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## Commentary

# A role for the β-amyloid precursor protein in memory?

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Alzheimer's disease[1] (AD), a progressive neurodegenerative disease, is the most common type of dementia occurring in mid-to-late life. Morphological and neurochemical studies have established that AD is associated with selective lesions of neuronal circuits in the neocortex, hippocampus, and basal forebrain cholinergic system. The principal consequence of these lesions is a diminution of synaptic inputs in these regions of the brain, leading to memory and attentional impairments (1). The principal neuropathological hallmarks of AD are the presence of neurofibrillary tangles, intracytoplasmic filaments of hyperphosphorylated forms of tau, and senile plaques, comprised of dystrophic neurites (abnormal neuronal processes) displayed in proximity to deposits of 39- to 42-aa β-amyloid (Aβ) peptides (2, 3). Aβ fibrillar aggregates act as a nidus for subsequent deposits of other proteins (4) and by mechanisms not presently understood and appear to be toxic to nerve cells (5). The mechanisms by which Aβ, tau, and associated polypeptides impact on the pathophysiology of AD are being actively investigated, with the underlying assumption that these molecular targets might offer opportunities for novel therapeutic interventions.

Much less is understood about the complexities underlying the cognitive and attentional deficits of patients with AD. It is to this arena that we are offered a tantalizing insight. In this issue of the *Proceedings*, Mezaine and colleagues (6) report that in behavioral paradigms, a secreted form of the β-amyloid precursor protein ($APP^{s\alpha}$) has memory-enhancing effects in normal and amnestic mice. The data are interpreted to suggest that $APP^{s\alpha}$ plays an important role in the formation and/or consolidation of memory. How compelling is this information and by what physiological mechanism(s) might these effects be facilitated? To discuss the potential significance of the new findings, it is useful to put into perspective our current understanding of the biology and function of the β-amyloid precursor protein (APP) and $APP^{s\alpha}$.

Aβ, the principal component of extracellular deposits in senile plaques, encompasses 28 amino acids of the ectodomain and 11–14 amino acids of the transmembrane domain of type I integral membrane proteins termed, for lack of a better name, APP (7). APP is ubiquitously expressed, and APP-like proteins have been described in evolutionarily distant organisms, including *Caenorhabditis elegans* (8) and *Drosophila melanogaster* (9). In cultured cells, APP mature through the constitutive secretory pathway, and some APP molecules are endoproteolytically cleaved at the cell surface within the Aβ sequence by an elusive α-secretase to release the ectodomain of APP ($APP^{s\alpha}$) into the medium; similar species are readily detected in human plasma and the cerebrospinal fluid (10–13). Alternative proteolysis of APP by yet-uncharacterized β-secretase and γ-secretase activities lead to the production of Aβ peptides (reviewed in ref. 14).

Very interesting, and highly pertinent to the report by Mezaine and colleagues, is the finding that pharmacological manipulation by several first messengers (e.g., phorbol esters, cholinergic agonists, and other neurotransmitters) that activate the phospholipase C/protein kinase C (PKC)-dependent pathway, enhance the antiamyloidogenic α-secretase pathway and subsequently, the secretion of $APP^{s\alpha}$ (15, 16). PKC-dependent secretion is the result of enhanced "budding" of APP-containing nascent vesicles from the trans-Golgi network and trafficking to the plasma membrane (17), the site of α-secretase activity (18, 19). Furthermore, enhanced PKC-dependent APP processing occurs at the expense of Aβ production (20). These results suggest that defects in signal-dependent regulation of APP cleavage might contribute to AD pathogenesis, as cholinergic neurotransmission and PKC activity are severely compromised in AD (reviewed in ref. 21). One prediction of this model is that the levels of $APP^{s\alpha}$ might be diminished in the cerebrospinal fluids (CSF) of patients with AD; in the context of the report by Mezaine and colleagues, the speculative suggestion put forth is that altered levels of $APP^{s\alpha}$ may underly the cognitive deficits in AD patients. Although analyses of CSF of patients diagnosed with probable AD do show significant decreases in $APP^{s\alpha}$ levels compared with age-matched control groups (22), any interpretations of these data are confounded by the fact that a variety of populations of neurons, a principal source of APP in the brain, invariably are reduced during the course of disease.

What have we learned about APP function? The reader is forewarned that there is no consensus about the function that APP or $APP^{s\alpha}$ subserves in the nervous system. In some experimental settings, APP appears to participate in neuroprotective activities; when embryonic rat hippocampal neurons are treated with $APP^{s\alpha}$, resting $[Ca^{2+}]_i$ is decreased and pretreatment of neurons with $APP^{s\alpha}$ reduces glutamate-mediated elevations in $[Ca^{2+}]_i$ and associated toxicity (23, 24). Evidence also has emerged that $APP^{s\alpha}$ influences synaptic plasticity; in cultured hippocampal neurons, single channel and whole-cell perforated patch clamp analysis revealed that $APP^{s\alpha}$ derived from either APP-695 or APP-751 activated high conductance charybdotoxin-sensitive potassium channels, leading to membrane hyperpolarization and suppressed glutamate receptor-mediated synaptic activity (25). These efforts notwithstanding, the underlying signaling mechanisms responsible for the observed effects of $APP^{s\alpha}$ are, in large part, undefined because of the paucity, if not complete absence, of information regarding the nature of the $APP^{s\alpha}$ "receptor." Equally perplexing is the function of membrane-bound APP-695, a species that is markedly induced during neuronal differentiation (26), abundantly expressed in adult neurons (27, 28), and transported within axons by the fast anterograde system to nerve terminals (29–32). It has been suggested that APP may play a role in the outgrowth or maintenance of axons or nerve terminals, a view supported by several studies documenting colocalization of APP with β1 integrins at focal contact sites of differentiating neuronal cells (33) and enhancement of neurite outgrowth (34, 35).



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Several lines of evidence suggest that APP may play a role in synapse formation and maintenance. For example, intracerebroventricular administration of a small peptide, corresponding to amino acids 319–335 of APP-695, into adult rats, resulted in increased synaptic density in the frontoparietal cortex and enhanced memory retention (36); this peptide previously had been shown to have mitogenic activity on cultured fibroblasts. In addition, transgenic expression of APP-695 to ≈1.5-fold over endogenous APP lead to increased density of synaptophysin-immunoreactive terminals and growth-associated protein 43 (GAP-43) expression (37). On the other hand, in 3-month-old transgenic mice that overexpress human APP to more than 5-fold over endogenous APP levels, animals exhibited normal learning and memory in spatial reference and alternation tasks. By 9–10 months of age, however, these animals were impaired on these tasks (38). It is not at all clear whether these behavioral manifestations are the result of APP overexpression, production/accumulation of $APP^s$, or A$\beta$ peptides, because cohorts of these animals exhibit dystrophic neurites and A$\beta$ deposits in the amygdala, hippocampus, and cortex very soon thereafter.

The obvious question is: does a knockout mouse help us, in any way, to assess APP function? Zheng and colleagues (39) generated mice with functionally ablated APP alleles; homozygous mice were viable and fertile, and with the exception of increased gliosis in the hippocampus and cortex, changes in neuronal number and cortical volume were unchanged relative to wild-type littermates. Behavioral studies of young APP null mice revealed a mild reduction in locomotor activity and forelimb grip strength; in an age-dependent manner, APP null mice exhibit deficits in cognitive function and long-term potentiation (40). Studies of cultured neurons from APP null mice reveal diminished viability of cells and reduction in outgrowth of neurites; neuritogenesis and dendritic arborization were restored when neurons were cocultured with astrocytes secreting soluble APP (41). Although the absence of dramatic neuronal phenotypes in APP null mice is disappointing, it is conceivable that loss of APP function is compensated by highly homologous amyloid precursor-like proteins (APLP1 and APLP2), which although lacking the A$\beta$ domain, nonetheless are expressed at high levels and have developmental and cellular distributions similar to APP (42, 43).

The studies by Mezaine *et al.* now show that in mice performing various learning tasks involving short-term or long-term memory, intracerebroventricular administration of $APP^{s\alpha}$, derived from either APP-695 or APP-751, enhances memory and blocks learning deficits induced by the systemic administration of the antimuscarinic agent scopolomine. The memory-enhancing effects of $APP^{s\alpha}$ were observed at low doses (0.05–5 ng) and were blocked by anti-APP antisera. Moreover, memory enhancement was observed when $APP^{s\alpha}$ was administered either after a training session in a visual discrimination or lever-press learning task, or before the acquisition trial in an object recognition task. The retrograde design of the posttraining paradigms often is viewed within a memory consolidation framework. By this view, physiological processes that underlie the storage of information are labile for a period of time after the experience during which interventions can produce either amnesia or enhancement of memory processes. A key feature of these sorts of studies is that the effectiveness of posttraining treatments is time dependent; although administration shortly after a training experience is effective, the same treatment given at longer delays is ineffective. In the case of the memory-enhancing effects of $APP^{s\alpha}$, the time dependency has yet to be fully tested; in view of the paucity of information regarding the physiological role(s) and mode(s) of action of soluble APP, any interpretation of these studies relevant to consolidation, although provocative and interesting, remain premature. Mechanistically, it is conceivable that $APP^{s\alpha}$ might stabilize or strengthen synapses involved in memory trace, and evidence has supported a role for APP or its soluble derivatives in synaptogenesis and interactions with extracellular matrix molecules, including heparin (44), laminin (45), and collagen (46). Is there a model that might provide a compelling insight regarding the function of $APP^{s\alpha}$ in memory? Certainly, the APP null mice, which exhibit deficits in cognition and long-term potentiation in APP, offer one clear avenue of investigation to test the restorative effects of exogenously administered $APP^{s\alpha}$ in these experimental paradigms.

The current studies suggest that $APP^{s\alpha}$ alters the function of cholinergic neurons or their targets because impairments caused by administration of scopolamine were alleviated by concurrent peptide treatment. That interpretation needs to include an important caveat: because $APP^{s\alpha}$ augmented performance when administered alone, the results obtained with combined treatments could reflect a facilitatory effect of the peptides that is quite independent of the deleterious effects of scopolamine; better performance could reflect a separate compensatory action rather than affecting the consequences of cholinergic blockade. In this regard, there is no consensus about the psychological mechanisms underlying antimuscarinic drug-induced deficits; cholinergic neurons innervate virtually the entire neuraxis and muscarinic receptors are distributed throughout the central nervous system (CNS). Thus, it is likely that systemically administered scopolamine would effect a multiplicity of CNS functions, including attention, working memory, and sensory gating, modalities that impact on global assessments of acquisition and performance of learned behaviors (47). This multiplicity of effects is particularly problematic when cholinergic agents are administered before training, as was the case in the object recognition task. We envision that future behavioral assessments in understanding the physiology of $APP^{s\alpha}$ likely will be achieved by using learning paradigms for which the underlying neuroanatomical circuitry is well defined, providing a basis for convergence between *in vivo* analysis and the study of cellular and molecular mechanisms.


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