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Restoring sAPPα functions as a potential treatment for Alzheimer's disease

Ahsan Habib[1,*], **Darrell Sawmiller**[1], and **Jun Tan**[1]

[1]Rashid Laboratory for Developmental Neurobiology, Silver Child Development Center, Department of Psychiatry and Behavioral Neurosciences, Morsani College of Medicine, University of South Florida, 3515 E Fletcher Ave. Tampa 33613, FL, USA

Abstract

Soluble amyloid precursor protein α (sAPPα), a secreted proteolytic fragment of non-amyloidogenic amyloid precursor protein (APP) processing, is known for numerous neuroprotective functions. These functions include but are not limited to proliferation, neuroprotection, synaptic plasticity, memory formation, neurogenesis and neuritogenesis in cell culture and animal models. In addition, sAPPα influences amyloid-β (Aβ) production by direct modulation of APP β-secretase proteolysis as well as Aβ-related or unrelated tau-pathology, hallmark pathologies of Alzheimer's disease (AD). Thus, the restoration of sAPPα levels and functions in the brain by increasing non-amyloidogenic APP processing and/or manipulation of its signaling could reduce AD pathology and cognitive impairment. It is likely that identification and characterization of sAPPα receptors in the brain, downstream effectors, and signaling pathways will pave the way for an attractive therapeutic target for AD prevention or intervention.

Keywords

sAPPα; APP; Aβ; Alzheimer's Disease; Receptor; Biomarker; Neuroprotection; Synaptic Plasticity; Memory; Neurogenesis; Aging; Cognitive Impairment; Therapeutics

Significance

Soluble amyloid precursor protein (sAPPα), a secreted proteolytic fragment of APP processing, elicits neuroprotection, synaptic plasticity, memory formation, neurogenesis and neuritogenesis, while reducing amyloid and tau pathology, in the brain. Since impairment of these processes underlies Alzheimer's disease, restoration of sAPPα levels and function by increasing non-amyloidogenic APP processing and/or manipulation of its signaling could

[*]Corresponding author: Ahsan Habib mhabib1@health.usf.edu.

Authors' information

AH is a graduate student of Molecular Pharmacology and Physiology at University of South Florida. DS is an Assistant Professor at Psychiatry and Behavioral Neurosciences department. JT is a Professor of Department of Psychiatry and Behavioral Neurosciences at University of South Florida, Tampa, Fl. USA. JT holds the Sliver Chair in Developmental Neurobiology.

Competing interests

The authors declare that they have no conflict of interest.

Authors' contribution

All authors drafted, contributed, read and approved our review.

reduce AD-related amyloid pathology and cognitive impairment. The present review summarizes recent work on functional neural properties of sAPPα, as well as its potential signaling mechanisms, and discusses several potential sAPPα-based therapies for AD and other dementias.

More than one hundred years have passed since Alois Alzheimer and Oskar Fisher's discovery of the two neuropathological hallmarks of Alzheimer's disease (AD), deposition of extracellular amyloid plaques and intracellular neurofibrillary tangles. Currently, AD is the most common type of age-associated dementia and there are no disease modifying treatments. The pathological features of AD are currently known to include: (a) extracellular amyloid plaques composed largely of amyloid-β (Aβ) peptides (Hardy and Allsop, 1991), (b) intracellular neurofibrillary tangles (NFTs) composed of the hyperphosphorylated microtubule associated protein tau (Goedert et al., 1991), (c) dysmorphic synapses and (d) neuronal loss (Palop and Mucke, 2010). The proteolytic cleavage of amyloid precursor protein (APP) by two different enzymes, β- (also called BACE1) and γ-secretases, is a critical step in AD development. In the non-amyloidogenic pathway, most of the APP is cleaved at the plasma membrane by α-secretase, which precludes Aβ formation but produces a large secreted N-terminal ectodomain of APP (sAPPα) of 105–125 kDa and small membrane-bound α-C-terminal fragment (CTF) (Haass and Selkoe, 1993). The membrane-bound α-CTF is cleaved by γ-secretase complex resulting in release of P3 peptide of 3 kDa and AICD (APP intracellular domain). In the amyloidogenic pathway, the remaining uncleaved APP is processed into the endosomal-lysosomal compartments by β-secretase results in soluble sAPPβ and membrane-bound β-CTF. The subsequent action of γ-secretase on β-CTF produces $Aβ_{40/42}$ peptides and AICD (Kang et al., 1987). In addition to α-, β- and γ-secretases cleavage, a recent study identified that APP can be cleaved by the metalloprotease meprin β, generating soluble N-terminal truncated APP (N-APP) and N-terminally truncated $Aβ_{2\text{-}X}$ peptide variants, which show increased aggregation potential compared to non-truncated $Aβ_{40}$ peptides (Jefferson et al., 2011); (Bien et al., 2012, Schonherr et al., 2016). Cleavage of APP by meprin β occurs prior to the endocytosis and different APP mutants affect the catalytic properties of the enzyme. More specifically, Swedish mutant APP does not undergo this cleavage and unable to produce this truncated Aβ variants. Another study showed that APP can also be cleaved by matrix metalloproteinases such as MT5-MMP, referred to as η-secretase, which releases a long-truncated ectodomain (sAPPη) and a membrane-bound CTF, termed CTFη (Willem et al. 2015). The membrane-bound CTFη is further cleaved by α- and β-secretases releasing both a long (Aη-α) and a short (Aη-β) peptide, respectively. The cleavage of η, cuts far from the N-terminus of the β-secretase cleavage site and produces fragments (92 or 108 amino acids), which end at either the β- or α-secretase site respectively (Willem et al., 2015) (Figure 1).

A number of *in vitro* and *in vivo* studies have demonstrated the toxic properties of Aβ peptides since the first identification of the APP gene in 1987 (Kang et al., 1987, Younkin, 1995). Administration of Aβ peptides (Maurice et al., 1996), their structural mimetics, and anti-Aβ antibodies (Cleary et al., 1995) have supported the deleterious functions of the peptide in terms of promoting cognitive deficits. Like sAPPα, sAPPβ has beneficial effects, is soluble in nature and secreted extracellularly but lacks 16 amino acids at the C-terminus. The potency of sAPPβ is found to be 100-times less than that of sAPPα, measured in its

ability to protect hippocampal neurons against excitotoxicity, glucose deprivation, and Aβ toxicity (Furukawa et al., 1996b, Barger and Harmon, 1997). In accord with this finding, other studies also reported the reduced potency of sAPPβ as a neuroprotective fragment (Turner et al., 2003); (Li et al., 1997). Like sAPPα, sAPPβ also supports axonal outgrowth (Chasseigneaux et al., 2011) and neural differentiation of human embryonic stem cells (Freude et al., 2011). In contrast to above effects, sAPPβ also causes neuronal cell death by binding to the death receptor 6 (DR6) (Nikolaev et al., 2009) and does not protect cell death induced by proteasome inhibitors (Copanaki et al., 2010). Further study showed that sAPPβ fragments are not involved in long-term potentiation (LTP) (Taylor et al., 2008). Perneczky and colleagues have reported that plasma levels of sAPPβ were significantly decreased (Perneczky et al., 2013) in AD patients compared to control and frontotemporal dementia (FTD) patients. However, sAPPβ levels were increased in cerebrospinal fluid (CSF) (Perneczky et al., 2011) of mild cognitive impairment (MCI) patients who had progressed to probable AD compared to control and patients with frontotemporal dementia (FTD).

Unlike sAPPβ and Aβ, sAPPα has demonstrated neurotrophic and neuroprotective functions. In contrast to its neuroprotective effects, we and others have shown that sAPPα attenuates Aβ pathology by binding to the allosteric site of BACE1 (Obregon et al., 2012, Peters-Libeu et al., 2015). Additionally, sAPPα has been shown to reduce tau hyperphosphorylation by inhibiting BACE1 and glycogen synthase kinase (GSK) 3β activity in cell culture and transgenic PSAPP mouse model (Deng et al., 2015). Surprisingly, the physiological functions and therapeutic importance of this fragment have received little attention. In this review, we have compiled physiological functions of sAPPα, especially in the context of AD. It is possible that this is not a complete list of potential sAPPα actions. We believe comprehensive understanding of the sAPPα functions, signaling pathways and downstream effectors could provide new therapeutic opportunities for effective AD drug development.

Modulation of APP processing and Aβ clearance by sAPPα-receptor interaction

a. Interaction of LRP1 and sAPPα

The physiological functions of sAPPα have been extensively studied in animal and in cell culture models. Earlier work pointed out the role of sAPPα as an extracellular ligand that modulates APP amyloidogenesis. LRP1 was initially identified as a receptor for APOE (Beisiegel et al., 1989), which regulates APP and Aβ metabolism (Kanekiyo and Bu, 2014). A study by Kounnas and colleagues (1995) first demonstrated that sAPP binds to the endocytic low-density lipoprotein (LDL) receptor-related protein (LRP1) *via* the Kunitz-type serine protease inhibitor (KPI) domain (Kounnas et al., 1995). Through the interaction with KPI, the LRP1 receptor enhances internalization of sAPPα into the endosomal and lysosomal compartments. As the KPI domain is essential for the sAPPα-LRP1 interaction, sAPPα695 isoform (lacking the KPI domain) acts as a weak LRP1 ligand. Both LRP1 antagonist (receptor-associated protein [RAP]) and heparin are able to inhibit the interaction. Interestingly, binding of RAP do not completely inhibit the effect and suggest the presence of receptors other than LRP1. Using LRP1-deficient cell lines, they showed that the binding

is dependent of LRP1 receptor (Kounnas et al., 1995). These data provide evidence that secreted APP is internalized into the cell *via* the LRP1 receptors and heparin modulates the binding and internalization of sAPPα. As sAPPα does not influence Aβ production, it would be very interesting to see if the secreted APP751 could affect generation of Aβ through sAPPα-(KPI)-LRP1 interaction. Furthermore, Knauer and co-worker (1996) demonstrated that LRP1 is also critical for internalization and generation of Aβ by cell surface (unprocessed) APP751 (containing the KPI domain). The interaction between APP and LRP1 receptor leads to increased trafficking of APP into the amyloidogenic endocytic pathway (Knauer et al., 1996). This finding further supports the data of Kounnas and colleagues by showing that sAPPα695, which lacks the KPI domain, does not undergo this interaction. To identify the sAPPα receptor specifically, Hoffmann and colleagues used histidine-tag labeling techniques to identify cell surface-bound sAPPα. Using immunocytochemistry and surface plasmon resonance spectroscopy, they demonstrated that sAPPα (1 and 10 nM) binds specifically on the cell surface microdomain (Hoffmann et al., 1999). In 2000 and subsequent years, Goto and Tanzi further studied the sAPPα-LRP1 interaction and demonstrated that a mini domain within LRP1, known as LRP-cluster II region, can bind specifically with the sAPPα-KPI domain (Goto and Tanzi, 2002). They also showed that inhibition of interaction of KPI and the cluster II region of LRP1 reduces generation of Aβ in Chinese hamster ovary cells overexpressing wild-type APP (Goto and Tanzi, 2002). A recent study suggests that all three isoforms of APP are expressed in brain but APP695 is a predominant isoform in neurons (Guo et al., 2012a). This finding suggests that LRP1 may not be an exclusive receptor for sAPPα in the brain. It is plausible that inhibition of the sAPPα-(KPI)-LRP1 interaction may force sAPPα to interact with Aβ. A proposed tentative sAPPα-Aβ interaction and subsequent clearance by LRP1 receptor is illustrated in Figure 2a. More recently, Pietrzik group (2016) demonstrated that deletion of mouse LRP1 receptors from endothelium cells of the blood brain barrier (BBB) significantly elevated soluble $A\beta_{42}$ in the brain and reduced it in blood plasma. This strongly supports LRP1-mediated clearance of Aβ across the BBB (Storck et al., 2016). It is plausible that sAPPα shuttles Aβ to the endothelial LRP1 at the abluminal side and shifts Aβ out the brain to the periphery as shown in Figure 2b. In accord with this hypothesis, our group (2015) found that sAPPα forms a complex with Aβ (corresponding to $APP_{672–688}$ region) and thereby enhances phagocytosis by monocytes. In addition, sAPPα enhances scavenger receptor class A (SR-A) mediated phagocytosis of Aβ by microglia (brain) and monocytes (peripheral system) as shown in Figure. 2c (Darlington et al., 2015). There is a need of further study to prove this hypothesis. On the other hand, Moir and Tanzi have showed that LRP1-mediated removal of Aβ involved in the formation of a complex with Aβ and APOE or alpha (2)-macroglobulin. They demonstrated that the KPI domain inhibits LRP1-mediated clearance of Aβ (Moir and Tanzi, 2005). Further investigation on sAPPα-LRP1 interaction and subsequent endocytosis of APP will characterize sAPPα-mediated efflux of Aβ from the brain.

b. Interaction of scavenger receptor SR-A and sAPPα

The microglial expression of SR-A has been shown to increase in brain injury (Bell et al., 1994) and in microglia surrounding the plaques (Honda et al., 1998). Santiago *et al.* (2001) found that activated platelets secrete sAPPα in the conditioned media, which competes with

both LDL and SR-A receptors. They showed that both sAPP751 and sAPP695 equally bind to the SR-A receptor suggesting that the binding is independent of the KPI domain. Although, they found that sAPPα (residues of 191–264) is involved in SR-A binding (Santiago-Garcia et al., 2001), however, deletion of the SR-A receptors do not affect the plaque numbers and neurodegeneration in transgenic mice expressing human APP (Huang et al., 1999). Interestingly, our recent work indicates that sAPPα forms a complex with $A\beta_{1–16}$ (corresponding to APP672–688) region, which augments the binding of this heterodimer complex with SR-A receptor. Our conclusion that scavenger receptor SR-A seems to be crucial for sAPPα-mediated clearance of Aβ (Darlington et al., 2015).

c. Interaction of sorting protein related receptor A (SORLA/LR11/SORL1) and sAPPα

A recent study demonstrated that variation within the two different clusters of intronic sequences of sorting protein related receptor A (SORLA/LR11/SORL1) is linked to sporadic AD (Rogaeva et al., 2007). Additional study data showed that overexpression of SORLA decreased production of Aβ and vice versa (Rogaeva et al., 2007). This finding is in good agreement with the reduced expression of SORLA in AD brain (Dodson et al., 2006). Using fluorescence resonance energy transfer (FRET) assay, Andersen *et al.* (2006) identified binding sites for APP-SORLA interactions (Andersen et al., 2006). They showed that two different sites of APP (APP28–123 and APP316–498) bind separately with SORLA (residues of 1044–1526). Utilizing plasmon resonance analysis and analytical ultracentrifugation techniques, the same study demonstrated that carbohydrate-linked (APP316–498) E2 domain of APP binds more favorably than the N-terminal (APP28–123) domain (Andersen et al., 2006). As the carbohydrate-linked domain (APP316–498) is an integral part of the sAPPα molecule, SORLA may be a plausible neuronal receptor. In agreement with this hypothesis, Hartl and colleagues have confirmed the sAPPα-SORLA interaction in cultured mouse cortical neurons showing that sAPPα downregulates cyclin dependent kinase (CDK) 5 activity by binding with the SORLA receptor (Hartl et al., 2013). As would be expected, the sAPPα-SORLA interaction increased expression of ORP150, which functions as a protective chaperone (Hartl et al., 2013). Like SORLA, Gustafsen *et al.* (2013) showed that sortilin acts as a neuronal receptors for sAPPα695. SORLA and sortilin both bind and mediate internalization of sAPPα into different intracellular compartments. Extracellular 6A domain of sAPPα interacts with sortilin in a pH dependent manner. As sortilin binds with both neuronal (sAPPα695) and non-neuronal (sAPPα751) isoforms, indicating the interaction could be independent of the KPI domain (Gustafsen et al., 2013).

d. Interaction of APP and of its different domains with sAPPα

Earlier works indicated APP as a cell-surface receptor that interacts with a variety of molecules in the extracellular environment. A recent investigation indicates that interaction of sAPPα ectodomain and full-length APP are crucial for neurite outgrowth. More specifically, they showed that neurotrophic activity of sAPPα is dependent on the membrane-bound full-length APP (Young-Pearse et al., 2008). To investigate if binding of sAPPα to the cell surface receptors is dependent on the membrane-bound (unprocessed) APP and of its homologues APLP1 and APLP2, Reinhard *et al.* (2013) demonstrated that sAPPα binds to the cell surface on a neuroblastoma cell line B103, which does not express APP, APLP1 and/or APLP2 (Reinhard et al., 2013). This suggests that binding of sAPPα is

independent of full-length APP and of its family members. This finding is in disagreement with the Young-Pearse group (2007), where they demonstrated that activity of sAPPα is dependent on the full-length APP (Young-Pearse et al., 2008). Reinhard *et al.* (2013) also found that the growth factor like domain (GFLD) of sAPPα binds to the heparan sulfate proteoglycan (HSPG) at a concentration of 100 nM. They concluded that GFLD binds with heparin and the E2 domain mediates interaction with the HSPG (Reinhard et al., 2013).

e. Interaction and effect of dimerization of APP and its homologs (APLP1/APLP2) with sAPPα

APP and other homologs such as APLP1 and APLP2 form homo- and/or hetero- dimer, which modulate the trafficking of APP into the endocytic compartments. The homodimerization of APP at the plasmamembrane drives it into the endocytic compartments and generates Aβ upon cleavage by BACE1 (Scheuermann et al., 2001, Kaden et al., 2008). While studying the effect of sAPPα, Gralle and others have demonstrated that sAPPα protects neuronal cells by disrupting the dimerization of APP as shown in Figure 2e (Gralle et al., 2009); (Khalifa et al., 2010). While looking at the binding mechanism, Wang and colleagues demonstrated that heparin binds with the antiparallel dimer of APP (Wang and Ha, 2004). In agreement with the heparin-APP interaction, Gralle and colleagues demonstrated that heparin induces dimerization of sAPPα in solution at high concentrations (Gralle et al., 2006). Using single molecule FRET analysis, they showed that heparan sulfate (HS) induces dimerization of APP, which is crucial for intracellular signaling upon binding with an extracellular ligand (Gralle et al., 2009). Previous research indicated that both unprocessed and secreted APP can bind with the heparan sulfate (Williamson et al., 1996) and heparin (Mok et al., 1997), respectively. In recent years, Dahms and colleagues extensively investigated the interaction of heparin with the ectodomain of APP. They demonstrated that the heparin and E1 domain interaction is very specific (low dissociation constant, Kd, indicative of high affinity) (Dahms et al., 2010). In addition to heparin-E1 interaction, the E2 domain of APLP1 can bind with HS chain of HSPG in two different ways. The first mechanism involves the specific binding of E2 domain with the nonreducing end of the highly sulfated HS chain of HSPG. The second mechanism involves the general binding of the E2-HS chain. A different but similar study demonstrated that heparin-induced dimerization of APP is mediated by E1 (subdomains GFLD and CuBD) and regulated by acidic domain (Hoefgen et al., 2014). Dahms and colleagues have further demonstrated that sAPPα brings the E2 domain close to the nonreducing end of HS and the process is enhanced by heparinase modification (Dahms et al., 2015). Previous research suggested that the trans-dimerization of sAPPα or APP-E1 domain is crucial for synaptic functions, which also possess a copper binding domain (D2, CuBD, at amino acids 124–189). While investigating the role of copper on APP-dimerization, it has been shown that copper induced both cis-and trans-dimerization of APP *in vitro* (Kd = 18 nM) and *in vivo* (Kd = 100 μM) but the process is independent of the heparin interaction (Baumkotter et al., 2014).

The role of sAPPα in neuroprotection

Multiple lines of evidence demonstrate that sAPPα protect neurons against a variety of insults in cell cultures and animal models. Initial studies using rat hippocampal and human

cortical neurons showed the protective role of sAPPα against hypoglycemic damage and glutamate mediated neurotoxicity (Mattson et al., 1993). In addition to the above findings, both sAPPα695 and sAPPα751 protect rat hippocampal neurons from iron mediated oxidative injury and Aβ-induced Ca^{2+} and free radical mediated neurotoxicity (Goodman and Mattson, 1994). These findings indicate that sAPPα regulates calcium homeostasis by inhibiting elevation of intracellular Ca^{2+} concentrations, the mechanism by which it enhances neuronal survival. Barger and Mattson further investigated the mechanism through which sAPPα shows the neuroprotective effect on hippocampal neurons. They showed that sAPPα increases the levels of cyclic nucleotides (cGMP) in neuronal cells, which inhibits elevation of cytosolic Ca^{2+} levels through inhibition of NMDA receptors (Barger et al., 1995). In a follow up study, the same group showed that elevation of cGMP by sAPPα is dependent on the activation of membrane-bound guanylate cyclase but independent of cytosolic (soluble) guanylate cyclase (Barger and Mattson, 1995). Using whole-cell patch-clamp and imaging techniques, Furukawa and colleagues extensively investigated sAPPα-mediated neuroprotective mechanisms in hippocampal neurons, showing that sAPPα (0.11 nM) suppresses neuronal excitability by activating K^+ channels and modulates glutamate neurotoxicity by inhibiting NMDA-currents (Furukawa et al., 1996a, Furukawa and Mattson, 1998).

In addition to neuronal cells, both astrocytes and microglia express all three major forms of APP and process mostly via amyloidogenic pathway. The level and magnitude of APP expression by non-neuronal cells (astroglial) is much more subtle than the neuronal cells (neurons). Hence, very few studies have reported the exact role of sAPPα on regulating astroglial functions. Barger *et al.* (1997) showed that sAPPα activate microglial inflammation (Barger and Harmon, 1997) and activation *via* c-Jun N-terminal kinases (JNK) and p38-MAPK pathway (Bodles and Barger, 2005). In contrast, a different study showed that primary cytokine such as IL-1α stimulates α-secretase activity and expression of ADAM-10 and ADAM-17which enhanced APP processing and sAPPα secretion through non-amyloidogenic pathway (Bandyopadhyay et al., 2006). However, the secretion and production of sAPPα is independent of c-JNK pathway but dependent on p38-MAPK pathway. A very recent study showed that inflammatory cytokines such as TNFα and IL-1β treated astrocytes enhance sAPPα production through non-amyloidogenic processing of APP by increasing membrane fluidity in neuronal cells (Yang et al., 2015). Further study is needed to clarify the role of sAPPα in activating astroglial cells and subsequent effect on neurons in the brain.

In accord with the cell culture findings, sAPPα also exerts neuroprotective effects in animal models following CNS injury. Administration of recombinant sAPPα in a rat model reduced hippocampal neuronal deaths against ischemic (Smith-Swintosky et al., 1994), spinal cord (Bowes et al., 1994), and traumatic brain injury (TBI) (Thornton et al., 2006, Corrigan et al., 2011). In addition to enhanced neuronal survival, surviving neuronal cells synthesize new proteins, attenuate amyloid pathology, improve cognition, and motor functions in a moderately brain-injured APP knockout (KO) mouse model (Corrigan et al., 2012). A successive study by the same group showed that the heparin binding site of sAPPα (residues of 96–110) protects against TBI (Corrigan et al., 2014). The cellular receptors and the downstream effectors involving these effects are largely unknown. In brief, the

neuroprotective effects of sAPPα could be through the modulation of ion channels and gene expressions (Mattson et al., 1997). While investigating the neuroprotective functions of sAPPα, several studies showed that sAPPα activates phosphatidylinositol-3-kinase (PI3K)/ Protein Kinase B (PKB/Akt) (Cheng et al., 2002, Jimenez et al., 2011); (Milosch et al., 2014), nuclear factor kappa B (NF-kB) (Guo et al., 1998), extracellular signal regulated kinase (ERK) (Greenberg et al., 1995, Cheng et al., 2002), and inhibits stress-induced c-JNK signaling (Kogel et al., 2005). Lastly, sAPPα mediated neuroprotection also involves activation and transcription of different factors and enzymes such as insulin-like growth factor 2, manganese superoxide dismutase, catalase, and transthyretin (Stein et al., 2004, Kogel et al., 2005).

The role of sAPPα in learning and memory formation

Alterations or loss of synapses (Terry et al., 1991) and cognitive decline (DeKosky et al., 1996) have been reported in healthy aging and in neurodegenerative diseases including but not limited to AD. However, the processes of memory formation in the brain are still largely unknown. Nevertheless, to identify the cognitive impairment, researchers and physicians frequently measure long-term potentiation (LTP) in basic and clinical research. In addition to impaired LTP, hippocampal and cortical studies have showed significant correlation between cognitive impairment and synaptic protein loss; clearly indicating that synapses are critical for memory formation and storage (Winocur et al., 2010). Many researchers have studied the role of APP in synaptic plasticity and memory formation. Not surprisingly, APP, a key protein in AD development, is highly expressed in the presynaptic terminals and plays a critical role in synaptic functions (Turner et al., 2003), LTP, (Seabrook et al., 1999) and memory formation (Huber et al., 1997, Mileusnic et al., 2000). Muller and Zheng group have independently studied the role of APP and its fragments in synapse formation and correlated those abnormalities with cognitive impairment using several APP mutant mouse models [See reviews by (Aydin et al., 2012, Guo et al., 2012b, Muller and Zheng, 2012)]. In addition, Jung and Herms published a comprehensive review on the role of APP in dendritic spine formation [for review please see (Jung and Herms, 2012)]. The details of those studies are beyond the scope of this review.

Initial studies by blocking the extracellular domain of APP with anti-APP antibodies showed behavioral and memory impairment in rat models (Doyle et al., 1990, Huber et al., 1993). Subsequently, using an APP (KO) hypomorphic mouse models, Muller and Zheng have demonstrated impaired behavioral functions in rodent models (Muller et al., 1994, Zheng et al., 1995, Zheng et al., 1996). In contrast to the effects of Aβ, APP and its proteolytic fragments particularly sAPPα, promoted enhanced synaptic plasticity (Ishida et al., 1997, Hick et al., 2015) and memory formation (Bour et al., 2004). Additionally, the positive correlation between decreased CSF levels of sAPPα and impaired cognitive functions in animal (Anderson et al., 1999) and human studies (Van Nostrand et al., 1992, Lannfelt et al., 1995, Almkvist et al., 1997) further suggested a role of sAPPα in cognition. To identify the mechanism, intracerebroventricular (ICV) administration of total sAPP antibodies (combined sAPPα and sAPPβ) targeted against the N-APP demonstrated memory deficits in rat models (Doyle et al., 1990, Huber et al., 1993). To investigate the role of sAPPα in learning and memory formation, recombinant sAPPα (0.5 pg/4μl/mice) (Bour et al., 2004)

and of its active domain (17 residues of sAPPα) (Roch et al., 1994) showed improved spatial memory in mice and memory retention in an aged rats, respectively. While investigating the role of sAPPα in LTP formation, induction of LTP has been shown to be associated with an increased secretion of APP and neural cell adhesion molecule in the dentate gyrus (DG) of a rat model (Fazeli et al., 1993). Furthermore, to investigate if sAPPα has a role in synaptic plasticity and spatial memory formation, administration of recombinant sAPPα increased and antibodies against endogenous sAPPα decreased LTP and NMDA transmission in an adult rat model (Taylor et al., 2008). NMDA receptors activation are shown to be involved in induction of nitric oxide from arginine, which subsequently increases cGMP, stimulates presynaptic (Arancio et al., 2001) soluble guanylyl cyclase (East and Garthwaite, 1991) and protein kinase G (PKG) signaling pathway (Zhuo et al., 1994). A different study in a drug induced-amnestic mouse model showed that both sAPPα695 and sAPPα751 are equally effective in enhancing memory at low doses (0.05–5000 pg) and the effect is independent of its KPI domain (Meziane et al., 1998). A recent study showed that sAPPα (10 nM) significantly increased protein synthesis at hippocampal synapses through cGMP signaling in an adult Sprague-Dawley rat model that might contribute synaptic plasticity (Claasen et al., 2009).

The APP KO mouse model exhibits anatomical, synaptic, and behavioral alterations. To investigate the role of APP and of its fragment sAPPα, Muller group have (2007) deleted the APP locus (APP-KO) and replaced it with an sAPPα knock-in (KI) gene at the same position, which constitutively expressed secreted sAPPα in the brain. They showed that sAPPα-KI mice had improved synaptic plasticity, cognition, and a rescue of all the deficits shown by APP-KO mice such as reductions in brain and body weight, grip strengths, exploratory impairments, alterations in circadian locomotor activity, as well as impairment of spatial learning and LTP (Ring et al., 2007). Interestingly, when sAPPα-KI mice were crossed with the APLP2 KO background model, most of the double mutants survived into adulthood. Despite the normal synaptic structure and transmission, these mice showed impaired LTP induction and maintenance coupled with working memory impairment. These findings suggest that sAPPα expression does not compensate the early developmental abnormalities in APLP2 KO mice and showed excessive nerve growth with widened nerve plates (Weyer et al., 2011). Contrary to the beneficial role of sAPPα, many studies have reported the increased level of sAPPα in autism studies (Bailey et al., 2008, Ray et al., 2011). The role of dysregulated secretion of sAPPα in autism is unknown.

Interestingly, to investigate the effect of sAPPβ in APP KO mouse, Li *et al.* (2010) constructed an sAPPβ KI mouse model. They found that secreted sAPPβ is highly stable in cell culture and in brain and CSF in this transgenic sAPPβ KI mouse model. Most of the offspring of the sAPPβ KI and APLP2 KO crossed mice died early due to the postnatal lethality. All surviving mice showed normal body weight and grip strength with abnormal nerve plate terminals (Li et al., 2010). The postnatal lethality of the APP/APLP2 double KO mouse was rescued by crossing sAPPα-KI with APLP2-deficient mice that showed impaired LTP function (Weyer et al., 2011). Due to the postnatal lethality of APP double KO mice, the effect of sAPPα was studied on conditional APP/APLP2 double KO mice model (Hick et al., 2015). These mice show reduced neurite length, dendritic branching, spine density, and spine head size in the hippocampus. They also demonstrated that exogenous

administration of sAPPα (10 nM), but not sAPPβ (even at 50 nM, do not show this effect), rescued impairment of LTP and memory deficits in this APP/APLP2 double conditional KO mouse model (Hick et al., 2015). These findings suggest that sAPPα has a crucial role in improvement of synaptic plasticity and cognitive impairment in transgenic APP mice. Recently, Muller group (2016) have published data indicating a rescue of the structural, electrophysiological, and behavioral deficits in APP/PS1ΔE9 mice using adeno-associated virus (AAV)-mediated expression of sAPPα (Fol et al., 2016). They concluded that sAPPα activated microglial cells, which might reduce soluble Aβ species and plaques by up regulating insulin-degrading enzyme (IDE) and triggering receptor expressed on myeloid cells 2 (TREM2) receptors.

The proliferative role of sAPPα in neuritogenesis and neurogenesis

The early expression of APP mRNA (at embryonic day 9.5) in a mouse model underscored the significance of this molecule in nervous system development (Salbaum and Ruddle, 1994). Moreover, crystal structure and computer modeling studies indicate that sAPPα (residues of 18–350) has a cysteine-rich growth factor like domain (Rossjohn et al., 1999) and plays a key role in outgrowth and survival of neurons in cell culture studies (Araki et al., 1991, Milward et al., 1992, Qiu et al., 1995, Perez et al., 1997). In line with the above findings, both soluble and membrane-bound APP independently increased neurite outgrowth and branching (Whitson et al., 1990, Milward et al., 1992, Qiu et al., 1995). In contrast, Young-Pearse and co-workers (2008) demonstrated that sAPPα regulates neurite outgrowth through interaction with full-length APP and integrin beta1 signaling (Young-Pearse et al., 2008). They concluded that the activity of sAPPα is dependent on the membrane-bound APP. Earlier work indicated that neuritotropic and heparin-binding sites of APP are distinct and a heparinase-insensitive region is responsible for the effect (Ninomiya et al., 1993). In a different study, Jin and colleagues (1994) have showed that the neuritotropic activity of sAPPα is located on a stretch of 17 amino acids (residues of 319–335), which includes the RERMS (APP 328–332) sequence (Jin et al., 1994). Subsequently, Small and others have showed that interaction of APP and HSPG is critical for neurite outgrowth. To identify the heparin-binding domain in APP, deletion mutation and peptide mapping experiments have revealed four heparin-binding sites in APP. Among the four different binding sites, one site (residues of 96–110 of sAPPα) has more affinity than the other three sites (Clarris et al., 1994, Small et al., 1994, Small et al., 1999). Additionally, a delta NL mutation in the APP gene which produces less sAPPα but more sAPPβ further supports those findings by showing defective neurite extension (Li et al., 1997). Both early and recent works showed that sAPPα stimulates proliferation of neural stem cells (NSCs) (Hayashi et al., 1994, Ohsawa et al., 1999), embryonic stem cells (Porayette et al., 2009), and adult progenitor cells (Caille et al., 2004, Demars et al., 2011). To investigate the signaling pathways involved in the neurite extensions, one study showed that sAPPα activated MAPK/ERK signaling *via* activation of NMDA receptors (Gakhar-Koppole et al., 2008). A recent study demonstrated that both sAPPα and sAPPβ were able to enhance axonal growth in cell culture at low (nanomolar) concentrations through early growth response protein 1 signaling (Chasseigneaux et al., 2011).

Ohsawa *et al.* identified the extracellular matrix glycoprotein fibulin-1, mainly produced by neurons, as a potential sAPPα binding partner in the brain (Ohsawa et al., 2001). The binding of sAPPα and fibulin-1 is dependent on Ca^{2+} and blocked by an antibody against the N-terminal region of APP. In addition, they showed that the N-terminal region of APP binds to fibulin-1 and prevent sAPP-mediated proliferation of neural stem cells. Both sAPP and fibulin-1 are secreted in extracellular environment, the consequence of this interaction demands further study.

P^{75} neurotrophin receptor (p^{75NTR}) belongs to a large family of transmembrane molecules of the tumor necrosis factor receptor superfamily. Ligand binding studies indicated the multiple functions of this receptor in regulating axonal growth, neuronal survival, synaptic transmission, and apoptosis (Dechant and Barde, 2002). A number of different studies showed that P^{75NTR} interacts with full-length APP (Fombonne et al., 2009), Aβ (Knowles et al., 2009), N-terminal APP (APP1–286, EC_{50} = 300 nM) (Nikolaev et al., 2009), sAPPα and sAPPβ (Hasebe et al., 2013). More specifically, the carboxyl-terminal region of sAPPα (residues of 314–612) interacts with P^{75NTR} (EC_{50} = 150 nM) and induced neurite outgrowth through activation of protein kinase A (PKA) signaling (Hasebe et al., 2013). These findings suggest that sAPPα (both N- and C- terminal) binds to $P75^{NTR}$ and initiates neurite outgrowth depending on the nature of binding as shown in Figure 2d.

The role of sAPPα in modulation of AD and aging

Multiple lines of evidence indicate that altered APP processing leads to an increased production of Aβ, which contributes to AD pathologies. Cleavage of APP by α- and γ-secretases not only prevents generation of toxic Aβ peptides but also produces neuroprotective sAPPα. Multiple lines of evidence indicate that sAPPα regulates the trafficking and processing of APP, which may decrease the risk of developing AD. The role of sAPPα as a modulator of γ-secretase complex came from an study which shows that sAPPα reduced the Aβ42/Aβ40 ratio by modulating the enzyme complex (Hou et al.). Additionally, modulation of BACE1 by sAPPα reduces generation of Aβ and plaques in cell culture and in a transgenic mouse model of AD (Obregon et al., 2012). In accord with this finding, Varghese group confirmed sAPPα as an endogenous inhibitor of BACE1 activity. They demonstrated that sAPPα decrease the enzymatic activity of BACE1 by binding to its allosteric site (Peters-Libeu et al., 2015). In addition, sAPPα, acting through unknown receptors, inhibited BACE1 and GSK3β activity, which reduced tau phosphorylation (Deng et al., 2015). This study also demonstrated that recombinant human sAPPα increased Ser-9 phosphorylation of GSK3β. Earlier work by Jimenez *et al.* (2011) demonstrated that GSK3β (Ser-9) phosphorylation decreased significantly in aged (18 months) APP/PS1 mice compared to young (6 months) mice (Jimenez et al., 2011). They also showed that soluble Aβ modulates the sAPPα-mediated neuroprotective PI3K/Akt/GSK3β signaling pathway in an aged mouse model as shown in Figure 2f. This indicated a key role of sAPPα in activation of survival pathway in an aged mouse model. The decreased level of hippocampal sAPPα coupled with reduced NMDA receptors and impaired LTP function further suggest the importance of this soluble fragment in an aged (24–27 months) rat model. In line with this finding, exogenous administration of sAPPα (100 nM) reduces age-associated deregulation of NMDA receptor function and LTP deficits (Moreno et al., 2015). Moreover,

sAPPα-mediated inhibition of apoptosis and dendritic degeneration *via* c- JNK pathway further underscored the importance of the fragment in aging studies (Copanaki et al., 2010).

Diagnostic value of sAPPα as AD biomarker

Several studies have measured the metabolites of APP cleavage such as sAPPα, sAPPβ, and total sAPP (sAPPα and sAPPβ together) in AD and other neurodegenerative diseases. The results are inconsistent and contradictory in many cases. The inconsistencies are partly due to the heterogeneity of the disease, inconsistencies in mini-mental status exam (MMSE) scores, presence of co-morbid conditions, specificity and sensitivity of the assays, cross-reactivity of the antibodies, differences in sampling, as well as processing and storage of CSF samples. Initial studies (Ghiso et al., 1989); (Weidemann et al., 1989) as well as a recent one conducted on patients with MMSE score greater than 20 (Lewczuk et al., 2010) demonstrated high CSF levels of sAPPα and sAPPβ in patients with CSF findings characteristic of AD. The later study lacks the healthy controls and co-morbid conditions in the cohort. In contrast, other studies measured a slight or no significant change in total sAPP levels in the CSF of AD patients compared to non-demented controls (Palmert et al., 1990); (Hock et al., 1998). Notably, the antibodies used in early studies failed to demonstrate the difference between sAPPα and sAPPβ so instead measured total sAPP. On the other hand, many recent studies found no significant changes between the two soluble fragments in AD and non-demented controls (Zetterberg and Blennow, 2008, Rosen et al., 2012, Brinkmalm et al., 2013). In contrast to the above studies, while other studies show significantly decreased levels of total and sAPPα, however, sAPPβ was found to be unchanged in AD patients compared to controls (Prior et al., 1991, Van Nostrand et al., 1992, Sennvik et al., 2000). In accord with these findings, patients carrying the Swedish mutation (a double mutation in the APP gene) showed significantly decreased levels of sAPPα in the CSF (Lannfelt et al., 1995). Significant negative correlations between CSF levels of sAPPα and cognitive impairment have been reported in Swedish mutant AD patients (Almkvist et al., 1997). More recent work by Kim and colleagues corroborated this finding, demonstrating that mutations in A Disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) significantly reduced levels of α-secretase and sAPPα in familial late-onset AD (Kim et al., 2009). While the level of sAPPα significantly decreased in familial (Swedish mutation) and in moderate-to-severe AD, the levels did not change in the early stage of sporadic AD and mild cognitive impairment. In contrast to sAPPα, the higher level of p-tau181 and reduced level of $A\beta_{42}$ serve as a diagnostic marker for AD (Blennow, 2004). Recently, in addition to sAPPα and sAPPβ, full-length soluble APP and sAPP complexes were detected in CSF samples (Cuchillo-Ibanez et al., 2015). Further investigation will clarify whether full-length sAPP complexes with itself and is falsely measured as sAPPα and/or sAPPβ.

A number of studies showed that apoliprotein 4 (APOE4), one of the variants of APOE, may also contribute to the CSF level of sAPPα in AD patients. APOE4, a risk factor for late-onset AD (Harold et al., 2009, Lambert et al., 2009), transports cholesterol in the brain (Liu et al., 2013). Most studies demonstrated that the APOE4 variant increased AD risk whereas the APOE2 variant decreased the risk of AD (Farrer et al., 1997). In line with these findings, addition of APOE4 to neuroblastoma SH-SY5Y cells (Cedazo-Minguez et al., 2001) and

cortical neurons carrying the Swedish mutation co-cultured with APOE4 astrocytes showed decreased level of sAPPα generation. Accordingly, sAPPα levels are significantly decreased in AD patients having two APOE4 alleles compared to one APOE4 allele. However, the levels of $A\beta_{42}$ and sAPPβ were found unchanged across other APOE genotypes (Vincent and Smith, 2001). This indicates that APOE4 might affect α-secretase cleavage of APP.

APP is involved in multiple physiological functions and variations in sAPPα generation occur in many different conditions in addition to AD. Reduced CSF concentrations of sAPPα has been reported in other conditions such as cerebrovascular and neurodegenerative diseases (Selnes et al., 2010, Steinacker et al., 2011), bipolar disorder (Jakobsson et al., 2013), amyotrophic lateral sclerosis (Steinacker et al., 2011) and idiopathic normal pressure hydrocephalus (Miyajima et al., 2013). The lower levels of sAPPα in other conditions indicate that critical clinical evaluation is necessary to rule out the other conditions. Although many association studies showed sAPPα as a predictive biomarker, more epidemiological data are needed to generate a robust and standard scale that is diagnostically precise and accurate.

The therapeutic potential of sAPPα

In this review, we summarized numerous physiological functions of sAPPα, which has been (Table 1) disrupted in the AD brain in several ways. These functions include, but are not limited to, neuroprotection (Goodman and Mattson, 1994, Gralle et al., 2009), neurite outgrowth (Araki et al., 1991, Gakhar-Koppole et al., 2008), elevation of LTP (Ishida et al., 1997, Hick et al., 2015), as well as stimulation and proliferation of neuronal (Ohsawa et al., 1999, Demars et al., 2011) and non-neuronal cells (Saitoh et al., 1989, Pietrzik et al., 1998). In addition, sAPPα directly inhibits β-secretase-mediated proteolysis of APP, thereby reducing generation of Aβ (Obregon et al., 2012). Furthermore, sAPPα also has the potential to reduce tau-pathology by inhibiting GSK3β and BACE1 activity as shown in Figure 2h (Deng et al., 2015). Moreover, both single and multiple low-dose infusion of human umbilical cord blood (Darlington et al., 2013) as well as derived monocytes significantly reduce Aβ and β-amyloid plaques, decrease APP processing, reactive microgliosis, associated astrocytosis and cognitive impairment in the PSAPP AD mouse model (Nikolic et al., 2008). While identifying the mechanism, further studies indicated that cord blood monocytes might have their own α-secretase or activate an endogenous α-secretase enzyme in the PSAPP mouse model. Interestingly, exogenous sAPPα reversed the deficiency of phagocytosis showed by aged blood monocytes (Darlington et al., 2015). Thus, restoration of sAPPα levels in the brain by shifting the amyloidogenic towards the non-amyloidogenic pathway could ameliorate AD-related amyloid and tau pathology, neuronal loss, and cognitive impairment. As such, increasing α-secretase activity is therefore an attractive strategy for treatment of AD.

Although, sAPPα provides neuroprotection, the only way to increase sAPPα level in the brain is by increasing α-secretase and/or decreasing β-secretase activity. The currently known α-secretase enzymes ADAM10, ADAM17 (TNFα converting enzyme, TACE), and ADAM9 reduce some degree of AD pathology (De Strooper et al., 2010) but these enzymes have other substrates. Although, TACE, ADAM10, and ADAM9 are mainly involved in APP

α-secretase cleavage, they also cleave various substrates involved in autoimmune and cardiovascular disease, neurodegeneration, neurodevelopmental disorders, infection, inflammation, and cancer (Arribas and Esselens, 2009; Crawford et al., 2009;(Peduto, 2009). Therefore, TACE and ADAM10 have been therapeutic targets for inflammation, cancer, and inflammation-associated cancer (Saftig and Reiss, 2011). Recently, dysregulation of ADAM10 activity has been shown to be associated with synaptic deficits in Fragile X Syndrome (Pasciuto et al., 2015). Despite the side effects, Farenholz and Postina have listed a variety of ways to enhance sAPPα production including but not limited to G-protein coupled muscarinic agonists, serotonin receptor 5HT4 agonists, neuropeptide pituitary adenylate cyclase-activating polypeptide, PKC activators, statins, retinoids, and caloric restriction (Fahrenholz and Postina, 2006); (Endres and Fahrenholz, 2010). In addition, a review by Vincent and Govitrapong summarized various natural and synthetic compounds such as acitretin, SirT1, statin, epigallocatechin-3 gallate, and, estrogen that are able to stimulate α-secretase activity selectively. They also emphasized the activation of protein kinase and G-protein-coupled receptors mediated upregulation of α-secretase activity (Vincent and Govitrapong, 2011).

It is imperative to identify the sAPPα-mediated signaling pathways and downstream effectors fully before using this fragment in therapeutic applications. Several studies suggest that sAPPα stimulates PI3K/Protein Kinase C (PKC)/Akt signaling in cell culture and animal models. Furthermore, Endres and Farenholz have summarized the modulation of the α-secretase ADAM10 gene expression by retinoic acid derivatives. They concluded that retinoids decrease generation of toxic Aβ and increase neuroprotective sAPPα (Endres and Fahrenholz, 2012). Recently, the Varghese group have summarized a review discussing the importance of sAPPα and enhancement of this fragments using many different approaches (Spilman P, 2015). They found that one of the α_{7}- nicotinic acetylcholine receptor partial agonist, tropisetron, significantly increased sAPPα in cell culture and in a mouse model (Spilman et al., 2014). The size of sAPPα fragment is too large to cross the BBB. More research is necessary to identify the small functional unit of sAPPα that crosses the BBB but retain functional properties. It has proven to be quite difficult to obtain a small functional unit of sAPPα, since the function is dependent on the conformational structure of this molecule. Recently, the Varghese group have demonstrated that sAPPα and sAPPβ adopt a completely different structure, although they are differ by only 16 amino acids residues at the C-terminus (Peters-Libeu et al., 2015). Transgenic mice engineered to overexpress sAPPα could be another way to accomplish this function. Currently, only one transgenic mouse line overexpressing human sAPPα is available for AD and Autism studies (Bailey et al., 2012). AAV (Fol et al., 2016) and Lentivirus mediated sAPPα gene delivery into the specific region of the brain could be another strategy to increase expression of this fragment locally.

Conclusions

The presence of amyloid plaques and NFT's is the pathognomonic feature delineating AD from other types of dementia. Currently, AD therapy focuses on the prevention and clearance of β-amyloid plaques and NFT from the brain. Unfortunately, none of the available strategies resulted in significant cognitive improvement in clinical trials. We

believe that restoration of sAPPα function using this fragment, or a mimetic thereof, in the very early stage of the disease will reduce or prevent cognitive impairment in AD and in other neurodegenerative diseases.

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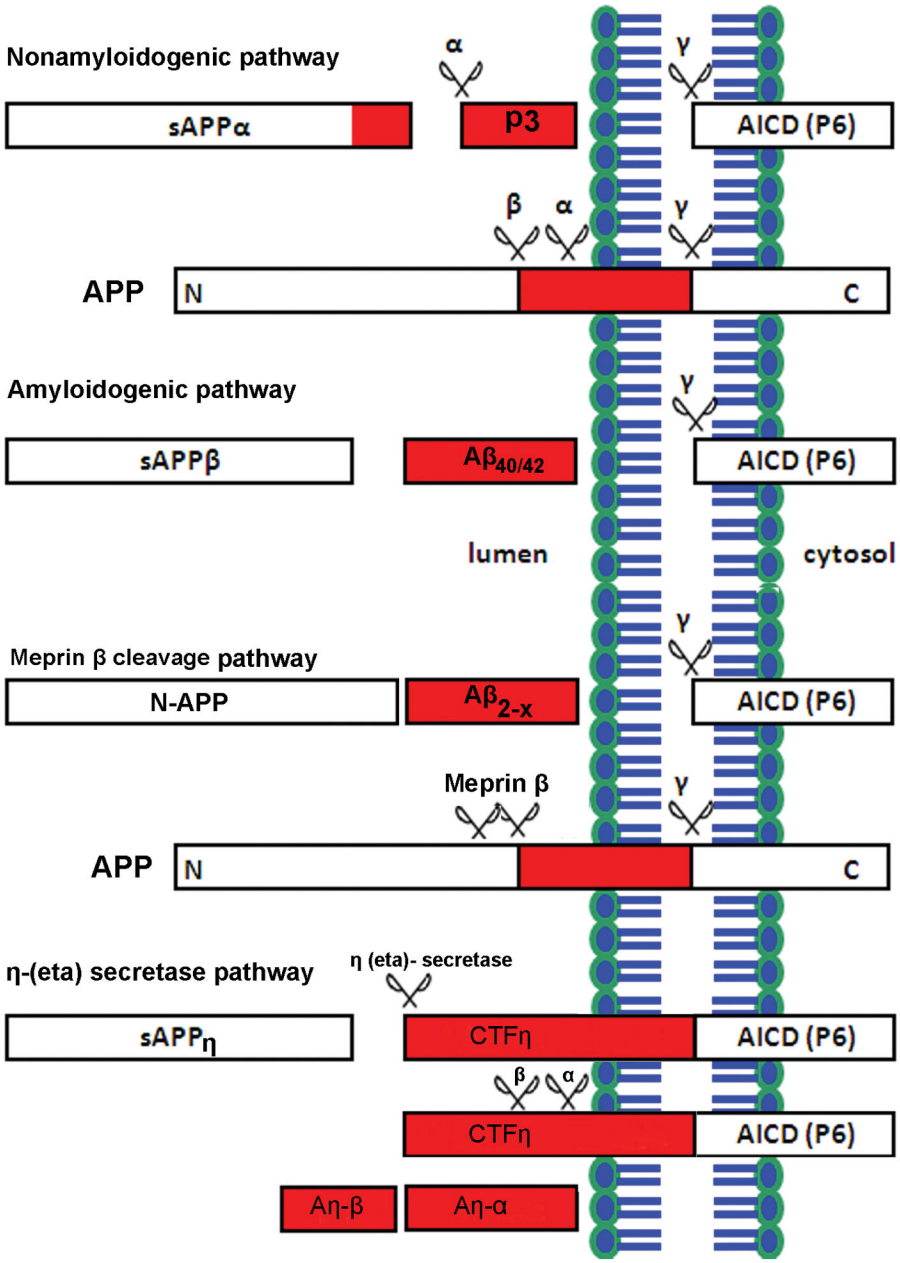

Figure 1. Schematic diagram of amyloid precursor protein (APP) processing pathways and cleavage products

The non-amyloidogenic APP processing pathway (upper) involves cleavages by α- and γ-secretases. Sequential cleavage of APP by α-secretase generates sAPPα and c-terminal fragment C83 (not shown). The subsequent cleavage of C83 by γ-secretase complex generate APP intracellular domain (AICD) and a short fragment called P3. The amyloidogenic APP processing pathway (lower) involves cleavages by β- and γ-secretases. Cleavage of APP by β-secretase generate sAPPβ and c-terminal fragment C99 (not shown). Subsequent cleavage of C99 by γ-secretase complex generate toxic species Aβ (40 or 42, depends on the cutting site) and AICD. This is termed as amyloidogenic pathway due to

generation and accumulation of Aβ species into plaque inside the brain. In addition to α-, β- and γ-secretases cleavage, APP is cleaved by metalloprotease meprin β, generating soluble N-terminal truncated APP (N-APP) or $Aβ_{2\text{-}X}$ variants. In addition to meprin β cleavage, the cleavage of APP by several matrix metalloproteinases such as MT5-MMP, referred to as η-secretase, releases a long-truncated ectodomain (sAPPη) and a membrane-bound carboxy-terminal fragment (CTF), termed CTFη. The membrane-bound CTFη is further cleaved by α- and β-secretases and release a long (Aη-α) and a short (Aη-β) peptide, respectively.

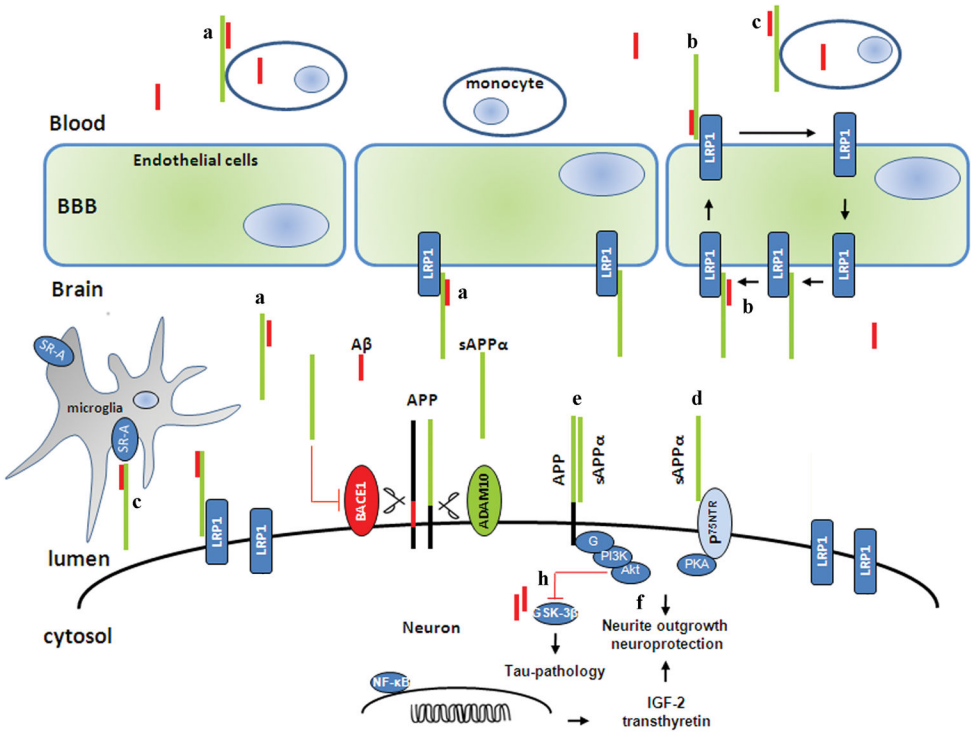

Figure 2. A schematic diagram presenting functions of APP processing metabolites Aβ (red) and sAPPα (green) inside the brain

Membrane-associated APP is processed through non-amyloidogenic or amyloidogenic pathway, resulting in the production of sAPPα (green) and Aβ (red), respectively. Depending on the cellular conditions, these two fragments can exist as monomer, and/or homo/heterodimer. The interaction of sAPPα and LRP1 receptor may induce internalization of Aβ into neuronal cells as an sAPPα/Aβ heterodimer. Additionally, we also hypothesize that LRP1 can transfer this heterodimer across blood-brain-barrier into peripheral circulation, and which then could be phagocytosed by monocytes (Figure 2a). We hypothesize that sAPPα could shuttle Aβ to the endothelial LRP1 at the abluminal side and remove Aβ out the brain to the periphery (Figure 2b). Additionally. SR-A as another possible receptor expressed on microglia cell surface, may also involved in sAPPα-mediated Aβ clearance by microglia (brain) and monocyte (peripheral system) (Figure 2c). The secreted sAPPα (both N- and C- terminal) fragements bind to their neuron membrane receptor $P75^{NTR}$ and initiate neurite outgrowth (Figure 2d). In addition, sAPPα protects neuronal cells by disrupting the dimerization of APP (Figure 2e). Furthermore, sAPPα can triggers expression of neuroprotective genes (IGF-2 and transthyretin) through NF-κB and PI3K/Akt signaling which provides neuronal outgrowth and survival (Figure 2f). sAPPα also reduce tau-pathology by inhibiting GSK3β and BACE1 activity (Figure 2h).

Table 1

Roles of sAPPα in neuroprotection, synaptic plasticity, neurogenesis and neurite outgrowth

Citation	Test Model	Functional domain and concentration	Treatment	Effect
Araki et al. 1991	Rat cerebral cortical neuron	sAPP695 and sAPP770 (40 nM)	Cortical neuron treated with sAPP695 and sAPP770	Neurite extension
Goodman and Mattson et al. 1994	Rat hippocampal cell culture	sAPP695 and sAPP751	Hippocampal culture treated with sAPP695 and sAPP751	Inhibit increase of intracellular $Ca2^{+}$ level and free radical
Mattson et al. 1993	Rat hippocampal, human cortical neuron	sAPP695 and sAPP751	Hippocampal, human cortical neuron treated with sAPP695 and sAPP751	Protect against hypoglycemic and glutamate neurotoxicity
Furukawa et al. 1996a and 1996b	Rat hippocampal neuron	N terminal- and C-terminal sAPPα(residues 591–612)	Hippocampal neuron treated with N terminal-sAPPα and C-terminal sAPPα (residues 591–612)	Suppress action potential; activation of K^{+} channel and cGMP; Heparinase reduces sAPPα activity
Furukawa and Mattson et al. 1998	Rat hippocampal neuron	sAPPα (0.01–1 nM)	Rat hippocampal neuron treated with sAPPα	Neuroprotection by activation by cGMP and suppression of NMDA.
Smith-Swintosky et al. 1994	Rat model	sAPP695 and sAPP751	Intracerebroventricular (icv) infusion of sAPPα in post ischemic injured	Neuronal survival and synthesis of new proteins in CA1
Bowes et al. 1994	Rabbit spinal cord ischemia model	sAPPα 17-mer peptide at 500 nM	Intrathecal infusion of (once per 3 days) sAPPα 20 min prior to the ischemia.	Reduce necrotic tissue; Increased synaptophysin synthesis
Thornton et al. 2006	Male Sprague-Dawley rat	sAPPα (0.2 mg/ml)	ICV infusion sAPPα (5 μl) after 30 min of traumatic brain injury (TBI) rat model	Improved motor function; Reduced cortical and CA1 caspase-3; Axonal injury at corpus callosum
Copanaki et al. 2010	Rat PC12 cells and mice hippocampal slices	sAPPα (0.1–50 nM)	sAPPα produced by HEK293 (APPWT) used to treat PC12 and mice hippocampal slices	Protect dendritic and neuronal damage in CA1; Inhibition of JNK and activation of PI3K/Akt signaling
Corrigan et al. 2011	Sprague-Dawley rat	N-terminal D1 (APP28–123), and C-terminal D6a/E2 (APP316–498) of sAPPα (25 μM)	ICV infusions of sAPPα D1 and D6a domain after 30 min in TBI rat model	Improved motor and cognitive function; Reduced axonal injury; Signaling through HSPG
Corrigan et al. 2012	APP KO mice	sAPPα (APP18–611) 25 μM	ICV infusions of sAPPα in APP KO after 30 min of moderate cortical injury	Improved motor and cognitive function; Reduced cortical and hippocampal damage
Corrigan et al. 2014	APP KO mice	sAPPα (APP96–110) 25 μM of D1 domain	ICV infusions of sAPPα in APP KO after 30 min of cortical injury	Rescue motor and cognitive deficits in APP KO mice; Reduced axonal injury
Roch et al. 1994	Rat (Adult)	sAPPα 17-mer peptide (residues 319–335) containing RERMS (APP328–332) (1 mM)	Intraventricular infusions of 17-mer peptide. After 14 days analyzed by behavioral and biochemical tests	Improved memory retention; Increased number of presynaptic terminals

Citation	Test Model	Functional domain and concentration	Treatment	Effect
				in the frontoparietal cortex
Ishida et al. 1997	ND	sAPPα (1–612) purified HEK293 (APPWT) (100 nM)	sAPPα infusion for 30–120 min followed by LTP measurement in hippocampus	Induce cGMP and enhancedLTP in CA1
Meziane et al. 1998	Male Swiss mice	sAPPα695 and sAPPα751 (0.05 pg-5 ng)	ICV infusions of sAPPα immediately after drug induced amnesia	Inhibit drug induced amnesia; Improved short-and long-term memory.
Andersen et al. 1999	Fischer 344-rat	Young (5–6 months) and Aged (24–25 months)	Total sAPP, sAPPα, Aβ measured in CSF of young and aged rat model	sAPPα reduce 50% in aged ; Improved spatial reference and working memory
Taylor et al. 2008	Sprague Dawley rat (adult)	sAPPα (11 nM) purified from HEK293 (APPWT) cells	Intrahippocampal infusion of sAPPα and anti-sAPP antibody	Enhanced LTP and NMDA currents in CA1; Improved spatial memory
Classen et al. 2009	Sprague Dawley rat (adult)	sAPPα and sAPPβ (10 nM)	Isolation of synaptoneurosome from hippocampus of adult (2–3 months) and aged (22–23 months) rat	Synaptic protein synthesis age and concentration dependent through PKG signaling; sAPPβ has no effect
Ring et al. 2007	sAPPα-KI and APP-KO mice	APP gene is replaced with sAPPα gene	Deficits of APP KO mice was fully rescued by sAPPα-KI mice	Improved LTP and cognition; Rescue brain and body weight, grip strength, exploratory and locomotor activity.
Weyer et al. 2011	sAPPα KI cross with APLP2 KO	sAPPα KI mice crossed with APLP2 KO background	Anatomical and behavioral assessment	Most of the mice survived; Cortical and hippocampal transmission normal; Impaired LTP and working memory; Excessive nerve growths
Li et al. 2010	sAPPβ KI cross with APLP2 KO	sAPPβ KI cross with APLP2 KO background	Anatomical and behavioral assessment	Mice died early due to postnatal lethality; Normal body weight and grip strength but abnormal nerve terminal
Hick et al. 2015	APP/APL2 double KO mice	sAPPα (10 nM), but sAPPβ (50 nM)	Conditional APP/APLP2 double KO in forebrain neurons using NexCre	sAPPα rescue impaired LTP; sAPPβ has no effect.
Fol et al. 2016	APP/PS1delE9 mice	sAPPα-AAV, (10^{10}vg/hippocampus)	sAPPα-AAV bilaterally injected into hippocampus and sacrificed after 5 months	Improved synaptic and cognitive deficits; Rescue spatial memory; Reduction of soluble Aβ and plaque loads.
Milward et al. 1992	Rat PC12 cells	Membrane-bound APP (10 ng) sAPPα (100 ng) per ml at (10^{-10}M)	Membrane-bound APP (10 ng) sAPPα (100 ng) treated for 18 hour.	Increased neurite length and branching; No change in neurite per cells.
Small et al. 1994;Clarris et al. 1994 and 1997	Chick sympathetic and mice hippocampal neurons	sAPPα (residues 96–110)	sAPPα (10 μg/ml)	Binding of sAPPα (residues 96–110) to HSPG stimulates neurite outgrowth

Citation	Test Model	Functional domain and concentration	Treatment	Effect
Qiu et al. 1995	Rat hippocampal neuronal culture	sAPPα (residues 361–648) (10 pM to 100 nM)	Rat hippocampal neurons treated with sAPPα for 26–28 hr	sAPPα751 and sAPPα770 promotes neurite outgrowth better than sAPPα695 in the presence of unprocessed APP
Ohsawa et al. 1995 and 1997	Rat embryonic neocortical explants	sAPPα695 and sAPPα770 (30 ng/ml); 16-mer (APP66–81) and 17-mer peptide containing RERMS sequence	Neocortical explants incubated with sAPPα695 and sAPPα770 (30 ng/ml)	N-sAPPα770 (residues 16–290) promote neurite outgrowth but C-sAPPα770 (residues 380–663) do not show this effect. 16-mer enhances neurite outgrowth but 17-mer peptide show neuronal survival
Jin et al. 1994 and Ninomiya et al. 1994	Rat neuronal line B103	sAPPα (10–100 nM) containing RERMS sequence (APP319–335)	B103 cell lacks APP and treated with sAPPα (10–100 nM) containing RERMS sequence (APP319–335)	Induction of neurite outgrowth
Young-Pearse et al. 2008	Primary E18 wild-type neurons;Sprague-Dawley rat	sAPPα (1–612-$(His)_6$	Primary E18 wild-type neurons treated with sAPPα for 3 days	sAPPα regulates the function of APP in neurite outgrowth
Gakhar-Koppole et al., 2008	Mouse neural precursor cells	Human recombinant sAPPα695 and sAPLP2	sAPPα treated with primary neuronal culture	Enhance neurite outgrowth through activation of cell surface APP, NMDAR and MAPK/ERK signaling
Chasseigneaux et al., 2011	Primary neuronal culture; C57BL/6J mice	Recombinant sAPPα and sAPPβ (100 nM)	sAPPα (100 nM) added to differentiated neurons	Both sAPPα and sAPPβ increased axonal elongation through MAPK/ERK/Egr1 signaling; Decrease of dendrites
Hasebe et al. 2013	Mice primary cortical neuron	sAPPα and sAPPβ (<100 nM)	sAPPα incubated with primary cortical culture for 24 h	Both sAPPα and sAPPβ bind to $P75^{NTR}$. But, sAPPα promotes neurite outgrowth