Am J Transl Res 2022;14(10):7260-7267
www.ajtr.org /ISSN:1943-8141/AJTR0146063

*Review Article*

# Research progress of apelin in acute ischemic brain injury

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Received August 21, 2022; Accepted October 12, 2022; Epub October 15, 2022; Published October 30, 2022

**Abstract:** Acute ischemic brain injury is a cerebrovascular disease with high clinical incidence. An increasing number of preclinical evidence has verified the complex interaction between autophagy disorder and mitochondrial damage. Endoplasmic reticulum stress, oxidative stress and excessive neuroinflammation are the main mechanisms of the neural injury induced by acute cerebral ischemia-reperfusion injury. Apelin and its receptors are widely distributed in various tissues and organs in the human body. Increasing evidence has suggested that apelin has a neuroprotective effect against excitatory toxicity injury, oxidative stress injury and induction of neuronal apoptosis, and it can play a neuroprotective role after acute cerebral ischemia-reperfusion injury. This review summarizes the progress of the neuroprotective effects and mechanisms of apelin, aiming to provide evidence for its therapeutic potential.

**Keywords:** Acute ischemic brain injury, apelin, apelin/APJ signaling pathway, neuroprotection, research progress

## Background

Cerebrovascular disease (CVD) refers to cerebral ischemic or hemorrhagic injury caused by thrombosis or cerebral vascular rupture, respectively. Acute ischemic brain injury is a common type of CVD seen in clinic, it is characterized by high morbidity, high disability, high mortality and high recurrence rate [1]. The mechanism of nerve damage induced by acute cerebral ischemia reperfusion is generally considered to be related to apoptosis, calcium ion overload, imbalance of oxidation and antioxidant capacity, excitatory amino acids toxicity and cellular inflammation [2]. In the process of ischemia, the body also activates endogenous protection mechanisms, and repairs the damaged brain regions by changing the expressions of various growth factors, DNA repair factors and anti-apoptotic proteins in the early stage of reperfusion [3]. In recent years, a lot of research has reported the biochemical markers of acute brain injury. Apelin has been reported to have a wide range of biological activity, which is closely related to the pathological mechanism of brain injury [4, 5].

Apelin is a metaprotein with 55 amino acids, which is formed by cutting the protoprotein with 77 amino acids at the N-terminal via a signaling peptide in the endoplasmic reticulum. Its gene is located on human chromosome xq25-26.1 [6]. Reverse transcription-polymerase chain reaction screening experiments have confirmed that apelin is distributed in the central nervous system, lung, kidney, heart, breast, placenta, vascular endothelial cells and endocardial cells in rat tissues [7]. Apelin is also widely expressed in human tissues, such as heart, lung, fat, pancreatic islets and other peripheral tissues. Studies have found that apelin can help to resist excitatory toxicity and oxidative stress and damage caused to nerve cells, and inhibit the apoptosis of nerve cells, thus paying a neuroprotective role in CVD, which makes it a promising novel target for the treatment of acute ischemic brain injury [8, 9]. With the increasing incidence of acute ischemic brain injury, the value of apelin in ischemic brain injury has become a hot topic in clinical research [10, 11].

## Mechanism analysis of nerve injury in acute ischemic brain injury

Nerve damage caused by acute cerebral ischemia is a complex pathophysiological process. In recent years, studies have found that injury

caused by the interruption of cerebral blood flow and reperfusion occurs via a rapid cascade reaction. The toxic effects of excitatory amino acids, free radical attack, intracellular $Ca^{2+}$ overload, oxidative stress response and inflammatory reactions determine the degree of injury and prognosis of the patients [12].

*Toxic effects of excitatory amino acids*

Glutamic acid (Glu) and other excitatory amino acids in the central nervous system play an important role in maintaining the normal signal transmission of neurons, but when its level is abnormally increased in the body, it also plays a significant excitatory toxicity role. After cerebral hypoxia-ischemia, nerve cells release a large amount of Glu. Moreover, the Glu uptake function can improve the extracellular Glu level significantly, resulting in phosphocreatine hydrolysis and increased triglycerides. The increased triglycerides can change protein kinase activity, elevate the sensitivity of cells to excitatory amino acids and other excitatory stimuli, and increase the intracellular $Ca^{2+}$ concentration, triggering the release of excitatory amino acids from nerve endings [13]. The above reactions repeatedly circulate in the body, inducing and aggravating nerve cell injury.

*Free radical attack*

Free radical-induced lipid peroxidation is one of the important mechanisms of acute cerebral ischemia-reperfusion injury. Its main pathways include: ① energy synthesis disorder and neuronal apoptosis caused by damaged mitochondrial membranes; ② destruction of the integrity of the cell structure by damage to the cell membrane; ③ massive release of lysosomes and hydrolyzed intracellular materials by damage to the lysosomal membrane [14-16]. In addition, when acute ischemic brain injury occurs, the free radical defense system is also damaged, and the activity of free radical scavengers such as superoxide dismutase (SOD) is reduced, resulting in reduced free radical scavenging rates. This series of reactions in turn exacerbates the damage caused by free radicals during ischemia, further aggravating cerebral perfusion damage and nerve damage [17].

*Intracellular $Ca^{2+}$ overload*

After acute cerebral ischemia, the failure of dependent ion pumps leads to the opening of voltage-dependent calcium channels and an increase of the permeability of cell membrane to $Ca^{2+}$, which causes the occurrence of intracellular $Ca^{2+}$ overload. Intracellular $Ca^{2+}$ overload can activate membrane phospholipase A to decompose membrane phospholipids. Besides, arachidonic acid, a product of membrane phospholipid degradation, can intensify smooth muscle contraction and platelet aggregation, thus aggravating brain injury [18]. At the same time, intracellular $Ca^{2+}$ overload can activate a variety of enzymes to affect the function of mitochondria, and produce a large number of free radicals and nitric oxide, which can aggravate cell acidosis and cause acute or delayed cell death.

*Oxidative stress response*

Oxidative stress is a cytotoxic reaction caused by the accumulation of reactive oxygen species in the body or cells due to serious imbalance between the production of intracellular free radicals and antioxidant defense. Reperfusion injury caused by cerebral ischemia can lead to a large number of free radicals in the tissue, which in turn induces oxidative stress. Oxidative stress induces the expression of apoptotic genes in cells, causing apoptosis of nerve cells, and inducing a post-ischemic chain reaction of brain tissue, thereby aggravating brain tissue damage [19].

*Inflammatory reaction*

The earliest response after acute ischemic brain injury is the release of inflammatory cytokines and the accumulation of leukocytes in the ischemic area, and it is also one of the key mechanisms of reperfusion injury. Among them, inflammatory cytokines include interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), platelets and activation factor (PAF), etc. These inflammatory cytokines can induce or promote ischemic brain injury by inducing or enhancing the expression of adhesion molecule G chemokines. Besides, the activation of PAF makes cells more prone to aggregation and agglutination, which can cause microvascular circulation disorders and even “no-reflow” phenomenon after reperfusion, thus inducing and aggravating brain injury [20]. Furthermore, many catabolic enzymes released by leukocytes entering brain tissue through endothelial cells can also damage brain tissue.

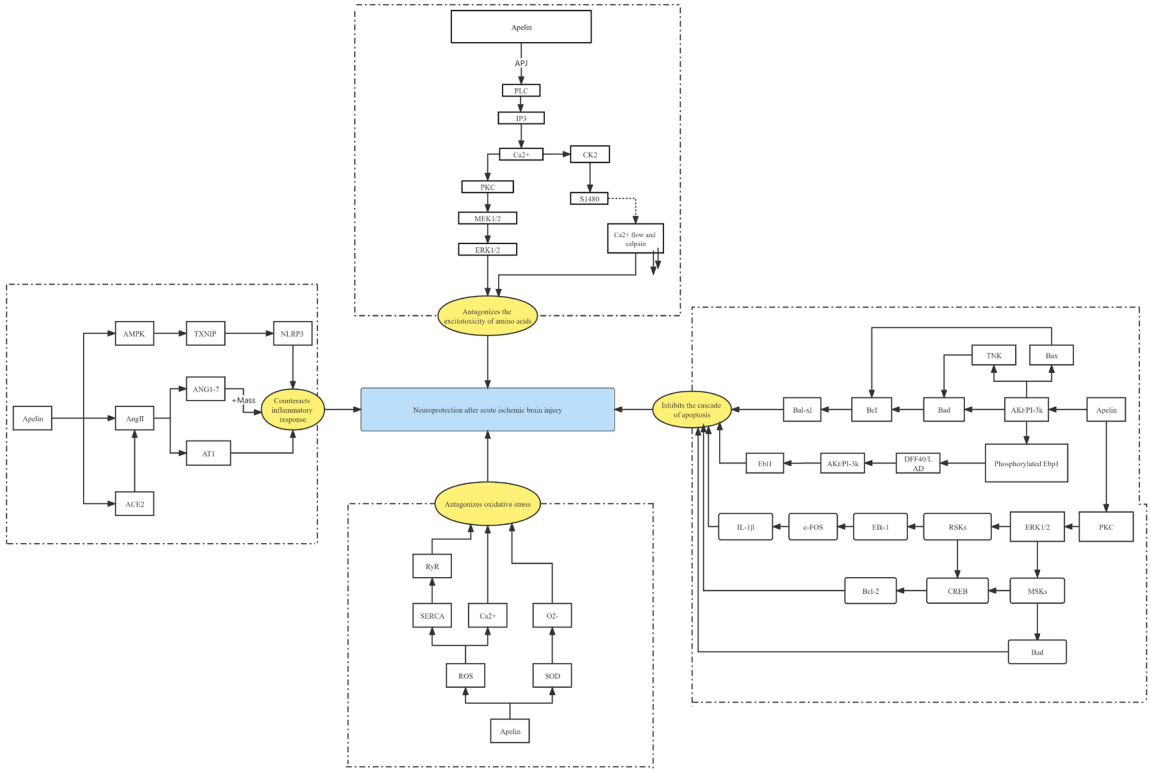


**Figure 1.** Mechanisms of neuroprotective effect of apelin.

## The neuroprotective effect of apelin after acute ischemic brain injury

A large number of studies have confirmed that apelin has a neuroprotective effect after acute ischemic brain injury. In the study of severe craniocerebral injury by Zhuang et al, it was found that apelin was independently related to the short-term mortality of patients with severe craniocerebral injury, and the main mechanism was that apelin could inhibit the autophagy of nerve cells, thus reducing the brain injury caused by trauma [21]. Liu et al. confirmed that apelin could reduce early brain injury after subarachnoid hemorrhage by inhibiting neuron apoptosis, and this effect might occur partly through activating the GLP-1R/PI3K/Akt signaling pathway [22]. In a study on the treatment of ischemic stroke, it was found that intraventricular injection of apelin significantly reduced the volume of cerebral infarction and cerebral edema, and inhibited apoptosis [23]. Caspase is closely related to apoptosis. In the caspase family, caspase-12 and caspase-3 are recognized as apoptosis factors related to inflammation and effector factors related to apoptosis. Zhu et al. showed that apelin could attenuate endoplasmic reticulum stress by inhibiting the expression of cleaved caspase-12 in MPTP/MPP+ treated mice and cells [24]. Li et al. found that apelin could promote apoptosis by inhibiting caspase-3 [25]. In addition, another experiment found that apelin could significantly down-regulate the expression of caspase-12 mRNA after acute ischemic brain injury [26]. These findings indicate that the brain can indeed block neuronal apoptosis caused by brain injury and reduce the inflammatory effect after acute ischemic brain injury by inhibiting the expression of caspase-12 via ultra-early apelin intervention.

## Mechanism of neuroprotective effect of apelin

Apelin can be used as a neuroprotective factor to protect neurons against multiple injuries through a variety of cellular and molecular mechanisms. The currently known neuroprotective mechanisms of apelin include resistance to amino acid excitotoxicity, inhibition of the apoptotic cascade, and responses to antioxidant stress and inflammation. See **Figure 1** for details.

*Apelin antagonizes the excitotoxicity of amino acids*

Excessive excitatory amino acids have neurotoxic effects on the nervous system, i.e., excitatory toxicity. Excitatory toxicity of amino acids can cause neuronal damage. The toxicity of excitatory amino acids is mainly mediated by N-methyl D-aspartate (NMDA) receptor in nerve cells [27]. After activating NMDA receptors, glutamate activates $Ca^{2+}$ channels, which promotes a large amount of $Ca^{2+}$ inflow and leads to intracellular $Ca^{2+}$ overload in the early stage of ischemia (main mechanism of excitatory toxicity damage in neurons). In this process, apelin can play a role in resisting excitatory toxicity damage by weakening $Ca^{2+}$ signal transduction, thus protecting nerve cells. In in the HIV model system of Franke et al. [28], the N-methyl D-aspartate receptor subtype 2B (NR2B) of the NMDA receptor was the main regulator of excitotoxicity, and the 1480 serine phosphorylation of NR2B regulated the sensitivity to excitotoxicity. Apelin can regulate the amino acid phosphorylation of NR2B and reduce calpain activation by activating inositol trisphosphate, protein kinase C (PKC), mitogen-activated protein kinase 1/2 and extracellular regulated protein kinase 1/2 (ERK1/2), thus protecting cerebral cortical neurons from glutamate or HIV-induced excitotoxic injury.

*Apelin inhibits the cascade of apoptosis*

Recent studies [29] have shown that apelin can accelerate the activation of Akt protein after brain injury, and participate in the inhibition of apoptosis through its phosphorylation. In addition, after apelin binds to the apelin receptor (APJ), it may be connected with the ras/RAF/me/ERK cell signal transduction pathway through PKC, and thus play its anti-apoptosis role [30]. To investigate the effects of apelin on apoptosis and autophagy in a model of cerebral ischemia/reperfusion injury, Zhou et al. [32] established a middle cerebral artery occlusion model in rats. Their results showed that up-regulation of Bcl-2, the inhibition of apoptosis and excessive autophagy caused by the activation of the mTOR signaling pathway were related to the neuroprotection induced by apelin-13, whether *in vivo* or *in vitro*. Letra et al. [33] also confirmed that apelin-13 could reduce neuronal apoptosis by increasing the ratio of Bcl-2/Bax and significantly reducing the expression of cleaved caspase-3. It can be concluded that apelin can antagonize the apoptosis of cells thus play a role preventing nerve injury after brain injury. In addition, apelin can scavenge oxygen free radicals to reduce cell death, and it may also change the permeability and membrane potential of the mitochondrial membrane by changing MPTP state, thus blocking the apoptosis pathway caused by endoplasmic reticulum stress [34].

*Apelin antagonizes oxidative stress*

Malondialdehyde (MDA) is one of the fatty acid decomposition products after lipid oxidation in tissues. Results from an experiment in mice found that apelin reduced the concentration of MDA in the body, and the ultra-early intervention of apelin significantly increased the activity of glutathione peroxidase in nerve tissue, thereby protecting nerve cells from oxidative stress [35]. In addition, the research by Shao et al. [36] showed that apelin could inhibit oxidative stress by down-regulating the levels of reactive oxygen species, MDA as well as inducible nitric oxide synthase, which further confirmed the antioxidant capacity of apelin.

*Apelin counteracts the inflammatory response*

The results of Yu et al. [37] showed that apelin had a positive correlation with inflammation in obese patients with type 2 diabetes. In the occurrence and development of brain injury and nerve injury, the inflammatory response also plays an important role. Xu et al. [38] found that the serum level of apelin in diabetic patients with peripheral neuropathy was higher than that in diabetic patients without peripheral neuropathy, which indicated that apelin was closely related to cranial nerve injury caused by neuroinflammation. Apelin's anti-inflammatory response involves multiple mechanisms. Shen et al. [39] confirmed that apelin-13 could reduce early brain injury by inhibiting inflammation and apoptosis after subarachnoid hemorrhage in rats through constructing a subarachnoid hemorrhage rat model. Mohseni et al. [40] showed that apelin-13 combined with APJ could reduce early brain injury caused by neuroinflammation mediated by the AMPK/TXNIP/NLRP3 signaling pathway. Apelin can inhibit the extracellular signal-regulated kinase (ERK) antagonist U0126 and the phosphatidylinositol 3-kinase inhibitor LY294002. Therefore,

its neuroprotective effect may be related to the activation of ERK and PI3K/Akt pathway. In addition, apelin can improve neurological deficit by reducing the expression of IL-1β, TNF-α, ICAM-1 and other inflammatory factors.

### The relationship between apelin and prognosis of acute ischemic brain injury

Many studies have reported the relationship between apelin and prognosis of patients with acute ischemic brain injury. Wang et al. [41] believed that there was an association between apelin-13 and death or severe disability in patients with acute ischemic brain injury. After one-year follow-up, they found that patients with high apelin-13 levels had low incidence of stroke and complex events, which indicated that serum apelin-13 might be a potential prognostic biomarker of acute ischemic brain injury. Sans-Roselló et al. [42] also found an association of apelin levels with markers related to the severity of ischemic heart failure. They additionally found that increased plasma apelin concentration in patients with ST-segment elevation myocardial infarction at admission was associated with an increased risk of death after 6 months, suggesting that early monitoring of apelin concentration had value in predicting patient outcomes. Bao et al. [43] established a rat model of cerebral hemorrhage and found that the neurological and motor function recovery of rats that received apelin intervention in the early stage after cerebral hemorrhage was significantly better than those of the rats without intervention. All these studies indicate that apelin has a neuroprotective effect and a significant correlation with the prognosis of patients with acute ischemic brain injury, so apelin may be able to serve as a potential therapeutic target.

### The development of drugs or interventions targeting apelin

Apelin is a peptide, and the blood-brain barrier prevents peptides from entering the central nervous system. Therefore, the limited bioavailability of apelin when administered orally also precludes its wide use as a drug. The current research direction is mainly devoted to prolonging the half-life of APJ agonists to enhance the binding ability. APJ agonists, Elabela/Toddler, apelin peptide analogs and small molecule substances are advantageous due to their metabolic stability and high pharmacological potency. Iturrioz et al. [44] have developed a neuropeptide APJ agonist with neural activity. This small molecule agonist can be used as a neuroprotective agent in the future for the treatment of a variety of nervous system diseases, including HIV-related cognitive diseases, ischemia, epilepsy and Alzheimer's disease, etc. Recently, through high-throughput screening, it has been found that the non-peptide small molecule APJ agonist E339-3D6 with a relative molecular mass of 1400 has a strong affinity for APJ, so it is considered to have a certain therapeutic potential [45]. Another small molecule APJ agonist ML233 with relative molecular mass of 359 has the characteristics of poor solubility, short half-life and high hepatotoxicity, so its clinical application is limited [46]. In addition, protamine and MM54 were also found to be antagonists of APJ.

### Conclusion

In summary, apelin plays a neuroprotective role by regulating the nervous system to protect against excitatory toxicity, neuronal apoptosis, oxidative stress and inflammatory response. Apelin plays a certain role in the occurrence, development and treatment of acute ischemic brain injury, and may become an important reference index for the diagnosis and treatment of acute ischemic brain injury. However, the specific mechanisms of the biological effects of apelin still need to be further studied. It is believed that with the deepening of further research, targeted therapy of apelin can become a promising strategy to improve the prognosis of patients with acute ischemic brain injury.

### Acknowledgements

This study was funded by grant 82100040 from National Natural Science Foundation of China, grants 2019JJ40329 and 2022JJ30640 from Hunan Natural Science Foundation, grants 18A494 and 19A054 from a project supported by Scientific Research Fund of Hunan Provincial Education Department, grant kq2004075 from Scientific Research Foundation of Changsha Science and Technology Bureau, grant kq1907035 from Changsha Municipal Natural Science Foundation, and grant 20201357 from the Foundation of Hunan Provincial Health Commission.

## Disclosure of conflict of interest

None.

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