several polypeptides each of which likely performs specific functions and (2) APP is part of a gene family that includes in mammals the APP-like proteins APLP1 and APLP2, which are highly conserved in several domains. Interestingly, APLP1 and APLP2 lack the Aβ region. Nevertheless, APLPs are similarly processed and genetic evidence indicates similar and partially redundant functions of APP family members (Heber et al. 2000; Herms et al. 2004). Structurally, membrane-bound APP/APLP holoproteins resemble cell surface receptors. Although their intracellular domains are devoid of any enzymatic activity, interaction screens have led to the identification of extracellular and numerous intracellular binding partners (including PTB domain proteins such as mDab1, JIP, X11/mints, Fe65 family proteins) that seem to anchor the APP/APLP C-termini to a complex protein network at the cell surface, which may transduce various cellular responses. At present, there is evidence supporting, on the one hand, a functional role of APP/APLPs as cell surface–bound signaling and/or adhesion molecules and, on the other hand, a functional role of APP-derived fragments shed from the cell surface into the extracellular space. Taking this into account, it is not too surprising that within the nervous system, the APP/APLPs and their proteolytic fragments have been implicated in a bewildering variety of processes such as neurogenesis, neuronal migration and positioning, neurite outgrowth and neuronal differentiation, neuronal adhesion, synaptogenesis, synaptic function, control of excitation/inhibition balance, neuroprotection, synaptic long-term and short-term plasticity, as well as learning and memory.

The physiological function of APP and APP family members

This series of reviews covers recent efforts to elucidate APP physiological functions at different levels of investigation ranging from structural biology, biochemistry, cell biology to genetics and genomics, as well as the analysis of in vivo functions in model organisms. Two reviews by Prox et al. (2011, this issue), and Endres and Fahrenholz (2011, this issue) describe in depth our current knowledge of the properties of α-, β- and γ-secretases, their regulation and neurobiological functions in health and disease. Although these secretases were initially identified as APP-cleaving enzymes, they have recently been shown to affect a multitude of other substrates and cellular pathways including ectodomain shedding of growth factors, intramembrane cleavage of receptors involved in development, tissue homeostasis and tumorigenesis. Endres and Fahrenholz (2011, this issue) describe the signaling pathways regulating the α-secretase ADAM10 and explore avenues to upregulate its activity (Endres and Fahrenholz 2011, this issue). This is important when attempting to shift processing therapeutically away from the amyloidogenic pathway and to understand how α-secretase gives rise to APPsα, the neurotrophic and neuroprotective cleavage product of APP that is also crucially involved in synaptic plasticity (see also Aydin et al. 2011; Kogel et al. 2011; Korte et al. 2011, this issue). Neurons are highly polarized cells with specific functions localized in dendritic and axonal compartments, most prominently at the synapse. Brunholz et al. (2011, this issue) review the various molecular mechanisms and components involved in the trafficking, maturation and subcellular distribution of APP along the biosynthetic secretory pathway and specifically address the mechanisms of APP axonal transport. During recent years, it has become clear that the generation of the various proteolytic APP cleavage products not only depends on the localization of APP as the substrate, but is also crucially governed by the distinct cellular localization of the secretases (Brunholz et al. 2011, this issue). All APP-cleaving enzymes are transmembrane proteins, and therefore, their activity strongly depends on

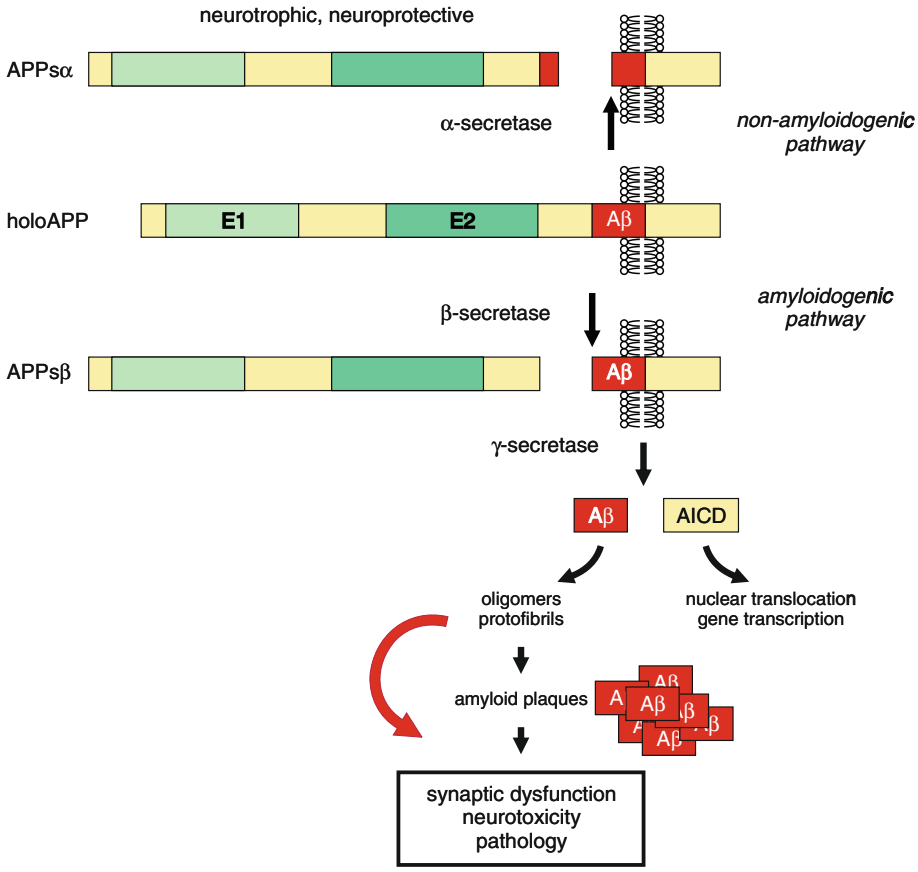

Fig. 1 Schematic overview of APP processing via the non-amyloidogenic (*top*) and the amyloidogenic (*bottom*) pathways. Among the various APP cleavage products, the secreted ectodomain APPsα has consistently been implicated in mediating neurotrophic and neuroprotective signaling, whereas Aβ and AICD are believed to induce predominantly neurotoxic effects. (AICD: APP intracellular domain; E1, E2: conserved extracellular domains). See text for further details

the local lipid environment. In this regard, cholesterol and sphingolipids have been shown to influence APP processing with cholesterol depletion favoring non-amyloidogenic APP processing. Interestingly, studies of APP-deficient cells and tissue in turn indicated an essential role of Aβ in regulating lipid homeostasis pointing toward complex reciprocal regulatory networks, as reviewed by Grimm et al. (2011, this issue). Since the apolipoprotein E4, which is part of low-density lipoproteins and responsible for lipid transport, is genetically associated with AD, Wagner and Pietrzik (2011, this issue) focus in their review on the interaction of APP with members of the low-density lipoprotein receptor family. This interaction critically depends on intracellular adapter molecules (e.g., Fe65); therefore, the authors discuss the functional consequences for APP processing and physiology.

There is accumulating evidence that APP and both APLPs are able to form homo- and heterodimers. APP dimers in cis orientation originate in the endoplasmic reticulum (Isbert et al. 2012), whereas APP dimers in trans orientation might form at the cell surface. Therefore, interactions in cis seem to affect APP processing, whereas interactions in trans may promote cell adhesion. Baumkötter et al. (2011, this issue) provide an overview of available structural data (X-ray and NMR studies) on the three-dimensional APP topology and discuss physiological consequences of APP trans-dimerization with regard to synaptogenesis.

Although biochemical and cellular approaches have been essential to elucidate many basal aspects of APP function, there is always the concern whether molecular interaction(s) and deduced signaling pathways (identified, e. g., via overexpression in transfected cells) are also relevant at the physiological level. Moreover, it is clear that the full extent of APP in vivo functions for the developing and adult nervous system can only be assessed in the context of an intact, that is, whole, organism. Crucial insights have been obtained by studies in invertebrate and mammalian model organism including *C. elegans*, *Drosophila* and mice (see reviews in this issue by Ewald and Li 2011; Poeck et al. 2011; Aydin et al. 2011; Korte et al. 2011; Jedlicka et al. 2011; Jung and Herms 2011; Kogel et al. 2011; Volknandt and Karas 2012). The impressive ease of genetic loss and gain of function screens in *C. elegans* and *Drosophila* establishes them as powerful model organisms. In contrast to mammals, both *C. elegans* and *Drosophila* express only a single APP orthologue. While flies lacking APPL are viable exhibiting synaptic defects and behavioral

abnormalities, a null mutation in the *C. elegans* APL-1 proved lethal. Two reviews by Ewald and Li (2011, this issue), and Poeck et al. (2011, this issue) describe current knowledge of APP functions in invertebrates highlighting functions for neuronal differentiation and synapse formation.

In mice, the analysis of APP functions is complicated by redundancy between APP and the related APLPs. Whereas APP knockout mice are viable, double and triple knockout mice die shortly after birth likely due to pronounced defects at the neuromuscular junction and at central synapses (Herms et al. 2004; Heber et al. 2000; Wang et al. 2005). Mammalian APP family functions are reviewed by Aydin and colleagues and by Korte et al. (2011, this issue), describing studies from mice lacking individual or combinations of APP family members. Recent advances in genetic techniques have made it possible to circumvent the perinatal lethality of APP/APLP2 double knockout mice, for example, by generating knockin mice that express APPsα on an APLP2-deficient background (Weyer et al. 2011). These studies showed essential roles of APP family proteins for synaptic plasticity, learning and memory (Aydin et al. 2011; Korte et al. 2011, this issue). Jedlicka et al. (2011, this issue) explore the consequences of APP deficiency in the mouse dentate gyrus using in vivo LTP recordings and show that APP deficiency may affect the presynaptic plasticity of synaptic transmission at the perforant path-granule cell synapse. Similar studies in the intact animal, in particular studies using conditional knockout mice with cell-type-specific deficiency for one or two APP family members, will be necessary to further unravel the in vivo function of the APP gene family. Neuroproteomic approaches have emerged as novel techniques to address the organization of functional protein networks that underlie neuronal differentiation processes and synaptic function. Volknandt and Karas (2012, this issue) review recent advances in proteomic analysis of synaptic vesicles and the presynaptic active zone and discuss their application for understanding APP physiology. The physiological role of APP at excitatory synapses is further highlighted by a review from Jung and Herms (2011, this issue). Advanced imaging techniques such as 2-photon microscopy in EGFP-expressing mice allow to visualize dendritic spines in the living animal and to follow the dynamics of individual spines over longer periods of time. Jung and Herms (2011, this issue) review recent data on the consequences of APP overexpression and deficiency for spine formation and stability. Finally, Kögel et al. (2011, this issue) provide an in-depth review about the role of APP family members for stress signaling and neuroprotection and summarize the cellular and molecular mechanisms believed to mediate these effects. They also summarize recent exciting experiments addressing how reduced non-amyloidogenic APP processing may affect brain aging.

Summary

Collectively, the reviews and studies compiled in this Special Issue cover a broad field of research on APP and its family members in physiology. They report recent insight into the diverse functions of these proteins and their cleavage products in normal brain physiology. In particular, they implicate APP/APLPs in cellular mechanisms that are considered the basis of higher cognitive functions, such as synaptic plasticity. Clearly, it is conceivable that lack of APP family proteins and their cleavage products could contribute to some of the symptoms seen in early AD, that is, at a time point when neurodegeneration is not as yet generalized and widespread. It will be fascinating to follow the future developments in this field, which holds promise to better understand the most common neurodegenerative disease associated with learning and memory deficits.

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