CNS Neurosciences & Therapeutics

REVIEW

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The Upside of APP at Synapses

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SUMMARY

The memory dysfunctions that characterize Alzheimer's disease (AD) are strongly correlated with synapse loss. The amyloid precursor protein (APP) and its cleavage product Aβ play central roles in synapse and memory loss, and thus are strongly implicated in the pathogenesis of AD. Numerous *in vitro* and transgenic AD mouse model studies have shown that overexpression of APP leads to Aβ accumulation, which causes decreased synaptic activity and dendritic spine density. However, the normal synaptic function of APP itself is not fully understood. Several recent studies have found that full-length APP promotes synaptic activity, synapse formation, and dendritic spine formation. These findings cast APP as a potential key player in learning and memory. It is of interest that the synaptic functions of full-length APP are opposite to the effects associated with pathological Aβ accumulation. In this review, we will summarize the normal functions of APP at synapses and spines along with other known functions of APP, including its role in cell motility, neuronal migration, and neurite outgrowth. These studies shed light on the physiological actions of APP, independent of Aβ effects, and thus lead to a better understanding of the synaptic dysfunctions associated with AD.

Introduction

Alzheimer's Disease (AD) is an age-related neurodegenerative disease characterized by the accumulation of neurofibrillary tangles and amyloid plaques, leading to progressive synapse loss and cognitive decline [1]. Amyloid plaques are composed predominantly of the Aβ peptide, a 40 or 42 amino acid peptide generated by a sequential cleavage of the amyloid precursor protein (APP) by processing enzymes β- and γ-secretases. This cleavage process also produces a large N-terminal secreted product (sAPPβ) and a soluble intracellular protein (AICD) (Figure 1). Alternatively, APP can be sequentially cleaved by α-secretase and γ-secretase, generating secreted APPα (sAPPα) and a P3 fragment, through a process known as the nonamyloidogenic pathway (Figure1). The products of the nonamyloidogenic pathway have been shown to have a neuroprotective effect and to increase neurite outgrowth and enhance learning and memory [2–4].

APP is a type 1 transmembrane glycoprotein and synaptic adhesion molecule with a large extracellular domain and a small cytoplasmic domain [5]. The cytoplasmic domain of APP has an NPXY motif, which interacts with several cytoplasmic adaptor proteins, including FE65, X11, and Dab1 [6–9]. Additionally, the extracellular domain of APP interacts with the extracellular matrix proteins TAG1, Reelin, and F-Spondin [10–13]. Although the physiological functions of APP and its interactions with intra- and extracellular binding proteins are not well understood, accumulating evidence suggests that intact APP may play a key role in promoting synapse formation and function. APP may, in fact, act protectively, rather than destructively. Understanding the physiological function of APP and its binding partners in the CNS is thus critical for providing insights leading to improved therapeutic options for AD. In the following sections, we will examine the physiological functions of APP, independent of the effects of Aβ, and how APP and its interactions with binding partners might affect synapse

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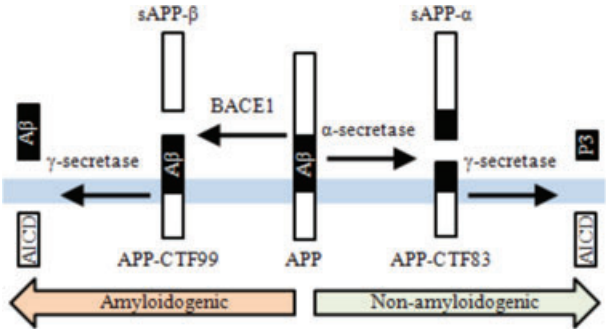

Figure 1 Diagram of APP Processing. APP can be processed via two pathways, amyloidogenic and nonamyloidogenic. In the amyloidogenic pathway, APP is cleaved by processing enzymes β and sequentially cleaved by γ-secretases, generating Aβ, a 40 or 42 amino acid peptide that forms the amyloid plaques. This process also produces a large N-terminal secreted product (sAPPβ) and a soluble intracellular protein (AICD). In the nonamyloidogenic pathway, APP is cleaved by α-secretase and sequentially cleaved by γ-secretase, generating secreted APPα (sAPPα) and a P3 fragment. The products of the nonamyloidogenic pathway have been shown to have a neuroprotective effect and to increase neurite outgrowth and enhance learning and memory [2–4].

formation, dendritic spine formation, dendritic neurite outgrowth, and learning and memory.

Synapse Formation

Recent developmental studies have demonstrated APP's involvement in synapse formation in a variety of contexts. We and others have shown that APP is present in pre- and postsynaptic compartments and is highly expressed between postnatal periods P1 and P36 [10,14,15]. This is a critical period for synaptogenesis and the development of neuronal processes [16]. Although APP is widely expressed in the brain, it preferentially localizes to synaptic puncta in both peripheral and central synapses [14,15,17,18]. Interestingly, a recent study using heterologous coculture systems has demonstrated that the extracellular domain of APP is especially important for promoting synapse formation [15]. These findings suggest that trans-synaptic interactions between pre- and postsynaptic APP contribute to the adhesion of synapses (Figure 2) [15].

APP and APP family members APLP1 and APLP2 also play an important role in synapse development in different systems, especially impacting presynaptic development. For example, Wang et al. found that APP/APLP2 double knockout mice display aberrant neuromuscular junction (NMJ) presynaptic marker proteins and postsynaptic acetylcholine receptors as well as excessive nerve terminal sprouting. Moreover, there was a dramatic reduction of synaptic vesicles at the presynaptic terminal, suggesting that APP and APLP2 are important regulators of the function and structure of developing neuromuscular synapses [19]. Another study found that the presynaptic active zone size and synaptic vesicle density were reduced in submandibular ganglion interneuronal synapses of APP/APLP2 double knockouts [20]. It has also been demonstrated that intraocular injection of APP siRNA significantly reduces APP expression in retinal ganglion cell presynaptic terminals

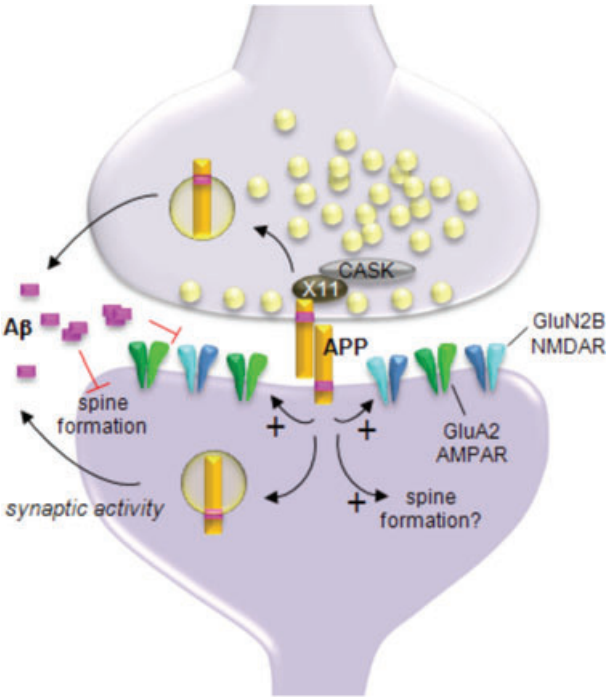

Figure 2 Schematic diagram of proposed APP and Aβ functions at excitatory synapses. APP is expressed pre- and postsynaptically and promotes synapse formation via trans-synaptic interactions of its extracellular domains. Full-length APP also may promote dendritic spine formation as well as surface expression of GluA2-containing AMPA receptors and GluN2B-containing NMDA receptors. Enhanced synaptic activity drives APP processing via the amyloidogenic β-secretase pathway, leading to subsequent spine loss and downregulation of glutamate receptors in a negative feedback loop.

in the superior colliculus, leading to decreased synaptic activity in response to visual stimulation, as measured by glucose utilization [21].

Furthermore, recent studies have shown that interaction between APPL is necessary for FasII-mediated synaptic growth and that overexpression of APP-like (APPL) homolog in Drosophila results in altered synaptic structure [22]. These findings suggest that interaction between Fas-II and APP is necessary for proper synaptic formation. Collectively, these findings demonstrate that APP and related proteins are important for synapse formation during development in diverse systems.

Dendritic Spine Formation

Dendritic spines are the primary sites of excitatory synaptic transmission in the central nervous system (CNS). In addition, dendritic spine number and size may reflect the number of excitatory synapses and the strength of those synapses, respectively. For example, larger spine heads are thought to have stronger, more stable synapses, while longer and thinner spines are less mature and more readily modified [23,24]. Although others have demonstrated that dendritic spines in APP overexpressed (and therefore Aβ-producing) transgenic mice are decreased [25,26], we have

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recently found that full-length APP, mutated so that it cannot be cleaved by β-secretase, promotes dendritic spine formation in primary hippocampal neurons [26]. In the following sections, we will discuss the controversial findings regarding the functions of APP in dendritic spine formation and attempt to reconcile them.

In primary hippocampal neurons, we found that overexpression of APP increases dendritic spine formation (Figure 2), an effect that is decreased by knockdown of endogenous APP with APP-shRNA [27]. Quantitative immunocytochemistry and morphometric analysis revealed a remarkably linear positive correlation between APP expression levels and spine density, strongly suggesting that APP is tightly integrated into the mechanisms that regulate spine number [27]. Although it is still unclear how APP exerts these effects, it should be noted that testing of APP deletion constructs revealed that full-length APP is necessary to enact changes in spine density. More importantly, all changes in spines were completely independent of Aβ.

Using Golgi analysis, we found that APP knockout mice exhibit decreased spine density in cortical layers II/III and CA1 regions of the hippocampus at 1 year of age, indicating that APP is important for maintaining spines *in vivo* [27]. Taken together with the increased post- and presynaptic markers of excitatory synapses in neuronal cultures of APP Tg mice, our data suggest that APP plays a role in maintaining excitatory synapses and spines.

However, our results appear to contradict the results of several studies showing that APP decreases dendritic spine formation, specifically in transgenic mouse models of AD. For example, two mutant APP transgenic mouse lines (J20 and APP/PS1), which overexpress APP and produce Aβ, showed spine loss and dystrophic neurites at 11 months of age [25,26,28]. These morphological abnormalities parallel those seen in human AD hippocampal tissue using diOlistic labeling of neurons [25]. Another study also found decreased dendritic spines in aged APP Tg2576 transgenic mice (producing Aβ) using multiphoton imaging [26]. We also find a similar loss in dendritic spines in 1-year-old APP Tg2576 mice [27]. It appears the apparent discrepancy lies in a key distinguishing feature of the latter studies, which is that all subjects or animals used were aged, and consequently exposed to considerable Aβ accumulation and/or Aβ plaques. Therefore, the spine loss seen in these studies could be attributed to the accumulation of Aβ, rather than to a normal function of APP. In support of this interpretation, we observed that APP Tg2576 mice actually displayed *higher* spine density than wild-type mice in the cortex and hippocampus at a younger age (1 month old) prior to the overaccumulation of soluble Aβ [27]. These results suggest that Aβ may be the primary pathway by which overexpression of APP leads to atrophy of dendritic spines in aged animals, and that Aβ production overrides the positive influence of APP to cause an age-related switch in APP effect from spine-promoting to spine-inhibiting (Figure 2).

Similarly, there are conflicting reports on the role of APP and its effects on dendritic spine formation in APP knockout animals. Most notably, Bittner et al. recently found that APP knockout mice display a 2-fold increase in dendritic spines in the cerebral cortex compared to wild-type animals, suggesting that APP antagonizes dendritic spine formation or stability [29]. It is unclear whether the inability to produce Aβ, the lack of APP, or the loss of some other APP proteolytic product is responsible for this phenotype. Nonetheless, the same may be said for any APP knockout study. The discrepancy between our APP knockout studies mentioned above [26], in which we found decreased spine density in mice aged 1 year, and that of Bittner et al. may therefore be a result of the difference in age of the mice (Lee et al. used 1-year-old mice, Bittner et al. used 4–6 months old mice) and different brain regions examined. Moreover, the two groups used different imaging methodology, another possible explanation for the contrasting findings.

Overall, it seems that APP's effects on dendritic spine formation may be more complex than once thought and may be regulated in a distinct spatiotemporal fashion at different synapses. Therefore, careful specification of age, brain region, and even cell type may be necessary when comparing findings (see Table 1), and generalizations or extrapolations should be made with caution. However, despite the controversy over its precise functions, it is evident that APP is involved in dendritic spine regulation. Further studies are necessary to determine the molecular mechanism by which APP affects dendritic spines. These studies may settle the debate of whether, when, and where APP increases or decreases spine formation.

Synaptic Transmission, Plasticity, and Learning and Memory

Current literature supports the idea that APP not only regulates synapse and spine formation, but also has direct actions on synaptic transmission and ion channel function. A recent study showed that APP knockout mice have increased levels of L-type calcium channel $Ca_V1.2$ and calcium currents in GABAergic inhibitory neurons within the striatum and hippocampus, suggesting that APP regulates synaptic properties of GABAergic neurons by modulating $Ca_V1.2$ [30]. In addition, sAPPα was shown to increase synaptic protein synthesis via a protein kinase G-dependent mechanism, providing a possible mechanism by which sAPPα contributes to synaptic signaling [31].

Interestingly, we found that APP also affects excitatory synaptic transmission by altering AMPA receptor (AMPAR) and NMDA receptor (NMDAR) trafficking. Recently, we demonstrated that APP increases cell surface levels of the GluA2 (or GluR2) subunit of AMPA receptors (or GluAs), but does not alter levels of GluA1 (or GluR1), suggesting that APP regulates certain AMPAR subunits, specifically GluA2 [26]. Considering that alterations in AMPAR subunit expression (particularly in the synaptic content of GluA2-containing AMPARs) can impact synaptic transmission and plasticity, these changes may also potentially alter the function of excitatory synapses [32]. The increase in GluA2 levels is expected to enhance excitatory synaptic transmission, especially because it occurred in the absence of a decrease in GluA1, suggesting an overall increase in AMPAR number at synapses. Using NMR analysis on APP knockout and APP Tg mice we found that APP expression leads to upregulation of glutamate production, which may reflect an increase in synapse number. Thus, APP appears to promote excitatory synaptic function. However, further studies are needed to clarify this, as well as the effects of increased GluA2 production on synaptic excitability.

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Table 1 The functions of APP and Aβ

	APP				Aβ			
	Brain regions	Age	Function	References	Brain regions	Age	Functions	References
Synapse formation	Widely expressed in brain, preferential localization at synaptic puncta in CNS and PNS	E16.5 – P0 NMJ; P0 hippocampal-HEK293 coculture	Promotes synapse formation, contributes to adhesion of synapses	[15]	Cortical and hippocampal neurons	DIV9	Decreases synapse formation	[65]
	Neuromuscular junctions	P0	Regulates function and structure	[19]				
	Submandibular ganglion interneuronal synapses	P0	Modulates presynaptic active zone size and synaptic vesicle density	[20]				
	Superior colliculus	Adult Long-Evans rats	Modulates synaptic activity in response to visual stimulation	[21]				
Dendritic spine formation	Primary hippocampal neurons	DIV21	Promotes dendritic spine formation, increases cell surface levels of the GluR2 (or GluA2) subunit of AMPAR; does not alter levels of GluR1 (or GluA1)	[27]	Cortical layers II/III Hippocampal CA1 pyramidal neurons	1 year	Decreases spine density (APP Tg<Wt)	[27]
	Corticial layers II/III and Hippocampal CA1 pyramidal neurons	1 month	Promotes glutamate synthesis	[27]	Hippocampus	11 months	Spine loss, dystrophic neurites	[25] [26] [28]
	Corticial layers II/III and Hippocampal CA1 pyramidal neurons	1 year	Promotes dendritic spine formation (APP KO< Wt)	[27]				
	Cerebral Cortex	4–6 months	Decreases dendritic spines (APP KO>Wt)	[29]	Cerebral Cortex	21–24 months	Decreases dendritic spines (APP Tg<Wt)	[26]

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Table 1 Continued

	APP				Aβ			
	Brain regions	Age	Function	References	Brain regions	Age	Functions	References
Synaptic transmission, plasticity and learning and memory	Striatum and Hippocampus	DIV10–14	Regulates synaptic properties of GABAergic neurons by modulating $Ca_v1.2$	[30]	Cortical neurons	DIV7–12	Decreases surface levels of NMDARs, promotes endocytosis of NMDARs, decreases NMDA-evoked currents, and reduces NMDAR signaling to CREB (APPswe < Wt).	[66]
	Hippocampus	Young (8–12 weeks)	Increases synaptic protein synthesis	[31]	Cortical and hippocampal	DIV12–19	Decreases and shrinks post-synaptic compartments, decreases and enlarges pre-synaptic compartments	[49]
	Hippocampus	Adult Sprague-Dawley rats	sAPPα causes clustering of NMDA receptor subtype NR1/ NR2B (or GluN1/GluN2B) complex on cell surface, enhances LTP, improves spatial memory	[38]	culture		Reduces PSD-95 and GluR1 surface expression (Tg2576 APP < Wt)	
		2–4 months	Intraventricular injection of sAPPα improves spatial memory	[37]				
		8–9 weeks	Improves learning and memory and behavioral performance (APP KO<Wt)	[42]	Cerebral cortex	6–12 months	Increases $STEP_{61}$ protein over time (age-dependent), increases catalytic activity (Tg2576 APP > Wt). decreases synaptic NMDAR (Tg2576 APP < Wt). (no change at 3 months).	[67]
					Prefrontal cortex	-	Increases $STEP_{61}$ in human AD patients	[67]
	Hippocampus	8–12 months	No effect on synaptic strength or synaptic protein levels (APP KO = Wt)	[44]	Hippocampus	3–4 months	Picomolar Aβ1–42 enhances LTP and learning and memory.	[41]

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Table 1 Continued

	APP				Aβ			
	Brain regions	Age	Function	References	Brain regions	Age	Functions	References
	Primary hippocampal culture	DIV18–20	Decreases excitatory synapses (APP KO> Wt). Decreases NMDAR- and AMPAR-mediated EPSCs (APP KO> Wt)	[46]	Hippocampus	Adult Long-Evans rats	Aβ1–42 enhances learning and memory formation (picomolar range).	[40]
					Hippocampus	15 months	No change in AMPAR or NMDAR protein or mRNA expression. Some decrease in AMPA binding site.(APPswe Tg < Wt)	[48]
					Frontal cortex	6 months	Decreases density of CaMKII clustering at synapses, leading to removal of AMPARs from cell surface (APPswe Tg<Wt)	[47]
					Hippocampus	16 months old	Decreases LTP and synaptic transmission (APPswe Tg< Wt). normal LTP at 2–8 months.	[50]
Neurite outgrowth	Growth cones & Growing Neurites throughout brain		Highly expressed	[51] [52]	Cortical and hippocampal neurons	DIV5-DIV9	Decreases neurite length and arborisation	[65]
			N-terminal secreted APP promotes dendrite outgrowth; interactions with extracellular matrix to promote neurite outgrowth	[53] [51]				
	PC12 cells		Phosphorylated APP is distributed in growth cones regulates neurite outgrowth	[52]				
			Interacts with Abelson (Abl) tyrosine kinase to promoted post-developmental axonal arborization in Drosophila	[4]				

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Table 1 Continued

	APP				Aβ			
	Brain regions	Age	Function	References	Brain regions	Age	Functions	References
	Neural stem cell-derived neurons		sAPPα promotes axonal and dendritic growth, induces neurite outgrowth through MAPK signaling, sAPPa and APP is necessary for neurite outgrowth	[54]				
	Primary Hippocampal Neurons		Increases neurite outgrowth, interacts with Reelin to further increase outgrowth; cytoplasmic domain of APP inhibits neurite outgrowth, decreases neurite branching via interaction with FE65	[10] [55] [56]				
Neuronal migration, motility and development			Necessary for appropriate neuronal positioning, cell adhesion, migration of keratinocytes and microglia, proliferation and differentiation, modulates neurogenesis via interaction with TAG1	[2] [61] [62] [13]				
	MDCK cells		Accelerates wound healing, interacts with FE65 to further accelerate wound healing	[59] [60]				
	Hippocampal region		Decreased neurogenesis	[63]				
	Retina and Tectum		Complex of APP, contactin 4, and NgCAM regulates growth of retinal axons during neuronal development	[64]				

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It has also been demonstrated by us and others that APP interacts with NMDA receptors (NMDARs) in order to regulate their trafficking [14]. NMDARs are calcium-permeable channels important for synaptic plasticity and spine regulation [33]. We have shown that APP overexpression increases cell surface levels of the GluN1 (or NR1) and GluN2B (or NR2B) subunits of NMDARs while knockdown of endogenous APP decreases these levels (Figure 2). However, APP expression (overexpression vs. knockdown) had no effect on cell surface levels of the GluN2A (or NR2A) subunit of NMDARs, suggesting that APP may cause clustering of certain NMDAR subtypes, specifically NR1/NR2B complex on the cell surface, but not NR1/NR2A complex. Consequently, in the same study we also found that reduction of APP decreased NMDAR-mediated whole cell current density and peak amplitude of miniature excitatory postsynaptic currents (mEPSCs). These results suggest a novel physiological role of postsynaptic APP in facilitating NMDAR function. While the exact mechanism of APP regulation of NR2B-containing NMDARs is unclear, considering that these receptors have slower decay kinetics than NR2A-containing NMDARs [34], NR2B-containing receptors would better summate input activity leading to enhanced synaptic plasticity. Indeed, a switch in NR2B-containing to NR2A-containing NMDARs has been implicated in closing the critical period of plasticity in sensory cortices [35,36].

Consistent with our cell biological studies implicating APP in regulation of dendritic spines and NMDAR trafficking, numerous behavioral studies suggest that APP influences synaptic plasticity as well as learning and memory. For example, administration of sAPPα has been shown to enhance long-term potentiation (LTP), a leading cellular model of memory, and improve spatial memory in mice [37,38]. Another study showed that APP is an important component of early phase memory formation [39]. Surprisingly, even a form of Aβ that is associated with AD progression (Aβ1–42) has been found to enhance learning and memory formation, especially at a picomolar range [40,41], suggesting that the normal function of Aβ (when not accumulated to pathological levels) may be beneficial for memory.

Nevertheless, reports of APP's effects on learning and memory have often been contradictory. Several studies have shown that APP knockout mice have impaired learning and memory and behavioral performance [42,43], while others have found that APP knockout mice have no significant alteration in synaptic strength or in synaptic protein levels [44,45]. Still others have reported that APP knockout mice have significantly *more* functional excitatory synapses compared to wild-type littermates as determined from an increase in the frequency of miniature excitatory postsynaptic current (mEPSCs) [46]. Another study showed that APP overexpressing transgenic mice have *decreased* cell surface levels of AMPARs as well as a decreased density of CaMKII clustering at synapses, suggesting that Aβ induced changes in CaMKII subcellular distribution, leading to the removal of AMPARs from synaptic membranes [47–49]. Primary neurons from APP transgenic mice also showed a decrease in LTP and synaptic transmission [50]. The apparent discrepancies described may be due to methodological differences, as well as variations in the developmental ages and bran regions studied in these reports. Moreover, some of these studies were performed *in vivo*, while others were performed *in vitro*, which could also have contributed to conflicting results. Additionally, several groups used aged APP overexpressing mice that predominantly express Aβ plaques, which, as discussed, possibly oppose the normal function of full-length APP.

Neurite Outgrowth

APP has been shown to be highly expressed within growth cones and growing neurites [51,52]. Several studies have found that APP promotes neurite outgrowth from cells in culture. Specifically, N-terminal secreted APP promoted dendrite outgrowth in primary hippocampal neurons [53]. Another study showed that N-terminal secreted APP interacts with components of the extracellular matrix, such as heparin sulfate proteoglycans (HSPGs). This association further increases neurite outgrowth [51]. Another study shows that APP, when phosphorylated at the Thr668 residue, is distributed in neuronal growth cones, and that the phosphorylated form of APP regulates neurite outgrowth in PC12 cells [52]. In addition, human APP and *Drosophila* APPL promoted postdevelopmental axonal arborization, depending on the interaction between the C-terminus of APP and Abelson (Abl) tyrosine kinase, suggesting a potential role for APP in axonal outgrowth following traumatic brain injury [4]. Furthermore, secreted sAPPα promoted axonal and dendritic growth [54] and induced neurite outgrowth in neural stem cell-derived neurons through MAP kinase signaling [3]. Young-Pearse et al. also found that sAPPα and full-length APP are necessary for neurite outgrowth. However, sAPPα does not affect neurite outgrowth in the absence of full-length APP, indicating that sAPPα regulates the effects of full-length APP on neurite outgrowth [2]. Recently, we found that full length APP increased dendritic neurite outgrowth, and that this effect was heightened by APP's interaction with Reelin. Therefore, the interaction between Reelin and APP may act cooperatively to enhance neurite development [10]. In contrast, it has also been reported that the cytoplasmic domain of APP inhibits neurite outgrowth in primary hippocampal neurons, providing evidence that the APP C-terminal domain could obstruct Reelin signaling [55]. Another study found that disrupting the interaction between APP and FE65 in hippocampal neurons increases neurite branching without affecting total neurite outgrowth, suggesting that APP negatively regulates neurite branching via an interaction with FE65 during early neuronal development [56].

Neuronal Migration, Motility, and Development

Several observations suggest physiological functions for APP in neuronal migration and motility. For example, mice lacking all three APP family members (APP, APLP1, & APLP2) die at various stages of development and demonstrate neuronal migration abnormalities in their brains. While APLP2-/-APLP1-/- and APLP2-/-APP-/- double mutants are not viable, triple mutants (APLP2-/-APLP1-/-APP-/-) survive through late embryonic stages and show aberrant migration of neuroblasts through the cortex, resulting in clusters of cells that migrate through the pial membrane [57]. Migration defects are also observed with *in utero* APP knockdown. APP knockdown *in utero* inhibits cortical plate entry of neuronal precursor cells, whereas APP overexpression causes migration of

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cells to overshoot the cortical plate. Thus, normal APP levels appear necessary for appropriate neuronal positioning [58].

Recent studies have also shown that APP is involved in cell motility. For example, we and others found that APP accelerates wound healing and that the interaction between APP and FE65 in MDCK cells further accelerates wound healing [59,60]. These results suggest that the cooperative interaction between APP and FE65 is involved in regulating cell motility. However, whether the interaction between APP and other binding partners may modulate cell motility is not well studied.

In addition, *in vitro* assays demonstrated that APP is needed for cell adhesion, migration, and proliferation of keratinocytes [61], and mobilization of microglia [62]. Another study found that transgenic adult mice with human wild-type APP show decreased neurogenesis (neuronal differentiation) in the hippocampal region [63]. Furthermore, during development of the retinotectal system, the complex of APP, contactin 4, and NgCAM is expressed in both the tectum and the retina, where it regulates the growth of retinal axons during neuronal development [64]. Ma et al. recently demonstrated another pathway by which APP affects early CNS development. They found that APP interacts with TAG1, a member of the F3 family, and that this interaction modulates neurogenesis [13]. These findings suggest that APP plays diverse and important roles during brain development.

Conclusions

Intense research has produced remarkable progress in uncovering the molecular properties of APP and Aβ. A general conclusion may be drawn from these studies: it is becoming increasingly clear that APP is a functionally complex molecule with multiple physiological responsibilities in a wide variety of pathways. These functions vary with development, age, brain region, or cell type, and may differ between full-length APP and its processing products. Thus, the effect of APP as a whole should be considered an integration of the subeffects of the holoprotein and its metabolic products, a dynamic equation that fluctuates according to the changing expression level of the different molecular species. In this view, the synaptic deficits seen in AD could be due not only to the pathological accumulation of Aβ, but also to the loss of synapse-promoting capabilities of intact APP or nonamyloidogenic components. A better understanding of the functions of APP and the regulation of its processing to Aβ will likely provide insights into both the pathogenesis of AD and novel therapeutic approaches aimed at restoring synaptic and cognitive ability—a scientific investment with tremendous upside potential.

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Conflict of Interest

For this review, the authors do not have conflict of interest to declare.

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