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What Does the APP Family Do in the Brain?

Ottavio Arancio[1,2,3,*]

[1]Department of Pathology and Cell Biology, Columbia University, 630W 168th Street, New York, NY 10032, USA

[2]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, 630W 168th Street, New York, NY 10032, USA

[3]Department of Medicine, Columbia University, 630W 168th Street, New York, NY 10032, USA

Abstract

Amyloid-β precursor protein (APP) is overshadowed by its degradation product, the Alzheimer protein Aβ. Lee et al. now find a role for the APP family in neuronal excitability, synaptic plasticity, and memory in adulthood, despite the lack of requirement for neuronal survival.

Amyloid-β precursor protein (APP) was named after the downstream product of its own processing, amyloid-β (Aβ). Aβ has dominated the scenes despite representing only ~6% of the whole APP because Aβ accumulates in the brain of those affected by Alzheimer's disease (AD). In addition, Aβ impairs memory and cell-to-cell communication, both of which are key features of the disease. Still, APP is much more than an Aβ factory. Besides being the source of different proteolytic products other than Aβ, including those derived from the soluble ectodomain and the intracellular domain, the APP in its entirety is a transmembrane protein that most likely plays fundamental roles in the central nervous system (CNS) during both development and adult life (Müller and Zheng, 2012). In this regard, recent findings suggesting that APP serves as a common downstream factor permitting soluble oligomeric forms of Aβ and tau to enter cells in the brain, affecting synaptic function and memory (Puzzo et al., 2017), might even re-write the history of AD. Thus, a more in-depth knowledge of full-length APP function might unravel important insights into disease onset and progression.

APP is a member of a gene family that includes the APP-like proteins 1 and 2 (APLP1 and ALPL2) in mammals (Müller and Zheng, 2012), two proteins that do not contain an Aβ-like domain despite their sequence homology with APP. APP, APLP1, and APLP2 have similar structures and undergo similar proteolytic processing (Müller and Zheng, 2012). The similarities between the three proteins are responsible for functional redundancy that compensates for the loss of essential gene functions in *APP* knock-out (KO) mice as supported by the evidence that $APP^{-/-}$, $APLP1^{-/-}$, $APLP2^{-/-}$ single mutants, and $APP^{-/-}/APLP1^{-/-}$ mice are viable, whereas combined $APLP1^{-/-}/APLP2^{-/-}$ double KOs, $APP^{-/-}/$

*Correspondence: oa1@columbia.edu.

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APLP1$^{-/-}$ *APLP2*$^{-/-}$ triple KOs, and 80% of the *APP*$^{-/-}$/*APLP2*$^{-/-}$ die postnatally (for a review on effects of *APP* and *APLP* KO combinations, see Müller and Zheng, 2012). Interestingly, lethal double mutants do not display obvious histopathological abnormalities in the brain or any other organ examined but show alterations in developing neuromuscular synapses as well as inter-neuronal synapses. Moreover, *APP*$^{-/-}$/*APLP1*$^{-/-}$/*APLP2*$^{-/-}$ triple KO mice show cranial abnormalities that resemble human type II lissencephaly. Finally, *APP* expression increases during differentiation and growth of neurons (Müller and Zheng, 2012). Taken together, these data indicate that *APP* family members have an essential role in normal brain development and early postnatal survival.

If there are certainties on the role of the APP family in the development of the CNS, the study of a physiological role of APP in adult life has been complicated by the combination of lethality of the double and triple mutants with functional redundancy within the three family members. A hint to a specific role of APP in postnatal life comes from studies on *APP*$^{-/-}$ mice that, because of compensation by the APLP proteins, reach adulthood. The analysis of APP functions *in vivo* shows that *APP*$^{-/-}$ mice have a complex phenotype including weight reduction, agenesis of the corpus callosum, difficulty in mating, hypersensitivity to seizures, defects in copper and lipid homeostasis, impaired grip strength, locomotor activity, exploratory activity, memory, and its electrophysiological correlate, long-term potentiation (LTP) (Müller and Zheng, 2012). Consistent with these findings, *APP*$^{-/-}$/*APLP2*$^{-/-}$ mice surviving early postnatal life show weight reduction, difficulty in mating and righting, ataxia, spinning behavior, and a head tilt, suggesting a deficit in balance and/or strength associated with reduced glutamate release (Fanutza et al., 2015). Moreover, APP is transported anterogradely by conventional kinesin in tubular vesicles together with β- and γ-secretase functioning as a receptor for the cargo transport (Müller and Zheng, 2012). Indeed, increased expression of APP or APPL (the *Drosophila* homolog of APP) causes axonal swellings with accumulation of organelles and synaptic vesicles in peripheral nerves of *Drosophila*. Nevertheless, many questions on the function of APP remain open because interpretation of studies on mice lacking normal APP function is complicated by several factors. LTP was found to be reduced only in older KO mice or when potentiation was evoked through a θ-burst stimulation (but not with a 100 Hz, 1 s tetanus in the presence of the GABAA receptor antagonist picrotoxin [Müller and Zheng, 2012]). Consistent with these findings, *APP* KO mice show an age-dependent defect in spatial memory (but muscle weakness and seizures confound the interpretation of the behavioral experiments) (Müller and Zheng, 2012). Thus, because of the limitations of the germline KO approach, there is the need for studies in which suppression of APP, APLP1, and ALPL2 function occurs both simultaneously and postnatally. The manuscript by Lee et al. (2020) addresses this need by presenting findings from mice in which combined APP, APLP1, and APLP2 were selectively inactivated postnatally in excitatory pyramidal neurons of the cerebral cortex.

The first surprising finding of the laborious enterprise undertaken by Lee et al. (2020) to generate the conditional triple KO (cTKO) mice is that the APP family is "dispensable for neuronal survival during aging." Differently than germline TKO mice presenting perinatal lethality, the cTKO mice were grossly normal with no neurodegeneration up to 2 years of age. The cortical volume and cortical neuron number were normal in cTKO mice, which also showed no increases in apoptosis or astrogliosis in the cerebral cortex. This is in

striking contrast with the finding that inactivation of Presenilins, which, similar to APP, are responsible for familial AD, results in a remarkable increase of apoptosis in the cerebral cortex starting at 2 months of age, followed by age-dependent loss of cortical neurons (Saura et al., 2004). Thus, differently than Presenilins, a loss-of-function mechanism is unlikely to underlie the effect of APP mutations in AD. Incidentally, this finding argues against the concept that neuronal hyperexcitability per se leads to neuronal loss at old ages, propelling studies aimed at better exploring the origin of neuronal death during hyperexcitability. Most importantly, because disease-causing mutations in APP are not believed to act as loss-of-function mutations, the demonstration by Lee et al. (2020) that the APP family is dispensable for neuronal survival during aging prompts future studies aimed at identifying the new function gained by APP during AD etiopathogenesis. Is the new APP function linked to the generation of one or more toxic degradation products derived from its processing or to disruption of a putative normal function of full-length APP? The work by Lee et al. (2020) will inspire studies onto the mechanisms(s) underlying AD etiopathogenesis through a thorough investigation of the function of the full-length APP in adult life.

Second, but not less importantly, cTKO mice allow tackling postnatal neuronal functions of the APP family members. Lee et al. (2020) found that cTKO mice display abnormal memory as outlined by their performance with the Morris water maze associated with a defect in LTP evoked through the θ-burst stimulation by 3 months of age. These findings are consistent with previous studies showing LTP and memory defects in *APP* KO mice. However, the LTP deficit in *APP* KO mice was apparent only in older mice and interpretation of their memory impairment is confounded by muscle weakness and seizures. Moreover, the defect in LTP and memory in cKO mice with selective APP deletion in excitatory forebrain neurons of the cortex and hippocampus in the APLP2 null background could be ascribed to lack of APP function in adult life due to possible developmental defects of these mice (Hick et al., 2015). Remarkably, the defects in LTP and memory found in Lee et al. (2020) are consistent with the dramatic reduction of memory assessed with the Morris water maze, contextual fear conditioning, and LTP after acute APP suppression obtained through intrahippocampal injections of APP small interfering RNA to avoid compensation (Puzzo et al., 2011). The current findings by Lee et al. (2020) unequivocally demonstrate that the *APP family is necessary for normal LTP and memory in adult mice*.

Where is the locus of alterations responsible for the defects in memory and LTP following suppression of the APP family? Lee et al. (2020) found evidence for *involvement of the APP family both at the pre- and post-synaptic level*. Specifically, they found enhancement of paired-pulse facilitation (PPF) and synaptic facilitation, two phenomena that are thought to be associated with presynaptic changes, together with reduced postsynaptic NMDA receptor-mediated responses in the hippocampal Schaffer collateral-CA1 pathway. These results are consistent with research on $APP^{-/-}/APLP2^{-/-}$ mice showing similar increased PPF and synaptic facilitation (Fanutza et al., 2015). However, they are not obvious because previous studies on $APP^{-/-}$ showed varying pre- or post-synaptic changes (Müller and Zheng, 2012). By creating a neuronal-specific cTKO model bypassing developmental requirement of APP family in the CNS, Lee et al. (2020) have definitely shown a cell-autonomous role of the APP family in the regulation of synaptic plasticity and memory in

mature excitatory neurons of the cerebral cortex due to alterations occurring both in the pre- and post-synaptic compartment.

What is the cause of the defects in memory and LTP following suppression of the APP family? Lee et al. (2020) found that *Kv7 channels, mediating the M-type potassium current, might be involved at least in part in the essential role of the APP family in LTP and memory through regulation of neuronal excitability*. Their pharmacological inhibition in hippocampal slices mimicked and largely occluded the neuronal excitability phenotypes observed in CA1 neurons from cTKO mice, including depolarized resting membrane potential, lower action potential threshold, and higher spike firing frequency. Thus, APP presence in adult life would lower neuronal excitability avoiding the negative effects of hyperexcitability. This conclusion is consistent with the findings that *APP* KO mice display hypersensitivity to seizures (Müller and Zheng, 2012), and *App*-Swedish knock-in rats show facilitated glutamate release (Tambini et al., 2019). Most importantly, given that *APP*-transgenic mice overexpressing mutant human APP also exhibited spontaneous seizure activity (Palop et al., 2007), it is tempting to conclude that APP dosage, more than its altered processing, is at the center of AD etiopathogenesis.

Overall, these data provide new insights on the role of the APP family in the adult CNS. Future studies will be necessary to explain the molecular mechanism underlying control of neuronal excitability, synaptic plasticity, and memory by the APP family. The work by Lee et al. (2020) raises a number of exciting questions. For instance, what is the molecular mechanism by which the APP family interacts with Kv7 channels and controls their function in neuronal excitability? How do Kv7 channels regulate synaptic plasticity in normal brain function and contribute to its dysregulation in disease? Do APP mutations affect Kv7 channels? If so, how do APP mutations affect Kv7 channels in familial AD? Given that the molecular interactions of APP, APLP1, and APLP2 are different (for example, JIP1 proteins interact with APP but not with APLP1 and APLP2 [Scheinfeld et al., 2003]), would analysis of single and double cKOs reveal differential involvement among the three members of the APP family in brain function? Irrespective of these questions, the current study underlines the importance of looking at AD from the perspective of the APP family and its members rather than the classical Ab-centric view.

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