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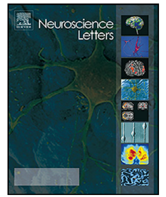

Research article

The neuroprotective effect of apelin-13 in a mouse model of intracerebral hemorrhage

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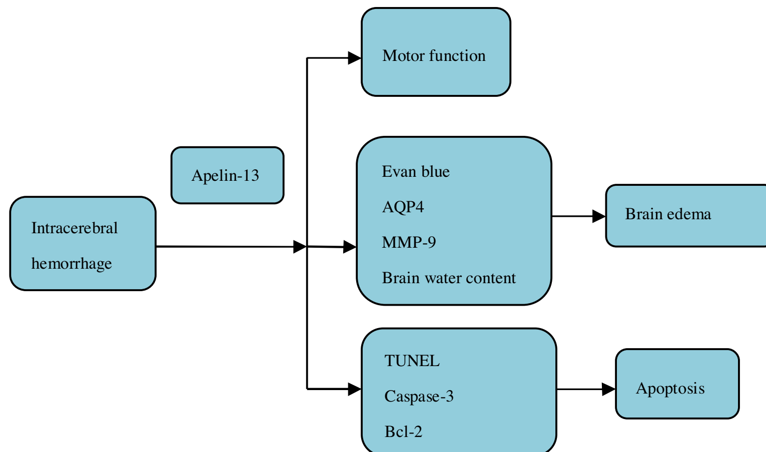
HIGHLIGHTS

- Apelin-13 significantly improved motor function after ICH.
- Apelin-13 can mitigate brain edema and inhibit apoptosis after ICH.
- Apelin-13 is a promising agent in the therapy for ICH.

GRAPHICAL ABSTRACT



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ABSTRACT

Adipocytokine apelin-13 is a peptide which could reportedly protect the brain against ischemic reperfusion injury and traumatic brain injury (TBI). Whether apelin-13 has any roles to play in intracerebral hemorrhage (ICH) has not been clarified. We aimed to investigate the roles of apelin-13 in ICH and effects on ICH-induced apoptosis. Firstly, CD-1 mice were subjected to infusion of Type IV collagenase (to induce ICH) or saline (for shams) into the left striatum. ICH animals received intracerebroventricular administration of vehicle, apelin-13 (50 μg dissolved in 5 μl saline) immediately after ICH. The motor function and the cerebral water content (CWC) as well as blood brain barrier (BBB) disruption were measured, coupled with determination of ICH-induced neural cell death by Terminal-deoxynucleoitidyl Transferase Mediated Nick End Labeling (TUNEL). The apoptosis-associated proteins caspase-3 and Bcl-2 as well as the brain edema-associated proteins aquaporin-4 (AQP4) and MMP-9 were all assessed with western blotting. The results showed that apelin-13 decreased CWC and reduced Evans blue leakage into

Abbreviations: ICH, intracerebral hemorrhage; BBB, Blood brain barrier; CWC, cerebral water content.

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injured hemispheres, with the motor function significantly improved. Additionally, apelin-13 also acutely decreased the number of ICH-induced TUNEL-positive ($TUNEL^+$) cells at 48 h after ICH. The expressions of AQP4, MMP-9, caspse-3 and Bcl-2 were all downregulated by apelin-13 at 24 h and 48 h after ICH. All these results revealed that apelin-13 attenuated brain edema and reduced cellular death by suppressing apoptosis after ICH in mice.

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1. Introduction

Nowadays, the mechanism of ICH injury has been a focus of attention. Previous studies have found that the clot-derived factors, physical trauma and ICH-induced mass effect can lead to brain edema, neuronal death and increase permeability of the BBB, triggering apoptosis and necrosis [10,26]. Brain edema is regarded as one of the most common lethal complications of ICH and causes changes in metabolite concentrations and alterations in cellular physiology, biochemistry and functionality of neuronal cells [24], all of which contribute to the detrimental functional outcomes [24].

Aquaporins (AQP) are a family of water channels, which permit selective bidirectional water movement in response to the osmotic gradient and are involved in intracranial edema [15]. AQP4, a predominant isoform in the brain, regulates fast water transport within the perivascular end feet of astrocytes [15].

Apelin is a peptide, which was originally isolated from a bovine stomach. It is also the endogenous ligand of the APJ receptor [22], which was firstly defined as analogous to AT1 angiotensin-I receptor [17]. There are several biologically active forms of apelin derived from a 77-amino acid prepropeptide precursor, such as apelin-13, apelin-17 and -36 [20,22]. However, apelin-13 displays much greater biological potency than apelin-36 [20,22]. Apelin-13 is a novel peptide identified as an important neuroprotective agent in the central nervous system [11,12]. The distribution pattern of apelinergic neurons in the CNS indicates diverse roles of apelin, such as controlling circadian rhythms, feeding behaviors, body fluid homeostasis or pituitary hormone release [9]. Moreover, apelin and APJ receptor are extensively expressed in neurons and oligodendrocytes but less in astrocytes [8]. APJ and apelin are highly expressed in the hypothalamo-neurohypophysial system, which regulates fluid homeostasis and controls the neuroendocrine response to stress. APJ and apelin in the forebrain and lower brainstem regions regulate cardiovascular functionality [16].

The potential benefits and neuroprotective effects of apelin-13 in the treatment of ischemia-reperfusion [1,27] have been identified: apelin-13 protects the brain against ischemic reperfusion injury and TBI [5,11] and significantly reduces TBI-induced cellular death by suppressing autophagy [5]. Apelin induces the expression of the junctional proteins claudin-5 and vascular endothelial cadherin in blood vessels, resulting in abundant cell-to-cell contact and the regulation of endothelial cell assembly [6,21]. Moreover, apelin attenuates ultraviolet radiation b (UVB)-induced edema and inflammation by promoting vascular functionalities [21].

Based on the above mentioned findings, we aimed to investigate whether apelin-13 could exert neuroprotection after ICH, and elucidate the role of apelin-13 in post-ICH brain edema and apoptosis.

2. Methods

2.1. Experimental protocol

All experimental procedures were in compliance with the NIH Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee, Xuzhou Medical College.

Mice were randomly assigned to Sham, Saline, Apelin-13 groups. Apelin-13 (Santa Cruz Biotechnology, sc-351718) was administered intracerebroventricularly (ICV; 50 μg dissolved in 5 μl saline) [3] immediately after ICH. Sham-operated mice, which did not undergo ICH injury, received the drug (Apelin-13) or vehicle (saline, 5 μl). Briefly, the ICV was performed at the left ventricular, according to the following stereotactic coordinates: 0.3 mm posterior and 1.0 mm lateral of the bregma, and 2.5 mm in depth. At the end of injection, the needle was maintained for 5 min to prevent reflux and slowly removed thereafter.

2.2. ICH model

The ICH procedures were conducted as previously described. Briefly, adult male CD-1 (20–25 g) mice were anesthetized under 4% chloral hydrate (0.4 mg/g) and were subjected to Type IV collagenase (0.075 U in 500 nl of saline) unilaterally into the left striatum at the following stereotactic coordinates: 1 mm anterior and 2.0 mm lateral of the bregma, 3.5 mm in depth. Collagenase was delivered over 5 min, with the needle in situ for an extra 5 min to prevent reflux. The open cranium was sealed with bone wax and the scalp sutured. Mice in the sham group only underwent sterile saline injection. The overall mortality rate was $<2\%$.

2.3. Assessment of motor functions

Motor tests were blindly performed and assessed for 6 days after ICH as previously described ($n = 15$ mice each) [3]. A six-point scoring system was employed, with 0 indicating animal inability on wire for 30 s, 1 indicating mouse on wire for 30 s, but not all paws on wire; 2 indicating mouse on wire with all paws except for the tail; 3 indicating mouse paws and tail on wire, but immobile; 4 indicating mouse motility with all paws plus tail on wire; 5 indicating mouse ambulation on one of the posts.

2.4. Measurements of cerebral water content

Briefly, mice were sacrificed by decapitation at 1 h, 6 h, 12 h, 24 h and 48 h after apelin-13 injection, respectively, followed by brain isolation and placement in a petri dish. The brain water content was measured with a drying method [24]. With the cerebellar tissue removed, the right and left hemispheres were isolated along the anatomic midline and the wet weight of each hemisphere measured. The tissues were completely dried in an oven at 100 °C for 5 days, with the dry weight of each hemisphere recorded. The percentage of water content (% water) was calculated according to the Elliott formula: % water = (wet weight − dry weight)/wet weight × 100.

2.5. Evaluation of blood–brain barrier permeability

2% solution of Evans Blue (Sigma-Aldrich Co. LLC, St. Louis, MO, USA) in normal saline (4 ml/kg of body weight) was injected into the caudal vein ($n = 6$ each). The dye was allowed to circulate

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