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News and reviews

Apelin, a promising target for Alzheimer disease prevention and treatment

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease with high outbreak rates. It is estimated that about 35 million individuals around the world suffered from dementia in 2010. AD is expected to increase twofold every 20 years and, by 2030, approximately 65 million people could suffer from this illness. AD is determined clinically by a cognitive impairment and pathologically by the production of amyloid beta (Aβ), neurofibrillary tangles, toxic free radicals and inflammatory mediators in the brain. There is still no treatment to cure or even alter the progressive course of this disease; however, many new therapies are being investigated and are at various stages of clinical trials.

Neuropeptides are signaling molecules used by neurons to communicate with each other. One of the important neuropeptides is apelin, which can be isolated from bovine stomach. Apelin and its receptor APJ have been shown to broadly disseminate in the neurons and oligodendrocytes of the central nervous system. Apelin-13 is known to be the predominant neuropeptide in neuroprotection. It is involved in the processes of memory and learning as well as the prevention of neuronal damage. Studies have shown that apelin can directly or indirectly prevent the production of Aβ and reduce its amounts by increasing its degradation. Phosphorylation and accumulation of tau protein may also be inhibited by apelin. Apelin is considered as an anti-inflammatory agent by preventing the production of inflammatory mediators such as interleukin-1β and tumor necrosis factor alpha. It has been shown that in vivo and in vitro anti-apoptotic effects of apelin have prevented the death of neurons.

In this review, we describe the various functions of apelin associated with AD and present an integrated overview of recent findings that, in general, recommend apelin as a promising therapeutic agent in the treatment of this ailment.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, and it is considered the most prevalent form of dementia in the elderly. Pathologically, it is characterized by intracellular neurofibrillary tangles (NFTs) and extracellular amyloid beta (Aβ) protein deposits that contribute to senile plaques (Selkoe, 1991). The mutation in the amyloid precursor protein (APP), *presenilin (PS)* 1 and 2 genes

Abbreviations: AAA, Abdominal aortic aneurysm; ABCA1, ATP-binding cassette transporter A1; ACE, Angiotensin converting enzyme; ACh, Acetylcholine; AChE, Acetyl choline esterase; AD, Alzheimer's disease; ApoE, Apo lipoprotein E; AMPK, AMP-activated protein kinase; APP, Amyloid precursor protein; AT1R, Angiotensin II type 1 receptors; AVP, arginine vasopressin; Aβ, Amyloid beta; BACE1, β-site APP-cleaving enzyme 1/β-secretase; BBB, blood-brain barrier; CAT, Catalase; cGMP, Guanosine monophosphate; CNS, Central nervous system; eNO, Endothelial nitric oxide; eNOS, Endothelial nitric oxide synthase; ERK, Extracellular signal-regulated kinase; FDA, Food and Drug Administration; GLP-1, Glucagon-like peptide-1; GSH-Px, Glutathione peroxidase; GSK, Glycogen synthase kinase; H_2O_2, Hydrogen peroxide; I/R, Ischemia/reperfusion; ICAM-I, Intercellular adhesion molecule I; IFN, Interferon; IL, Interleukin; ICV, intracerebroventricular; IP_3, Inositol triphosphate; JNK, c-Jun N-terminal kinase; LRP-1, Low-density lipoprotein receptor related protein-1; MAPK, Mitogen-activated protein kinase; MEK, Mitogen activated protein kinase kinase; MCP-1, Monocyte chemoattractant protein-1; MIP-1α, Macrophage inflammatory protein-1α; MPO, Myeloperoxidase; NEP, Neprilysin; NFT, Neurofibrillary tangles; NMDAR, *N*-methyl D-aspartate receptor; OxS, Oxidative stress; PI3K, phosphatidylinositide 3-kinases; PKB/AKT, Protein kinase B; PKC, Protein kinase C; PLA2, Phospholipase A2; PS, Presenilin; PTZ, Pentylenetetrazole; QUIN, Quinolinic acid; RAGE, Receptor for advanced glycation end products; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; SD, Serum deprivation; SOD, Superoxide dismutase; TGF, Transforming growth factor; TNF-α, Tumor necrosis factor alpha

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causes high levels of Aβ production, thus resulting in the early onset of AD. Moreover, the ε4allele of Apo lipoprotein E (ApoE) is associated with an increased risk of late-onset AD (St George-Hyslop, 2000; Takeda et al., 2004). Other important factors involved in the pathogenesis of AD include neurotransmitter dysfunctions such as acetylcholine (Coyle et al., 1983), *N*-methyl D-aspartate receptor (NMDAR)-mediated excitotoxicity (Hynd et al., 2004), oxidative damage (Lin and Beal, 2006), and inflammation from cytokines and chemokines (Akiyama et al., 2000).

Apelin is a neuropeptide isolated from bovine stomach extracts and is used by neurons to communicate with each other. It is an endogenous ligand for the APJ receptor (Tatemoto et al., 1998). The apelin/APJ system has several important functions in the body, such as blood pressure regulation, cardiac contractility, immunity, glucose metabolism, water homeostasis, cell proliferation, angiogenesis, and neuroprotection (Wu et al., 2017). A study has been shown that serum levels of apelin-13 decreased in AD patients (EREN et al., 2012). In rats with cerebral ischemia/reperfusion (I/R) injury, treatment by apelin-13 significantly decreased neurological deficits and the infarct volume (Xin et al., 2015). In cerebral ischemia mice model, apelin-13 injection significantly protected blood-brain barrier (BBB) from injury through decreasing BBB permeability, elevated vascular endothelial growth factor, upregulated endothelial nitric oxide synthase (eNOS), and downregulated inducible NOS (Chu et al., 2017a). In $SOD1^{G93A}$ mouse model of amyotrophic lateral sclerosis, it has been indicated that apelin deficiency caused decreasing the number of motor neurons and earlier appearance of disease phenotypes and also, accelerated the progression of disease via microglia activation in spinal cord (Kasai et al., 2011). In mice with glioblastoma, an aggressive brain tumor, APJ antagonist, MM54,treatment caused significantly decrease in tumor growth and disrupted the expansion of tumor associated neurological symptoms (Harford-Wright et al., 2017). It is reported that intracerebroventricular (ICV) injection of apelin-13 in traumatic brain injury mice model resulted in reducing of brain damage via autophagy suppressing (Bao et al., 2015). In stressed rats it has been shown that apelin-13 injection accelerated antidepressant-like and recognition memory improving activities via activating phosphatidyl inositol 3-kinases (PI3K) and extracellular signal-regulated kinase1/2 (ERK1/2) signaling pathways. It has been revealed that the hippocampus is a Critical Site of apelin antidepressant-like activity (Li et al., 2016; Xiao et al., 2018). In Parkinsonism rats, apelin-13 injection into the substantia nigra significantly reduced cognitive impairments (Haghparast et al., 2018). In this review, we examine the various factors and mechanisms mediated by apelin that may contribute to the prevention and treatment of AD.

2. Apelin

The APJ receptor ligand apelin firstly in 1998 was segregated from bovine stomach tissue. Human preproapelin gene located on chromosome Xq25–26.1. The apelin preproproteins consist of 77 amino acid residues that are cleaved into biologically active C-terminal fragments of various sizes. The apelin peptides, including 13 (65–77), 17 (61–77), and 36 (42–77) amino acids (Fig. 1), are all capable of binding to APJ (Lee et al., 2000a; Tatemoto et al., 1998). Among apelin isoforms, apelin-13 has the highest plasma concentration and plays the most

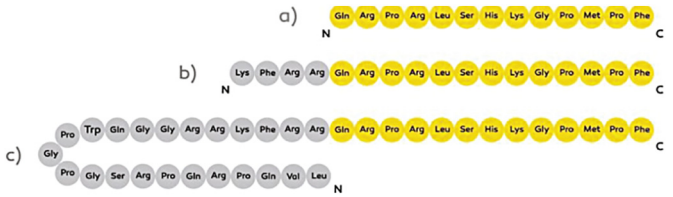

Fig. 1. Amino acid sequences of various biologically active forms of apelin. a) apelin13 (65–77), b) apelin17 (61–77), c) apelin36 (42–77).

significant role in neuroprotection (Cheng et al., 2012; Zhen et al., 2013). In humans, apelin mRNA are expressed in various parts of the central nervous system such as the hippocampus, thalamus, hypothalamus, the basal forebrain, frontal cortex, corpus callosum, amygdala, substantia nigra, pituitary, and the spinal cord, as well as in peripheral organs such as placenta, kidney, heart, lung, and mammary gland (Kleinz and Davenport, 2005). Early on, apelin was recognized as an effective factor in lowering blood pressure by increasing endothelial nitric oxide (eNO) (Tatemoto et al., 2001b). APJ receptor identified as a coreceptor for human immunodeficiency virus type 1. It has been demonstrated that apelin by binding to APJ can block virus entry into the cells expressing APJ (Cayabyab et al., 2000). Experimental studies indicated that apelin led to protection against heart I/R injury in rats (Zeng et al., 2009), reducing in left ventricular preload and afterload and improving of cardiac contractility in C57/Bl/6 mice (Ashley et al., 2005), and reducing of the infarct size and normalization of the impaired cardiac function in C57BL/6 J mice with myocardial infarction (Xu et al., 2017). In patients along with chronic heart failure, apelin treatment caused peripheral and coronary vasodilatation and augmented cardiac output (Japp et al., 2010). Also it has been shown that apelin-13 plays an important role in improvment of post myocardial infarction repair through myocardial progenitor cells elevation in the infarcted hearts (Li et al., 2012). It has been shown that apelin-13 administration in patients with type 2 diabetes improves insulin sensitivity (Gourdy et al., 2017). Intravenous injection of apelin in mice potentially lowered blood glucose through elevating of glucose utilization in skeletal muscle and adipose tissue, and on the other hand, in high fat diet C57Bl6/J mice with hyperinsulinemia, hyperglycemia and obesity, apelin injection restored glucose tolerance and increased glucose utilization in peripheral tissues (Dray et al., 2008). In obes mice, apelin injection decreased body weight, adiposity, and blood triglycerides and fatty acids (Castan-Laurell et al., 2011). In rats with renal I/R injury, Apelin-13 treatment blocked increasing of inflammatory mediators and transforming growth factor (TGF)-β1, as well as apoptosis and subsequently, normalized the injury induced renal dysfunction (Chen et al., 2015b). Apelin plays a key role in inducing angiogenesis in phatological conditions including myocardial infarction, ischemic stroke, critical limb ischemia, tumor, cirrhosis, obesity, diabetes and other related diseases (Wu et al., 2017). Apelin expression increased in variety of cancers and indicated that plays a role in the progression of various cancers including lung cancer, gastroesophageal cancer, colonic cancer, hepatocellular carcinoma, prostate cancer, endometrial cancer, oral squamous cell carcinoma and brain cancer (Yang et al., 2016a).

Different functions of apelin in the CNS have been documented in various studies. ICV administration of apelin-13 in rats caused significantly increasing in drinking behavior and water intake and also elevated plasma levels of adrenocorticotropic hormone (ACTH) and corticosterone and decreased plasma levels of prolactin, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Taheri et al., 2002). It has been revealed that apelin has a diuretic activity and play an crucial role in body fluid homeostasis control by regulation of arginine vasopressin (AVP) neurons activity and AVP release (De Mota et al., 2004). ICV administration of apelin in lactating rats inhibited the activity of magnocellular and parvocellular oxytocin neurons and subsequently, reduced the amount of milk ejected (Bodineau et al., 2011). It has been reported that apelin-13 with dopamine, NO and prostaglandins cooperation, involved in the regulation of behavioral, endocrine and homeostatic responses in the CNS (Jaszberenyi et al., 2004).

3. The pathogenesis of AD and the targets of apelin

3.1. Apelin/endothelial nitric oxide and AD

The absence of eNO in the brain increases the amount of APP and β-