Apelinergic System in Brain Diseases

Subjects: Clinical Neurology

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Apelin, a peptide initially isolated from bovine stomach extract, is an endogenous ligand for the Apelin Receptor (APLNR). Subsequently, a second peptide, ELABELA, that can bind to the receptor has been identified. The Apelin receptor and its endogenous ligands are widely distributed in mammalian organs. A growing body of evidence suggests that this system participates in various signalling cascades that can regulate cell proliferation, blood pressure, fluid homeostasis, feeding behaviour, and pituitary hormone release. Additional research has been done to elucidate the system's potential role in neurogenesis, the pathophysiology of Glioblastoma multiforme, and the protective effects of apelin peptides on some neurological and psychiatric disorders-ischemic stroke, epilepsy, Parkinson's, and Alzheimer's disease. Mounting evidence suggests that the apelinergic system is a prominent player in the pathogenesis of different neuronal and mental diseases, such as stroke, epilepsy, Alzheimer's disease, and Parkinson's, among others.

Keywords: Apelin ; neurogenesis ; gene expression

1. Apelinergic System Involvement in Ischemic Stroke

Ischemic stroke is the most common cause of disability and death worldwide [1]. Damage caused by cerebral blood vessel occlusion leads to the regional increase in Ca^{2+} (via NMDAR activation), depolarization of the mitochondrial membrane, caspase activation, neuronal cell death, and cerebral edema. Infusion of apelin-13 in mice reduces the infarct zone volume [2], cerebral edema, and caspase-3 activation but does not alter the neurological deficits [3]. Apelin-36 in lower concentrations can also reduce the infarct volume, but unlike apelin-13, it also improves neurological function after ischemia/reperfusion injury. LY294002, a potent inhibitor of PI3K, reduced the phosphorylation of Akt, thus, lowering the activity of the PI3K/Akt pathway activated by the APLNR ligands. Applying this substance to the ischemic stroke model treated with apelin-13 or 36 elevates the pro-apoptotic proteins caspase-3 and BAX, confirming that the antiapoptotic effect of apelin-36 is induced by PI3K/Akt pathway [4].

Apelin-13 treatment significantly reduced the levels of neutrophil infiltration in the ischemic penumbra and the levels of the pro-inflammatory mediators IL-1β, TNF-α, and ICAM-1. Moreover, it can also lower the number of cells activated in the penumbral region, thus, inducing a neuroprotective effect by blocking or suppressing neuroinflammation [2][5]. Intranasal administration of Apelin-13 effectively reduced the number of apoptotic cells and of activated microglial cells, increasing the expression of antiapoptotic factors (Bcl-2). It could also reduce the pro-inflammatory cytokines and chemokines TNF-a, IL-1b, MIP-1a, and MCP-1 and increase the anti-inflammatory cytokine IL-10. Angiogenesis in the peri-infarct region can be explained by the enhanced activity of pro-angiogenic factors VEGF and MMP9, which were also elevated after treatment with apelin-13. Because of the enhanced angiogenesis after treatment, better recovery was reported compared to non-treated animals [6]. Upon treatment with apelin, an upregulation of the expression of VEGF and VEGF-2 can be observed. This elevation is associated with the protective effects of apelin, mediated by ERK and PI3K/Akt pathways, which can be blocked by intraventricular injection with an anti-VEGF antibody [5].

Following cerebral ischemia in primates, *APLNR* and *Apelin mRNA* was strongly induced in monkey SVZa and caudate nucleus [7].

2. Apelinergic System Involvement in Epilepsy

Neurons in the mammalian neocortex are either excitatory, glutamatergic projecting neurons or inhibitory, GABAergic interneurons that branch in the local circuits. A disbalance in the excitation levels leads to pathological hyperexcitability manifested by spontaneous and recurrent seizures [8][9].

Extended epileptic periods and poorly managed or drug-resistant epilepsy can cause neuronal loss either by apoptosis or necrosis. The observed overexpression of Apelin in patients with drug-resistant temporal lobe epilepsy and rats with lithium–pilocarpine-induced epilepsy may be a compensatory mechanism [10]. Apelin can salvage the hippocampal

neurons from the effects of excitotoxicity by downregulating metabotropic Glutamate Receptor-1 (mGluR1), increasing phosphorylation of Akt, and upregulating Bcl2, thus, reducing caspase-3 activation [11]. Treatment with brain-specific micro-RNA-182 (miR-182) that blocks Apelin leads to increased apoptosis in epilepsy models. Blocking miR-182 can increase the effects on Apelin, lower pro-apoptotic proteins (Bax; caspase-3), and increase the antiapoptotic ones (Bcl-2) [11].

Treatment with apelin-13 in an experimental rat epilepsy model prevented the induction of seizures and neuronal loss. This effect is lost when F13A, an APLNR receptor antagonist, is applied [12]. Apelin can exert a level of neuroprotection in the PTZ model of epilepsy thanks to its ability to maintain mitochondrial potentials, reduce intracellular Ca^{2+}, and inhibit ROS generation and COX2 (Cyclooxygenase 2) [13].

3. Apelinergic System Involvement in Neurogenesis and Glioblastoma Multiforme

Glioblastomas are brain tumors showing high invasiveness, angiogenesis, and an unusual tumor environment. There is substantial evidence showing that Glioblastoma multiforme is derived from SVZa stem cells [14].

Apelin is secreted from the endothelial cell near Glioblastoma stem-like cells (GSCs). It mediates self-renewal, but it is not associated with proliferation. Apelin protein expression is also correlated with the levels of vascularization of GBM [15].

Silencing the apelin Signalling pathway either by knocking down or blocking the APLNR reduces tumor volume, vascularization, and proliferation [16]. GSC are in a quiescent state maintained by the vascular niche in the tumor, which is the main reason for the inefficiency of chemotherapies [17]. Interestingly, applying an antagonist of APLNR in combination with chemotherapies improves the response and decreases the GSC numbers. This effect is possibly mediated by activation of GSK3β (Glycogen synthase kinase-3 pathway) [15][16][18]. Nuclear GSK3β phosphorylates KDM1A at s683, which can interact with USP22, thus, increasing the stability of KDM1A. KDM1A is responsible for the demethylation of histone H3K4 leading to the downregulation of genes (*BMP2*, *CDKN1A*, and *GATA6*) associated with stem cell self-renewal [19].

ELABELA was also shown to be expressed in GSCs. Moreover, brain tumor datasets have shown that expression levels of ELABELA are linked to tumor grading and patient survival [20].

Current therapies relying on anti-VEGF mAb usually target tumor angiogenesis. Unfortunately, such therapies have not increased patient survival [21]. These treatments have been shown to decrease the apelin expression inside the tumor, thus, increasing its invasiveness [22]. Interestingly, using a partial agonist for APLNR (apelin-F13A) combined with anti-VEGF therapy lessens the invasiveness and angiogenesis properties of GBM [22][23].

4. Apelinergic System Involvement in Alzheimer's Disease (AD)

Alzheimer's disease is a progressive neurodegenerative disorder characterized by the deposition of intracellular senile plaques composed of insoluble neurofibrillary tangles and extracellular amyloid β (Aβ) peptides. Neuronal loss in the hippocampus and neocortex leads to memory loss and cognitive impairments [24][25].

In newly discovered AD patients, the levels of Apelin-13 were lower compared to healthy individuals [26].

Apelin-13 can reduce memory deficits in a mouse model of Alzheimer's disease. [27][28] Aβ deposition in neurons induces apoptosis and autophagy, which can be attenuated by Apelin-13 treatment. The molecular basis of these neuroprotective effects in AD models is: (i). Decreased autophagy pathway (e.g., LC3II/I), (ii). Increase of autophagic clearance (HDAC6), (iii). Decreased apoptosis (caspase-3), and (iv). Increasing survival of neurons through the mTOR pathway [27].

Neuroinflammation plays a critical role in the pathophysiology of Alzheimer's disease. Important components of the neuroinflammation response, including microglial and astroglial activation and pro-inflammatory cytokine (e.g., IL-1β and TNF-α) production are attenuated from Apelin-13 [28].

Apelin can also increase the expression of hippocampal neurotrophins/neurotrophin receptors, such as Brain-Derived Neurotrophic Factor (BDNF) and Tropomyosin receptor kinase B (TrkB), which are typically at low levels in Alzheimer's mouse models. Blocking the TrkB receptor with an apelin antagonist, K252a, blocked the apelin-13 effects, showing that the beneficial effects of apelin in the hippocampus are mediated by activation of the BDNF/TrkB Signaling pathway. Synaptophysin (SYP) generally used for evaluating synaptic transmission plasticity is downregulated in AD and restores

its normal levels upon reapplication of apelin-13 [28]. Tissue necrosis is also initiated in AD by activation of the proteins RIP1 and RIP3, controlled by TNF-α. Reduction of RIP1, RIP3, and TNF-α is observed when apelin is applied [29]. Wan et al. have provided an in-depth review of the role of apelin in AD and its mechanism of neuroprotection [30].

5. Apelinergic System Involvement in Parkinson's Disease (PD)

Parkinson's disease (PD) is a neurodegenerative disorder affecting the dopaminergic neurons in the substantia nigra. It manifests with motor dysfunctions, including muscle rigidity, tremor, slow movement, and cognitive impairments, including depression, anxiety, and in later stages, dementia. The main histological hallmark of the disease is the aggregation of a misfolded protein called α-synuclein, which accumulates and becomes cytotoxic [31][32]. Additionally, factors such as mitochondrial dysfunction, inflammation, oxidative stress, and synaptic dysfunction can play a crucial role in the pathophysiology of the disease. To show the role of apelin-13, Pouresmaeili-Babaki et al. used SH-SY5Y cells treated with 6-hydroxydopamine (6-OHDA), which is a widely used cell model for PD. Upon treatment with 6-OHDA, dopaminergic cell death can be observed. Application of Apelin-13 is capable of inhibiting cytochrome-3 release and activation of caspase-3, effects through activation of APLNR/PI3K/Akt Signalling pathway [33]. The same group was able to show also that Apelin can improve memory and cognitive deficits in a Parkinson's disease model treated with 6-hydroxydopamine (6-OHDA) [34].

Another study, utilizing the same SH-SY5Y cell line but induced cell damage by applications of 1-methyl-4-phenyl-pyridine (MPP+) showed that apelin-13 could attenuate the neurotoxicity and the Endoplasmic Reticulum Stress (ER stress), the level of GRP78, CHOP and cleaved caspase-12 and significantly increase the levels of phosphorylated ERK1/2, thus, preventing the apoptosis [35]. Similarly, another study using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP) to induce Parkinson-like damage has shown that apelin-13 significantly increases autophagy by upregulation of LC3B and Beclin1 and down-regulation of p62. Apelin-13 was also capable of inhibiting the effect of the GRP78/ IRE1α/XBP1s/CHOP pathway associated with ER stress [36].

The neuroprotective effect of apelin was also shown in the methamphetamine PC12 cell model. Applying methamphetamine increased the generation of ROS, autophagy, and apoptosis, which were reduced by apelin [37]. Furthermore, some evidence suggests that it can also alleviate motor deficits [36] and prevent pathological alterations to the synaptic elements in the striatum and substantia nigra [38].

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