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The paradigm of amyloid precursor protein in amyotrophic lateral sclerosis: The potential role of the $_{682}$YENPTY$_{687}$ motif

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ABSTRACT

Neurodegenerative diseases are characterized by the progressive decline of neuronal function in several brain areas, and are always associated with cognitive, psychiatric, or motor deficits due to the atrophy of certain neuronal populations.

Most neurodegenerative diseases share common pathological mechanisms, such as neurotoxic protein misfolding, oxidative stress, and impairment of autophagy machinery.

Amyotrophic lateral sclerosis (ALS) is one of the most common adult-onset motor neuron disorders worldwide. It is clinically characterized by the selective and progressive loss of motor neurons in the motor cortex, brain stem, and spinal cord, ultimately leading to muscle atrophy and rapidly progressive paralysis.

Multiple recent studies have indicated that the amyloid precursor protein (APP) and its proteolytic fragments are not only drivers of Alzheimer's disease (AD) but also one of the earliest signatures in ALS, preceding or anticipating neuromuscular junction instability and denervation. Indeed, altered levels of APP peptides have been found in the brain, muscles, skin, and cerebrospinal fluid of ALS patients.

In this short review, we discuss the nature and extent of research evidence on the role of APP peptides in ALS, focusing on the intracellular C-terminal peptide and its regulatory motif $_{682}$YENPTY$_{687}$, with the overall aim of providing new frameworks and perspectives for intervention and identifying key questions for future investigations.

1. Introduction

Over the past few years, common pathways involved in neurodegenerative diseases have been highlighted [1]. Indeed, neurodegenerative disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS), show various degrees of overlapping pathology, not only in clinical appearance but also at the single-protein level or in an entire signalling cascade.

One case is that of the amyloid precursor protein (APP), a protein primarily at the center of AD research. An increasing number of studies have proposed APP as an active contributor to certain forms of ALS [2]. In line with this concept, APP is expressed at the neuromuscular junction (NMJ) [3] and is required for the normal development and function of the NMJ [4,5] suggesting that alterations in the signalling or processing of APP might influence NMJ function and are likely to predispose patients to motor neuron diseases (MND), such as ALS. Accordingly, alterations in the APP pathway have been proposed to represent an ALS signature preceding or anticipating the pathology [1,6].

ALS and AD are age-associated sporadic disorders with no precisely identified genetic causes but with a large number of susceptibility genes in which selective and progressive dysfunctions of specific neuronal populations occur [1,7]. Although apparently unrelated, as AD is primarily a central nervous system disease and ALS targets the peripheral nervous system, approximately 30 % of ALS patients show neuritic plaques and neurofibrillary tangles, especially in the amygdala, hippocampus, and entorhinal and insular cortices [6,8].

In addition, both AD and ALS show accumulation and deposition of a specific misfolded protein, APP in AD and TDP-43 in ALS, conferring vulnerability to specific neuronal populations [9] affecting mitochondrial and autophagy functions [10,11] and triggering neurotoxic mechanisms [12].

In this short review, we provide evidence for the role of APP peptides in ALS, and underline new frameworks and perspectives for future research.

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Findings regarding the pathophysiology of AD and ALS and their similarities are beyond the scope of this review, as many outstanding reports have extensively discussed this area of research [13,14].

In particular, because APP contains multiple structural and functional domains, we focused our review mainly on the properties of APP intracellular domains and its regulatory motif $_{682}$YENPTY$_{687}$.

2. Lights and shadows of APP in ALS

APP is expressed in both neuronal and non-neuronal cells and is largely distributed in extra-neuronal tissues [15]. APP is present at synaptic sites in both the central and peripheral nervous systems, including the NMJ, and plays an essential role in the development of neuromuscular synapses [3,4].

APP is post-transcriptionally processed into three major isoforms with differential cellular and tissue expression patterns. The three main isoforms of APP described to date are APP_{695}, APP_{751} and APP_{770}, depending on the number of amino acids, and are produced through alternative splicing of exons 7 and 8, which encode the Kunitz protease inhibitor and OX-2 domains, respectively [16]. APP_{695} lacks both domains, whereas the APP_{751} isoform containes only KPI domain in the extracellular sequence. APP_{770} in addition to KPI domain, contains an OX-2 domain [17]. APP_{751} and APP_{770} are ubiquitously expressed, whereas APP_{695} is predominantly expressed in neurons [18,19].

APP belongs to an evolutionarily conserved type I transmembrane glycoprotein family that includes two paralogues, amyloid precursor-like proteins 1 and 2 (APLP1 and APLP2), with similar structures and membrane topologies [20]. Notably, previous studies using knockout mice have emphasized the high functional redundancy of APP, APLP1, and APLP2 [21]. These proteins contain several conserved motifs that are shared between all vertebrates, including E1 and E2 domains in the extracellular region and a short intracellular C-terminal domain (AICD) that contains the highest conserved consensus motif, Y_{682}ENPTY$_{687}$ [22]. The latter is thought to be crucial for AICD binding to adaptor proteins, and for APP trafficking and localization in cells [23]. Notably, while Aβ originates solely from APP, AICD originates from APP, APLP1, and APLP2 [20].

Aβ peptides, the major components of amyloid fibrils in AD, are the result of sequential cleavage of β- and γ-secretase. Briefly, β-secretase cleavage generates a soluble APP peptide (sAPPβ) secreted in extracellular compartments and an intracellular C-terminal fragment (CTF99). CTF99 is then cleaved by γ-secretase to produce Aβ40 and Aβ42 peptides and AICD, which appears to regulate the transcription of certain genes [24,25]. AICD is rapidly metabolized by insulin-degrading enzyme [26,27] and the endosomal/lysosomal system [28]. Alternatively, α-secretase cleaves APP within the Aβ sequence, thus precluding Aβ formation and generating sAPPα with neurotrophic properties and the CTF83 peptide, which is further processed by γ-secretase to yield AICD and p3 fragment [29–32].

Increased β-secretase activity has been observed in animal models of ALS and nerve injury [33,34]. Similarly, a lack of α-secretase expression associated with increased β-secretase expression and activation of the amyloid cascade of APP, leading to increases in amyloid-β and AICD peptides, has been reported in the hippocampi of ALS patients [35]. In addition, deficits in lysosomal autophagic pathways have been demonstrated to activate the γ-secretase complex and lead to Aβ42 accumulation in cultured human muscle fibers [36]. Pharmacological inhibition of β-secretase enhances peripheral functional recovery after sciatic nerve ablation and increases axonal sprouting due to partial nerve injury [37]. Treatment with a monoclonal antibody (MAb) that blocks β-secretase cleavage prevents an increase in APP expression, phosphorylation, processing, and inflammatory processes [33,34].

β-Secretase cleavage to generate Aβ peptides and AICD occurs preferentially in the APP_{695} isoform, although increased expression of APP_{751} and APP_{770} has been detected in the brains of patients with AD and is associated with increased Aβ deposition [38,39]. Interestingly, prolonged activation of extrasynaptic NMDA receptors, which has been associated to neurodegenerative diseases [40,41], shifts APP splicing from APP_{695} to KPI-containing APP isoforms in neurons and triggers APP processing to produce Aβ [40]. This might imply that dysregulated splicing of APP mRNA occurs in pathological conditions and might allow discrimination of different pathologies in which APP has been demonstrated to be involved, including PD and ALS. Indeed, most reports focusing on the role of the APP gene in ALS face difficulties in discriminating between the three isoforms and refer to APP generically [22]. In this regard, a recent study reported the development of a new PCR procedure that can accurately measure and quantify the transcript copy numbers of all three major isoforms, APP_{695}, APP_{751}, and APP_{770} [42].

It is noteworthy that specific adaptors might bind APP_{695}, APP_{751}, and APP_{770} because of the differences in their APP sequences, APP/KPI versus APP_{695}, thus affecting APP endocytosis, trafficking, and metabolism in neuronal cells. Accordingly, sequence differences between APP_{695}, APP_{751}, and APP_{770} may regulate the transport of APP_{695} along a distinct processing route, leading to β-secretase cleavage, whereas APP/KPI isoforms are excluded from this pathway or located in a distinct subcellular compartment. In this context, the identification of these different adaptor proteins may be useful for designing innovative strategies for the differential diagnosis of neurodegenerative diseases associated with altered APP levels.

Notably, only AICD generated by β- and γ-secretase cleavage translocates to the nucleus, where several potential target genes have been identified Table 1 [25]. Although γ-secretase cuts AICD in several subcellular locations, AICD generated by α-secretase cleavage at the plasma membrane has a lower likelihood of reaching the nucleus because of its short half-life and longer distance from the cell surface [43]. In contrast, AICD produced in the endosomes by β- and γ-secretase cleavage can reach the nuclear vicinity before γ-cleavage releases AICD owing to dynein- and microtubule-mediated transport systems [44].

Interestingly, less AICD is produced in amyloidogenic APP processing than in non-amyloidogenic processing, raising the question of whether a reduction in AICD levels results in the loss of physiological functions or the gain of new functions.

Some of these genes, such as those encoding the Aβ-degrading enzyme, neprilysin (NEP), are implicated in APP metabolism. Although the direct involvement of NEP in ALS has not yet been defined, it is known that NEP not only participates in the regulation of various brain functions but also in movement regulation [59,60]. Loss of NEP expression results in altered locomotor activity [61].

Other putative AICD target genes are α2-actin and transgelin, which are involved in the regulation of actin cytoskeleton dynamics [44]. Notably, many mutations in ALS-related genes that affect cytoskeletal integrity and dynamics have been identified [62]. For instance, mutations in proteins that regulate actin polymerization, including superoxide dismutase (SOD1), TDP-43, FUS, and Profilin1

Table 1
Putative genes regulated by AICD.
Source: Adapted from Muller et al. [44].

Protein	References
α2-actin and transgelin	[44]
Neprilysin (Aβ degradation factor)	[45]
GSK3 β (glycogen synthase kinase)	[46–50]
p53 (Tumor suppressor)	[51,52]
AchE1, AchE2 (Acetyl choline esterase)	[53,54]
Thymidylate synthase	[45,55]
(HES) Hairy and Enhancer of split (differentiation factor)	[56]
LRP1 (Lipoprotein Receptor)	[57]
EGFR (Epidermal growth factor receptor)	[58]

(PFN1), have been identified in patients with ALS, causing an increased tendency to aggregate and leading to the formation of cytoplasmic inclusions [63]. Notably, mutations in PFN1 (C71G, M114T, G118V, A20T, T109M, Q139L, and E117G) [64,65] and other cytoskeletal-related proteins such as Tubulin A4A (TUBA4A) [66] and kinesin family member 5A (KIF5A) [67] have been identified in familial ALS patients. The ability of mutant PFN1 to associate with actin is impaired in ALS, and mutant PFN1 motoneurons exhibit morphological abnormalities characterized by smaller growth cones and shorter axons [68].

Indeed, the disruption of cytoskeletal integrity and/or motor neuron-dependent transport are key features of ALS. This highlights the necessity of potentially differentiating variants of these genes that might act as primary causes of the disease from those that might become risk factors or disease modifiers of the pathology. In addition, the possibility that altered levels of AICD in ALS might influence the expression of some of these genes and activate neurotoxic downstream pathways is an aspect not enough speculated that might deserve attention.

Glycogen synthase kinase 3β (GSK3β) promotes tau hyperphosphorylation and neurofibrillary tangle formation in AD [69]. Dysregulations of GSK3β signalling has also been recognized in ALS [70]. In this regard, increased levels of GSK3β expression and phosphorylation of the Tyr_{216} residue have been reported in the spinal cord, frontal and temporal cortices, and hippocampus of patients with ALS [71–73].

The tumor suppressor genes p53 and cyclin B1, and D1 or KAI1 are pro-apoptotic factors and cell cycle reentry, respectively, and are involved in neuronal death processes, also included ALS (Reviewed by Szybińska et al. [74]. Consistently, activation of p53 and an altered Bcl-x/Bax ratio were also observed in the ventral horns of the lumbar spinal cord of SOD1 transgenic mice harboring a single amino acid substitution of glycine to arginine at codon 86 (SOD1 G86R) mice [75]. p53 [76] and other apoptotic markers, such as Rb, Bax, Fas, and caspases [77] are increased in the motor cortex and spinal ventral horns of postmortem brain tissues [74,78].

APP regulates Cu/Zn SOD1 expression and function, which is one of the major targets of oxidative damage in the brains of AD patients [79,80] and its mutations have been linked to familial ALS [81]. In ALS neurons, Aβ acts as an early and short-lived change [82] directly interacting with superoxide dismutase 1 (SOD1), decreasing its enzymatic activity [83] and accelerating the onset of motor impairment [84]. Accordingly, increased Aβ immunoreactivity has been reported in the perikaryal region of anterior horn neurons of patients with familial and sporadic forms of ALS, and proximal axonal swelling was detected in mild lesions or in the early stage of the pathology [85] supporting the concept that ALS is a disease not confined to the motor system [86–88]. Indeed, neurodegeneration in patients with ALS also involves brain areas such as the dorsolateral prefrontal cortex, anterior cingulate, hippocampus, dentate gyrus (DG), parietal lobe, substantia nigra, cerebellum, amygdala, and basal ganglia [86,89–91] and amyloid cascade-related biomarkers have been found in the cerebral spinal fluid of patients with ALS and frontotemporal dementia (FTD) [92,93]. Additionally, an increase in Aβ levels has been observed in the skin and muscles of ALS patients [93,94].

Similar results were obtained in SOD1 transgenic mice harboring a single amino acid substitution of glycine to alanine at codon 93 (SOD1-G93A), which is commonly used to model ALS, where Aβ peptide accumulation and increased APP levels have been detected in a restricted subpopulation of vulnerable muscle fibers and in the spinal cord [2]. Interestingly, genetic ablation of APP ($APP^{-/-}$) in SOD1-G93A mice significantly prevents neuromuscular junction loss, reduces disease progression, and promotes motor neuron survival, further supporting the idea that APP and Aβ peptides might contribute to ALS pathology by accelerating muscle denervation [2]. The hypothesis that Aβ can also be neurotoxic in the peripheral nervous system was further supported by evidence from murine models of familial AD overexpressing Aβ, in which the susceptibility of motor neurons to Aβ peptides, progressive degeneration of skeletal muscle, and age-dependent axonal degeneration in the spinal cord have been described [95–97].

3. The $_{682}$YENPTY$_{687}$-mediated APP processing regulation: possible implications in ALS

As mentioned above, APP processing can result in the production of Aβ peptides, which contribute to AD or the secretion of the sAPPα peptide as well as intracellular AICD.

The production of sAPP(α or β) and AICD metabolites largely depends on the level of Tyr_{682} phosphorylation of the highly conserved $_{682}$YENPTY$_{687}$ motif on AICD (referred to as neuronal APP_{695} numbering). The $_{682}$YENPTY$_{687}$ motif represents a docking site for multiple interacting proteins. $_{682}$YENPTY$_{687}$ phosphorylation changes the AICD conformation, which shifts the cis/trans isoforms, resulting in loss of affinity for binding proteins. Notably in both APP_{695} as well as APP_{751} and APP_{771} the $_{682}$YENPTY$_{687}$ motif is preserved.

For instance, Grb2, Shc, Grb7, and Crk interact with APP only when Tyr682 is phosphorylated, whereas Fe65, Fe65L1, and Fe65L2 interact with APP only when this tyrosine is not phosphorylated (reviewed by Matrone et al. [23]) Table 2.

In this regard, the $_{682}$YENPTY$_{687}$ binding protein, Fe65 acts as an AICD stabilizer in the nuclear compartment, where it binds to histone acetylase Tip60 to form AFT complexes and prevents APP amyloidogenic processing [118]. Notably, decreased Fe65 expression has been identified in patients with ALS, in which the accumulation of APP and Aβ has also been detected, suggesting that the AICD-Fe65 complex is internalized into the nucleus, as occurs when the APP amyloidogenic signalling pathway is activated [86].

Similarly, the $_{682}$YENPTY$_{687}$ binding proteins Clathrin and AP2 control APP endocytosis, as well as many other transmembrane proteins, and proper trafficking to the early endosome and back to the plasma membrane, thus preventing APP accumulation in the late endosome and lysosome, where because of the acidic environment, APP is preferentially cleaved by β secretase [119] thereby initiating amyloidogenic processing [116,120]. Although a direct link between ALS and the Clathrin and AP2 adaptors has not yet been demonstrated, alterations in the transport of endosomes or lysosomes have been proposed to be likely causative of the pathology, as in many other neurodegenerative diseases [121]. Accordingly, several genes involved in endosomal maturation, lysosome biogenesis, and vesicle trafficking have been linked to ALS [122], suggesting that these

Table 2
Some of the most common $_{682}$YENPTY$_{687}$ adaptor proteins.

Protein	References
Fe65 (fe65l1, fe65l2)	[98–100]
Mint/X11 (mint1, mint2, mint3)	[101]
Numb	[56]
JIP (JIP1, JIP3) (Islet-brain1/C-Jun N-terminal kinase interacting protein-1)	[102]
PAT (PAT1, PAT1A) (Protein interacting with APP tail 1)	[103]
Pin1 (peptidyl-prolyl isomerases. PPIase)	[104]
FKBP12	[105]
SHCA/SHCC (Src homology and collagen homology)	[106,107]
GRB2 (growth factor receptor-bound protein 2)	[108]
Dab1, dab2 (Disabled Regulator protein)	[109,110]
Crk	[111]
cAbl (Tyrosine kinase)	[112]
Fyn (Tyrosine kinase)	[113–115]
Clathrin, AP2 (adaptor protein 2)	[116]
SorLA (Sortilin-related receptor)	[117]

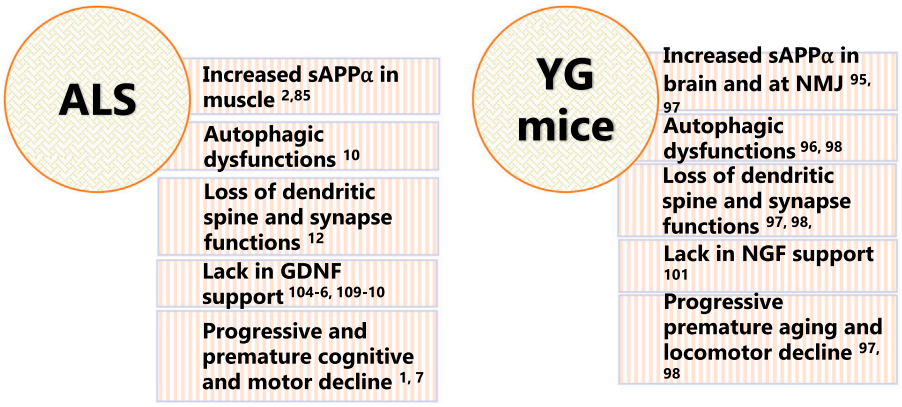

Fig. 1. Similarities between ALS SOD1-G93A and APP YG mice.

pathways are altered in ALS. In addition, changes in the expression of proteins responsible for endocytic trafficking have been detected in ALS patients [123,124]. Among others, SorLA, which belongs to the VPS10Ps protein family and interacts with the $_{682}$YENPTY$_{687}$ motif of APP [125], decreases in the anterior horn cells (AHCs) of patients with ALS compared to controls [126]. Notably, abundant SorLA expression has been detected in neurons throughout the central nervous system, including the cortex, hippocampus, cerebellum, and spinal cord, which controls retromer-dependent sorting of APP and prevents APP amyloidogenic processing [125,127,128].

Referring to another $_{682}$YENPTY$_{687}$ binding protein, Notch, studies have reported that Notch and APP compete for α- and γ-secretase cleavage. Interestingly, inactivation of the Notch pathway and a reduction in α-secretase expression have been described in the hippocampus of patients with motor neuron deficits. Such alterations are associated with increased β-secretase expression and the activation of the amyloidogenic cascade, leading to Aβ and AICD accumulation [35,129,130]. Of note Notch 1 is essential for hippocampal neurogenesis [131,132] and the Notch receptor is expressed in neural stem cells [131]. Consistently, inactivation of the Notch pathway results in inhibition of neurogenesis, and Notch signalling is repressed in the hippocampi of patients with ALS [133]. Interestingly, some drugs that increase Notch signalling have been found to promote hippocampal neurogenesis [134]. Similarly, a rat model of AD showed that soluble Aβ_{42} suppresses Notch1 expression [135].

The $_{682}$YENPTY$_{687}$ adaptor protein Numb is involved in stem cell maintenance and differentiation, as well as in neuritogenesis, and antagonizes Notch-1 signalling [136,137]. Numb is reduced one week after the spinal cord lesion or after motor neuron ablation and then restored at one month [129] in animal models of ALS, in line with other evidence of decreased neurogenesis in patients with ALS [35,133]. Nevertheless, the role of Numb, as well as the other APP adaptor protein Shh, has also been reported in the regulation of adult neurogenesis [138] and the expression of these proteins has been found to be downregulated in animal models of motor neuron degeneration [129].

Furthermore, c-Abl [49,139] and Fyn tyrosine kinase (TK) phosphorylate the APP Tyr$_{682}$ residue of APP under physiological or pathological conditions, although Fyn appears to be primarily responsible for aberrant Tr$_{682}$ phosphorylation in AD neurons [115]. Interestingly, an increase in the amount of c-Abl mRNA, phosphorylated c-Abl and Fyn TK has been detected in motor neurons of ALS [140–142]. Consistently, treatment with c-Abl and Fyn inhibitors, such as dasatinib and bosutinib, or the new compound SC75741, has been shown to exert protective effects on motor neuron degeneration in G93A-SOD1 transgenic ALS mice [142] as well as iPSC-derived motor neurons from patients with ALS [141,143,144]. In addition, multiple studies have associated mutations in genes encoding different kinases with ALS [145,146], suggesting that alterations in the function of specific kinases and/or their downstream targets are crucial to neuronal survival, and that protein kinase inhibitors may be a reasonable target for the design of innovative ALS treatment [147,148].

Multiple lines of evidence indicate that regulation of APP trafficking might prevent Aβ generation. Consistently, increased sAPPα levels appeared to be associated with a reduced risk of developing AD [149–152].

Interestingly, variations in sAPPα production have also been reported in conditions other than AD such as cerebrovascular and neurodegenerative diseases [153], bipolar disorder [154] and ALS [92,93].

In particular, sAPPα is upregulated in the muscles of mouse models of familial ALS and in patients [1,2,94], whereas low sAPPα concentrations have been found in the CSF of patients with ALS with a rapidly progressive course of the disease [92]. However, whether the increase in sAPPα represents a cell survival response to molecular changes caused by MND [86] or a neurotoxic process to promote neuronal death is a matter of debate.

Interestingly, Barbagallo et al. previously demonstrated that sAPPα production largely depends on Tyr$_{682}$ phosphorylation of the $_{682}$YENPTY$_{687}$ motif of APP in neurons [155]. Accordingly, when Tyr$_{682}$ is not phosphorylated, APP is largely located in the plasma membrane where it is processed by α-secretase to generate sAPPα. In contrast, when APP is phosphorylated at the Tyr$_{682}$ residue, APP endocytosis and trafficking inside neurons are affected, resulting in APP accumulation in acidic neuronal compartments, such as late endosomes and lysosomes, where it is preferentially cleaved to generate sAPPβ peptides [114,116,125]. Consistently, APP YG knock-in mice, in which Tyr$_{682}$ is not phosphorylated because it is replaced by glycine (YG), show aberrant sAPPα production in the brain and motor neurons [155,156]. In addition, YG mice display a progressive reduction in muscular strength, motor functions and abilities, and learning performance [157]. Such deficits are associated with age-dependent cognitive decline, autophagic dysfunction, and progressive dendritic spine loss [125], mirroring some of the crucial features reported in patients [158] (Fig. 1).

Notably, the YG background, when introduced into an APLP2 null background failed to rescue early postnatal lethality or neuromuscular synaptic defects present in APLP2 null mice, supporting the role of the Tyr$_{682}$ residue and $_{682}$YENPTY$_{687}$ motif in regulating NMJ neurodevelopment and function [156].

In accordance with the importance of Tyr$_{682}$ phosphorylation on the $_{682}$YENPTY$_{687}$ motif in controlling sAPPα release and preventing aberrant sAPPα secretion, when the APP background lacking the $_{682}$YENPTY$_{687}$ domain was reintroduced into APP-knockout mice, an increased cell surface expression of sAPPα was detected [159].

Interestingly, YG hippocampal neurons fail to differentiate properly in vitro because of deficits in nerve growth factor (NGF) response [160]. In fact, the lack of Tyr_{682} phosphorylation prevents the association between APP and the NGF receptor TrkA, resulting in TrkA perinuclear accumulation and causing APP redistribution towards the non-amyloidogenic pathway with the accumulation of sAPPα and AICD peptides [160]. This critical role of NGF in APP trafficking, control of neuronal functions, and prevention of dysfunction largely reminds us of the crosstalk between glial cell-derived neurotrophic factor (GDNF) and APP at the neuromuscular junctions [161,162]. GDNF controls muscle and Schwann cell functions [163]. Deficits in GDNF and APP signalling have been associated with ALS. GDNF is decreased in the serum of patients with ALS, whereas sAPPα levels are increased in the same fluid [164]. APP regulates GDNF gene expression [164,165]. NGF promotes trophic effects and protects neurons from AD-related processes [166]; when GDNF is administered directly to muscles, it improves muscle-nerve synapse performance and promotes motor neuron activity and survival [167]. In addition, overexpression of GDNF in muscles extends the lifespan of ALS mice [168]. Whether GDNF activity and secretion levels change depending on APP Tyr_{682} phosphorylation is worth investigating.

4. Conclusions

Considerable knowledge gaps and clinical challenges associated with neurodegenerative diseases remain unaddressed. Perhaps the biggest challenge is to better define and understand the factors that initiate the pathology and drive cellular dysfunction in the disease. Numerous studies suggest that neurodegenerative diseases share not only clinical phenotypes but also molecular mediators (s). Although the findings discussed here portray only part of the broad literature on AD and ALS and their roles in these diseases, it is likely sufficient to delineate some of the critical questions for the next phase of studies.

Herein, we discuss a novel hypothesis that might deserve to be expanded and sustained in the future regarding the potential role of the conserved $_{682}$YENPTY$_{687}$ motif located on the AICD of APP in ALS and speculate that modifications in the $_{682}$YENPTY$_{687}$ peptide might represent an early signature of the disease, as previously described in AD [23,120].

The $_{682}$YENPTY$_{687}$ peptide has been consistently viewed as an active and critical player in controlling APP function and preventing the switch from the non-amyloidogenic to amyloidogenic pathway through phosphorylation of the Tyr_{682} residue [23,120]. However, the idea that this peptide can also regulate APP activity in other pathologies such as ALS has never been speculated. Importantly, evidence regarding the role of $_{682}$YENPTY$_{687}$ peptide in regulating the levels of sAPPα in motor neurons and influencing the correct development of NMJ has been reported previously [33,34,82,164]. Indeed, Tyr_{682} phosphorylation of the $_{682}$YENPTY$_{687}$ motif controls APP trafficking and prevents amyloidogenic APP processing to generate Aβ [157,160]. Conversely, the lack of Tyr_{682} phosphorylation in YG mice causes an increase in sAPPα levels, autophagic deficits, locomotor deficiency, and cognitive deficits, all of which have been observed in ALS patients [155,157]. Consistently, an aberrant increase in sAPPα levels has been detected in the dysfunctional NMJ of patients with ALS [1,2,94].

These findings raise the question of whether a possible malfunction of the $_{682}$YENPTY$_{687}$ pathway might influence Tyr_{682} phosphorylation and predispose APP to aberrant production of sAPPα in patients with ALS.

Based on these perspectives, this short review provides new and important directions for the investigation of ALS.

Author statement

I declare that this manuscript is original and has not been published before and is not currently, being considered for publication elsewhere., I confirm that the manuscript has only one author and that there are no other persons who, satisfied the criteria for authorship and are not listed., I will be the responsible for communicating with the editor about progress, submissions of revisions and final approval of proofs.

Conflict of Interest

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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