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Impact of the apelin/APJ axis in the pathogenesis of Parkinson's disease with therapeutic potential

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Abstract

The pathogenesis of Parkinson's disease (PD) remains elusive. There is still no available disease-modifying strategy against PD, whose management is mainly symptomatic. A growing amount of preclinical evidence shows that a complex interplay between autophagy dysregulation, mitochondrial impairment, endoplasmic reticulum stress, oxidative stress, and excessive neuroinflammation underlies PD pathogenesis. Identifying key molecules linking these pathological cellular processes may substantially aid in our deeper understanding of PD pathophysiology and the development of novel effective therapeutic approaches. Emerging preclinical evidence indicates that apelin, an endogenous neuropeptide acting as a ligand of the orphan G protein-coupled receptor APJ, may play a key neuroprotective role in PD pathogenesis, via inhibition of apoptosis and dopaminergic neuronal loss, autophagy enhancement, antioxidant effects, endoplasmic reticulum stress suppression, as well as prevention of synaptic dysregulation in the striatum, excessive neuroinflammation, and glutamate-induced excitotoxicity. Underlying signaling pathways involve phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin, extracellular signal-regulated kinase 1/2, and inositol requiring kinase 1α/XBP1/C/EBP homologous protein. Herein, we discuss the role of apelin/APJ axis and associated molecular mechanisms on the pathogenesis of PD *in vitro* and *in vivo* and provide evidence for its challenging therapeutic potential.

KEYWORDS

adipokine, apelin-13, apelin-36, apelinergic, biomarker, brain-gut peptide

Abbreviations: ACE2, angiotensin-converting enzyme 2; ACTH, adrenocorticotropic hormone; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AMPK, 5′-AMP-activated protein kinase; AT1, angiotensin II type-1 receptor; ATF4, activating transcription factor 4; ATF6, activating transcription factor 6; ATG13, autophagy-related protein 13; Atg101, autophagy-related protein 101; ASK1, apoptosis signal-regulating kinase 1; BBB, blood–brain barrier; BMPs, bone morphogenic proteins; cAMP, cyclic adenosine monophosphate; CAT, catalase; CHOP, C/EBP homologous protein; CNS, central nervous system; DAG, diacylglycerol; DHA, docosahexaenoic acid; ER, endoplasmic reticulum; ERK1/2, Extracellular signal-regulated kinase 1/2; ERS, Endoplasmic reticulum stress; GBA, glucocerebrosidase; GFAP, glial fibrillary acidic protein; GH, growth hormone; GPCR, G protein-coupled receptor; GRP78, glucose-regulated protein 78; GSH, glutathione; GSK-3β, glycogen synthase kinase 3 b; HIF-1α, hypoxia-inducible factor 1α; HMGB1, high mobility group box 1; HPA, hypothalamic–pituitary–adrenal; Iba1, ionized calcium-binding adapter molecule-1; ICAM-1, intercellular adhesion molecule-1; IGF-1, insulin-like growth factor 1; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; IP3, inositol 1,4,5-triphosphate; IRE1α, inositol requiring kinase 1α; JNK, c-Jun N-terminal kinase; LC3B-II, microtubule-associated protein 1A/1B light chain 3B-II; LRRK2, leucine-rich repeat kinase 2; MAPKs, Mitogen-activated protein kinases; mGluRs, metabotropic glutamate receptors; MPTP, 1-Methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; MPO, myeloperoxidase; mTOR, Mammalian target of rapamycin; NLRP3, NOD-like receptor pyrin domain-containing 3 protein; NMDA, *N*-methyl-D-aspartate; NRF2, nuclear factor erythroid 2-related factor 2; 6-OHDA, 6-hydroxydopamine; PCSK3, proprotein convertase subtilisin kexin type 3; PD, Parkinson's disease; PEG, polyethylene glycol; PEG-apelin-36, PEG-conjugated apelin-36; PERK, protein kinase R-like endoplasmic reticulum kinase; PI3K, phosphoinositide 3-kinase; PINK1, PTEN (phosphatase and tensin homologue)-induced kinase 1; XBP1, X-box binding protein 1; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; PLCb, phospholipase C beta; PSD-95, postsynaptic density protein 95; RAS, renin–angiotensin–aldosterone system; RB1CC1/FIP200, RB1-inducible coiled-coil 1; ROS, reactive oxygen species; SNP, single-nucleotide polymorphism; SNpc, Substantia nigra pars compacta; SOD, superoxide dismutase; SP1, Sp1 transcription factor; STAT3, signal transducer and activator of transcription 3; SQSTM1, sequestosome 1; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; TXNIP, thioredoxin-interacting protein; ULK1, Unc-51 like autophagy activating kinase 1; UPR, unfolded protein response.

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1 | INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD), affecting 1%–2% of the population above the age of 65 (Forman et al., 2004). Due to the aging population, it is expected that its prevalence will double by 2030 (Dorsey et al., 2007). The main clinical characteristics of PD include bradykinesia, rigidity, postural instability, and resting tremor, as well as non-motor symptoms, such as cognitive impairment, depression, psychotic manifestations, and autonomic dysfunction (DeMaagd & Philip, 2015). The neuropathological hallmarks of PD are the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), as well as the accumulation of Lewy bodies and Lewy neurites consisting of aggregated α-synuclein in the degenerating neurons. However, neuropathological findings are also present in several other brain regions, such as the dorsal motor nucleus of the vagus nerve, locus coeruleus, raphe nucleus, and cerebral cortex (Dickson, 2018). Current treatment including levodopa and dopaminergic agonists is mainly symptomatic with potentially severe side effects such as levodopa-induced dyskinesias, and there is still no available therapy halting disease progression (DeMaagd & Philip, 2015). PD pathogenesis remains elusive with both genetic and environmental factors contributing to its development. Specific neurotoxins such as 6-hydroxydopamine (6-OHDA), rotenone, paraquat, and 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) are widely used for experimental PD models (Acar et al., 2019). Preclinical evidence shows that a complex interplay between mitochondrial impairment, autophagy dysregulation, endoplasmic reticulum stress (ERS), neuroinflammation, oxidative damage, abnormal protein degradation, and dysfunction of synaptic plasticity underlies PD pathophysiology (Thomas, 2009). Identifying the key molecules that link these cellular processes may significantly aid in our deeper understanding of PD pathogenesis and the development of novel effective therapeutic approaches.

Significance

Parkinson's disease (PD) is the second most common neurodegenerative disorder with still elusive pathogenesis and in constant search for novel molecular targets. In this review, we discuss the emerging neuroprotective role of the endogenous neuropeptide apelin in PD pathophysiology. Experimental data indicate that apelin acts as a ligand to the orphan G protein-coupled receptor APJ to elicit its functions which include the inhibition of neuronal apoptosis, enhancement of autophagy, and antioxidant effects. Moreover, apelin/APJ signaling axis suppresses endoplasmic reticulum stress, inflammation, and synaptic dysregulation via several pathways, highlighting its therapeutic potential against PD development and progression.

2 | PHARMACOLOGY OF APELIN AND APJ

Apelin is an endogenous neuropeptide discovered by Tatemoto et al. (1998) and firstly isolated from bovine stomach tissue (Lee et al., 2000). Apelin acts as a ligand for its orphan receptor APJ—encoded by *APLNR* gene—which belongs to the family of G protein-coupled receptors (GPCR) possessing seven transmembrane domains (Pope et al., 2012). In humans, apelin is encoded by the *APLN* gene located on the long arm of X chromosome (Xq25-q26.1) and encodes pre-proapelin, a 77-amino acid precursor peptide (Lee et al., 2000). The enzymatic hydrolysis of this native apelin peptide gives rise to several active peptide fragments able to activate APJ that consist of 12, 13, 15, 16, 17, 19, 28, 31, 36, or 55 amino acids (Antushevich & Wojcik, 2018; Haghparast et al., 2018). Each form displays a distinct receptor binding affinity, and induces different APJ trafficking (Chen et al., 2020). Apelin-36 is considered to be the parent apelin variant (Antushevich & Wojcik, 2018), while apelin-13 is the most effective activator of APJ (Mughal & O'Rourke, 2018), followed by apelin-17 and apelin-36 (Pouresmaeili-Babaki et al., 2018). Post-translational modifications also affect the half-life and apelin-mediated cellular responses. One such modification is the removal of the C-terminal phenylalanine of apelin isoforms by angiotensin-converting enzyme 2 (ACE2), a plasma metalloprotease (Lv et al., 2020). This process has been associated with short half-lives of circulating apelin peptides and reduced cellular responses, although the exact role of C-terminal truncation remains unclear (Shin et al., 2017). Another post-translational modification of apelin is the spontaneous cyclization of the N-terminal glutamine of apelin-13 to pyroglutamate, giving rise to pyr-apelin-13, an isoform with increased stability and longer half-life in circulation (Lv et al., 2020), possibly due to the loss of the free primary N-terminal amine recognized by N-terminal exoprotease (Shin et al., 2017). In addition, neprilysin, a zinc-dependent metalloprotease, has been reported to inactivate apelin, by cleaving an important sequence of the conserved C-terminal 12 residues required for its activity (McKinnie et al., 2016).

APJ is encoded by a gene located on chromosome 11 and displays about 50% homology to the angiotensin II type-1 receptor (AT1)—a major component of the renin–angiotensin–aldosterone system (RAS)—although it is unable to bind to angiotensin II (Murphy et al., 1991; O'Dowd et al., 1993). Aside from apelin, the hormonal peptide Apela/Elabela/Toddler has been recently reported as a ligand of APJ (Kurowska et al., 2018); however, in humans, its expression is restricted to kidney and pluripotent cells (Wu et al., 2017).

In rodents and humans, apelin and its receptor APJ are widely expressed in both the central nervous system (CNS) and the periphery, including the spleen, placenta, lung, stomach, intestine, heart, and adipose tissue, where apelin acts as an adipokine (Kleinz & Davenport, 2005). Apelin/APJ-related pathways have been implicated in several physiological and pathological processes, such as angiogenesis, blood pressure regulation, nitric oxide-mediated

vasodilation, pituitary hormone release, obesity, insulin secretion and sensitivity, glucose and lipid metabolism, fluid homeostasis, immune responses, and cancer.

APJ interacts with G proteins (mainly Gα-$G\alpha_i$ and $G\alpha_q$, but also Gβ and Gγ), leading to the activation of several different signaling pathways. In particular, apelin/APJ activates via $G\alpha_i$, the phosphoinositide 3-kinase (PI3K)/Akt [also named protein kinase B (PKB)] and protein kinase C (PKC)/extracellular signal-regulated kinase 1/2 (ERK 1/2) pathways, thereby being involved in several cellular processes including the regulation of apoptosis, cell proliferation, neuroinflammation, and oxidative stress (Kurowska et al., 2018; Tian et al., 2020). $G\alpha_i$ is also implicated in the downregulation of protein kinase A (PKA) by inhibiting the adenylyl cyclase-mediated cyclic adenosine monophosphate (cAMP) production (Tian et al., 2020). Ga_q can upregulate phospholipase C beta (PLCb), triggering the generation of diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3), leading to the initiation of PKC cascade and the intracellular release of Ca^{2+}, respectively (Tian et al., 2020). APJ can also induce a β-arrestin-mediated G protein-independent response involving the desensitization and internalization of APJ, although the exact signaling remains obscure (Tian et al., 2020; Wu et al., 2017).

APJ signaling is heterologous, since the receptor interacts with several G proteins and mediates diverse effects in different tissues and cell types (Chapman et al., 2014). Upon binding to APJ, the different isoforms of its two endogenous ligands (apelin and toddler) may activate different signaling cascades (Chapman et al., 2014). APJ heteromer formation with the AT1 receptor, κ-opioid receptor, and bradykinin 1 receptor may also affect the downstream signaling (Chapman et al., 2014). Both the type and magnitude of downstream APJ-mediated effects may be context- and cell type-dependent, based on $G_{\alpha i}$ and $G_{\alpha q}$ coupling preferences (Table 1) (Chapman et al., 2014). Apelin-13 seems to be the most effective activator of $G_{\alpha i}$-mediated ERK phosphorylation (Masri et al., 2006). Although the binding affinities of the apelin-13-bound APJ for $G_{\alpha i1}$ and $G_{\alpha i2}$ are almost equivalent, apelin-36/apelin-13–APJ interaction induces the preferential coupling to $G_{\alpha i2}$ (Chapman et al., 2014). Although current evidence regarding the preferential APJ-mediated downstream signaling is limited, diverse conformations of "activated" APJ—which may be differentially induced by the different apelin isoforms—may have critical functional consequences (Chapman et al., 2014). Like apelin, toddler exists in several endogenous isoforms; the expression profiles of apelin and toddler differ substantially during embryonic development, and although the exact intracellular pathways of toddler remain unknown, it seems that these two ligands induce diverse functional cellular effects (Chapman et al., 2014) (Table 1).

APJ, as a typical GPCR, undergoes several post-translational modifications, such as phosphorylation, glycosylation, and palmitoylation, which may affect its turnover rate (O'Carroll et al., 2013). For example, the palmitoylation of the C-terminal domain of GPCR has been shown to affect the internalization, dimerization, and ligand binding, and the glycosylation of the N-terminal domain has been implicated in receptor expression, stability, and ligand binding (O'Carroll et al., 2013).

In the CNS, apelin and APJ are expressed in neuronal cells, oligodendrocytes, and astrocytes, and they are highly implicated in neuronal pathways (O'Carroll et al., 2000; Pouresmaeili-Babaki et al., 2018). Apelin is widely distributed throughout the brain in the cerebral cortex, SN, striatum, subthalamic nucleus, olfactory tract, dorsal raphe nucleus, medulla, ventral tegmental area, corpus callosum, hypothalamus, hippocampus, amygdala, cerebellum, and spinal cord (Kurowska et al., 2018; Pouresmaeili-Babaki et al., 2018). This expression pattern has raised significant interest in the implication of apelinergic system in neurological disorders. Apelin has been suggested to be able to cross the blood–brain barrier (BBB), although the exact mechanism has not been clarified yet (Higuchi et al., 2007; Lee et al., 2019). *In vivo* evidence has revealed that apelin-13 displays a neuroprotective role in the animal models of cerebral ischemia/reperfusion injury (He et al., 2015), subarachnoid hemorrhage (Xu et al., 2019), epilepsy (Dong et al., 2020), as well as neurodegenerative disorders including amyotrophic lateral sclerosis (Kasai et al., 2011) and AD (Luo et al., 2019).

Accumulating *in vitro* and *in vivo* evidence highlights the crucial role of apelin/APJ pathway in many of the key aspects of PD pathophysiology, including apoptosis, autophagy impairment, oxidative stress, neuroinflammation, and striatal synaptic dysregulation via various mechanisms (Table 2). APJ protein expression has been found to be decreased in 6-OHDA-treated human neuroblastoma SH-SY5Y cells, which possess dopamine neuron properties (Pouresmaeili-Babaki et al., 2018). Intracerebroventricular injection of apelin-13 could also rescue the dopaminergic neuronal loss in the striatum and the levels of tyrosine hydroxylase in the SN of rotenone-treated rat models of PD (Chen et al., 2020). In addition, intranigral injection of apelin-13 on

TABLE 1 APJ ligands, G protein interaction and associated signaling pathways

APJ ligand	G protein interaction	Pathway involved	Reference
Apelin-13	$G\alpha_{i1}$, $G\alpha_{i2}$, and $G\alpha_{i3}$	PI3K, MAPK ERK1/2, AMPK/mTOR/ULK1, IRE1α/XBP1/CHOP	Chapman et al. (2014), Masri et al. (2006), Mughal and O'Rourke (2018)
Apelin-36	$G\alpha_{i2}$ and Ga_q	PI3K/Akt/mTOR, ERS	Antushevich and Wójcik (2018), Chapman et al. (2014), Pouresmaeili-Babaki et al. (2018)
ELABELA/Toddler/Apela	$G\alpha_{i1}$, $G\alpha_{i/o}$, $G\alpha_{q/11}$ and β-arrestin	PI3K/Akt, PKC and PKC-independent RAS/MAPK pathways	Chapman et al. (2014), Kurowska et al. (2018), Wu et al. (2017)

TABLE 2 The neuroprotective effects of apelin isoforms in different models of Parkinson's disease

Apelin isoform	Model of PD	Effects and relevant pathways	References
Apelin-13	*In vitro* (6-OHDA-treated SH-SY5Y cells)	• Interacts with APJ to activate PI3K signaling, protects against neurotoxicity and apoptosis • Inhibits caspase-3 activation, cytochrome c release, preserves mitochondrial membrane potential • Reduces ROS production	Pouresmaeili-Babaki et al. (2018)
Apelin-13	*In vitro* (MPP+-treated SH-SY5Y cells)	• Inhibits apoptosis, increases ERK1/2 phosphorylation without affecting p38 phosphorylation • Protects against apoptosis via downregulation of ERS, UPR activation • Reduces CHOP, GRP78, and cleaved caspase-12, upregulates ERK1/2 signaling	Jiang et al. (2018)
Apelin-13	*In vitro* (rotenone-treated SH-SY5Y cells)	• Inhibits caspase-3 cleavage, reduces pro-apoptotic factor Bax expression, elevates anti-apoptotic bcl-2 expression, protects from neurotoxicity and apoptosis • Activates autophagy via upregulation of AMPK/mTOR/ULK1 signaling pathway, contributes to neuroprotection • Abolishes reduction of mitochondrial membrane potential	Chen et al. (2020)
Apelin-36	*In vitro* (MPP+-treated SH-SY5Y cells)	• Inhibits apoptosis, by regulating PI3K/Akt/mTOR signaling pathway • Induces autophagy by increasing LC3BII/LC3B-I ratio, reducing p62 expression via PI3K/Akt/mTOR axis • Reverses α-synuclein increased expression • Enhances cell survival, increases tyrosine hydroxylase expression by suppressing ERS-mediated apoptosis • Alleviates ERS-induced neuronal loss, suppresses ERS, reduces GRP78, CHOP, cleaved caspase-12	Zhu, Dou, Jiang, Bai, et al. (2019); Zhu, Dou, Wang, et al. (2019)
Apelin-36	*In vivo* (MPTP-treated C57/BL mice)	• Inhibits ERS in the SNpc, reduces CHOP, GRP78, cleaved caspase-12 in dopaminergic neurons • Reduces α-synuclein overexpression/accumulation in dopaminergic neurons of the SNpc • Regulates oxidative stress, autophagy, and apoptosis • Protects against dopaminergic neuronal loss in the SN, accompanied by motor improvement (at rotarod test)	Zhu, Dou, Wang, et al. (2019)
Apelin-13	*In vivo* (MPTP-treated mice)	• Enhances autophagy associated with increase of LC3B-II and reduces p62 • Protects dopaminergic neuronal cells by suppressing ERS (reduces GRP78, downregulates IRE1α/XBP1/CHOP signaling pathway in SNpc) • Reverses α-synuclein overexpression in SNpc • Improves motor behavior (at rotarod test)	Zhu, Dou, Jiang, Chen, et al. (2019)

(Continues)

TABLE 2 (Continued)

Apelin isoform	Model of PD	Effects and relevant pathways	References
Apelin-13	*In vivo* (6-OHDA-treated rats)	• Increases dopamine D1, D2 receptors, decreases mGluR1 expression in striatum • Increases striatal PSD-95, neuroligin, and neurexin levels compared to controls • Reduces motor impairment • Improves motor skill learning and motor performance (at the accelerating rotarod test), induces better recovery in catalepsy time (at bar test), improves motor coordination and balance (at beam and the beam traversal tests) • Attenuates dopaminergic neuronal death in the SN • Prevents SN damage (at apomorphine-induced rotational test) • Ameliorates cognitive performance • Improves spatial learning ability (at Morris water maze test), novel object recognition, spatial working memory (at novel object recognition test and object location task)	Haghparast et al. (2018, 2019)

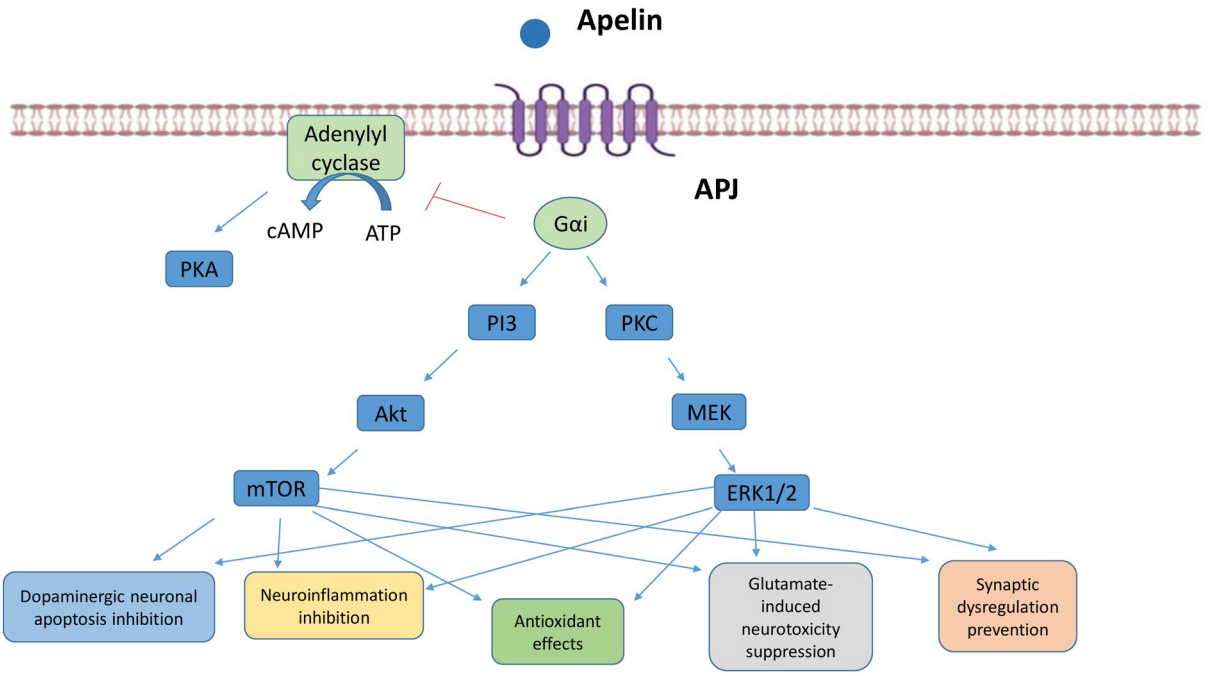

FIGURE 1 Impact of Apelin/APJ signaling via Ga_i pathway in PD pathogenesis. Apelin binds to its G protein-coupled receptor APJ, which interacts with G proteins (mainly Gα-$G\alpha_i$ and $G\alpha_q$-, but also Gβ and Gγ), resulting in the activation of several signaling pathways. Via $G\alpha_i$, apelin/APJ activates phosphoinositide 3-kinase (PI3K)/Akt and protein kinase C (PKC)/extracellular signal-regulated kinase 1/2 (ERK 1/2) pathways, thereby being involved in the regulation of apoptosis, neuroinflammation, and oxidative stress. $G\alpha_i$ is involved in the downregulation of protein kinase A (PKA) by inhibiting the adenylyl cyclase-mediated generation of cyclic adenosine monophosphate (cAMP) from ATP

MPTP-treated mice could inhibit the dopaminergic neuronal loss in the SNpc of the animals (Zhu, Dou, Jiang, Chen, et al., 2019).

The role of apelin in physiological and pathological conditions, including neurological disorders, has previously been discussed (Luo et al., 2020; Lv et al., 2020). However, given the growing preclinical evidence on the role of apelin/APJ axis in PD pathogenesis and the lack of a recent comprehensive review focusing particularly on PD, herein we discuss the emerging role of this pathway in PD pathophysiology (Figures 1 and 2) and its potential as a novel but challenging therapeutic target.

3 | THE IMPLICATION OF APELIN/APJ PATHWAY IN APOPTOSIS IN PD

It is well recognized that oxidative stress, microglia activation and excessive neuroinflammation are major characteristics of PD pathology. These responses exert detrimental effects on dopaminergic neurons, resulting in their apoptosis and potentially leading to neurodegeneration (Jha et al., 2015). Impaired balance between the key cellular anti-apoptotic and pro-apoptotic pathways plays a major role in PD pathogenesis (Jha et al., 2015). Among them, the dysregulation of PI3K/Akt and mitogen-activated protein kinases (MAPKs) including ERK 1/2 cascades is highly involved in this process (Jha et al., 2015).

Apelin has been shown to display anti-apoptotic properties in mouse cortical neuronal cultures (Zeng et al., 2010), and intracerebroventricular injection of apelin-13 could significantly ameliorate cerebral ischemia/reperfusion injury by inhibiting neuronal apoptosis in rat models (Yan et al., 2015). The anti-apoptotic activity of apelin is mediated via the APJ/PI3K/Akt signaling pathway in PC12 cells (Figure 1) (Zou et al., 2016). Akt is a crucial regulator of PI3K-mediated cell survival, and Akt signaling activation can inhibit cell death induced by pro-apoptotic stimuli (Datta et al., 1999). Akt inhibits apoptosis by preventing the process of procaspases to their active forms, the release of cytochrome c from mitochondria, and the alterations in the inner mitochondrial membrane potential (Kennedy et al., 1999). Hence, apelin-mediated PI3K-induced Akt activation may be able to prevent apoptosis possibly by preserving mitochondrial membrane potential (Taneja et al., 2004).

Aside from the Akt pathway, MAPK pathway has been also implicated in the anti-apoptotic role of apelin, since apelin-13 could protect against ischemic/reperfusion injury-induced neuronal apoptosis at least partly by upregulating the ERK1/2 pathway, resulting in increased bcl-2 expression (Figure 2) (Yang et al., 2014). In bone marrow-derived mesenchymal stem cell models, apelin-13 could also act in an anti-apoptotic manner by preventing mitochondria depolarization, release of cytochrome c, and activation of caspase-3 (Zeng et al., 2012). Apelin-13 was also able to majorly reduce brain edema and inhibit neuronal apoptosis via downregulation of caspase-3 (Khaksari et al., 2012). Apelin-36 could also attenuate apoptosis in rat models of ischemic stroke, with the ERS being significantly involved in this effect (Qiu et al., 2017).

A growing amount of preclinical evidence has demonstrated that apelin-13 may exert neuroprotective effects in PD by inhibiting apoptosis. More specifically, *in vitro* evidence has shown that apelin-13 pretreatment was able to protect SH-SY5Y cells against 6-OHDA-induced neurotoxicity and apoptosis, accompanied by

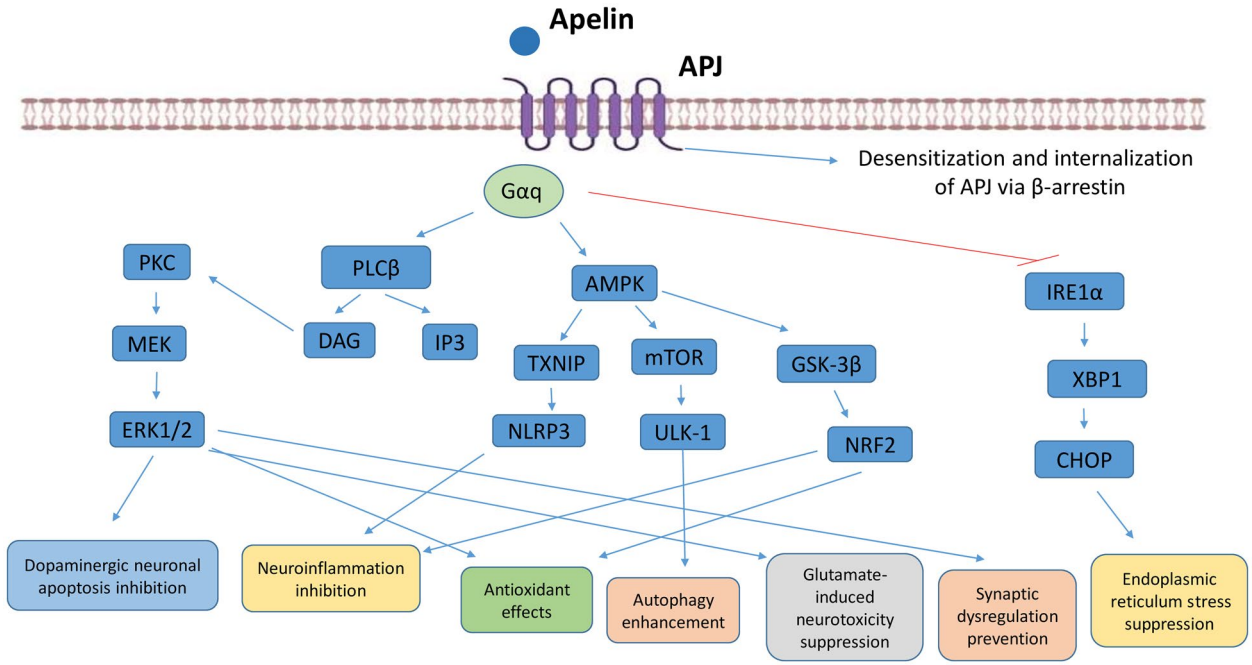

FIGURE 2 Impact of Apelin/APJ signaling via Ga_q and β-arrestin pathway in PD pathogenesis. Ga_q upregulates phospholipase C beta (PLCb), triggering the generation of diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3), resulting in the activation of protein kinase C (PKC) cascade. APJ can also trigger a β-arrestin-mediated G protein-independent response involving the desensitization and internalization of APJ. Apelin-13 has been shown to act neuroprotectively in *in vitro* models of PD, by activating autophagy through the activation of AMPK/mTOR/ULK1 signaling pathway. Based on ischemia-reperfusion models, apelin-13 might also protect against neuroinflammation and oxidative stress by activating the adenosine monophosphate kinase (AMPK)/glycogen synthase kinase 3 b (GSK-3β)/nuclear factor erythroid 2-related factor 2 (NRF2) pathway. Based on subarachnoid hemorrhage models, apelin may reduce neuroinflammation by regulating AMPK/TXNIP/NLRP3 signaling pathway. Apelin can suppress endoplasmic reticulum stress via downregulation of the IRE1α/XBP1/CHOP signaling pathway. Apelin can inhibit glutamate-induced neuronal excitotoxicity through its receptor APJ, by activating Akt and ERK1/2. Apelin might also reduce α-synuclein accumulation although the exact mechanisms remain unclear

the suppression of caspase-3 activation and cytochrome c release (Pouresmaeili-Babaki et al., 2018). These effects were mediated through the interaction of apelin-13 with APJ, resulting in the activation of PI3K signaling cascade (Pouresmaeili-Babaki et al., 2018).

Another study has indicated that apelin-13 was able to inhibit the MPP^+-induced apoptosis of SH-SY5Y cells, accompanied by an increased phosphorylation of ERK1/2 without affecting p38 phosphorylation (Jiang et al., 2018). Apelin-13 has been previously shown to activate ERK1/2 but not p38 through the coupling of APJ to Gi2 protein (Bai et al., 2008). Phosho-ERK1/2 expression is activated by Gi2 protein and enhanced by β-arrestin protein, potentially explaining why apelin-13 only upregulated ERK1/2 and not p38 (Jiang et al., 2018). In accordance, apelin-13 pretreatment could protect SH-SY5Y cells from rotenone-induced neurotoxicity and apoptosis, by inhibiting the rotenone-induced caspase-3 cleavage and activation (Chen et al., 2020).

Aside from apelin-13, apelin-36 pretreatment has also been reported to inhibit MPP^+-induced apoptosis of SH-SY5Y cells, by regulating PI3K/Akt/mTOR signaling pathway (Zhu, Dou, Jiang, Bai, et al., 2019). In addition, apelin-36 could significantly enhance the survival of MPP^+-treated SH-SY5Y cells, as well as increase tyrosine hydroxylase expression, by suppressing the ERS-mediated apoptosis (Zhu, Dou, Wang, et al., 2019). A recent *in vivo* study also demonstrated that the neuroprotective effects of apelin-36 were mediated via the inhibition of the apoptosis signal-regulating kinase 1 (ASK1)/c-Jun N-terminal kinase (JNK) signaling pathway and subsequent inactivation of caspase-3 in MPTP-lesioned PD model mice (Zhu et al., 2020).

Collectively, accumulating evidence demonstrates that apelin/APJ axis protects against dopaminergic neurodegeneration in neurotoxin-induced *in vitro* PD models by inhibiting apoptosis, through the upregulation of both PI3K/Akt and ERK1/2 signaling pathways.

4 | THE ROLE OF APELIN/APJ PATHWAY IN AUTOPHAGY IMPAIRMENT IN PD

Autophagy is a highly conserved homeostatic lysosomal-dependent process resulting in the degradation and removal of damaged or misfolded proteins and organelles (Curry et al., 2018). 5′-AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) axis is a key pathway implicated in autophagy regulation (Curry et al., 2018). In particular, AMPK/mTOR/Unc-51 like autophagy activating kinase 1 (ULK1) signaling has been shown to be essential for the induction of autophagy (Alers et al., 2012); mTOR is a serine/threonine kinase that under nutrient starvation dissociates from the autophagy-related protein 13 (Atg13)/RB1-inducible coiled-coil 1 (RB1CC1/FIP200)/autophagy-related protein 101 (Atg101) complex, facilitating ULK1 activation and autophagy induction (Wang et al., 2018). mTOR acts as a negative modulator of autophagy, and its upstream regulation is mediated by PI3K and Akt phosphorylation (Zhu, Dou, Jiang, Bai, et al., 2019). Autophagosomes are then fused with lysosomes, where their ingredients are degraded by lysosomal hydrolases (Wang et al., 2018). The microtubule-associated protein 1A/1B light chain 3B-II (LC3B-II) is produced during the autophagic process and is a widely used marker of autophagosomes (Zhu, Dou, Jiang, Chen, et al., 2019). p62/sequestosome 1 (SQSTM1) expression negatively correlates with autophagy activity and acts by coupling to LC3B (Zhu, Dou, Jiang, Chen, et al., 2019).

It is well recognized that dysregulation of autophagy is highly implicated in the pathogenesis of neurodegenerative disorders including PD. Impaired autophagy machinery has been associated with abnormal α-synuclein accumulation, mitochondrial dysfunction, dopaminergic neuronal death, and extracellular release of α-synuclein (Hou et al., 2020; Minakaki et al., 2018). The expression of PI3K, Akt, and mTOR has been demonstrated to be upregulated in MPP^+-treated SH-SY5Y cells (Khwanraj et al., 2016). Furthermore, proteins encoded by several genes related to autosomal dominant or recessive forms of PD, such as α-synuclein, PTEN (phosphatase and tensin homologue)-induced kinase 1 (PINK1), Parkin, leucine-rich repeat kinase 2 (LRRK2), DJ-1, glucocerebrosidase (GBA), and ATPA13A2, are also implicated in the regulation of autophagy (Zhang et al., 2015). Potential autophagy enhancers, including rapamycin, carbamazepine, and valproic acid have demonstrated neuroprotective properties in animal models of PD (Pan et al., 2008; Xiong et al., 2011).

Apelin-13 has been indicated to enhance adenosine monophosphate-activated protein kinase (AMPK) phosphorylation in ischemic stroke models, and AMPK signaling contributes to the apelin-13-mediated neuroprotective properties (Duan et al., 2019). On the contrary, there is also evidence showing that apelin-13 may reduce traumatic brain damage-induced injury by blocking autophagy (Bao et al., 2015). AMPK is an evolutionarily conserved serine/threonine kinase playing key roles in maintaining cellular energy homeostasis, mitochondrial metabolism, and autophagy, being also implicated in PD pathophysiology (Curry et al., 2018).

Apelin-13 has been shown to act neuroprotectively in *in vitro* models of PD, by activating autophagy through the upregulation of AMPK/mTOR/ULK1 signaling pathway (Chen et al., 2020). These effects were accompanied by a reduction of rotenone-induced α-synuclein overexpression (Chen et al., 2020). Regarding the underlying molecular mechanisms, apelin-13 was indicated to stimulate the phosphorylation of AMPKα and ULK1, as well as suppress mTOR phosphorylation in these cells (Chen et al., 2020). Apelin-13/APJ interaction, AMPK/mTOR/ULK1 signaling pathway, and subsequent autophagy enhancement were essential for the protective role of apelin-13 in these cells (Chen et al., 2020). *In vivo* evidence has shown that intranigral apelin-13 injection could act neuroprotectively in MPTP-treated mice by enhancing autophagy, since it was associated with increase in LC3B-II and reduction of p62 (Zhu, Dou, Jiang, Chen, et al., 2019).

The neuroprotective effects of apelin-36 in MPP^+-treated SH-SY5Y cells have also been shown to be mediated by induction of autophagy via the PI3K/Akt/mTOR axis (Zhu, Dou, Jiang, Bai, et al., 2019).

Collectively, both apelin-13 and apelin-36 exert potential neuroprotective effects in *in vitro* and *in vivo* models of PD by enhancing

autophagy, through their interaction with APJ, resulting in the activation of AMPK/mTOR/ULK1 pathway.

5 | THE ROLE OF APELIN/APJ AXIS IN OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN PD

Oxidative stress has been well documented to play a major role in PD pathogenesis, by inducing dopaminergic neuronal loss via several mechanisms. Reactive oxygen species (ROS) production can activate the caspases' cascade, resulting in neuronal apoptosis (Simon et al., 2000). Increased ROS promotes mitochondrial dysfunction, which further increases oxidative stress, thereby forming a vicious cycle (Mosley et al., 2006; Wu et al., 2017). Further, oxidative stress enhances neuroinflammation resulting in dopaminergic degeneration (Mosley et al., 2006).

Importantly, in cell cultures of mouse cortical neurons, apelin-13 could inhibit ROS generation, acting in an antioxidant manner (Zeng et al., 2010). Another recent study showed that apelin-13 could protect against ischemic/reperfusion-induced neuroinflammation and oxidative stress by activating the AMPK/glycogen synthase kinase 3 b (GSK-3β)/nuclear factor erythroid 2-related factor 2 (NRF2) pathway, leading to the increased expression of antioxidant enzymes, including glutathione (GSH), catalase, and superoxide dismutase (SOD) (Figure 2) (Duan et al., 2019). Hence, apelinergic system may protect against oxidative stress-induced neuroinflammation and neuronal death by inhibiting ROS production and increasing ROS scavenging.

In this context, *in vitro* evidence has revealed that apelin-13 pretreatment could reduce ROS production, preserve the mitochondrial membrane potential, and inhibit the release of cytochrome c in 6-OHDA-treated SH-SY5Y cells (Pouresmaeili-Babaki et al., 2018), and abolish the decrease in mitochondrial membrane potential in rotenone-treated SH-SY5Y cells (Chen et al., 2020).

A recent *in vivo* study demonstrated that apelin-36 partially prevented dopamine depletion in the striatum of MPTP-induced PD model mice, at least partially via improving the antioxidant cellular mechanisms including SOD and GSH (Zhu et al., 2020). In addition, apelin-36 downregulated inducible nitric oxide synthase and nitrated α-synuclein expression in this study, further supporting its neuroprotective role in PD by acting in an antioxidant manner (Zhu et al., 2020).

However, the exact mechanisms underlying the antioxidant properties of apelin/APJ axis in PD, as well as its effects on mitochondrial regulation remain largely unknown.

6 | THE POTENTIAL IMPLICATION OF APELIN/APJ AXIS IN NEUROINFLAMMATION IN PD

Apelin-13 has been demonstrated to exert a regulatory role in neuroinflammation, by inhibiting the expression of pro-inflammatory cytokines and suppressing the activity of microglia, astrocytes, and other inflammatory cells (Xin et al., 2015; Xu et al., 2019). Apelin-13 could inhibit cerebral infarct volume in a rat model of ischemic stroke by inhibiting the expression of pro-inflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α), and intercellular adhesion molecule-1 (ICAM-1), a cell-surface glycoprotein belonging to the immunoglobulin protein superfamily (Xin et al., 2015). Additionally, ionized calcium-binding adapter molecule-1 (Iba1), glial fibrillary acidic protein (GFAP)—a marker of astrocytes—and high mobility group box 1 (HMGB1)—a protein highly implicated in inflammation—levels were reduced after apelin-13 treatment in this study, suggesting that apelin-13 exerted neuroprotective effects by inhibiting microglia and astrocytes, resulting in the suppression of excessive inflammation in the brain. Apelin-13 has been recently shown to inhibit neuroinflammation by altering M1 polarization of microglia to M2 phenotype potentially with a signal transducer and activator of transcription 3 (STAT3)-mediated manner (Zhou et al., 2019), which sheds more light on the underlying molecular mechanisms. STAT3 is a key regulator of cell growth, differentiation, and survival, being also involved in brain inflammation (Chen et al., 2013). Microglia, the innate immune cells of the CNS, can both detect pathogens and eliminate cell debris and also contribute to neuronal regeneration after tissue damage (Cherry et al., 2014). For these purposes, they may acquire two different activated phenotypes: M1 type, which produces pro-inflammatory cytokines and ROS causing cytotoxic effects, and M2 type, which generally produces anti-inflammatory cytokines, inhibits tissue damage, and stimulates regeneration thereby acting in a neuroprotective manner (Cherry et al., 2014).

The exogenous administration of apelin-13 binding to APJ could attenuate early brain injury and neuroinflammation after subarachnoid hemorrhage in rats, by inhibiting microglia activation and oxidative stress through the reduction of the levels of NOD-like receptor pyrin domain-containing 3 protein (NLRP3), TNF-α, IL-1β, and myeloperoxidase (MPO), at least partially by modulating AMPK/thioredoxin-interacting protein (TXNIP)/NLRP3 signaling pathway (Xu et al., 2019). MPP^+-induced neurodegeneration has been associated with the upregulation of TXNIP/NLRP3 pathway *in vitro* (Zeng et al., 2019). As discussed above, PI3/Akt/mTOR pathway is majorly implicated in the neuroprotective role of apelin in PD, and PI3K/Akt/mTOR pathway has been demonstrated to promote the formation of inflammasome in MPTP-induced mouse models of PD (Figure 1) (Giacoppo et al., 2017).

Taken together, since neuroinflammation, microglia overactivation, and HMGB1-mediated pathways may play crucial roles in models of PD (Angelopoulou et al., 2018), the role of apelin/APJ axis in neuroinflammation in PD definitely deserves further study.

7 | THE EFFECTS OF APELIN/APJ PATHWAY IN ERS IN PD

Endoplasmic reticulum (ER) is involved in the protein folding, trafficking, and lipid metabolism. Oxidative stress, misfolded proteins,

and other toxic stimuli can cause ERS, which activates unfolded protein response (UPR) with the aim to remove the damaged elements (Shacham et al., 2019). Growing evidence highlights the key role of ERS in PD pathogenesis. Under toxic stimuli, glucose-regulated protein 78 (GRP78), a Hsp70 family ATPase, becomes overactivated and is separated from three ER transmembrane proteins involving protein kinase R-like endoplasmic reticulum kinase (PERK), inositol requiring kinase 1α (IRE1α), and activating transcription factor 6 (ATF6), resulting in UPR activation (Lee, 2005; Shacham et al., 2019). Caspase-12 and C/EBP homologous protein (CHOP) are two critical factors for the initiation of the ERS-induced apoptosis (Marciniak et al., 2004). It has been demonstrated that ERS, as depicted by the increased levels of GRP78, CHOP, and cleaved caspase-12, is overactivated in the SNpc of animal models of PD models, and ERS suppression was able to slow down the neurodegenerative process (Zhang et al., 2017). ERS leads to the upregulation of IRE1α/X-box binding protein 1 (XBP1)/CHOP signaling pathway (Janyou et al., 2015), and p-IRE1α, XBP1s, and CHOP have been shown to be increased in *in vivo* PD models (Avagliano et al., 2016). Telmisartan (an AT1 receptor blocker) has been shown to exert neuroprotective effects in rat models of PD by inhibiting ERS-induced increased levels of GRP78 and cleaved caspase-12 (Tong et al., 2016). Of note, apelin pretreatment could reduce ERS in diabetic mice by downregulating the expression of GRP78, IRE1α, and PERK, suggesting the role of apelin in ERS regulation (Figure 2) (Chen et al., 2011). Given the fact that the neuroprotective role of telmisartan in PD was mediated by regulating GRP78 levels, the 50% homology of APJ to AT1 receptor, and the ability of APJ to form heteromer with AT1 receptor as abovementioned, it can be hypothesized that apelin axis may be also implicated in the beneficial effects of telmisartan in PD. Apelin-36 was also able to act neuroprotectively in rat models of ischemic stroke inhibiting ERS-induced increased expression of CHOP and GRP78 (Qiu et al., 2017).

Apelin-13 has been demonstrated to protect against MPP^+-induced apoptosis of SH-SY5Y cells via downregulation of ERS and UPR activation, since apelin-13 pretreatment was associated with reduced MPP^+-induced CHOP, GRP78, and cleaved caspase-12 upregulation in these cells, accompanied by the upregulation of ERK1/2 signaling (Jiang et al., 2018). In this context, *in vivo* evidence has shown that apelin-13 could protect dopaminergic neuronal cells in MPTP-treated mice by suppressing endoplasmic reticulum stress and enhancing autophagy (Zhu, Dou, Jiang, Chen, et al., 2019). More specifically, intranigral apelin-13 injection was associated with reduced GRP78 levels and downregulation of the IRE1α/XBP1/CHOP signaling pathway in the SNpc of MPTP-treated mice (Zhu, Dou, Jiang, Chen, et al., 2019).

In accordance, apelin-36 has been shown to inhibit MPTP induced ERS in the SNpc of mice models of PD, which was accompanied by a reduced expression of CHOP, GRP78, and cleaved caspase-12 in the dopaminergic neurons (Zhu, Dou, Wang, et al., 2019). Furthermore, apelin-36 was able to alleviate ERS-induced neuronal loss and suppress ERS in *in vitro* PD models, since it could reduce the expression of GRP78, CHOP, and cleaved caspase-12 in MPP^+-treated SH-SY5Y cells (Zhu, Dou, Wang, et al., 2019).

Of note, it has also been demonstrated that apelin expression can be downregulated by ERS in hepatocytes *in vitro* (Jeong et al., 2014), thereby forming a vicious feedback loop. This mechanism should be also investigated in the case of PD-related neurodegeneration. In summary, apelin-13 and apelin-36 seem to protect against dopaminergic neuronal apoptosis *in vitro* and *in vivo* by suppressing ERS, mainly by regulating IRE1α/XBP1/CHOP axis.

8 | THE POTENTIAL ROLE OF APELIN/APJ AXIS IN α-SYNUCLEIN EXPRESSION AND ACCUMULATION

The intranigral injection of apelin-13 has been demonstrated to reverse the MPTP-induced α-synuclein overexpression in the SNpc of the mouse models of PD (Zhu, Dou, Wang, et al., 2019). In addition, apelin-36 could reverse the MPP^+-induced α-synuclein increased expression in SH-SY5Y cells (Zhu, Dou, Jiang, Bai, et al., 2019; Zhu, Dou, Wang, et al., 2019). Apelin-36 treatment was associated with reduced MPTP induced elevated expression and accumulation of α-synuclein in the dopaminergic neurons of the SNpc of the MPTP treated mice (Zhu, Dou, Wang, et al., 2019). The molecular pathways implicated in this effect are still obscure; however, given the known involvement of autophagy impairment and ERS in abnormal α-synuclein accumulation, it can be proposed that the protective role of apelin in these processes may lead to the reduced α-synuclein levels; however, other underlying mechanisms remain to be further explored.

9 | THE IMPLICATION OF APELIN/APJ PATHWAY IN THE DYSFUNCTION OF SYNAPTIC PLASTICITY AND GLUTAMATE-INDUCED NEUROTOXICITY IN PD

In PD, dopaminergic neuronal degeneration in the SNpc results in the loss of dopamine and disruption of dopaminergic synapses in the striatum (Haghparast et al., 2019). The damage of the nigrostriatal dopaminergic pathway can also dysregulate the striatal neuronal circuity, which in turn impairs synaptic plasticity (Calabresi et al., 2014). In the basal ganglia, the interplay between glutamate and dopamine critically affects motor and cognitive behavior (Amalric, 2015). The concomitant overactivation of *N*-methyl-D-aspartate (NMDA) and D1 receptors may exert detrimental effects on the structural and functional synaptic integrity (Zhang et al., 2009). Several synaptic membrane-associated proteins play a crucial role in maintaining synaptic plasticity and promoting a balance between excitatory and inhibitory synapses in the brain (Haghparast et al., 2019). Among them, postsynaptic density protein 95 (PSD-95) is one of the major scaffolding molecules of the dendritic spines in the medium spiny neurons, the primary neuronal type in the striatum. PSD-95 can regulate the trafficking of dopamine D1,

NMDA receptors in the striatum, affecting their downstream intracellular signaling (Zhang et al., 2009). More specifically, PSD-95, NMDA, and D1 receptors form a multi-protein complex. PSD-95 can uncouple D1 receptor trafficking and signaling from regulation by NMDA receptors, thereby weakening D1/NMDA receptors interaction and their abnormal concomitant overactivation (Zhang et al., 2009). Neurexins and neuroligins are cell-adhesion synaptic proteins connecting pre- and postsynaptic neurons, modulating excitatory and inhibitory transmission (Sudhof, 2008). PSD-95, neurexin 1, and neuroligin levels are downregulated in the denervated striatum of 6-OHDA-induced rat models of PD, suggesting its role in PD pathophysiology (Haghparast et al., 2019). In addition, metabotropic glutamate receptors (mGluRs) are major regulators of glutamatergic dysfunction in PD (Amalric, 2015). Antagonism of group I mGluR and activation of groups II and III mGluR may inhibit motor impairment and improve levodopa-induced dyskinesia in animal models of PD via the modulation of synaptic transmission in the striatum (Amalric, 2015).

Of note, the behavioral effects of apelin-13 have been abolished by haloperidol, a selective dopamine receptor antagonist (Jaszberenyi et al., 2004), implying that apelin-13 might be implicated in D1 receptor signaling in PD. Moreover, apelin/APJ axis activation could prevent glutamate-mediated neuronal excitotoxicity (O'Donnell et al., 2007), suggesting its key role in glutamate dysfunction in neurodegeneration. In addition, apelin-13, -17, -36, and -77 have been shown to protect hippocampal neurons against excitotoxicity by triggering the phosphorylation of Akt kinases and ERK1/2, as well as prevent NMDA-induced neurotoxicity (O'Donnell et al., 2007).

Interestingly, the neuroprotective role of apelin-13 in 6-OHDA-induced rat models of PD has been accompanied by an increased expression of dopamine D2 and D1 receptors, as well as a decreased expression of mGluR1 in their striatum (Haghparast et al., 2019). Furthermore, apelin-13-treated 6-OHDA-treated rats displayed significantly increased striatal levels of PSD-95, neuroligin, and neurexin in this study (Haghparast et al., 2019). The underlying molecular mechanisms of these effects of apelin-13 have not been clarified yet. However, it has been demonstrated that apelin can reduce glutamate-induced neuronal excitotoxicity through its receptor APJ, by activating Akt and ERK1/2, inhibiting cAMP production, and suppressing adenylyl cyclase formation, resulting in the restoration of the intracellular Ca^{2+} concentration and downregulation of TNF-α expression (Figure 2) (Haghparast et al., 2019; Ishimaru et al., 2017). Hence, this signaling pathway could underlie the protective effects of apelin in PD against glutamate dysregulation and synaptic dysfunction and should be further explored.

10 | THE EFFECTS OF APELIN/APJ AXIS ON MOTOR AND COGNITIVE FUNCTION IN PD *IN VIVO*

The neuroprotective effects of apelin/APJ axis have been significantly associated with improved behavioral effects *in vivo*. Apelin treatment was accompanied by a reduced motor impairment of 6-OHDA-induced rat models of PD (Haghparast et al., 2019). Compared to controls, apelin-treated rats displayed improved motor skill learning and motor performance, better recovery in catalepsy time, as well as improved motor coordination and balance (Haghparast et al., 2019). These behavioral effects were associated with attenuation of dopaminergic neuronal death in the SN (Haghparast et al., 2019). In accordance, apomorphine-induced rotational test has demonstrated that 6-OHDA-induced SN damage could be prevented by apelin-13 in rat models of PD (Haghparast et al., 2018). Given the well-recognized correlation between apomorphine-induced rotational behavior and nigrostriatal dopamine levels in unilaterally 6-OHDA-treated rats (Hudson et al., 1993), it has been proposed that apelin is associated with restoration of nigrostriatal pathway in these PD animal models (Haghparast et al., 2018). The intranigral injection of apelin-13 in MPTP-treated mice has been associated with improvement in motor behavior as evaluated by the rotarod test (Zhu, Dou, Jiang, Chen, et al., 2019). In agreement with this evidence, apelin-36 has been shown to protect against dopaminergic neuronal loss in the SN of MPTP treated C57/BL mouse models of PD, accompanied by motor improvement as evaluated by the rotarod test (Zhu, Dou, Wang, et al., 2019).

As mentioned above, cognitive impairment is one of the most common and debilitating non-motor symptoms of PD (DeMaagd & Philip, 2015). Apelin and APJ are widely expressed in brain regions implicated in cognitive function, memory, and learning such as hippocampus (O'Carroll et al., 2000), suggesting that apelin/APJ pathway may play a key role in cognitive dysfunction related to neurodegenerative disorders, such as PD. There is controversial evidence about the role of apelin in cognition, since both beneficial and detrimental effects have been documented (Han et al., 2014; Telegdy et al., 2013). Apelin-13 has been shown to inhibit brain injury-induced cognitive impairment (Bao et al., 2015), and improve recognition memory in stressed rat models via PI3K and ERK pathways (Li et al., 2016). Apelin-13 could also significantly ameliorate cognitive performance in 6-OHDA-treated rats (Haghparast et al., 2018). More specifically, apelin-13 treatment was indicated to improve the spatial learning ability of the animals in the Morris water maze test, as well as to improve novel object recognition and spatial working memory, as evaluated by the novel object recognition test and object location task, respectively (Haghparast et al., 2018).

11 | DISCUSSION AND FUTURE DIRECTIONS

Accumulating *in vitro* and *in vivo* evidence highlights the emerging neuroprotective role of apelin/APJ axis in the key pathophysiological mechanisms underlying PD pathogenesis. Apelin/APJ pathway activation may inhibit apoptosis and dopaminergic neuronal loss, enhance autophagy, exert antioxidant effects, suppress endoplasmic reticulum stress, prevent excessive neuroinflammation, and protect against synaptic dysregulation in the striatum and glutamate-induced

excitotoxicity. The main underlying signaling pathways include PI3K/Akt/mTOR, ERK1/2, and IRE1α/XBP1/CHOP.

However, all *in vivo* studies described herein have used neurotoxin-induced animal models of PD. Although these models represent a widely used model mimicking PD in humans, the investigation of apelin/APJ axis should be also explored in genetic models of PD, which possess intrinsic differences from neurotoxin-induced models and are considered to reflect more effectively at least some of the aspects of human PD pathophysiology (Kin et al., 2019). In this regard, models overexpressing α-synuclein, PINK1 knockout mouse models which are considered to represent prodromal PD, and the recently developed DJ-1 knockout rat models (Kin et al., 2019) could be also helpful for understanding of the role of apelin in PD. Since there is no neurotoxin or genetic model which completely reproduces human PD pathophysiology, combined neurotoxin and genetic models may reflect more effectively the multifactorial nature of PD pathogenesis and progression, attributed to both environmental factors and genetic vulnerability (Kin et al., 2019). In addition, preformed fibrils (PFFs) made of recombinant α-synuclein have been used to create models of PD reflecting the neuron-to-neuron propagation of aggregated α-synuclein and spreading throughout the CNS (Chung et al., 2019). The role of apelin should be also examined in these models too, in order to clarify its role in α-synuclein spreading.

An important issue that should be considered is the potential upstream regulators of apelin in PD, which could affect its expression or activity. In this regard, a recent study has demonstrated that treatment of MPTP-induced mouse models of PD with n-3 fatty acid docosahexaenoic acid (DHA) affected the expression of apelin and its receptor APJ in the cerebellum and pons, but not in the cerebrum of the animals (Acar et al., 2019). DHA is one of the main fatty acids of the brain, required for effective neuronal structure and signaling. DHAH, a hydroxylated derivative of DHA, has demonstrated neuroprotective properties in animal models of PD by potentially reducing oxidative stress and neuroinflammation (Hernando et al., 2019). Functional neuroimaging has revealed that cerebellar circuits might be implicated in the impaired dual motor and cognitive task performance observed in patients with PD (Gao et al., 2017). The loss of noradrenergic neurons in the locus coeruleus in the pons has been reported in patients with PD (Acar et al., 2019), and depression in PD has been considered to be at least partially associated with the degeneration of the serotoninergic neurons in the raphe nucleus in the pons (Faggiani et al., 2015). DHA has been previously shown to upregulate the gene transcription of apelin through its action on retinoid or nuclear receptors in the brain of mice (de Urquiza et al., 2000). Taken together, these findings suggest that DHA might regulate apelin and its receptor expression in a tissue-specific manner in PD, which could account for some of the non-motor PD clinical features.

As mentioned above, apelin is widely distributed in several peripheral tissues, in which specific factors have been shown to regulate its expression. For instance, apelin expression in adipocytes is increased by insulin, growth hormone (GH), and TNF-α (Boucher et al., 2005). Endocannabinoid combined with lipopolysaccharide has been indicated to enhance APJ and apelin expression in adipocytes of diabetic and obese mice (Geurts et al., 2011), and emerging evidence highlights the neuroprotective potential of the endocannabinoid system in PD (Patricio et al., 2020). Furthermore, hypoxia could promote apelin expression in human adipocytes via the hypoxia-inducible factor 1α (HIF-1α) (Geiger et al., 2011). HIF-1α plays a crucial role in the survival of dopaminergic neurons, and upregulation of its expression has been demonstrated to play a neuroprotective role in animal models of PD (Kandil et al., 2019). Additionally, some bone morphogenic proteins (BMPs)—which belong to the transforming growth factor-β (TGF-β) family—such as BMP4 and 7 could reduce apelin expression in endothelial cells (Poirier et al., 2012). Interestingly, neuron-glial BMP-signaling cascade has been shown to mediate LRRK2-induced and paraquat-induced neurodegeneration (Maksoud et al., 2019). Sp1 transcription factor (SP1) can also regulate apelin gene expression (Wu et al., 2017) and plays a major role in neuroinflammatory and apoptotic response in PD (R. Wang et al., 2020). Furthermore, activating transcription factor 4 (ATF4) is also involved in the transcriptional regulation of apelin (Wu et al., 2017), and ATF4 enhances dopaminergic cell death induced by α-synuclein aggregates, MPP^+, and 6-OHDA (Demmings et al., 2020). In addition, APJ expression can be upregulated by insulin-like growth factor 1 (IGF-1) (Roche et al., 2016) and IGF-1 may suppress α-synuclein aggregation via PI3K/Akt pathway (Kao, 2009). Therefore, the endocannabinoid system, HIF-1α, ATF4, SP1, IGF-1, and BMP-related pathways should be also investigated as potential regulatory elements in apelin expression in PD.

Apelin/APJ interaction not only modulates downstream intracellular signaling, but also regulates the internalization of APJ. The excess activation of APJ results in disrupted responsiveness of the cell to its ligands (Kleinz & Davenport, 2005). Internalized APJ after interacting with apelin-13 has been shown to recycle much sooner to the cell membrane in comparison to the apelin-36-induced APJ internalization (Zhou et al., 2003). Moreover, apelin deficiency has been shown to inhibit APJ mRNA levels (Wu et al., 2017). These effects of apelin on APJ internalization and expression may also affect the final effects of apelin/APJ axis and need to be further elucidated in the case of PD.

Regarding the use of apelin/APJ system as a therapeutic target, some important bioavailability issues should be considered. First, oral administration of peptides is associated with limited bioavailability because of enzymatic breakdown and poor intestinal absorption. Novel delivery approaches, such as nano-encapsulation and polyethylene glycol (PEG)-ylation have been developed for the increase in the half-life and/or activity of apelin (Mughal & O'Rourke, 2018). In this context, a synthetic non-peptidic agonist of APJ, known as E339-3D6, as well as PEG-conjugated apelin-36 (PEG-apelin-36) with a much longer circulating life have also been recently employed (Yu et al., 2014). Importantly, apelin needs to cross the BBB in order to act on the neurons in the CNS, highlighting the need for the design of small molecules such as non-peptidic APJ agonists mimicking its action that could penetrate BBB. For the effective delivery of pharmaceutical agents into the CNS, there has

been extensive research in the development of drug delivery nanovehicles, such as nanoparticles, liposomes, micelles, dendrimers, and carbon nanotubes (Teleanu et al., 2018). Most *in vivo* studies have used intraventricular injection of apelin, but this strategy cannot be clinically applied. Other less invasive drug delivery systems should be developed. For this purpose, intranasal delivery in mice has been successfully used in a recent study investigating its effects in the treatment of ischemic stroke (Chen et al., 2015), suggesting that this method may also be applied in other neurological disorders including PD.

Since apelin and APJ are abundantly expressed in several peripheral tissues, systemic administration of apelin agonists may cause severe side effects (Wu et al., 2017). Potential side effects include cardiovascular events, such as vasodilation and subsequent hypotension which has been observed in animal models (Kleinz & Davenport, 2005). Given the autonomic dysfunction and orthostatic hypotension particularly in PD (DeMaagd & Philip, 2015), this activity raises some additional concerns. Apelin may also affect hypothalamic–pituitary–adrenal (HPA) axis; it has been demonstrated that intracerebroventricular apelin-13 may significantly raise both plasma adrenocorticotropic hormone (ACTH) and corticosterone in rat models (Taheri et al., 2002). Intravenous apelin-12 administration has been also shown to increase gastric acid secretion (Lv et al., 2013), which could also affect its tolerability in patients with PD.

Another factor that should be considered is the cleavage or inactivation of apelin. Apelin isoforms can be cleaved by ACE2, which plays a key role in the RAS (Kleinz & Davenport, 2005). In this regard, one apelin analog resistant to ACE2 cleavage, mimicking the activity of apelin has been also synthesized (Yu et al., 2014). In addition, apelin-36 and apelin-55 can also be processed by proprotein convertase subtilisin kexin type 3 (PCSK3) (Lv et al., 2020). The role of these enzymes in apelin processing should be also investigated in the case of PD, since they could affect its activity.

Based on preclinical and clinical evidence, it has been suggested that α-synuclein aggregation may start at the gastrointestinal tract, through which it could be transferred via the vagus nerve into the CNS (Yan et al., 2018). In the gastrointestinal tract, the highest concentration of apelin has been detected in the stomach, followed by the proximal part of the intestine (Antushevich & Wojcik, 2018). It has been also revealed that the highest levels of gastrointestinal α-synuclein were also detected in the stomach (Yan et al., 2018), highlighting their potential interaction in the periphery which should be further explored. For this purpose, PFF α-synuclein-induced animal models of PD reflecting α-synuclein cell-to-cell transmission may be used for the investigation of the role of apelin in this aspect of PD pathophysiology.

In addition, patients with Crohn's disease show increased levels of apelin expression in colon tissues and the mesenteric adipose tissue (Ge et al., 2018); given the known shared genetic variants of the LRRK2 gene associated with both PD and Crohn's disease (Hui et al., 2018), the role of apelin in this genetic form of PD could be investigated in future studies.

Of note, a clinical study has demonstrated that the single-nucleotide polymorphism (SNP) rs9943582 in the *APLNR* gene was associated with increased risk of ischemic stroke (Hata et al., 2007). Currently, to the best of our knowledge, no associations between *APLNR* or *APLN* SNPs and PD have been reported. However, given the implication of apelin/APJ axis in PD, the potential association between *APLNR* or *APLN* gene variants and PD risk should be also explored. Since *APLN* is located on the X chromosome, it could be hypothesized that *APLN* SNPs might be associated with the sex differences in incidence and prevalence of PD, which both are 1.5–2 times higher in men than women (Haaxma et al., 2007). In this context, there is some evidence that the association between common variants of *APLN* gene and hypertension might depend on gender, although meta-analytic evidence did not confirm this hypothesis (R. Zhang et al., 2012).

Interestingly, it has been demonstrated that serum apelin-12 levels in non-patient smokers were significantly higher than healthy non-smokers (Gholamnejad et al., 2019). Given the known well-established association between smoking and reduced risk of PD (Angelopoulou et al., 2019), the potential role of interaction between apelin and tobacco should be further investigated with regard to PD development. In addition, serum uric acid levels have been demonstrated to be significantly lower in patients with PD compared to controls (Wen et al., 2017), as well as in genetic forms of PD such as p.A53T α-synuclein gene mutation carriers (Koros et al., 2020). Since apelin-13 has been shown to reduce uric acid-induced oxidative stress by downregulating RAS in adipose tissue (Zhang et al., 2019), the involvement of apelin-13 in the effects of uric acid on PD development may be important.

The detection of plasma apelin levels exhibits a promising biomarker potential in both neurological and non-neurological diseases. For instance, patients with cardiovascular disorders display lower plasma apelin levels compared to healthy controls, and apelin levels vary according to the severity of heart failure (Kadoglou et al., 2010; Mughal & O'Rourke, 2018). On the contrary, apelin plasma levels are higher in patients with obesity or diabetes (Mughal & O'Rourke, 2018). Patients with multiple sclerosis have higher serum apelin-13 levels compared to controls (Alpua et al., 2018), while patients with autistic spectrum disorder seem to display lower plasma apelin levels compared to controls (Boso et al., 2007). Importantly, it has been indicated that apelin concentration in plasma may decrease with age, since its levels in aged rat models are half of those in younger adults (Sauvant et al., 2014). Hence, the future investigation of the role of apelin as a potential biomarker of PD should also consider the age, body weight factors along with other comorbidities.

12 | CONCLUSION

Emerging preclinical evidence shows that apelin/APJ axis may play a crucial neuroprotective role in PD pathogenesis, via inhibition of apoptosis and dopaminergic neuronal loss, autophagy enhancement, antioxidant effects, endoplasmic reticulum stress

suppression, as well as prevention of synaptic dysregulation in the striatum and glutamate-induced excitotoxicity. However, because of the different active apelin isoforms, upstream regulators, and downstream signaling pathways of apelin, further investigation into the exact effects of the apelin/APJ system in PD is obviously needed before its potential use as a therapeutic target in clinical practice.

COMPETING INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Conceptualization, *Methodology*, *Software*, E.A.; *Data curation*, *Writing-Original draft preparation*, A.B. and Y.N.P.; *Visualization*, *Investigation*, E.A.; *Supervision*, C.P.; *Software*, *Validation*, E.A. and Y.N.P.; *Writing-Reviewing and Editing*, C.P.

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REFERENCES

Acar, N., Parlak, H., Ozkan, A., Soylu, H., Avcı, S., Ustunel, I., Izgut-Uysal, V. N., & Agar, A. (2019). The effect of docosahexaenoic acid on apelin distribution of nervous system in the experimental mouse model of Parkinson's disease. *Tissue and Cell*, *56*, 41–51. https://doi.org/10.1016/j.tice.2018.12.002

Alers, S., Loffler, A. S., Wesselborg, S., & Stork, B. (2012). Role of AMPK-mTOR-Ulk1/2 in the regulation of autophagy: Cross talk, shortcuts, and feedbacks. *Molecular and Cellular Biology*, *32*(1), 2–11. https://doi.org/10.1128/MCB.06159-11

Alpua, M., Turkel, Y., Dag, E., & Kisa, U. (2018). Apelin-13: A promising biomarker for multiple sclerosis? *Annals of the Indian Academy of Neurology*, *21*(2), 126–129. https://doi.org/10.4103/aian.AIAN_377_17

Amalric, M. (2015). Targeting metabotropic glutamate receptors (mGluRs) in Parkinson's disease. *Current Opinion in Pharmacology*, *20*, 29–34. https://doi.org/10.1016/j.coph.2014.11.001

Angelopoulou, E., Bozi, M., Simitsi, A.-M., Koros, C., Antonelou, R., Papagiannakis, N., Maniati, M., Poula, D., Stamelou, M., Vassilatis, D. K., Michalopoulos, I., Geronikolou, S., Scarmeas, N., & Stefanis, L. (2019). The relationship between environmental factors and different Parkinson's disease subtypes in Greece: Data analysis of the Hellenic Biobank of Parkinson's disease. *Parkinsonism & Related Disorders*, *67*, 105–112. https://doi.org/10.1016/j.parkreldis.2019.08.013

Angelopoulou, E., Piperi, C., & Papavassiliou, A. G. (2018). High-mobility group box 1 in Parkinson's disease: From pathogenesis to therapeutic approaches. *Journal of Neurochemistry*, *146*(3), 211–218. https://doi.org/10.1111/jnc.14450

Antushevich, H., & Wojcik, M. (2018). Review: Apelin in disease. *Clinica Chimica Acta*, *483*, 241–248. https://doi.org/10.1016/j.cca.2018.05.012

Avagliano, C., Russo, R., De Caro, C., Cristiano, C., La Rana, G., Piegari, G., Paciello, O., Citraro, R., Russo, E., De Sarro, G., Meli, R., Mattace Raso, G., & Calignano, A. (2016). Palmitoylethanolamide protects mice against 6-OHDA-induced neurotoxicity and endoplasmic reticulum stress: In vivo and in vitro evidence. *Pharmacological Research*, *113*(Pt A), 276–289. https://doi.org/10.1016/j.phrs.2016.09.004

Bai, B., Tang, J., Liu, H., Chen, J., Li, Y., & Song, W. (2008). Apelin-13 induces ERK1/2 but not p38 MAPK activation through coupling of the human apelin receptor to the Gi2 pathway. *Acta Biochimica et Biophysica Sinica*, *40*(4), 311–318. https://doi.org/10.1111/j.1745-7270.2008.00403.x

Bao, H. J., Zhang, L., Han, W. C., & Dai, D. K. (2015). Apelin-13 attenuates traumatic brain injury-induced damage by suppressing autophagy. *Neurochemical Research*, *40*(1), 89–97. https://doi.org/10.1007/s11064-014-1469-x

Boso, M., Emanuele, E., Politi, P., Pace, A., Arra, M., Ucelli di Nemi, S., & Barale, F. (2007). Reduced plasma apelin levels in patients with autistic spectrum disorder. *Archives of Medical Research*, *38*(1), 70–74. https://doi.org/10.1016/j.arcmed.2006.08.003

Boucher, J., Masri, B., Daviaud, D., Gesta, S., Guigné, C., Mazzucotelli, A., Castan-Laurell, I., Tack, I., Knibiehler, B., Carpéné, C., Audigier, Y., Saulnier-Blache, J.-S., & Valet, P. (2005). Apelin, a newly identified adipokine up-regulated by insulin and obesity. *Endocrinology*, *146*(4), 1764–1771. https://doi.org/10.1210/en.2004-1427

Calabresi, P., Picconi, B., Tozzi, A., Ghiglieri, V., & Di Filippo, M. (2014). Direct and indirect pathways of basal ganglia: A critical reappraisal. *Nature Neuroscience*, *17*(8), 1022–1030. https://doi.org/10.1038/nn.3743

Chapman, N. A., Dupre, D. J., & Rainey, J. K. (2014). The apelin receptor: Physiology, pathology, cell signalling, and ligand modulation of a peptide-activated class A GPCR. *Biochemistry and Cell Biology*, *92*(6), 431–440. https://doi.org/10.1139/bcb-2014-0072

Chen, D., Lee, J., Gu, X., Wei, L., & Yu, S. P. (2015). Intranasal delivery of apelin-13 is neuroprotective and promotes angiogenesis after ischemic stroke in mice. *ASN Neuro*, *7*(5), 175909141560511. https://doi.org/10.1177/1759091415605114

Chen, E., Xu, D., Lan, X., Jia, B., Sun, L., Zheng, J. C., & Peng, H. (2013). A novel role of the STAT3 pathway in brain inflammation-induced human neural progenitor cell differentiation. *Current Molecular Medicine*, *13*(9), 1474–1484. https://doi.org/10.2174/15665240113139990076

Chen, H., Zheng, C., Zhang, X., Li, J., Li, J., Zheng, L., & Huang, K. (2011). Apelin alleviates diabetes-associated endoplasmic reticulum stress in the pancreas of Akita mice. *Peptides*, *32*(8), 1634–1639. https://doi.org/10.1016/j.peptides.2011.06.025

Chen, P., Wang, Y., Chen, L., Song, N., & Xie, J. (2020). Apelin-13 protects dopaminergic neurons against rotenone-induced neurotoxicity through the AMPK/mTOR/ULK1 mediated autophagy activation. *International Journal of Molecular Sciences*, *21*(21), 8376. https://doi.org/10.3390/ijms21218376

Cherry, J. D., Olschowka, J. A., & O'Banion, M. K. (2014). Neuroinflammation and M2 microglia: The good, the bad, and the inflamed. *Journal of Neuroinflammation*, *11*, 98. https://doi.org/10.1186/1742-2094-11-98

Chung, H. K., Ho, H. A., Perez-Acuna, D., & Lee, S. J. (2019). Modeling alpha-synuclein propagation with preformed fibril injections. *Journal of Movement Disorders*, *12*(3), 139–151. https://doi.org/10.14802/jmd.19046

Curry, D. W., Stutz, B., Andrews, Z. B., & Elsworth, J. D. (2018). Targeting AMPK signaling as a neuroprotective strategy in Parkinson's disease. *Journal of Parkinson's Disease*, *8*(2), 161–181. https://doi.org/10.3233/JPD-171296

Datta, S. R., Brunet, A., & Greenberg, M. E. (1999). Cellular survival: A play in three Akts. *Genes and Development*, *13*(22), 2905–2927. https://doi.org/10.1101/gad.13.22.2905

de Urquiza, A. M., Liu, S., Sjoberg, M., Zetterstrom, R. H., Griffiths, W., Sjovall, J., & Perlmann, T. (2000). Docosahexaenoic acid, a ligand for the retinoid X receptor in mouse brain. *Science*, *290*(5499), 2140–2144. https://doi.org/10.1126/science.290.5499.2140

DeMaagd, G., & Philip, A. (2015). Parkinson's disease and its management: Part 1: Disease entity, risk factors, pathophysiology, clinical presentation, and diagnosis. *Pharmacy and Therapeutics*, *40*(8), 504–532.

Demmings, M. D., Tennyson, E. C., Petroff, G. N., Tarnowski-Garner, H. E., & Cregan, S. P. (2020). Activating transcription factor-4 promotes

neuronal death induced by Parkinson's disease neurotoxins and alpha-synuclein aggregates. *Cell Death and Differentiation*. https://doi.org/10.1038/s41418-020-00688-6

Dickson, D. W. (2018). Neuropathology of Parkinson disease. *Parkinsonism & Related Disorders*, *46*(Suppl. 1), S30–S33. https://doi.org/10.1016/j.parkreldis.2017.07.033

Dong, H., Dong, B., Zhang, N., Liu, S., & Zhao, H. (2020). microRNA-182 negatively influences the neuroprotective effect of apelin against neuronal injury in epilepsy. *Neuropsychiatric Disease and Treatment*, *16*, 327–338. https://doi.org/10.2147/NDT.S238826

Dorsey, E. R., Constantinescu, R., Thompson, J. P., Biglan, K. M., Holloway, R. G., Kieburtz, K., Marshall, F. J., Ravina, B. M., Schifitto, G., Siderowf, A., & Tanner, C. M. (2007). Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*, *68*(5), 384–386. https://doi.org/10.1212/01.wnl.0000247740.47667.03

Duan, J., Cui, J., Yang, Z., Guo, C., Cao, J., Xi, M., & Wen, A. (2019). Neuroprotective effect of Apelin 13 on ischemic stroke by activating AMPK/GSK-3beta/Nrf2 signaling. *Journal of Neuroinflammation*, *16*(1), 24. https://doi.org/10.1186/s12974-019-1406-7

Faggiani, E., Delaville, C., & Benazzouz, A. (2015). The combined depletion of monoamines alters the effectiveness of subthalamic deep brain stimulation. *Neurobiology of Diseases*, *82*, 342–348. https://doi.org/10.1016/j.nbd.2015.07.010

Forman, M. S., Trojanowski, J. Q., & Lee, V. M. (2004). Neurodegenerative diseases: A decade of discoveries paves the way for therapeutic breakthroughs. *Nature Medicine*, *10*(10), 1055–1063. https://doi.org/10.1038/nm1113

Gao, L., Zhang, J., Hou, Y., Hallett, M., Chan, P., & Wu, T. (2017). The cerebellum in dual-task performance in Parkinson's disease. *Scientific Reports*, *7*, 45662. https://doi.org/10.1038/srep45662

Ge, Y., Li, Y. I., Chen, Q., Zhu, W., Zuo, L., Guo, Z., Gong, J., Cao, L., Gu, L., & Li, J. (2018). Adipokine apelin ameliorates chronic colitis in Il-10(-/-) mice by promoting intestinal lymphatic functions. *Biochemical Pharmacology*, *148*, 202–212. https://doi.org/10.1016/j.bcp.2018.01.011

Geiger, K., Muendlein, A., Stark, N., Saely, C. H., Wabitsch, M., Fraunberger, P., & Drexel, H. (2011). Hypoxia induces apelin expression in human adipocytes. *Hormone and Metabolic Research*, *43*(6), 380–385. https://doi.org/10.1055/s-0031-1273767

Geurts, L., Lazarevic, V., Derrien, M., Everard, A., Van Roye, M., Knauf, C., Valet, P., Girard, M., Muccioli, G. G., François, P., de Vos, W. M., Schrenzel, J., Delzenne, N. M., & Cani, P. D. (2011). Altered gut microbiota and endocannabinoid system tone in obese and diabetic leptin-resistant mice: Impact on apelin regulation in adipose tissue. *Frontiers in Microbiology*, *2*, 149. https://doi.org/10.3389/fmicb.2011.00149

Gholamnejad, M., Meghrazi, K., Akhgar, M., & Shaianmehr, M. (2019). The assessment of serum apelin-12 level in a variety of pulmonary malignancies in smokers. *Addict Health*, *11*(2), 93–99. https://doi.org/10.22122/ahj.v11i2.228

Giacoppo, S., Bramanti, P., & Mazzon, E. (2017). Triggering of inflammasome by impaired autophagy in response to acute experimental Parkinson's disease: Involvement of the PI3K/Akt/mTOR pathway. *NeuroReport*, *28*(15), 996–1007. https://doi.org/10.1097/WNR.0000000000000871

Haaxma, C. A., Bloem, B. R., Borm, G. F., Oyen, W. J. G., Leenders, K. L., Eshuis, S., Booij, J., Dluzen, D. E., & Horstink, M. W. I. M. (2007). Gender differences in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *78*(8), 819–824. https://doi.org/10.1136/jnnp.2006.103788

Haghparast, E., Esmaeili-Mahani, S., Abbasnejad, M., & Sheibani, V. (2018). Apelin-13 ameliorates cognitive impairments in 6-hydroxydopamine-induced substantia nigra lesion in rats. *Neuropeptides*, *68*, 28–35. https://doi.org/10.1016/j.npep.2018.01.001

Haghparast, E., Sheibani, V., Abbasnejad, M., & Esmaeili-Mahani, S. (2019). Apelin-13 attenuates motor impairments and prevents the changes in synaptic plasticity-related molecules in the striatum of Parkinsonism rats. *Peptides*, *117*, 170091. https://doi.org/10.1016/j.peptides.2019.05.003

Han, R. W., Xu, H. J., Zhang, R. S., & Wang, R. (2014). The role of apelin-13 in novel object recognition memory. *Peptides*, *62*, 155–158. https://doi.org/10.1016/j.peptides.2014.10.003

Hata, J., Matsuda, K., Ninomiya, T., Yonemoto, K., Matsushita, T., Ohnishi, Y., Saito, S., Kitazono, T., Ibayashi, S., Iida, M., Kiyohara, Y., Nakamura, Y., & Kubo, M. (2007). Functional SNP in an Sp1-binding site of AGTRL1 gene is associated with susceptibility to brain infarction. *Human Molecular Genetics*, *16*(6), 630–639. https://doi.org/10.1093/hmg/ddm005

He, L., Xu, J., Chen, L., & Li, L. (2015). Apelin/APJ signaling in hypoxia-related diseases. *Clinica Chimica Acta*, *451*(Pt B), 191–198. https://doi.org/10.1016/j.cca.2015.09.029

Hernando, S., Requejo, C., Herran, E., Ruiz-Ortega, J. A., Morera-Herreras, T., Lafuente, J. V., Ugedo, L., Gainza, E., Pedraz, J. L., Igartua, M., & Hernandez, R. M. (2019). Beneficial effects of n-3 polyunsaturated fatty acids administration in a partial lesion model of Parkinson's disease: The role of glia and NRf2 regulation. *Neurobiology of Diseases*, *121*, 252–262. https://doi.org/10.1016/j.nbd.2018.10.001

Higuchi, K., Masaki, T., Gotoh, K., Chiba, S., Katsuragi, I., Tanaka, K., Kakuma, T., & Yoshimatsu, H. (2007). Apelin, an APJ receptor ligand, regulates body adiposity and favors the messenger ribonucleic acid expression of uncoupling proteins in mice. *Endocrinology*, *148*(6), 2690–2697. https://doi.org/10.1210/en.2006-1270

Hou, X., Watzlawik, J. O., Fiesel, F. C., & Springer, W. (2020). Autophagy in Parkinson's disease. *Journal of Molecular Biology*, *432*(8), 2651–2672. https://doi.org/10.1016/j.jmb.2020.01.037

Hudson, J. L., van Horne, C. G., Strömberg, I., Brock, S., Clayton, J., Masserano, J., Hoffer, B. J., & Gerhardt, G. A. (1993). Correlation of apomorphine- and amphetamine-induced turning with nigrostriatal dopamine content in unilateral 6-hydroxydopamine lesioned rats. *Brain Research*, *626*(1–2), 167–174. https://doi.org/10.1016/0006-8993(93)90576-9

Hui, K. Y., Fernandez-Hernandez, H., Hu, J., Schaffner, A., Pankratz, N., Hsu, N. Y., Chuang, L. S., Carmi, S., Villaverde, N., Li, X., Rivas, M., Levine, A. P., Bao, X., Labrias, P. R., Haritunians, T., Ruane, D., Gettler, K., Chen, E., & Li, D., … Peter, I. (2018). Functional variants in the LRRK2 gene confer shared effects on risk for Crohn's disease and Parkinson's disease. *Science Translational Medicine*, *10*(423), eaai7795. https://doi.org/10.1126/scitranslmed.aai7795

Ishimaru, Y., Sumino, A., Kajioka, D., Shibagaki, F., Yamamuro, A., Yoshioka, Y., & Maeda, S. (2017). Apelin protects against NMDA-induced retinal neuronal death via an APJ receptor by activating Akt and ERK1/2, and suppressing TNF-alpha expression in mice. *Journal of Pharmacological Sciences*, *133*(1), 34–41. https://doi.org/10.1016/j.jphs.2016.12.002

Janyou, A., Changtam, C., Suksamrarn, A., Tocharus, C., & Tocharus, J. (2015). Suppression effects of O-demethyldemethoxycurcumin on thapsigargin triggered on endoplasmic reticulum stress in SK-N-SH cells. *Neurotoxicology*, *50*, 92–100. https://doi.org/10.1016/j.neuro.2015.08.005

Jaszberenyi, M., Bujdoso, E., & Telegdy, G. (2004). Behavioral, neuroendocrine and thermoregulatory actions of apelin-13. *Neuroscience*, *129*(3), 811–816. https://doi.org/10.1016/j.neuroscience.2004.08.007

Jeong, K., Oh, Y., Kim, S.-J., Kim, H., Park, K.-C., Kim, S. S., Ha, J., Kang, I., & Choe, W. (2014). Apelin is transcriptionally regulated by ER stress-induced ATF4 expression via a p38 MAPK-dependent pathway. *Apoptosis*, *19*(9), 1399–1410. https://doi.org/10.1007/s10495-014-1013-0

Jha, S. K., Jha, N. K., Kar, R., Ambasta, R. K., & Kumar, P. (2015). p38 MAPK and PI3K/AKT signalling cascades in Parkinson's disease. *International Journal of Molecular and Cellular Medicine*, *4*(2), 67–86.

Jiang, Y., Liu, H., Ji, B., Wang, Z., Wang, C., Yang, C., Pan, Y., Chen, J., Cheng, B., & Bai, B. O. (2018). Apelin13 attenuates ER stressassociated apoptosis induced by MPP+ in SHSY5Y cells. *International Journal of Molecular Medicine*, *42*(3), 1732–1740. https://doi.org/10.3892/ijmm.2018.3719

Kadoglou, N. P., Lampropoulos, S., Kapelouzou, A., Gkontopoulos, A., Theofilogiannakos, E. K., Fotiadis, G., & Kottas, G. (2010). Serum levels of apelin and ghrelin in patients with acute coronary syndromes and established coronary artery disease–KOZANI STUDY. *Translational Research*, *155*(5), 238–246. https://doi.org/10.1016/j.trsl.2010.01.004

Kandil, E. A., Sayed, R. H., Ahmed, L. A., Abd El Fattah, M. A., & El-Sayeh, B. M. (2019). Hypoxia-inducible factor 1 alpha and nuclear-related receptor 1 as targets for neuroprotection by albendazole in a rat rotenone model of Parkinson's disease. *Clinical and Experimental Pharmacology and Physiology*, *46*(12), 1141–1150. https://doi.org/10.1111/1440-1681.13162

Kao, S. Y. (2009). Rescue of alpha-synuclein cytotoxicity by insulin-like growth factors. *Biochemical and Biophysical Research Communications*, *385*(3), 434–438. https://doi.org/10.1016/j.bbrc.2009.05.089

Kasai, A., Kinjo, T., Ishihara, R., Sakai, I., Ishimaru, Y., Yoshioka, Y., Yamamuro, A., Ishige, K., Ito, Y., & Maeda, S. (2011). Apelin deficiency accelerates the progression of amyotrophic lateral sclerosis. *PLoS ONE*, *6*(8), e23968. https://doi.org/10.1371/journal.pone.0023968

Kennedy, S. G., Kandel, E. S., Cross, T. K., & Hay, N. (1999). Akt/Protein kinase B inhibits cell death by preventing the release of cytochrome c from mitochondria. *Molecular and Cellular Biology*, *19*(8), 5800–5810. https://doi.org/10.1128/mcb.19.8.5800

Khaksari, M., Aboutaleb, N., Nasirinezhad, F., Vakili, A., & Madjd, Z. (2012). Apelin-13 protects the brain against ischemic reperfusion injury and cerebral edema in a transient model of focal cerebral ischemia. *Journal of Molecular Neuroscience*, *48*(1), 201–208. https://doi.org/10.1007/s12031-012-9808-3

Khwanraj, K., Madlah, S., Grataitong, K., & Dharmasaroja, P. (2016). Comparative mRNA expression of eEF1A Isoforms and a PI3K/Akt/mTOR pathway in a cellular model of Parkinson's disease. *Parkinson's Disease*, *2016*, 8716016. https://doi.org/10.1155/2016/8716016

Kin, K., Yasuhara, T., Kameda, M., & Date, I. (2019). Animal models for Parkinson's disease research: Trends in the 2000s. *International Journal of Molecular Sciences*, *20*(21), 5402. https://doi.org/10.3390/ijms20215402

Kleinz, M. J., & Davenport, A. P. (2005). Emerging roles of apelin in biology and medicine. *Pharmacology and Therapeutics*, *107*(2), 198–211. https://doi.org/10.1016/j.pharmthera.2005.04.001

Koros, C., Simitsi, A.-M., Papadimitriou, D., Bougea, A., Prentakis, A., Papagiannakis, N., Pachi, I., Bozi, M., Antonelou, R., Angelopoulou, E., Beratis, I., Papageorgiou, S. G., Trapali, X. G., Stamelou, M., & Stefanis, L. (2020). Serum uric acid level as a biomarker in idiopathic and genetic (p. A53T alpha-synuclein carriers) Parkinson's disease: Data from the PPMI study. *Journal of Parkinson's Disease*, *10*(2), 481–487. https://doi.org/10.3233/JPD-191860

Kurowska, P., Barbe, A., Rozycka, M., Chmielinska, J., Dupont, J., & Rak, A. (2018). Apelin in reproductive physiology and pathology of different species: A critical review. *International Journal of Endocrinology*, *2018*, 9170480. https://doi.org/10.1155/2018/9170480

Lee, A. S. (2005). The ER chaperone and signaling regulator GRP78/BiP as a monitor of endoplasmic reticulum stress. *Methods*, *35*(4), 373–381. https://doi.org/10.1016/j.ymeth.2004.10.010

Lee, D. K., Cheng, R., Nguyen, T., Fan, T., Kariyawasam, A. P., Liu, Y., Osmond, D. H., George, S. R., & O'Dowd, B. F. (2000). Characterization of apelin, the ligand for the APJ receptor. *Journal of Neurochemistry*, *74*(1), 34–41. https://doi.org/10.1046/j.1471-4159.2000.0740034.x

Lee Mosley, R., Benner, E. J., Kadiu, I., Thomas, M., Boska, M. D., Hasan, K., Laurie, C., & Gendelman, H. E. (2006). Neuroinflammation, oxidative stress and the pathogenesis of Parkinson's disease. *Clinical Neuroscience Research*, *6*(5), 261–281. https://doi.org/10.1016/j.cnr.2006.09.006

Lee, T. H., Cheng, K. K., Hoo, R. L., Siu, P. M., & Yau, S. Y. (2019). The novel perspectives of adipokines on brain health. *International Journal of Molecular Sciences*, *20*(22), 5638. https://doi.org/10.3390/ijms20225638

Li, E., Deng, H., Wang, B., Fu, W., You, Y., & Tian, S. (2016). Apelin-13 exerts antidepressant-like and recognition memory improving activities in stressed rats. *European Neuropsychopharmacology*, *26*(3), 420–430. https://doi.org/10.1016/j.euroneuro.2016.01.007

Luo, H., Han, L., & Xu, J. (2020). Apelin/APJ system: A novel promising target for neurodegenerative diseases. *Journal of Cellular Physiology*, *235*(2), 638–657. https://doi.org/10.1002/jcp.29001

Luo, H., Xiang, Y., Qu, X., Liu, H., Liu, C., Li, G., Han, L. I., & Qin, X. (2019). Apelin-13 suppresses neuroinflammation against cognitive deficit in a streptozotocin-induced rat model of Alzheimer's disease through activation of BDNF-TrkB signaling pathway. *Frontiers in Pharmacology*, *10*, 395. https://doi.org/10.3389/fphar.2019.00395

Lv, S. Y., Chen, W. D., & Wang, Y. D. (2020). The Apelin/APJ system in psychosis and neuropathy. *Frontiers in Pharmacology*, *11*, 320. https://doi.org/10.3389/fphar.2020.00320

Lv, S. Y., Yang, Y. J., & Chen, Q. (2013). Regulation of feeding behavior, gastrointestinal function and fluid homeostasis by apelin. *Peptides*, *44*, 87–92. https://doi.org/10.1016/j.peptides.2013.03.024

Maksoud, E., Liao, E. H., & Haghighi, A. P. (2019). A neuron-glial transsignaling cascade mediates LRRK2-induced neurodegeneration. *Cell Reports*, *26*(7), 1774–1786.e1774. https://doi.org/10.1016/j.celrep.2019.01.077

Marciniak, S. J., Yun, C. Y., Oyadomari, S., Novoa, I., Zhang, Y., Jungreis, R., & Ron, D. (2004). CHOP induces death by promoting protein synthesis and oxidation in the stressed endoplasmic reticulum. *Genes and Development*, *18*(24), 3066–3077. https://doi.org/10.1101/gad.1250704

Masri, B., Morin, N., Pedebernade, L., Knibiehler, B., & Audigier, Y. (2006). The apelin receptor is coupled to Gi1 or Gi2 protein and is differentially desensitized by apelin fragments. *Journal of Biological Chemistry*, *281*(27), 18317–18326. https://doi.org/10.1074/jbc.M600606200

McKinnie, S. M., Fischer, C., Tran, K. M., Wang, W., Mosquera, F., Oudit, G. Y., & Vederas, J. C. (2016). The metalloprotease neprilysin degrades and inactivates apelin peptides. *ChemBioChem*, *17*(16), 1495–1498. https://doi.org/10.1002/cbic.201600244

Minakaki, G., Menges, S., Kittel, A., Emmanouilidou, E., Schaeffner, I., Barkovits, K., Bergmann, A., Rockenstein, E., Adame, A., Marxreiter, F., Mollenhauer, B., Galasko, D., Buzás, E. I., Schlötzer-Schrehardt, U., Marcus, K., Xiang, W., Lie, D. C., Vekrellis, K., Masliah, E., … Klucken, J. (2018). Autophagy inhibition promotes SNCA/alpha-synuclein release and transfer via extracellular vesicles with a hybrid autophagosome-exosome-like phenotype. *Autophagy*, *14*(1), 98–119. https://doi.org/10.1080/15548627.2017.1395992

Mughal, A., & O'Rourke, S. T. (2018). Vascular effects of apelin: Mechanisms and therapeutic potential. *Pharmacology and Therapeutics*, *190*, 139–147. https://doi.org/10.1016/j.pharmthera.2018.05.013

Murphy, T. J., Alexander, R. W., Griendling, K. K., Runge, M. S., & Bernstein, K. E. (1991). Isolation of a cDNA encoding the vascular type-1 angiotensin II receptor. *Nature*, *351*(6323), 233–236. https://doi.org/10.1038/351233a0

O'Carroll, A. M., Lolait, S. J., Harris, L. E., & Pope, G. R. (2013). The apelin receptor APJ: Journey from an orphan to a multifaceted regulator of homeostasis. *Journal of Endocrinology*, *219*(1), R13–R35. https://doi.org/10.1530/JOE-13-0227

O'Carroll, A. M., Selby, T. L., Palkovits, M., & Lolait, S. J. (2000). Distribution of mRNA encoding B78/apj, the rat homologue of the human APJ receptor, and its endogenous ligand apelin in brain and peripheral tissues. *Biochimica et Biophysica Acta*, *1492*(1), 72–80. https://doi.org/10.1016/s0167-4781(00)00072-5

O'Donnell, L. A., Agrawal, A., Sabnekar, P., Dichter, M. A., Lynch, D. R., & Kolson, D. L. (2007). Apelin, an endogenous neuronal peptide, protects hippocampal neurons against excitotoxic injury. *Journal of Neurochemistry*, *102*(6), 1905–1917. https://doi.org/10.1111/j.1471-4159.2007.04645.x

O'Dowd, B. F., Heiber, M., Chan, A., Heng, H. H. Q., Tsui, L.-C., Kennedy, J. L., Shi, X., Petronis, A., George, S. R., & Nguyen, T. (1993). A human gene that shows identity with the gene encoding the angiotensin receptor is located on chromosome 11. *Gene*, *136*(1–2), 355–360. https://doi.org/10.1016/0378-1119(93)90495-o

Pan, T., Kondo, S., Zhu, W., Xie, W., Jankovic, J., & Le, W. (2008). Neuroprotection of rapamycin in lactacystin-induced neurodegeneration via autophagy enhancement. *Neurobiology of Diseases*, *32*(1), 16–25. https://doi.org/10.1016/j.nbd.2008.06.003

Patricio, F., Morales-Andrade, A. A., Patricio-Martinez, A., & Limon, I. D. (2020). Cannabidiol as a therapeutic target: Evidence of its neuroprotective and neuromodulatory function in Parkinson's disease. *Frontiers in Pharmacology*, *11*, 595635. https://doi.org/10.3389/fphar.2020.595635

Poirier, O., Ciumas, M., Eyries, M., Montagne, K., Nadaud, S., & Soubrier, F. (2012). Inhibition of apelin expression by BMP signaling in endothelial cells. *American Journal of Physiology: Cell Physiology*, *303*(11), C1139–C1145. https://doi.org/10.1152/ajpcell.00168.2012

Pope, G. R., Roberts, E. M., Lolait, S. J., & O'Carroll, A. M. (2012). Central and peripheral apelin receptor distribution in the mouse: Species differences with rat. *Peptides*, *33*(1), 139–148. https://doi.org/10.1016/j.peptides.2011.12.005

Pouresmaeili-Babaki, E., Esmaeili-Mahani, S., Abbasnejad, M., & Ravan, H. (2018). Protective effect of neuropeptide apelin-13 on 6-hydroxydopamine-induced neurotoxicity in SH-SY5Y dopaminergic cells: Involvement of its antioxidant and antiapoptotic properties. *Rejuvenation Research*, *21*(2), 162–167. https://doi.org/10.1089/rej.2017.1951

Qiu, J., Wang, X., Wu, F., Wan, L., Cheng, B., Wu, Y., & Bai, B. (2017). Low dose of apelin-36 attenuates ER stress-associated apoptosis in rats with ischemic stroke. *Frontiers in Neurology*, *8*, 556. https://doi.org/10.3389/fneur.2017.00556

Roche, J., Rame, C., Reverchon, M., Mellouk, N., Cornuau, M., Guerif, F., Froment, P., & Dupont, J. (2016). Apelin (APLN) and apelin receptor (APLNR) in human ovary: Expression, signaling, and regulation of steroidogenesis in primary human luteinized granulosa cells. *Biology of Reproduction*, *95*(5), 104. https://doi.org/10.1095/biolreprod.116.141754

Sauvant, J., Delpech, J.-C., Palin, K., De Mota, N., Dudit, J., Aubert, A., Orcel, H., Roux, P., Layé, S., Moos, F., Llorens-Cortes, C., & Nadjar, A. (2014). Mechanisms involved in dual vasopressin/apelin neuron dysfunction during aging. *PLoS ONE*, *9*(2), e87421. https://doi.org/10.1371/journal.pone.0087421

Shacham, T., Sharma, N., & Lederkremer, G. Z. (2019). Protein misfolding and ER stress in Huntington's disease. *Frontiers in Molecular Biosciences*, *6*, 20. https://doi.org/10.3389/fmolb.2019.00020

Shin, K., Kenward, C., & Rainey, J. K. (2017). Apelinergic system structure and function. *Comprehensive Physiology*, *8*(1), 407–450. https://doi.org/10.1002/cphy.c170028

Simon, H. U., Haj-Yehia, A., & Levi-Schaffer, F. (2000). Role of reactive oxygen species (ROS) in apoptosis induction. *Apoptosis*, *5*(5), 415–418. https://doi.org/10.1023/a:1009616228304

Sudhof, T. C. (2008). Neuroligins and neurexins link synaptic function to cognitive disease. *Nature*, *455*(7215), 903–911. https://doi.org/10.1038/nature07456

Taheri, S., Murphy, K., Cohen, M., Sujkovic, E., Kennedy, A., Dhillo, W., Dakin, C., Sajedi, A., Ghatei, M., & Bloom, S. (2002). The effects of centrally administered apelin-13 on food intake, water intake and pituitary hormone release in rats. *Biochemical and Biophysical Research Communications*, *291*(5), 1208–1212. https://doi.org/10.1006/bbrc.2002.6575

Taneja, R., Parodo, J., Jia, S. H., Kapus, A., Rotstein, O. D., & Marshall, J. C. (2004). Delayed neutrophil apoptosis in sepsis is associated with maintenance of mitochondrial transmembrane potential and reduced caspase-9 activity. *Critical Care Medicine*, *32*(7), 1460–1469. https://doi.org/10.1097/01.ccm.0000129975.26905.77

Tatemoto, K., Hosoya, M., Habata, Y., Fujii, R., Kakegawa, T., Zou, M.-X., Kawamata, Y., Fukusumi, S., Hinuma, S., Kitada, C., Kurokawa, T., Onda, H., & Fujino, M. (1998). Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. *Biochemical and Biophysical Research Communications*, *251*(2), 471–476. https://doi.org/10.1006/bbrc.1998.9489

Teleanu, D. M., Chircov, C., Grumezescu, A. M., Volceanov, A., & Teleanu, R. I. (2018). Blood-brain delivery methods using nanotechnology. *Pharmaceutics*, *10*(4), 269. https://doi.org/10.3390/pharmaceutics10040269

Telegdy, G., Adamik, A., & Jaszberenyi, M. (2013). Involvement of neurotransmitters in the action of apelin-13 on passive avoidance learning in mice. *Peptides*, *39*, 171–174. https://doi.org/10.1016/j.peptides.2012.10.011

Thomas, B. (2009). Parkinson's disease: From molecular pathways in disease to therapeutic approaches. *Antioxidants & Redox Signaling*, *11*(9), 2077–2082. https://doi.org/10.1089/ars.2009.2697

Tian, Y., Chen, R., Jiang, Y., Bai, B., Yang, T., & Liu, H. (2020). The protective effects and mechanisms of Apelin/APJ system on ischemic stroke: A promising therapeutic target. *Frontiers in Neurology*, *11*, 75. https://doi.org/10.3389/fneur.2020.00075

Tong, Q., Wu, L., Jiang, T., Ou, Z., Zhang, Y., & Zhu, D. (2016). Inhibition of endoplasmic reticulum stress-activated IRE1alpha-TRAF2-caspase-12 apoptotic pathway is involved in the neuroprotective effects of telmisartan in the rotenone rat model of Parkinson's disease. *European Journal of Pharmacology*, *776*, 106–115. https://doi.org/10.1016/j.ejphar.2016.02.042

Wang, J.-F., Mei, Z.-G., Fu, Y., Yang, S.-B., Zhang, S.-Z., Huang, W.-F., Xiong, L. I., Zhou, H.-J., Tao, W., & Feng, Z.-T. (2018). Puerarin protects rat brain against ischemia/reperfusion injury by suppressing autophagy via the AMPK-mTOR-ULK1 signaling pathway. *Neural Regeneration Research*, *13*(6), 989–998. https://doi.org/10.4103/1673-5374.233441

Wang, R., Yang, Y., Wang, H., He, Y., & Li, C. (2020). MiR-29c protects against inflammation and apoptosis in Parkinson's disease model in vivo and in vitro by targeting SP1. *Clinical and Experimental Pharmacology and Physiology*, *47*(3), 372–382. https://doi.org/10.1111/1440-1681.13212

Wen, M., Zhou, B. O., Chen, Y.-H., Ma, Z.-L., Gou, Y., Zhang, C.-L., Yu, W.-F., & Jiao, L. (2017). Serum uric acid levels in patients with Parkinson's disease: A meta-analysis. *PLoS ONE*, *12*(3), e0173731. https://doi.org/10.1371/journal.pone.0173731

Wu, Y., Wang, X., Zhou, X., Cheng, B., Li, G., & Bai, B. (2017). Temporal expression of apelin/apelin receptor in ischemic stroke and its therapeutic potential. *Frontiers in Molecular Neuroscience*, *10*, 1. https://doi.org/10.3389/fnmol.2017.00001

Xin, Q., Cheng, B., Pan, Y., Liu, H., Yang, C., Chen, J., & Bai, B. (2015). Neuroprotective effects of apelin-13 on experimental ischemic stroke through suppression of inflammation. *Peptides*, *63*, 55–62. https://doi.org/10.1016/j.peptides.2014.09.016

Xiong, N., Jia, M., Chen, C., Xiong, J., Zhang, Z., Huang, J., Hou, L., Yang, H., Cao, X., Liang, Z., Sun, S., Lin, Z., & Wang, T. (2011). Potential autophagy enhancers attenuate rotenone-induced toxicity in SH-SY5Y. *Neuroscience*, *199*, 292–302. https://doi.org/10.1016/j.neuroscience.2011.10.031

Xu, W., Li, T., Gao, L., Zheng, J., Yan, J., Zhang, J., & Shao, A. (2019). Apelin-13/APJ system attenuates early brain injury via suppression of endoplasmic reticulum stress-associated TXNIP/NLRP3 inflammasome activation and oxidative stress in a AMPK-dependent

manner after subarachnoid hemorrhage in rats. *Journal of Neuroinflammation*, *16*(1), 247. https://doi.org/10.1186/s12974-019-1620-3

Yan, F., Chen, Y., Li, M., Wang, Y., Zhang, W., Chen, X., & Ye, Q. (2018). Gastrointestinal nervous system alpha-synuclein as a potential biomarker of Parkinson disease. *Medicine*, *97*(28), e11337. https://doi.org/10.1097/MD.0000000000011337

Yan, X. G., Cheng, B. H., Wang, X., Ding, L. C., Liu, H. Q., Chen, J., & Bai, B. (2015). Lateral intracerebroventricular injection of Apelin-13 inhibits apoptosis after cerebral ischemia/reperfusion injury. *Neural Regeneration Research*, *10*(5), 766–771. https://doi.org/10.4103/1673-5374.157243

Yang, Y., Zhang, X., Cui, H., Zhang, C., Zhu, C., & Li, L. (2014). Apelin-13 protects the brain against ischemia/reperfusion injury through activating PI3K/Akt and ERK1/2 signaling pathways. *Neuroscience Letters*, *568*, 44–49. https://doi.org/10.1016/j.neulet.2014.03.037

Yu, X.-H., Tang, Z.-B., Liu, L.-J., Qian, H., Tang, S.-L., Zhang, D.-W., Tian, G.-P., & Tang, C.-K. (2014). Apelin and its receptor APJ in cardiovascular diseases. *Clinica Chimica Acta*, *428*, 1–8. https://doi.org/10.1016/j.cca.2013.09.001

Zeng, R., Luo, D. X., Li, H. P., Zhang, Q. S., Lei, S. S., & Chen, J. H. (2019). MicroRNA-135b alleviates MPP(+)-mediated Parkinson's disease in in vitro model through suppressing FoxO1-induced NLRP3 inflammasome and pyroptosis. *Journal of Clinical Neuroscience*, *65*, 125–133. https://doi.org/10.1016/j.jocn.2019.04.004

Zeng, X., Yu, S. P., Taylor, T., Ogle, M., & Wei, L. (2012). Protective effect of apelin on cultured rat bone marrow mesenchymal stem cells against apoptosis. *Stem Cell Research*, *8*(3), 357–367. https://doi.org/10.1016/j.scr.2011.12.004

Zeng, X. J., Yu, S. P., Zhang, L., & Wei, L. (2010). Neuroprotective effect of the endogenous neural peptide apelin in cultured mouse cortical neurons. *Experimental Cell Research*, *316*(11), 1773–1783. https://doi.org/10.1016/j.yexcr.2010.02.005

Zhang, H., Duan, C., & Yang, H. (2015). Defective autophagy in Parkinson's disease: Lessons from genetics. *Molecular Neurobiology*, *51*(1), 89–104. https://doi.org/10.1007/s12035-014-8787-5

Zhang, J., Lin, X., Xu, J., & Tang, F. (2019). Apelin-13 reduces oxidative stress induced by uric acid via downregulation of renin-angiotensin system in adipose tissue. *Toxicology Letters*, *305*, 51–57. https://doi.org/10.1016/j.toxlet.2019.01.014

Zhang, J., Xu, T. X., Hallett, P. J., Watanabe, M., Grant, S. G., Isacson, O., & Yao, W. D. (2009). PSD-95 uncouples dopamine-glutamate interaction in the D1/PSD-95/NMDA receptor complex. *Journal of Neuroscience*, *29*(9), 2948–2960. https://doi.org/10.1523/JNEUROSCI.4424-08.2009

Zhang, J., Zhang, Z., Bao, J., Yu, Z., Cai, M., Li, X., Wu, T., Xiang, J., & Cai, D. (2017). Jia-Jian-Di-Huang-Yin-Zi decoction reduces apoptosis induced by both mitochondrial and endoplasmic reticulum caspase12 pathways in the mouse model of Parkinson's disease. *Journal of Ethnopharmacology*, *203*, 69–79. https://doi.org/10.1016/j.jep.2016.12.053

Zhang, R., Lu, J., Hu, C., Wang, C., Yu, W., Jiang, F., & Jia, W. (2012). Associations of common variants at APLN and hypertension in Chinese subjects with and without diabetes. *Experimental Diabetes Research*, *2012*, 917496. https://doi.org/10.1155/2012/917496

Zhou, N., Fan, X., Mukhtar, M., Fang, J., Patel, C. A., DuBois, G. C., & Pomerantz, R. J. (2003). Cell-cell fusion and internalization of the CNS-based, HIV-1 co-receptor, APJ. *Virology*, *307*(1), 22–36. https://doi.org/10.1016/s0042-6822(02)00021-1

Zhou, S., Guo, X., Chen, S., Xu, Z., Duan, W., & Zeng, B. (2019). Apelin-13 regulates LPS-induced N9 microglia polarization involving STAT3 signaling pathway. *Neuropeptides*, *76*, 101938. https://doi.org/10.1016/j.npep.2019.101938

Zhu, J., Dou, S., Jiang, Y., Bai, B., Chen, J., Wang, C., & Cheng, B. (2019). Apelin-36 exerts the cytoprotective effect against MPP(+)-induced cytotoxicity in SH-SY5Y cells through PI3K/Akt/mTOR autophagy pathway. *Life Sciences*, *224*, 95–108. https://doi.org/10.1016/j.lfs.2019.03.047

Zhu, J., Dou, S., Jiang, Y., Chen, J., Wang, C., & Cheng, B. (2019). Apelin-13 protects dopaminergic neurons in MPTP-induced Parkinson's disease model mice through inhibiting endoplasmic reticulum stress and promoting autophagy. *Brain Research*, *1715*, 203–212. https://doi.org/10.1016/j.brainres.2019.03.027

Zhu, J., Dou, S., Wang, C., Jiang, Y., Wang, C., & Cheng, B. (2019). Apelin-36 mitigates MPTP/MPP(+)-induced neurotoxicity: Involvement of alpha-synuclein and endoplasmic reticulum stress. *Brain Research*, *1721*, 146334. https://doi.org/10.1016/j.brainres.2019.146334

Zhu, J., Gao, W., Shan, X., Wang, C., Wang, H., Shao, Z., Dou, S., Jiang, Y., Wang, C., & Cheng, B. (2020). Apelin-36 mediates neuroprotective effects by regulating oxidative stress, autophagy and apoptosis in MPTP-induced Parkinson's disease model mice. *Brain Research*, *1726*, 146493. https://doi.org/10.1016/j.brainres.2019.146493

Zou, Y., Wang, B., Fu, W., Zhou, S., Nie, Y., & Tian, S. (2016). Apelin-13 protects PC12 cells from corticosterone-induced apoptosis through PI3K and ERKs activation. *Neurochemical Research*, *41*(7), 1635–1644. https://doi.org/10.1007/s11064-016-1878-0

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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