Cleavage of the amyloid precursor protein (APP) by α-secretase generates an extracellularly released fragment termed secreted APP-alpha (APPα). Not only is this process of interest due to the cleavage of APP within the amyloid-beta sequence, but APPα itself has many physiological properties that suggest its great potential as a therapeutic target. For example, APPα is neurotrophic, neuroprotective, neurogenic, a stimulator of protein synthesis and gene expression, and enhances long-term potentiation (LTP) and memory. While most early studies have been conducted in vitro, effectiveness in animal models is now being confirmed. These studies have revealed that either upregulating α-secretase activity, acutely administering APPα or chronic delivery of APPα via a gene therapy approach can effectively treat mouse models of Alzheimer’s disease (AD) and other disorders such as traumatic head injury. Together these findings suggest the need for intensifying research efforts to harness the therapeutic potential of this multifunctional protein.

Keywords: Alzheimer’s disease, amyloid precursor protein, APPα, synaptic plasticity, neuroprotection

INTRODUCTION

Secreted amyloid precursor protein-alpha (APPα, also known as soluble APPsα), when generated from the neuronally expressed APP695 isoform by the action of α-secretase (Figure 1), is a 612 amino acid protein that was first shown in the mid-1990s to promote the survival and growth of cultured neurons under physiological and non-physiological conditions (e.g., glucose and oxygen deprivation, amyloid-β (Aβ) toxicity; Mattson et al., 1993; Barger and Mattson, 1996a; Furukawa et al., 1996). These observations have been supported and extended by myriad reports over the intervening years (Ryan et al., 2013; Hefter et al., 2016) and has generated suggestions that the promotion of α-secretase cleavage of APP and increasing APPα levels could be a therapeutic strategy for the treatment of Alzheimer’s disease (AD; Turner et al., 2003; Ring et al., 2007; Postina, 2012; Hick et al., 2015; Fol et al., 2016; Habib et al., 2016) and possibly other neurological disorders. The purpose of this review is to consider the extent to which APPα generation may be disrupted in AD, and summarize the many positive functions of APPα that could be lost in the disease. In addition we will discuss the potential that either enhancement of non-amyloidogenic processing of APP or upregulating the expression of APPα by other means has for preventing or at least slowing the progression of AD as well as treating other neurological disorders.
APP PROCESSING

APP is a single pass type I transmembrane protein that undergoes complex proteolytical processing by several enzymes termed secretases. In the amyloidogenic pathway, APP processing is initiated by β-secretase (β-amloid cleaving enzyme, BACE-1), a transmembrane aspartate-type protease (for review see Vassar et al., 2014) that cleaves APP at the N-terminus of Aβ, leading to the secretion of the soluble ectodomain APPβ (Figure 1A). In the competing and physiologically predominant non-amyloidogenic pathway, α-secretase cleaves APP within the Aβ region (Figure 1A), in a process that can be stimulated by neuronal and synaptic activity (Hoey et al., 2009; Hoe et al., 2012). This not only prevents the formation of Aβ peptides but also leads to the secretion of the ectodomain APPα, which is only 16 amino acids longer than APPßβ (Figure 1B), into the extracellular space. Several members of the ADAM (a disintegrin and metalloprotease) family including ADAM9, ADAM10 and ADAM17, transmembrane Zn-proteases located at the cell surface, are able to cleave APP at the α-secretase site in vitro (reviewed by Saftig and Lichtenhalter, 2015). In neurons ADAM10 serves as the major physiological α-secretase as demonstrated by pharmacological inhibition and knockdown in vivo, as well as brain-specific knockout (KO) in vitro (Kuhn et al., 2010; Colombo et al., 2013; Prox et al., 2013). Subsequent processing of the membrane tethered C-terminal fragment resulting from β-secretase activity (CTFβ) by γ-secretase liberates Aβ and the APP intracellular domain (AICD), while CTFα processing yields the p3 fragment. γ-secretase cleavage occurs within the membrane by a complex of transmembrane proteins containing as a catalytic core presenilin (PS) 1 or 2. In wild-type neurons the predominant Aβ species generated is Aβ40, whereas familial forms of AD (FAD) linked to PS1 mutations result in a higher proportion of longer, more aggregation prone Aβ species including Aβ42 and Aβ43 that are believed to trigger plaque deposition (Veugelen et al., 2016).

ALZHEIMER’S DISEASE

AD is a progressive neurodegenerative disease for which aging is the most significant risk factor. It has traditionally been diagnosed by the appearance of functional deficits that frequently begin with self-reporting of impaired episodic memory (Dubois et al., 2007). Definitive diagnosis, however, requires post-mortem confirmation, although in recent times a number of biomarkers are providing new ways of diagnosing in life, such as medial temporal lobe atrophy with hippocampi volume loss, abnormal cerebrospinal fluid levels of the neurotoxic Aβ peptide and tau protein, plus positron emission tomography evidence for amyloid plaques and reduced glucose metabolism (Jack and Holtzman, 2013). While the proximal causes of sporadic AD are largely unknown, the familial forms arise when any one of several autosomal dominant mutations in genes regulating the production and clearance of Aβ are present (Dubois et al., 2007, 2010).

The post-mortem neuropathology of AD is characterized by the extensive development of extracellular plaques containing Aβ that are generated by amyloidogenic processing of APP (Figure 1A), intraneuronal hyperphosphorylated tau leading to neurofibrillary tangles, neuroinflammation and cell loss. Moreover, accumulation of intraneuronal Aβ has been observed as an early event in transgenic animal models (Kumar et al., 2013) and may contribute to pathogenesis (Zou et al., 2015; Ji et al., 2016). Sub-clinical progression of AD may occur over 15–20 years prior to diagnosis (Jack and Holtzman, 2013). This early phase of the disease is characterized by the formation of soluble oligomeric forms of Aβ that cause neuronal dysfunction and toxicity that may underpin early cognitive deficits. At the center of this early dysfunction in particular is impairment of synaptic function. Investigations in both AD patients and in mouse models of AD have revealed significant reductions in dendritic spine density in both cortical and subcortical regions early in the disease that are highly correlated with the appearance of cognitive deficits (Scheff et al., 1990, 2006; Terry et al., 1991; Spires-Jones and Knafo, 2012). Compensatory enlargement of remaining synapses has been reported and may mitigate some of the early losses in spine density; as AD progresses, however, spine loss exceeds synaptic growth leading to a net reduction in synaptic transmission (Scheff et al., 1990). Further progression of AD results in loss of dendritic complexity (reduced length, less branching, changes in dendrite diameter) and eventually cell death (Alpár et al., 2006).

An important pathology associated with synaptic dysfunction is the impairment in the synaptic plasticity mechanisms hypothesized to underpin learning and memory. The most extensively studied form of synaptic plasticity, long-term potentiation (LTP), is reliably impaired in most animal models of AD and can also be caused by extracts obtained from post-mortem AD brain (Oddo et al., 2003; Shankar et al., 2008; Li et al., 2011). The impairment of LTP observed in animal models and from raised Aβ levels may in part relate to altered transmission and loss of dendritic spines (reviewed by Spires-Jones and Knafo, 2012), as well as impairments in N-methyl-D-aspartate (NMDA) receptor expression and inhibition of LTP-associated de novo protein synthesis (Snyder et al., 2005; Li et al., 2011).

The treatment of AD has proven to be extremely challenging. Despite an exhaustive array of clinical trials that now number in the hundreds (Schneider et al., 2014), no disease-modifying treatments have proven effective for clinical use, although there is renewed hope arising from a recent study that has given very promising results from anti-Aβ antibody treatment (Sevigny et al., 2016). On the other hand, a lack of significant cognitive improvements was recently reported for a phase III clinical trial in patients with mild AD (EXPEDITION-3) using Solanezumab, an anti-Aβ antibody that binds only soluble Aβ (Hawkes, 2016). Thus, at present only two classes of drugs have been approved by the Food and Drug Administration for AD treatment and these only address the symptoms of the disease (Geldenhuys and Darvesh, 2015). Acetylcholinesterase inhibitors (e.g., donepezil)

1http://www.ctad-alzheimer.com/live-webcast
target the reduced cholinergic innervation of the hippocampus and cortex resulting from the loss of basal forebrain cholinergic neurons (Whitehouse et al., 1982), and memantine targets the increased tonic activation of extrasynaptic NMDA receptors that leads to activation of apoptotic pathways and neuronal death (Hardingham and Bading, 2010). While these treatments provide some symptomatic relief, their efficacy invariably reduces over time and ultimately they fail to halt or reverse the progression of the disease. Therefore, it is vital that new treatment options continue to be explored.

A SHIFT IN THE BALANCE OF \( \alpha \)-SECRETASE VERSUS \( \beta \)-SECRETASE ACTIVITY?

The amyloid cascade hypothesis has been the most widely supported explanation of the pathology that drives the progression of AD (De Strooper and Karran, 2016; Selkoe and Hardy, 2016), although other elements of the neuropathology are gaining increasing attention (Herrup, 2015; Rius-Pérez et al., 2015; Briggs et al., 2016). The amyloid cascade hypothesis contends that there is either a shift in APP processing towards the amyloidogenic pathway, or there is a reduction in A\( \beta \) clearance which results in the excessive accumulation of A\( \beta \) and a shift in the ratio of the various A\( \beta \) species to favor A\( \beta \)42. There is also evidence that BACE1 is upregulated during aging and AD, thus favoring amyloidogenic APP processing (Fukumoto et al., 2002, 2004; Holsinger et al., 2002; Yang et al., 2003; Li et al., 2004; Ahmed et al., 2010).

With the firm focus on increased levels of both soluble and insoluble A\( \beta \) in the brain and cerebrospinal fluid (CSF) in AD, relatively little attention has been given to a possible associated reduction in \( \alpha \)-secretase activity and thus a shift away from the production of APP\( \alpha \) that might amplify the toxic effects of A\( \beta \), hyperphosphorylated tau and other neuropathologies. However, the evidence for a reduction in APP\( \alpha \) levels in AD is mixed. Measuring mixed alpha and beta forms of secreted APP, Kibbey et al. (1993) reported that levels of APP\( \alpha \) in the CSF of AD patients were 3.5 times lower than that in healthy controls. Subsequent studies specifically measuring APP\( \alpha \) in CSF supported this finding (Lannfelt et al., 1995; Almkvist et al., 1997; Sennvik et al., 2000), and positive correlations between reduced APP\( \alpha \) levels and diminished performance in cognitive testing in both AD patients (Almkvist et al., 1997) and normal aged rats (Anderson et al., 1999) have been reported. The loss
of cholinergic innervation from the basal forebrain to the cortex and hippocampus in the very earliest stages of AD may underlie the loss of APPsα production and this may be the driver for the shift to amyloidogenic processing of APP (Obregon et al., 2012).

On the other hand, there is also evidence that APPsα levels may not be changed in the early stages of sporadic AD (Perneckzy et al., 2014). Several studies using newly developed methodologies have reported that APPsα CSF and blood plasma levels are unchanged in sporadic AD patients (Olsson et al., 2003; Perneckzy et al., 2011, 2013; Rosén et al., 2012; Brinkmalm et al., 2013) with decreases only in advanced AD (Rosén et al., 2012) and in AD patients carrying the ApoE ε4 allele (Olsson et al., 2003). One study has even reported an increase in APPsα levels in the CSF of AD patients (Rosén et al., 2012). Thus, a complete understanding of the pattern of APPsα production in AD and its significance will require more detailed study of AD patients and testing in animal models of the disease.

While the production of APPsα in the brain still needs to be fully understood, evidence from studies in humans and animals indicates that reduced APPsα levels can exacerbate AD symptoms. A mutation at the α-secretase cleavage site of human APP (APP770K687N) was found to cause early onset dementia. The mutation severely reduced α-cleavage and thus APPsα production, but at the same time led to the production of highly toxic Aβ species, hampering a clear interpretation of the specific impact of low APPsα levels (Kaden et al., 2012). However, Epis et al. (2010) demonstrated that hippocampal ADAM10/SAP97 levels (a complex required for synaptic ADAM10 localization) are reduced in AD patients, while activity-attenuating mutations in the prodomain of the human ADAM10 gene have been associated with AD (Kim et al., 2009; Suh et al., 2013). Reducing ADAM10 activity in adult mice by impairing its trafficking (Epis et al., 2010) or through forebrain-specific conditional ADAM10 KO (Prox et al., 2013) shifted APP processing towards Aβ production. Together these data suggest that reduced APPsα levels may contribute to the early stages of sporadic AD.

**PROPERTIES AND FUNCTIONS OF APPsα**

The possible significance of any impairments in ADAM10 activity or in the expression of APPsα becomes quickly apparent when one considers that this protein exerts a large number of growth factor-like properties when applied exogenously to neural tissue. Understanding the functionality of this protein, and its mechanisms of action, is crucial not only for understanding its biology in normal tissue, but also for providing critical information that will underpin any attempt to harness its potential therapeutic benefits (Figure 2).

**NEUROPROTECTION**

APPsα has strong neuroprotective properties that mitigate in cultured neurons the effects of a range of pro-apoptotic insults including hypoglycemia and glutamate toxicity (Mattson et al., 1993; Furukawa et al., 1996) and, importantly, Aβ-induced toxicity (Goodman and Mattson, 1994; Barger and Mattson, 1996a,b; Furukawa et al., 1996; Guo et al., 1998). More recently, we and others have demonstrated that the effects of other disease-associated insults such as excessive NMDA receptor activation (Ryan et al., 2013) and proteasomal impairments (Copanaki et al., 2010; Kundu et al., 2016) can be mitigated by APPsα administration. APPsα inhibits the upregulation of the co-chaperone BAG3 and suppresses BAG3-mediated aggresome formation under conditions of proteasomal stress (Kundu et al., 2016). Moreover, APPsα is a key activator of the PI3K/Akt survival signaling pathway that is triggered in response to serum withdrawal in cultured neurons (Milosch et al., 2014). Although the mechanisms conferring neuroprotection are only partially understood (for review see Kögel et al., 2012), some of these effects depend on the binding of APPsα to cell surface APP, that via its C-terminal domain can interact with G0 protein to trigger the pro-survival Akt kinase pathway (Milosch et al., 2014).

While most previous studies focused on cell death, the impact of APP on cellular and neuronal network functions during metabolic stress remain largely unknown. In this regard, Hefter et al. (2016) recently studied hypoxia-induced loss of function and recovery upon re-oxygenation in mouse hippocampal slices. While APP-KO mice showed impaired functional recovery after transient hypoxia, this could be largely rescued by APPsα expression or by pharmacological block of L-type calcium channels. Voltage-gated Ca²⁺ channels are, in
addition to NMDARs and internal Ca\(^{2+}\) stores, major sources of intracellular calcium contributing to traumatic/ischemic insults and AD pathogenesis. These data indicated that APP, in particular APP\(\alpha\), supports neuronal resistance against acute hypoxia by regulating calcium homeostasis (Hefter et al., 2016).

In addition to these in vitro studies, there is also evidence that APP\(\alpha\) may protect against acute forms of brain injury in vivo. Smith-Swintosky et al. (1994) demonstrated that APP\(\alpha\) ameliorates neuron loss in the hippocampus under conditions of transient ischemia, consistent with subsequent findings that APP-KO mice show increased acute mortality upon ischemia (Koike et al., 2012). In addition, a series of recent experiments have shown a protective effect of APP\(\alpha\) in traumatic brain injury (reviewed by Plummer et al., 2016). Intracerebroventricular (ICV) administration of APP\(\alpha\) following traumatic injury in rats significantly reduced cell and axonal death and improved motor outcomes (Corrigan et al., 2014). While APP-KO mice are more vulnerable to traumatic brain injury this could be rescued by recombinant APP\(\alpha\) or peptides derived from it (Corrigan et al., 2014; Plummer et al., 2016). Together these data indicate that endogenous APP\(\alpha\) is neuroprotective under injury conditions and suggest that these properties may be exploited in a therapeutic setting.

In a positive feedback cycle, APP\(\alpha\) may promote the further production of APP\(\alpha\) by blocking the amyloidogenic pathway through binding to and inhibiting the \(\beta\)-secretase BACE1 (Peters-Libeu et al., 2015), leading to a reduction in A\(\beta\) production (Obregon et al., 2012; but see also Fol et al., 2016). Further protection against \(\alpha\)-secretase toxicity by APP\(\alpha\) may arise from the inhibition of the tau phosphorylating enzyme GSK3\(\beta\), thus reducing tau hyperphosphorylation and the subsequent production of NFTs (Deng et al., 2015).

TROPHIC FUNCTIONS: CELL PROLIFERATION AND ADULT NEUROGENESIS

In addition to neuroprotection, APP\(\alpha\) exerts trophic functions both in vitro and in vivo. Early studies indicated that APP\(\alpha\) restores the growth of fibroblasts in which endogenous APP expression had been attenuated (Saitoh et al., 1989), stimulates thyroid epithelial cell growth (Pietrzik et al., 1998) and enhances the proliferation of rat fetal neural stem cells (Hayashi et al., 1994; Ohsawa et al., 1999). While these trophic functions appear beneficial under physiological conditions, enhanced APP\(\alpha\) expression has been detected in different tumors including glioblastoma (for review see Chasseigneaux and Allinquant, 2012). APP\(\alpha\) has also been implicated in adult neurogenesis. APP knockdown in adult mice resulted in reduced numbers of neurospheres that could be cultured form the ventricular zone (Caillé et al., 2004) and an APP-Fc fusion protein (Fc domain of IgG fused to the APP ectodomain) was shown to bind to the subventricular zone of adult mice (Caillé et al., 2004), suggesting that APP\(\alpha\) may stimulate neuronal stem/progenitor cell proliferation. Consistent with these findings, APP\(\alpha\) infusion into the lateral ventricle increased the number of EGF-responsive progenitor cells (Caillé et al., 2004), while pharmacological blockade of \(\alpha\)-secretase by infusion of the inhibitor batimatstat decreased the number of neuronal progenitors in vivo (Caillé et al., 2004). This was further corroborated by in vitro studies indicating that APP\(\alpha\) stimulates the proliferation of cultured neuronal precursor cells (NPCs) from the adult subventricular zone even in the absence of EGF (Demars et al., 2011) and also NPCs from the dentate gyrus (Baratchi et al., 2012). Consistent with the latter finding, transgenic overexpression of ADAM10 led to increased hippocampal neurogenesis (Suh et al., 2013). In addition, intraventricular injection of APP\(\alpha\) rescued the age-dependent decline in the number of NPCs in vivo (Demars et al., 2013). Taken together these findings indicate a prominent role of APP\(\alpha\) in adult neuronal progenitor cell proliferation.

ROLE FOR NEURITE OUTGROWTH, SYNAPTOGENESIS AND SPINE DENSITY

Several in vitro studies indicated that APP\(\alpha\) can promote neurite (Clarris et al., 1994; Small et al., 1994) and axonal outgrowth (Young-Pearse et al., 2008). Several APP domains important for these functions have been identified including the N-terminal APP\(96-110\) region located in the first heparin-binding domain and the APP\(319-335\) region which contains the RERMS motif (Ninomiya et al., 1994). Studies from animal models also indicate a crucial role for APP\(\alpha\) in synaptogenesis and modulation of spine density. Using organotypic hippocampal cultures we have demonstrated a pronounced decrease in spine density and reductions in the number of mushroom spines thought to represent mature synapses in CA1 pyramidal neurons of APP-KO mice. Interestingly, APP\(\alpha\) expression alone was sufficient to prevent the defects in spine density observed in APP-KO mice, as APP\(\alpha\) knock-in mice that lack transmembrane APP and express solely the secreted APP\(\alpha\) fragment exhibited unaltered spine density and spine type distribution (Weyer et al., 2014). In line with this, APP\(\alpha\) could also partially restore spine density deficits of cultured APP-KO neurons (Tyan et al., 2012). In turn, these findings imply that autocrine or paracrine APP\(\alpha\) signaling, important for spine formation and/or maintenance, involves a so far unknown receptor distinct from APP itself. Further support for a synaptotrophic role of APP\(\alpha\) comes from transgenic mice with moderate overexpression of human wild-type APP (Mucke et al., 1996) or indirect up-regulation of APP\(\alpha\) by transgenic expression of the \(\alpha\)-secretase ADAM10 (Bell et al., 2008), which both led to increased synaptic density. In Tg2576 mice, expression of mutant hAPP increased spine density in CA1 and cortical neurons of young mice prior to plaque deposition presumably via APP\(\alpha\), whereas spine density was decreased in aged animals, likely due to A\(\beta\)-mediated synaptotoxic effects (Lee et al., 2010). This suggests that APP\(\alpha\) might counteract A\(\beta\)-mediated effects on spine density during early stages of pathogenesis. Recent evidence indicates
that APP also regulates spine plasticity. Using two-photon in vivo microscopy, (Zou et al., 2016) analyzed cortical spine dynamics in vivo and reported decreased spine turnover rates (formation of new spines or loss of established spines) in APP-KO mice. Moreover, when housed under environmental enrichment, APP-KO mice failed to respond with an increase in spine density (Zou et al., 2016), suggesting that not only a reduction in spine numbers but also alterations in spine dynamics could contribute to deficits in synaptic plasticity and behavior found in APP mutant mice (Dawson et al., 1999; Seabrook et al., 1999; Ring et al., 2007). It remains to be seen which domains of APP or which proteolytic fragment is important for this function. The mechanism underlying the effects of APPα on spines is presently unknown, although NMDARs could play a crucial role. APP-KO mice have decreased levels of extracellular D-serine (Zou et al., 2016), an essential endogenous co-factor of NMDAR activation (Panatier et al., 2006). Taken together these findings indicate important synaptogenic and synaptic modifying properties of APPα that may be of therapeutic value (Fol et al., 2016; see also below).

SYNAPTIC PLASTICITY

Synaptic plasticity phenomena, such as LTP and long-term depression (LTD), are fundamental to learning and memory and are thus also central to normal cognitive function. In mouse models of AD, LTD is consistently impaired in an age-dependent fashion (Oddo et al., 2003; Vigot et al., 2006), and in some cases LTD is facilitated (Megill et al., 2015), while humans with diagnosed AD also show impaired synaptic plasticity (Trebbastoni et al., 2016). It is interesting to note then that APPα has the capacity to facilitate LTD and thus has the potential to counter the LTD-impairing effects of Aβ. In an early study, Ishida et al. (1997) demonstrated that APPα increased the frequency dependency of LTD induction in CA1 from 1 Hz to 10 Hz and facilitated LTD expression induced by 100 Hz stimulation, possibly by a protein kinase G (PKG)-dependent mechanism. Moreover, we showed in anesthetized rats that exogenously applied APPα exerted an inverted U-shaped dose-dependent facilitation of LTD in the dentate gyrus, although too high a dose impaired LTD (Taylor et al., 2008). Moreover, APPα antibodies as well as an α-secretase inhibitor impaired LTD, and the latter effect could be rescued by exogenous APPα but not by APPβ, despite its lacking only the 16 C-terminal residues when compared to APPα (Figure 1B). The inhibition of LTD appeared to be mediated, at least in part, through a reduction of NMDAR currents generated during the high-frequency stimulation (HFS). No effects on basal AMPA or NMDA receptor currents were observed, suggesting that endogenous APPα may be released during the HFS to contribute to LTD. However this point requires further study, as the effect of α-secretase inhibition on tetanic NMDA receptor currents was small, and other studies have reported both a decrease (Furukawa and Mattson, 1998) and an increase in single NMDA receptor currents (Moreno et al., 2015) in response to exogenous APPα delivery. More recently, we generated conditional APP/APLP2 double KO (termed NexCre cDKO) mice that lack APP expression and thus APPα secretion in excitatory forebrain neurons on a global APLP2-KO background (Hick et al., 2015). Consistent with findings by Taylor et al. (2008), this led to impairments in hippocampal LTD that were also reflected in impairments in hippocampus-dependent learning and memory tasks, including deficits in Morris water maze and radial maze performance (Hick et al., 2015). Interestingly, we demonstrated that acute treatment of brain slices with nanomolar amounts of recombinant APPα, but not APPβ, rescued the impairment of LTD (Hick et al., 2015). These findings indicate a crucial ability specifically for APPα to support synaptic plasticity of mature hippocampal synapses on a rapid time scale. Similar differential effects of APPα vs. APPβ have been reported in assays of neuroprotection, with APPβ being far less effective (reviewed by Chasseigneaux and Allinquant, 2012). Thus, the crucial functional domain of APPα may reside within terminal APPα-CT16 residues, and/or their presence alters the conformation of APPα in a critical way. Indeed, there is evidence from recent structural analysis by small angle X-ray diffraction studies that the threedimensional structure of APPα is very different from APPβ (Peters-Libeu et al., 2015). This study further suggested that the N-terminal E1 domains folds back towards the C-terminal juxtamembrane domain in APPβ (Peters-Libeu et al., 2015). Thus, epitopes that are accessible in APPα or when provided as peptides may become masked in APPβ. This may have important functional implications as distinct 3D structures may enable or prevent binding to different receptors. Although the receptor(s) mediating the acute effects of APPα on synaptic plasticity are currently unknown, they are not the endogenous APP and APLP2 that are both lacking in NexCre cDKO mice (Hick et al., 2015).

APPα also appears to play an important role in processes of natural aging. Not only is memory performance correlated with APPα levels (Anderson et al., 1999), but aging-related deficits in both LTD and cognitive behavior can be rescued by exogenous APPα (Moreno et al., 2015; Xiong et al., 2016).

GENE EXPRESSION AND PROTEIN SYNTHESIS

Full expression of LTD requires gene expression and de novo protein synthesis, and this raises the question of whether APPα itself directly regulates protein synthesis and the processes of translation and transcription that underlie it. Barger and Mattson (1996a) suggested that APPα could regulate transcription through activation of the transcription factor NF-kappa B (NFkB), and extensive gene expression responses to relatively brief delivery of exogenous APPα have been reported (Stein et al., 2004; Ryan et al., 2013). Gene expression responses occurred in as little as 15 min and these slowly changed from predominantly upregulation to predominantly downregulation during 24 h of APPα treatment (Ryan et al., 2013). Upregulation occurred for immediate early gene transcription factors and for NFκB- and CREB-regulated
genes, as well as regulation of late response genes known to be involved in cell survival, inflammatory responses, apoptosis and neurogenesis. These findings were further corroborated by Aydin et al. (2011).

Although APP\(\alpha\) can regulate coupled transcriptional and translational processes, it can also directly regulate protein synthesis. Claasen et al. (2009) found, using rat hippocampal synaptoneurosomes that are not transcriptionally competent, that APP\(\alpha\) initiated de novo protein synthesis in the dendritic compartment that was sensitive to the translation inhibitor cycloheximide. This effect was: (1) dose-dependent with higher concentrations failing to affect baseline protein synthesis; (2) age-dependent with a much reduced effect in tissue from aged rats; and (3) abolished by a PKG inhibitor and partially blocked by inhibitors of calcium/calmodulin protein kinase II (CaMKII), and mitogen-activated protein kinases (MAPKs). It appears likely therefore that at least part of the LTP facilitation by APP\(\alpha\) is through regulated transcriptional and translational processes, but this hypothesis has yet to be directly tested.

**MEMORY**

Intracerebral administration of antibodies against the APP\(\alpha\) region of APP is able to cause learning and memory impairments in rat inhibitory avoidance (Doyle et al., 1990; Huber et al., 1993) as well as chick inhibitory avoidance (Mileusnic et al., 2000) tasks. Similarly, inhibition of \(\alpha\)-secretase impaired rat spatial watermaze memory (Taylor et al., 2008) while APP knock-out impaired mouse spatial learning (Ring et al., 2007). Although these treatments are not specific manipulations of APP\(\alpha\), it is notable that memory deficits could be prevented in a number of experiments by acute administration of either full-length APP\(\alpha\) (Taylor et al., 2008) or APP\(\alpha\) fragments (Mileusnic et al., 2000), or by genetic over-expression of full-length APP\(\alpha\) (Ring et al., 2007). APP\(\alpha\) and its fragments have also been used to rescue memory under other conditions of impairment, such as caused by the muscarinic receptor antagonist scopolamine (Meziane et al., 1998), A\(\beta\) (Mileusnic et al., 2004), head injury (Corrigan et al., 2012), and aging (Xiong et al., 2016). Moreover, viral vector mediated over-expression of APP\(\alpha\) rescued memory in a mouse model of AD (Fol et al., 2016).

There is also evidence that normal memory can be enhanced by exogenous APP\(\alpha\) or peptide fragments. Full-length APP\(\alpha\) enhanced go-no-go discrimination and operant lever pressing in rats (Meziane et al., 1998) while a 17-mer fragment (derived from the heparin binding domain located in the conserved E2 domain) facilitated spatial memory in the watermaze task for aged but non-memory impaired rats (Roch et al., 1994). A 5-mer peptide internal to that fragment converted short-term avoidance memory to long-term memory in chicks (Mileusnic et al., 2004). These findings need to be treated with caution, however, because transgenic over-expression of APP\(\alpha\) from gestation has been shown to lead to the development of autism-like markers such as hypoactivity and impaired sociability (Bailey et al., 2013), as well as aberrant T-lymphocyte development and function (Bailey et al., 2011).

**APP\(\alpha\) AS A THERAPEUTIC TARGET**

The neurotrophic, neuroprotective, neurogenic, synaptogenic as well as neuronal plasticity and memory enhancing properties establish APP\(\alpha\) as an attractive therapeutic target during the early stages of AD and possibly also later. In this regard it should be kept in mind that due to the highly plastic nature of synapses, their dysfunction and loss are reversible processes. Thus, synaptic repair stimulated by trophic APP\(\alpha\) may ameliorate pathophysiology and improve clinical outcome as a complementary approach to eliminating toxic factors.

APP\(\alpha\) levels may either be enhanced by shifting APP processing towards the non-amyloidogenic pathway or by direct delivery/expressions of exogenous APP\(\alpha\) (Figure 1).

Inhibiting amyloidogenic APP processing, e. g., by targeting the A\(\beta\)-generating secretases has been a major focus of AD research over last two decades (e.g., Yan and Vassar, 2014; Geldenhuys and Darvesh, 2015) and several advanced BACE inhibitors are in phase 3 clinical trials (Cumming et al., 2012). However, using systematic proteomic approaches, it has become clear that all secretases have numerous substrates besides APP (Saftig and Lichtenthaler, 2015; Kuhn et al., 2016). Pharmacological inhibition of secretases may therefore have serious drawbacks due to mechanism-based side effects on other targets that are important for normal brain physiology. These concerns were further fueled by recent findings demonstrating that BACE inhibition upregulates non-canonical APP processing and production of A\(\eta\) fragments that impair neuronal activity and LTP (Willem et al., 2015).

With respect to the alternative approach, enhancement of non-amyloidogenic APP processing may be achieved by upregulating \(\alpha\)-secretase expression at the transcriptional level or by modulating its subcellular trafficking or activity (for review see Endres and Fahrenholz, 2012; Postina, 2012; Saftig and Lichtenthaler, 2015; Habib et al., 2016).

**Transcriptional Activation of ADAM10**

The human ADAM10 promoter contains two retinoic acid response elements and ADAM expression can be upregulated at the transcriptional level by the vitamin A analog acitretin in cells and in transgenic AD mouse models leading to increased APP\(\alpha\) and reduced A\(\beta\) production (Tippmann et al., 2009). In a small clinical trial with AD patients, acitretin, that is already approved to treat psoriasis, was well tolerated and caused a significant increase in APP\(\alpha\) levels that was detectable in CSF samples of treated patients (Endres et al., 2014). Long-term studies with larger patient cohorts are planned. Melatonin, which decreases during aging and in AD patients, has been shown to efficiently decrease A\(\beta\) levels when administered at early stages of pathogenesis in Tg2576 AD mice (Matsubara et al., 2003). Recently, detailed in vitro studies indicated that the underlying mechanism involves plasma membrane-located melatonin receptor activation, and ERK1/2 phosphorylation.

**APP\(\alpha\) as a Therapeutic Target**
leading to increased APP\(\alpha\) levels via transcriptional activation of ADAM10 and ADAM17 (Shukla et al., 2015). Moreover, and in line with data from Moreno et al. (2015) and Xiong et al. (2016), melatonin partially restored APP\(\alpha\) levels and spatial learning in aged mice (Mukda et al., 2016).

**Post-Transcriptional Activation of \(\alpha\)-Secretase**

Although the precise mechanisms of activation are not fully understood, it is clear that \(\alpha\)-secretase activity, as judged by enhanced APP\(\alpha\) levels, can be directly or indirectly upregulated via ion channels, G-protein coupled receptors (GPCRs) and receptor tyrosine kinases. In particular, receptor-activated protein kinase C, MAP kinases, PI3 kinase and Ca\(^{2+}\) signaling have been shown to contribute to \(\alpha\)-secretase activation. In many cases, however, it has not been directly studied which enzymes mediate increased APP\(\alpha\) production. In these cases processing may involve ADAM10 and/or ADAM17 and possibly further metalloproteases that have been shown to have APP cleaving activity *in vitro* (Saftig and Lichtenthaler, 2015). A detailed description of these various pharmacological approaches is beyond the scope of this review, the reader is referred to a series of recent reviews (see Postina, 2012; Saftig and Lichtenthaler, 2015; Habib et al., 2016; Spilman et al., 2016).

Upregulation of \(\alpha\)-secretase activity was reported for etazolate, an allosteric activator of GABA\(A\) receptors, which increased APP\(\alpha\) in rat cortical neurons and guinea pig brain (Marcade et al., 2008), improved memory in aged rats (Drott et al., 2010) and proved protective against traumatic brain injury (Siopi et al., 2013). The neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP) potently increased APP\(\alpha\) levels in vivo, an effect that was abrogated by an antagonist of the GPCR PAC1, by a hydroxamate-based ADAM inhibitor and by inhibitors of MAP kinases and PI3 kinases (Kojro et al., 2006). *In vivo*, APP\(\alpha\) production in the brain was stimulated by long-term intranasal PACAP application. The effects of PACAP application were not limited to increased APP\(\alpha\) levels but were instead pleiotropic, including upregulation of the PAC1 receptor, BDNF and of the anti-apoptotic Bcl-2 protein (Rat et al., 2011). While these *in vivo* effects, including improved object recognition in transgenic AD model mice (Rat et al., 2011), appear favorable for treatment, Gardoni et al reported that PACAP treatment of primary hippocampal neurons led to postsynaptic ADAM10 accumulation and N-cadherin-dependent reductions in spine head volume and reduced postsynaptic GluR1 expression (Gardoni et al., 2012). Thus a more detailed *in vivo* characterization appears warranted.

Activation of serotonin type 4 receptors (5-HT\(_4\)R)s, another class of neuronally expressed GPCR, promotes the activity of ADAM10 and APP\(\alpha\) generation. The 5-HT\(_4\)R was shown to directly interact with the mature form of ADAM10 and agonist stimulation of the receptor accelerated ADAM10 activity by cAMP/Epac (cAMP-responsive Rap1 guanine nucleotide exchange factor) signaling (Cochet et al., 2013). Tesserue et al. (2013) reported that chronic 5-HT\(_4\) receptor activation lowered A\(\beta\) production in transgenic hAPP/PS1 AD model mice but the authors found no evidence for a direct activation of ADAM10. The underlying mechanism appears more complex and may involve decreased APP and BACE-1 expression and elevated astroglial and microglial responses. More recently, donecopride, a promising synthetic multitargeted ligand that functions both as a partial agonist of 5-HT\(_4\)R and as an acetylcholinesterase inhibitor, has been developed and shown to have memory enhancing ability (Lecoutey et al., 2014).

**Direct Expression of APP\(\alpha\) in the CNS**

Although \(\alpha\)-secretase-targeting pharmacological strategies are potentially promising, there remains the concern regarding lack of specificity (see for example Gardoni et al., 2012). Acitretin may induce other genes with retinoid response elements in their promoters and upregulation of \(\alpha\)-secretase activity (ADAM10, 17 or others) will likely lead to the processing of many additional substrates. In this regard, Kuhn et al. (2016) recently demonstrated that ADAM10 has over 40 neuronal substrates including some involved in tumorigenesis. Thus, it is still unclear whether increasing \(\alpha\)-secretase activity in neural tissue will ultimately be of therapeutic benefit for patients. An approach to circumvent these problems is the direct delivery of APP\(\alpha\) into the brain.

While previous studies demonstrated the neuroprotective properties of APP\(\alpha\) against acute forms of brain injury (Van Den Heuvel et al., 1999; Thornton et al., 2006; Corrigan et al., 2012, 2014; Plummer et al., 2016) the situation is quite different in neurodegenerative diseases such as AD, characterized by chronic production and accumulation of neurototoxic molecules including A\(\beta\). Another challenge is the need for sustained expression of neurotrophic/neuroprotective factors. This calls for a gene therapy approach. During recent years gene therapy approaches to neurological disorders including AD have been explored in preclinical studies and also entered phase I/II clinical trials (Tuszynski et al., 2015; Choudhury et al., 2016b; Fol et al., 2016; Hocquemiller et al., 2016). For the CNS, adenovirus (AAV) vector systems have been most commonly used due to their safety, non-pathogenic nature, the ability to transduce dividing and non-dividing cells, particularly neurons *in vivo*, the wide volumetric distribution of vector particles in tissue and the ability to mediate long-term gene expression *in vivo* (Choudhury et al., 2016a; Hocquemiller et al., 2016).

Recently, we employed AAV9-mediated gene transfer of APP\(\alpha\) into the brain to explore its potential to ameliorate or rescue structural, electrophysiological and behavioral deficits of transgenic APP/PS1 AD model mice. A single bilateral injection of AAV-APP\(\alpha\) particles was sufficient to mediate long-lasting APP\(\alpha\) expression over 5 months that was well tolerated without apparent side effects. Interestingly, sustained APP\(\alpha\) overexpression in aged APP/PS1 mice with already preexisting pathology and amyloidosis restored LTP, ameliorated spine density deficits and also rescued spatial reference memory assessed by the Morris water maze. Moreover, we demonstrated a significant reduction of soluble A\(\beta\) species and plaque load. In addition, APP\(\alpha\) treatment induced the recruitment of microglia with a ramified morphology into the vicinity of plaques and upregulated IDE and TREM2 expression suggesting enhanced plaque clearance (Fol et al., 2016). These data...
further corroborate the therapeutic potential of APP\textsubscript{\alpha} for AD that raises hope to translate these findings into clinical application.

To this end further experimental studies including different routes of viral vector application, dose optimization and studies in larger animals are needed. Several routes of vector administration to the CNS have been developed: (i) direct injection into the brain parenchyma; (ii) CSF-based delivery using ICV, cisternal or lumbar intrathecal (IT) administration; and (iii) intravascular (e.g., intravenous) administration. Intracranial injection has been explored not only for diseases with anatomically restricted pathology such as Parkinson’s disease (reviewed in Choudhury et al., 2016b; Hocquemiller et al., 2016), but also for neuropathic lysosomal storage diseases (LSD) that affect large brain regions. For LSDs, multiple intraparenchymal injections were used in phase I/II clinical trials that showed the safety of the approach and also lead to encouraging clinical outcome (Leone et al., 2012; Tardieu et al., 2014). Vector delivery via the CSF, in particular intracisternal and IT is a less invasive alternative strategy that is particularly promising for the delivery of secreted proteins such as growth factors and lysosomal proteins, and has been successfully used to express Apolipoprotein E in AD model mice (Hudry et al., 2013). Systemic, intravascular administration is the least invasive route and has the potential to enable widespread vector distribution as every cell in the brain being a maximum of 40 microns from the microvasculature (Wong et al., 2013). In this regard encouraging progress has been made, as serotype AAV9 and AAVrh.10 have been shown to cross to some extent the blood brain barrier (BBB; reviewed in Hocquemiller et al., 2016; Saraiva et al., 2016), apparently by active transcytosis through endothelial cells (Merkel et al., 2017). The development of modified AAV vectors with re-engineered capsids should improve this further (Choudhury et al., 2016a; Deverman et al., 2016; Jackson et al., 2016). One of the main challenges for AD gene therapy is the widespread pathology that affects several anatomic regions involved in learning and memory. Thus, protocols that either target regions affected early during disease and/or widespread gene delivery to several anatomical regions are required.

A non-invasive alternative to viral vector mediated gene transfer are formulations of recombinant APP\textsubscript{\alpha} protein, sub-domains or active peptides that enable transport across the BBB. This includes intranasal delivery that has been successfully used in preclinical models of CNS diseases (Lochhead and Thorne, 2012). Examples for AD are the intranasal delivery of insulin (Mao et al., 2016) or PACAP (Rat et al., 2011) to enhance non-amyloidogenic APP processing in transgenic mouse models. Liposomes and nano-particle based approaches are emerging as further options (Kreuter, 2014; Khalin et al., 2016). Finally, transient opening of the BBB by transcranial focused or scanning ultrasound in combination with microbubbles might be used to further enhance delivery of viral vectors, proteins such as APP\textsubscript{\alpha} (or active fragments) and nano-particles (Thévenot et al., 2012; Leinenga et al., 2016).

Collectively, these various approaches all appear to merit further investigation. However it needs to be kept in mind that many challenges lie ahead for translating these approaches to the human brain, especially given its size and thus the widespread volume of brain tissue that needs to be treated. Moreover, the preclinical animal models being currently used do not fully recapitulate the human disease features, and thus successes in animal models need to be treated with caution. Nonetheless, despite these challenges the neuroprotective and synaptic repair inducing properties of APP\textsubscript{\alpha} make it a worthy target for future research aiming to treat AD, as well holding other neurological disorders.

AUTHOR CONTRIBUTIONS

BGM, MR, WCA and UCM co-wrote this review. MR designed the figures.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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