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Minireview

The amyloid precursor protein and postnatal neurogenesis/neuroregeneration

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Abstract

The amyloid precursor protein (APP) is the source of amyloid-beta (Aβ) peptide, produced via its sequential cleavage β- and γ-secretases. Various biophysical forms of Aβ (and the mutations of APP which results in their elevated levels) have been implicated in the etiology and early onset of Alzheimer's disease. APP's evolutionary conservation and the existence of APP-like isoforms (APLP1 and APLP2) which lack the Aβ sequence, however, suggest that these might have important physiological functions that are unrelated to Aβ production. Soluble N-terminal fragments of APP have been known to be neuroprotective, and the interaction of its cytoplasmic C-terminus with a myriad of proteins associates it with diverse processes such as axonal transport and transcriptional regulation. The notion for an essential postnatal function of APP has been demonstrated genetically, as mice deficient in both APP and APLP2 or all three APP isoforms exhibit early postnatal lethality and neuroanatomical abnormalities. Recent findings have also brought to light two possible functions of the APP family in the brain-regulation of neural progenitor cell proliferation and axonal outgrowth after injury. Interestingly, these two apparently related neurogenic/neuroregenerative functions of APP involve two separate domains of the molecule.

Keywords: Amyloid precursor protein; Neurogenesis; Neuronal regeneration

The amyloid precursor protein (APP) [1,2] is a member of an evolutionarily conserved family of type I membrane proteins. Mammals have two APP-like paralogues, APLP-1 and APLP-2 [3]. The evolutionary conservation of the APP gene family also extends to invertebrates, with the *Drosophila* gene product known as APPL and the *Caenorhabditis elegans* homologue named APL-1. Perhaps, the most well-known aspect of APP biology is as the precursor for amyloid-beta (Aβ) peptide. There is little doubt that the latter, be it in the form of insoluble extracellular amyloid plaques [4], or as soluble intraneuronal and synaptically targeting extraneuronal oligomers, is an etiological agent of Alzheimer's disease (AD) [5,6].

In the amyloidogenic pathway of APP processing, Aβ is generated by sequential cleavages of β-secretase (BACE) and the presenilin-containing γ-secretase complex [7]. The latter, termed presenilin-dependent regulated intramembrane proteolysis (PS-RIP) [8,9], appears to be an important and conserved cellular process for the signaling by some growth factor receptors (such as ErbB-4) and the liberation of membrane bound transcription factors such as Notch [10]. APP could also be proteolytically processed in an alternative, non-amyloidogenic path, where it is cleaved by α-secretases [11], at a site which will preclude BACE cleavage. This cleavage releases a soluble sAPPα fragment which, in contrast to Aβ, could in fact be neuroprotective [12,13].

Other than APP orthologues, all other members of the APP-related gene family do not possess Aβ sequences. Amyloidogenesis is therefore unlikely to be the main physiological function of this protein family. Although in vitro

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interactions provided some clues as to the physiological roles of APP, earlier investigations into its function in vivo were thwarted by the rather subtle neurological deficits in APP-deficient (as well as APLP1 and 2-deficient) mice. The functional redundancy between mammalian APP, APLP-1, and APLP-2 became clear when it was first shown that APP/APLP-2 [14], and subsequently, APLP-1 and APLP-2 double knockouts [15,16], exhibit early postnatal lethality. APP/APLP-2 double knockouts have structurally and functionally defective neuromuscular synapses, with excessive nerve terminal sprouting, reduced synaptic vesicle numbers at the presynaptic compartment, and an observable aberrant apposition of presynaptic markers with postsynaptic acetylcholine receptors. APP/APLP-1 double knockouts are viable, but these also exhibit early postnatal death in conjunction with a haplodeficiency of APLP-2 [16]. The triple knockouts are postnatally lethal and exhibit cranial abnormalities. These include cortical dysplasias resembling the phenotype found in human type II lissencephaly and a partial loss of cortical Cajal retzius cells [17]. These phenotypes of the APP/APLP-1/APLP-2 triple knockout are suggestive of defects in the survival of specific central nervous system cell types and the migration of neuroblasts.

It is therefore clear that the APP and APPLs have important developmental and postnatal functions. These functions are gradually being elucidated, and could be broadly associated with either APP's N-terminal extracellular domain, or mediated via the C-terminal cytoplasmic domain. The former pictures the APP functioning like a growth factor (either in a soluble or membrane bound form) or a cell adhesion molecule. The latter is in line with APP's interaction with cytoskeletal components and coordination of subcellular dynamics, as well as potential regulatory role in gene transcription, perhaps in the form of an APP intracellular domain (AICD). The various elucidated as well as potential functions of both intracellular and extracellular portions of APP had been extensively reviewed [18–20]. We focus here on neurogenic roles of the APP family as revealed by recent in vivo investigations. Both portions of the molecule, as described below, have recently been shown to have roles in neurogenesis and neuronal regeneration, respectively.

APP and proliferation of adult neural progenitors at the subventricular zone

The non-amyloidogenic sAPP had been implicated in enhancement of synaptogenesis, neurite outgrowth, and neuronal survival. In particular, sAPP has been known for some time now to be able to stimulate the proliferation of neural progenitor cells in culture [21,22], as does the ectodomain of APLP-2 [23]. A possible role for the N-terminus of APP in stem cell growth has received support in that crystal structure analysis at 1.8 Å resolution of the cysteine-rich N-terminal heparin-binding domain of APP (residues 28–123) revealed that it has similarities with other cysteine-rich growth factors, such as the hepatocyte growth factor [24]. A demonstration of a stem cell neurogenic role in vivo has however been lacking. A report by Caille et al. [25] therefore provided some much anticipated evidence in this light.

In investigating possible saturable, high affinity binding sites for sAPP in the brain, the authors found that an immunoglobulin heavy chain (Fc) linked fusion sAPP protein (sAPP-Fc) binds prominently to cells at the subventricular zone (SVZ). The SVZ is one of two adult CNS sites that harbor neural progenitors that are capable of producing neurons in the adult brain [26] (the other site being the dentate gyrus of the hippocampus). It has various cell types—the radial glial-like type B cells are the primary precursors to the rapidly dividing (transit amplifying) type C cells, which in turn generate type A cells. The latter are neuroblasts that migrate to the olfactory bulb [27]. sAPP-Fc was found to bind to both epidermal growth factor (EGF) receptor positive type C and the type A neuroblasts. Notably, sAPP-Fc binding was not observed at the hippocampal dentate gyrus, which is a good indication of the binding specificity observed at the SVZ.

The significance of sAPP-Fc's binding to SVZ cells was further investigated by culturing the EGF-responsive type C neural progenitors, which form neurospheres in culture in the presence of EGF. These neurospheres bind sAPP-Fc and secrete sAPP, the latter in a manner that is dose-dependent on EGF concentration. sAPP-Fc itself does not appear to induce proliferation. That this secreted sAPP might have an autocrine/paracrine function in enhancing EGF-induced proliferation is however shown by the fact that bromodeoxyuridine (BrdU) uptake by the neurospheres was significantly reduced by treatment with two different APP monoclonal antibodies (22C11, which targets a N-terminal APP fragment of amino acids 66–82; and 6E10, which binds to an APP region between amino acids 597 and 613). The fractions of differentiated neuronal cell type (neurons, astrocytes or oligodendrocytes) that could be derived from these neurospheres were not affected by the APP blocking antibodies, indicating that sAPP-Fc has no significant effect on the outcome of the neural precursor differentiation in vitro. Corroborating the observations in cell culture, infusion of sAPP-Fc into the lateral ventricle of adult mice increased the number of neurosphere yield in subsequent culture, as well as the number of BrdU-positive cells counted in whole mount preparations. On the other hand, infusion of the α-secretase inhibitor batimastat and antisense oligonucleotides against APP decreased the proliferative parameters described, which could be rescued by co-infusion of sAPP-Fc.

In an interesting extension of their analysis, the authors also showed that a corresponding Fc fusion protein of APLP-2 (sAPLP2-Fc), but not that of APLP-1 (sAPLP1-Fc), stained the SVZ cells in a similar manner to sAPP-Fc. sAPLP2-Fc could likewise stimulate EGF-responsive SVZ cells in vivo to a similar extent compared to sAPP-Fc. These results are suggestive of the two

members of the family serving possibly similar and redundant functions in the SVZ.

The results of Caile et al., summarized above have important implications for APP and APLP-2 functioning as rather specific growth factors or co-factors for CNS neuroprogenitors. A possible endogenous source of APP or APLP ectodomains at the SVZ has in fact been noted in a subpopulation of cells which expresses astrocytic markers [28]. That a growth factor-like function may be essential for mammalian postnatal survival (as illustrated by the phenotype of the double knockouts) could be further reconciled by the fact that sAPP is also known as an autocrine regulator of basal cell proliferation in the skin epidermis under the control of transforming growth factor (TGF)-α [29,30], stimulating proliferation and migration of keratinocytes as well as melanin particle exocytosis by melanocytes in vitro [31]. In similar regard, sAPP is also known to stimulate both differentiation and proliferation of thyroid follicle epithelial cells [32]. In no case, however, has any specific sAPP receptor been identified and the respective proliferative signaling pathways dissected in detail (although MAP kinase activation by sAPP has been demonstrated [33]).

In fact, unlike the cytoplasmic C-terminus of APP, the N-terminus is surprisingly devoid of known specific neuronal interacting proteins. Candidate interacting proteins thus far known include ApoE [34], the class A scavenger receptor [35], and the extracellular matrix protein fibulin [36]. One most recently identified protein associating with the N-terminus of APP is F-spondin [37]. In this case, F-spondin binding to APP inhibits its proteolytic cleavage by BACE-1 and appears to modulate APP-dependent transactivation of Tip60-mediated transcription. F-spondin has been shown to promote neurite outgrowth of both CNS [38] and peripheral nervous system neurons [39], as well as functioning in developmental axonal pathfinding and neuronal regeneration [40,41]. The latter role coincides with a recent in vivo demonstration of APP's potential role in axonal regeneration, which we now turn our attention to.

APP, postdevelopmental neurite arborization and neuronal regeneration after injury

It is amazing how much we have learned about various aspects of nervous system development from invertebrate models. In a recent report, Leyssen et al. [42] had, however, used a *Drosophila* model to unveil a postnatal function of APP. The neurons they focused on are sLNv, a well-characterized group of *Drosophila* brain neurons which regulates circadian rhythm. These have a simple and stereotypical morphology and therefore allowed high resolution microscopic analysis of axonal arborization phenotypes. Flies deficient in the *Drosophila* orthologue of APPL ($appl^d$) appear to have normal development of sLNv. The authors observed that overexpression of the human neuronal isoform of APP (APP695) and APPL in sLNv neurons, while having no effect on their developmental patterns, greatly increased their axonal extension and the area of axonal arbour in adult flies. This increase is quantifiable and is dependent on APP gene dosage. The authors further mapped the region of APP responsible for the axonal arborization gain-of-function phenotype to a YENPTY motif located at the C-terminus of the protein. This motif is known to be required for the binding of various adaptor proteins like Fe65, Mint, and Dab1. Dab1's interaction with APP, in particular, requires the integrity of both the tyr (Y) residues of this motif [43]. As mutations of either Y residues abolished APP's ability to induce axonal arborization, the APP effect is likely mediated through Dab1.

The mammalian Dab, mDab-1, has been implicated in neuronal development. It is an adaptor which engages the Abl tyrosine kinase [44], an oncogene whose product is associated with the regulation of axonal growth cone motility through modulation of the actin cytoskeleton (see [45] for a review). A link between Abl and APP was known previously, as APP is tyrosine-phosphorylated in cells expressing a constitutively active Abl [46]. When the authors overexpressed APP in flies heterozygous for the Abl mutations Abl^1 and Abl^4, both strong hypomorphs, APP-induced axonal arborization was significantly suppressed. Coexpression of APP with a kinase-dead mutant of Abl also suppressed arborization. In fact, overexpression of BCR-Abl, an activated form of Abl (not subjected to intramolecular self-inhibition), could by itself induce axonal extension and arborization in a similar manner to APP expression. This phenotype is induced even in the *Drosophila* APPL-deficient mutant $appl^d$. The Abl tyrosine kinase therefore appears to act downstream of APP in inducing axonal arborization, probably by modulating growth cone actin dynamics. The authors also found that null alleles of *chickadee*, the *Drosophila* homologue of the mammalian actin-binding protein profilin, also suppressed APP axonal arborization activity.

The gain-of-function phenotype in postnatal neurons observed with APP overexpression is in stark contrast to the lack of a phenotype in APPL-deficient flies. This indicates that APP upregulation may have a postnatal physiological (or pathophysiological) role rather than a developmental function. In checking this possibility, the authors observed that *Drosophila* head injury (by the insertion of an insect pin through the fly's head) resulted in a dramatic upregulation of APPL levels at the injured brain areas. High level of APPL was sustained for up to 7 days after injury. A neuroprotective role for APPL upregulation after injury was implicated by the observation that $appl^d$ mutants, while not impaired in survival under normal conditions, had a significantly higher rate of mortality compared to wild type flies after brain injury.

Although biochemical interaction studies have identified a plethora of molecules that interact with the APP intracellular domain (AICD), concrete evidence for a physiological significance of these interactions is often lacking. An interesting point to note here is that, as mentioned by the

authors (as unpublished observations), while membrane bound C-terminal fragment of APP-induced axonal arborization, the intracellular AICD fragment released by γ-secretase activity does not. If true, in conjunction with previous reports of cytotoxicity of APP C-terminal peptides [19,47–49], γ-secretase-mediated amyloidogenesis appears to be detrimental to adult CNS neurons in multiple ways. While verification of their findings in mouse or other mammalian model would indeed be necessary, the work of Leyssen et al., as such provided valuable in vivo data implicating a neuronal pathophysiological role for APP.

Epilogue

The evolutionary conservation of the APP and related genes is best explained by their products serving an important developmental or postnatal function. Genetic analysis clearly illustrates, in spite of obvious redundancy, the importance of APP and APLPs in postnatal function. The in vivo studies discussed here opened up new avenues to further explore the role of APP family members in postnatal neurogenesis as well as axonal regeneration after injury. Of course, attempts to study endogenous, postnatal roles of APP in vertebrates in vivo still face confounding complications due to the large number of proteolytic fragments that are generated from the parent APP molecule, and the difficulty at times of telling which is more important pertaining to the phenomenon in question. For example, it would always be much easier to check the effect of sAPP on long-term potentiation or long-term depression using hippocampal slide cultures in vitro [50] than investigations of a role for APP or sAPP in learning and memory in vivo (particularly in Alzheimic models). The latter would obviously face potential interference from multiple aspects of Aβ-mediated pathology. The generation of suitably genetically manipulated animals, with brain region specific deletion or overexpression of the genes in various combinations, would probably be necessary for further breakthroughs in our understanding of the physiological role of the APP family proteins.

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