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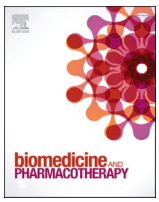

Review

α7nACh receptor, a promising target to reduce BBB damage by regulating inflammation and autophagy after ischemic stroke

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ABSTRACT

Increased blood-brain barrier (BBB) permeability can lead to cerebral vasogenic edema and hemorrhagic transformation (HT) after reperfusion with tissue plasminogen activator (tPA), the only United States Food and Drug Administration (FDA)-approved treatment for acute ischemia stroke (AIS). The therapeutic benefits of tPA after AIS are partially outweighed by a more than a six-fold increase in the risk of symptomatic intracerebral hemorrhage. Therefore, strategies to protect the integrity of BBB are urgently needed to reduce HT and vasogenic edema after tPA thrombolysis or endovascular thrombectomy. Interestingly, an NIH study showed that smokers treated with tPA had a significantly lower prevalence of brain hemorrhage than nonsmokers, suggesting that cigarette smoking may protect patients treated with tPA from the side effects of cerebral hemorrhage. Importantly, we recently showed that treatment with nicotine reduces AIS-induced BBB damage and that modulating α7nAChR by modulation could reduce ischemia/reperfusion-induced BBB damage, suggesting that α7nAChR could be a potential target to reduce BBB after AIS. In this review, we first provide an overview of stroke and the impact of α7nAChR activation on BBB damage. Next, we discuss the features and mechanism of BBB destruction after AIS. We then discuss the effect of nicotine effect on BBB integrity as well as the mechanism underlying those effects. Finally, we discuss the side effects and potential strategies for modulating α7nAChR to reduce AIS-induced BBB damage.

1. General introduction

A salvageable penumbra is the prerequisite for thrombolytic therapy after acute ischemic stroke (AIS) [1]. Recombinant tissue plasminogen activator (r-tPA) is the only FDA-approved drug for AIS treatment. It can significantly reduce the rate of disability and mortality in patients after AIS, however, a large number of studies have shown that tPA thrombolysis, while crucial for stroke treatment, can also cause damage to the blood-brain barrier (BBB), leading to vasogenic brain edema and intracerebral hemorrhage [2]. Therefore, the therapeutic benefits of tPA in AIS are partially affected by a significant upregulated risk of hemorrhagic transformation (HT) [2].

Interestingly, although cigarette smoking is a prominent risk factor that increases the risk of stroke by approximately 50 %, analysis of a landmark National Institutes of Health (NIH) r-tPA stroke trial has demonstrated that the prevalence of HT among tPA-treated smokers (4 %) was significantly lower than that among the non-smoking tPA-treated patients (13 %), indicating that cigarette smoking can protect

Abbreviations: ABCA1, ATP-Binding cassette transporter A-1; AIS, acute ischemic stroke; BBB, blood-brain barrier; BM, basement membrane; Cav-1, caveolin-1; CNS, central nervous system; DAMPs, danger-associated molecular patterns; ECM, extracellular matrix; ICAM-1, intercellular adhesion molecule 1; ICH, intracerebral hemorrhage; IL-1, interleukin-1; HMGB1, high mobility group box-1 protein; HT, hemorrhagic transformation; I/R, ischemia and reperfusion; MCAO, middle cerebral artery occlusion; MMP, matrix metalloproteinases; NAChR, nicotinic acetylcholine receptor; NF-κb, nuclear factor kappa B; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; Nrf2, nuclear factor erythroid-2-related factor 2; OGD, oxygen-glucose deprivation; ROS, reactive oxygen species; SAH, subarachnoid hemorrhage; TNF-α, tumor necrosis factor α; TJPs, tight junction proteins; TPA, tissue plasminogen activator; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VNS, vagus nerve stimulation.

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tPA-treated patients from HT [3,4]. Therefore, it seems paradoxical that cigarette smoking, the known risk factor for stroke, might trigger a signaling cascade to protect the BBB from damage, thereby decreasing HT potentially caused by tPA treatment following AIS

Recent research has revealed the modulatory role of the cholinergic anti-inflammatory pathway. This pathway functions by activating nicotinic acetylcholine receptors (nAChRs) in immune cells, leading to the inhibition of cytokine release [5]. Moreover, previous studies have shown that activation of nAChR can attenuate AIS-induced brain damage [6,7]. Furthermore, activation of the α7nAChR subtype is neuroprotective in various conditions, alleviating BBB damage caused by ischemia and reperfusion (I/R) [8–10], intracerebral hemorrhage (ICH) [11,12], and subarachnoid hemorrhage (SAH) [13]. Additionally, activation of nAChR has been shown to reduce BBB damage after experimental traumatic brain injury [14]. This review will explore and discuss the main findings of the protective effect of activating nAChR on ischemic stroke-induced BBB damage.

2. Physiologic structure and function of the BBB

The BBB, which consists of endothelial cells, pericytes, astrocytes, neurons, and the extracellular matrix is necessary for keeping homeostasis of the central nervous system (CNS) [15]. It can prevent the entry of certain substances (mostly harmful) from the bloodstream into the brain tissue and plays a key role in maintaining an optimal environment for the functioning and homeostasis of the central nervous system (CNS) [16,17].

2.1. Endothelial cell, tight junction protein, and transcytosis

Anatomically, the BBB endothelium is characterized by the lack of open windows, minimal cytosolic activity, and the presence of tight junction proteins (TJPs), which form a continuous and impermeable barrier to regulate the movement of solutes between endothelial cells. The degree of BBB integrity is determined by the degree of paracellular and transcellular transport[18]. TJPs between brain endothelial cells greatly limit paracellular transit [19].

Transcytosis increase is another way to increase permeability for endothelial cells (ECs)[20]. Under the physiological condition of the brain, ECs have a limited number of endocytosis vesicles, mediating the low rate of transcytosis between blood and the brain. Although electron microscopy has demonstrated that ECs in the brain have 80–84 % fewer endocytosed vesicles than ECs in peripheral capillaries, transcytosis remains the major pathway for the transport of large molecular weight solutes across the BBB[21].

2.2. Basement membrane (BM)

The BM surrounds both the vascular endothelial cells and the pericytes to establish a connection with the surrounding cells [22]. The BM is produced and maintained by the cooperation of endothelial cells, peripheral cells, and astrocytes [23]. BM also includes the matrix adhesion receptors of the cells, which can change the cytoskeleton structure of the endothelial cells. BM is essential for the integrity of the TJP as well as the BBB [24].

2.3. Extracellular matrix (ECM)

BM are generated and maintained by ECM proteins that are secreted by ECs and astrocytes. Cellular and matrix components are connected by ECM receptors which are expressed at the brain microvasculature, such as integrins and dystroglycan upon physiological and pathophysiological conditions [15]. For example, by interacting with integrin and non-integrin receptors, laminin can exert a lot of key functions in the CNS in both physiological and pathological conditions[25]. For example, Yao et al. (2014) reported that by binding to the integrin α2 receptor, laminin can prevent pericyte differentiation from the BBB-stabilizing resting stage to the BBB-disrupting contractile stage and that missing astrocytic laminin downregulates AQP4 and TJPs expression, indicating that astrocytic laminin can regulate pericyte differentiation and maintain the integrity of BBB [26]. In addition, the deletion of astrocytic laminin can impair the function of vascular smooth muscle cells and lead to hemorrhagic stroke [27].

2.4. Transporter proteins

To accommodate all the other components needed to maintain brain homeostasis, the BBB is equipped with an array of different transporter proteins to ensure that essential molecules can easily enter the brain [28]. Transporter proteins include the following five main types: active efflux transporters, carrier-mediated transporters, receptor-mediated transporters, uptake-mediated transporters, and ion transporters. For example, ABC transporter proteins can actively prevent the accumulation of drugs and other substances in the brain[29].

2.5. Pericytes and astrocytes

Pericytes are blood vessel wall cells that grow close to the brain endothelium; they help maintain the BBB integrity, regulate cerebral blood flow, play an important role in neovascularization, and help with microvascular stabilization and removal of brain wastes[30]. An important feature of astrocyte interaction with the BBB is the perivascular end-foot and reduced astrocyte expression interferes with the expression of TJPs[31].

3. Disruption of BBB integrity after ischemic stroke

BBB disruption is a general event after AIS and is regarded as the indicator of HT[2]. In the past three decades, reperfusion-related BBB damage after AIS has been widely investigated [32]. Upon thrombolysis, BBB disruption can be produced by three major aspects: oxygen and glucose deprivation-induced BBB damage during the acute ischemia stage, oxidative stress and inflammation-aggravated damage during the reperfusion stage [2], and tPA extravasation-induced damage when entering into the perivascular space [33]. We have previously revealed BBB damage in the ventral striatum and preoptic area as early as 2 hours following cerebral ischemia [34–38], these brain regions are common sites of cerebral hemorrhage after tPA thrombolysis [2]. Clinical imaging studies suggest a significantly increased risk of cerebral hemorrhage (up to 80 %) following thrombolytic therapy in patients with acute cerebral ischemia who have BBB disruption as well as cerebral hemorrhage identified before treatment[39]. It is of note, tPA extravasation into the perivascular spaces could have detrimental effects to worsen ischemic damage to neuron and BBB integrity [33]. In addition to reperfusion-produced disruption, BBB injury during the acute ischemia phase, especially within the 3-h thrombolytic time window is also reported [34]. Disruption of the BBB can lead to leakage of blood components into the brain tissue, causing progressive edema and swelling [40].

Whether the ischemic brain could safely bear the blood flow return depends on the status of BBB integrity at thrombolytic treatment. Accumulating evidence indicate that HT can occur after reperfusion with tPA thrombolysis [41] or endovascular thrombectomy [42] if BBB integrity has been damaged during the acute ischemia stage. Notably, disruption of BBB integrity at the ischemia stage with the thrombolytic time window is emerging as both a precursor and a potential target to reduce HT in the clinic [2]. Thus, BBB protection at the ischemia stage could become a promising strategy to alleviate HT [2].

3.1. The features of BBB destruction after ischemic stroke

3.1.1. Endothelial cell alterations after AIS and potential therapeutic targets

Ischemic stroke disrupts the blood-brain barrier (BBB) by decreasing TJP expression and increasing transporter protein and endocytosis activity. These changes heighten BBB permeability, a hallmark pathological feature of stroke [43]. The loss of TJPs between brain capillary endothelial cells is an indicator of BBB disruption [44]. For example, claudin-5 reorganization has been shown to play a critical role in ischemia-induced BBB damage after AIS[35]. In addition, rapid endothelial cytoskeletal reorganization can enable early BBB disruption and long-term ischemic reperfusion brain injury[45].

Examination using transmission electron microscope and immunoelectron microscopy of caveolin-1 (Cav-1) revealed an increase in the number of caveolae in the endothelium after I/R[46]. Glycocalyx is essential for BBB integrity by inhibiting Cav-1-dependent endothelial transcytosis after ischemic stroke[47]. In addition, Cav-1 plays an important role in I/R-induced BBB damage and can facilitate the internalization and degradation of ATP-Binding cassette transporter A-1 (ABCA1) [48], while deficiency of ABCA1 can exacerbate BBB and white matter damage after ischemic stroke [49].

3.1.2. Alterations and potential therapeutic targets in pericytes and astrocytes after AIS

Astrocytes can maintain the post-stroke barrier integrity of endothelial cells by regulating TJPs components[15]. For example, reversible disruption of TJPs complexes in the BBB following astrocyte loss was found in an animal model of ischemic stroke[31]. In addition, astrocytes can secrete vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), chemokines, and cytokines, they can exacerbate BBB damage and brain injury after brain trauma and ischemic stroke [50].

Pericytes can guide endothelial cells to the correct location, stabilize the actin filaments in endothelial cells and inhibit their loss, and clean neuronal debris during injury [22]. Pericyte loss can lead to increased endothelial transcytosis without affecting TJPs integrity[51]. During the late phase of stroke, pericytes can promote neurons to uptake a variety of blood-derived neurotoxic materials, reduce microcirculation, and induce chronic neuronal dysfunction and degenerative changes[52]. Oxidative stress during ischemia triggers pericyte apoptosis and subsequent rigor mortis, leading to a prolonged reduction in blood flow and rupture of the BBB[53]. Human pluripotent stem cell-generating pericytes effectively promote neurological recovery by re-establishing BBB integrity and preventing neuronal apoptosis after transplantation into a transient middle cerebral artery occlusion (tMCAO) mouse model with BBB disruption[54].

3.1.3. Changes in BM and ECM and potential targets for AIS

There is a close temporal correlation between TJPs and α5β1 and Ang1, the angiogenic markers, in the penumbra of the ischemic hemisphere, suggesting that α5β1 and Ang1 may have a potential role in promoting repair of BBB integrity after ischemic stroke[55]. In addition, endothelial cell-specific α5 integrin knockout mice (α5 KO) have improved BBB integrity, and inhibition of α5 integrin *in vitro* can lead to increased barrier integrity of brain endothelial cells following oxygen-glucose deprivation (OGD)[56]. Moreover, the upregulated integrin α5β3 can promote angiogenesis, and improve neural function recovery after cerebral ischemic stroke and the integrin α5β3 inhibitor can reduce VEGF-induced BBB leakage, alleviate inflammatory reaction, and ameliorate fibrinogen deposition [57]. Cyclo-RGDfV (cRGDfV), a selective inhibitor of integrin α5β3, can reduce focal ischemia-induced BBB disruption by inhibiting VEGF-mediated vascular breakdown [58], can improve outcomes after MCAO by protecting BBB integrity [59]. Moreover, endothelial α6β4 integrin can maintain vascular integrity and TJPs expression, reduce neuroinflammation induced by experimental autoimmune encephalomyelitis [60] and PARP inhibition in leukocytes protects the BBB and diminishes inflammation via effects on integrins/cytoskeleton [61].

3.2. The mechanism of BBB injury after cerebral ischemia and reperfusion

Inflammation, free radicals, VEGF, high mobility group box-1 protein (HMGB1), and MMP have been reported to induce cerebral hemorrhage after thrombolysis of tPA by disrupting BBB [62]. Reperfusion-related BBB damage has been investigated widely[63], and several mechanisms are proposed to explain reperfusion-related BBB damage, including free radical-induced oxidative stress damage [64–68], inflammatory disruption [69], vascular activation, and dysregulated extracellular proteolysis [32,70–72].

3.2.1. Inflammation

Inflammation, as one of the important pathogenic mechanisms of ischemic stroke, has been shown to play a role in BBB damage [73]. In the acute phase of ischemic stroke, both systemic and local inflammatory responses have adversely affected the prognosis of stroke [74–76]. Previous studies have shown that long-term systemic inflammatory response can aggravate neurological damage after focal cerebral ischemia in rats[77]. Therefore, inhibiting inflammation provides a therapeutic possibility for patients with stroke to improve functional recovery Figs. 1 and 2.

3.2.2. Cytokines and adhesion molecules

Microglia are macrophages present in the brain, and their activation has a major impact on the BBB in brain diseases[19]. In the inflammatory state, activated microglia are transformed into phagocytic cells and secrete various cytokines. Previous studies have shown that after ischemia activation of glial cells initiates an early immune response and secretes pro-inflammatory cytokines or inflammatory mediators such as tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), and reactive oxygen species (ROS) [78–80]. These inflammatory factors can cause subsequent damage to ECM, neurons, and endothelial cells, leading to neuron death, BBB destruction, and HT. For example, proinflammatory cytokines TNF-α, and IL-1 can stimulate microglia to actively secrete HMGB1, forming a positive feedback process, and aggravating inflammatory response and cerebral I/R injury. Both early and secondary inflammatory reactions can cause BBB damage, which in turn leads to vasogenic cerebral edema and cerebral palsy[81].

After ischemia, the infiltration and accumulation of peripheral immune cells and molecules in the brain and the release of proinflammatory cytokines can exacerbate BBB injury [82]. The cytokines, such as IL-1 and IL-6, can also increase the expression of intercellular adhesion molecule 1 (ICAM-1), L-selectin, and P-selections. By inducing white blood cells to adhere to endothelial cells, intracellular signals are generated, which causes the cytoskeleton to rearrange and the cell gap to increase, thus contributing to the damage of BBB [83], on the other hand, these cytokines can promote infiltration of white blood cells in brain parenchyma and mediate inflammatory cascade reaction, further aggravating cerebral infarction and BBB injury [84]. Cerebral ischemia stroke can upregulate the expression of adhesion molecules, including integrin and E-selectin, ICAM-1, and vascular cell adhesion molecule 1 (VCAM-1) in the ischemic hemisphere. The adhesion molecules can promote a massive “second wave” of immune cells entering into the brain parenchyma through the damaged BBB, resulting in deteriorative neuroinflammation in the lesioned brain, which also contributes to the “second wave” of BBB disruption[85].

3.2.3. MMPs

MMPs play a crucial role in disrupting the BBB integrity. These enzymes target various components of the BBB, including the extracellular matrix (ECM) and TJPs. MMPs degrade ECM components like collagen, lipoproteins, and glycoproteins, weakening the structural support for

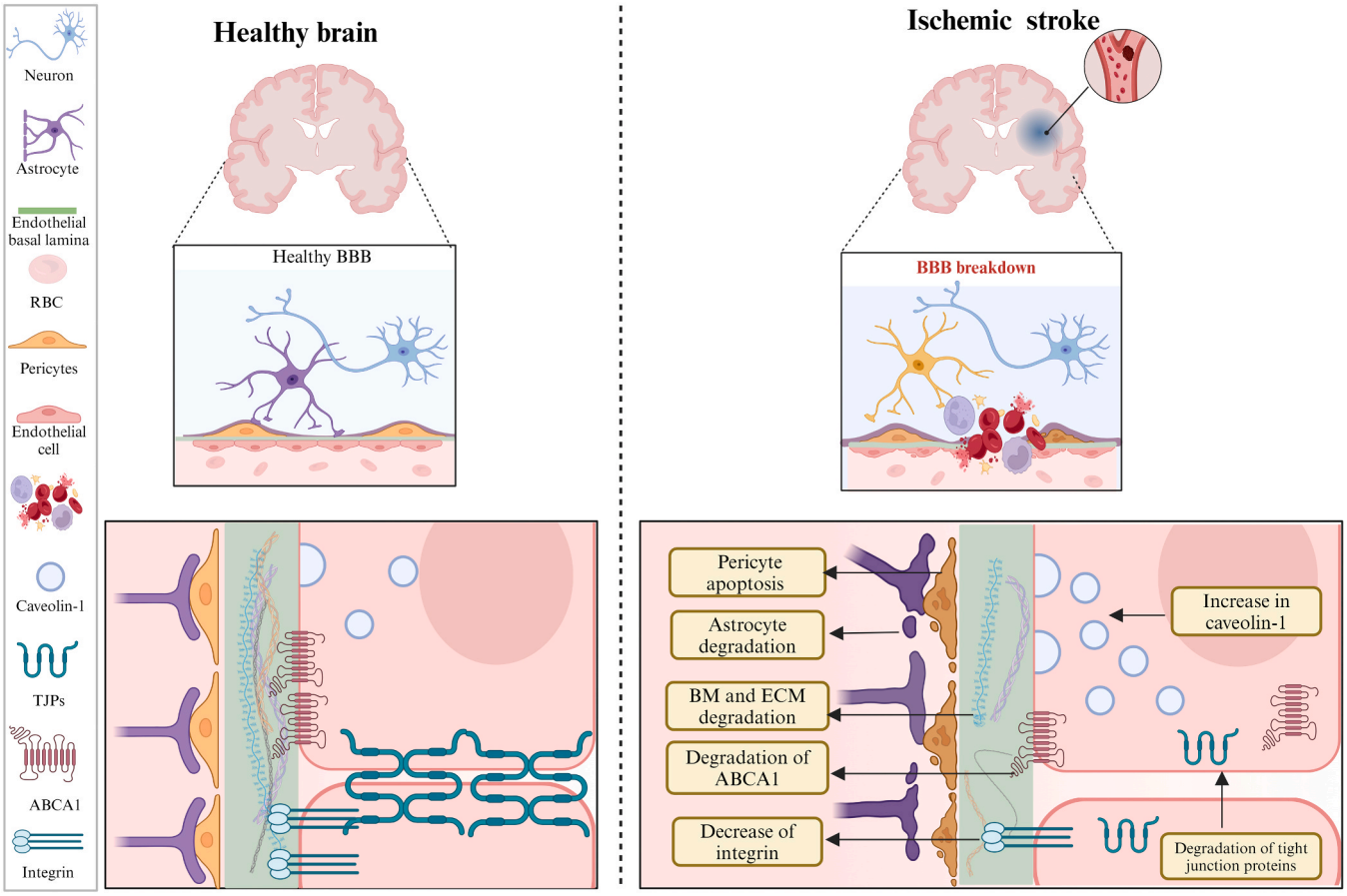

Fig. 1. The features of BBB destruction after ischemic stroke. Ischemia-induced degradation of tight junction protein (TJP), abnormalities of the transporter protein ABCA1 expressed on endothelial cells, astrocyte degeneration, pericyte apoptosis, degeneration of the basement membrane (BM) and extracellular matrix (ECM), and increase of caveolin-1.

the BBB. Moreover, they directly cleave TJPs, which are essential for maintaining a selective barrier between the bloodstream and the brain. This combined MMP action disrupts the BBB's ability to restrict the passage of molecules and immune cells, potentially contributing to various neurological diseased conditions, making them promising targets for therapeutic development [68,86]. After cerebral ischemia, accumulation of zinc in microvessels activated MMP-9 and MMP-2, which resulted in the degradation of TJPs occludin and claudin-5, and disrupted the integrity of BBB [87]. The inhibitors of MMP-2 and MMP-9 can reduce BBB damage by inhibiting the degradation of TJPs after cerebral ischemia [34,35]. We have previously shown that MMP-2 is a key factor in BBB damage during the thrombolysis time window[34–38], and MMP-2 and 9 play an important role in reperfusion-induced BBB damage [68].

Numerous studies have shown that tPA disrupts BBB integrity by activating MMP-9 [2,62,86,88,89] leading to cerebral hemorrhage. Moreover, many compounds have been shown to reduce MMP-9 damage to BBB in animal models and reduce cerebral hemorrhage caused by tPA thrombolysis [86,90]. Caveolin-1 (Cav-1) is important in tPA-induced MMP-9 elevation in endothelial cells [88]. Cav-1 is known to play important roles in regulating MMP activity [88] and BBB permeability in focal cerebral I/R injury [72]. Increased Cav-1 expression precedes decreased expression of occludin and claudin-5 during BBB breakdown [91].

3.2.4. HMGB1

Impaired brain tissue in the ischemic core releases a class of endogenous alerters, also known as danger-associated molecular patterns (DAMPs), which are released from necrotic brain cells in the infarct core. The DAMPs activate inflammatory cells by binding to the corresponding receptors and initiate the secondary inflammatory cascade through cytokine release [92,93]. Several DAMPs such as ATP, nucleic acids, and HMGB1, are critically involved in the inflammatory disruption after ischemic stroke [94].

HMGB1, a non-histone nucleoprotein involved in the maintenance of chromosome structure [95], is one of the most critical pro-inflammatory factors after ischemic stroke [78]. It can link acute neuronal death and delayed neuroinflammation in the postischemic brain [96]. It is of note, that HMGB1 is involved in brain damage in ischemic stroke as a DAMP [75,96–98]. Under normal physiological conditions, HMGB1 resides primarily within the nuclei of neurons and astrocytes. Following cerebral ischemic injury, HMGB1 translocates to the cytoplasm and is released extracellularly, triggering an inflammatory response. In addition, the expression of HMGB1 was significantly upregulated in reactive astrocytes after white matter injury [99] and focal cerebral ischemia [100]. Following I/R, HMGB1 is released extracellularly within 2–4 hours, increasing vascular permeability and aggravating BBB damage. Conversely, neutralizing extracellular HMGB1 can alleviate BBB damage and reduce infarct size [98,101]. For example, HMGB-1 was released from astrocytes upon different stresses, including OGD[102], tMCAO[103] and lipopolysaccharide [104].

3.2.5. Autophagy

Autophagy has an important role in endothelial damage and BBB disruption after ischemic stroke [105]. For example, the upregulation expression of LC3B in brain microvascular endothelial cells (BMECs), abnormal aggregation of claudin-5 and its co-localization with LC3B were detected in the BMECs after ischemic stroke [106]. In addition,

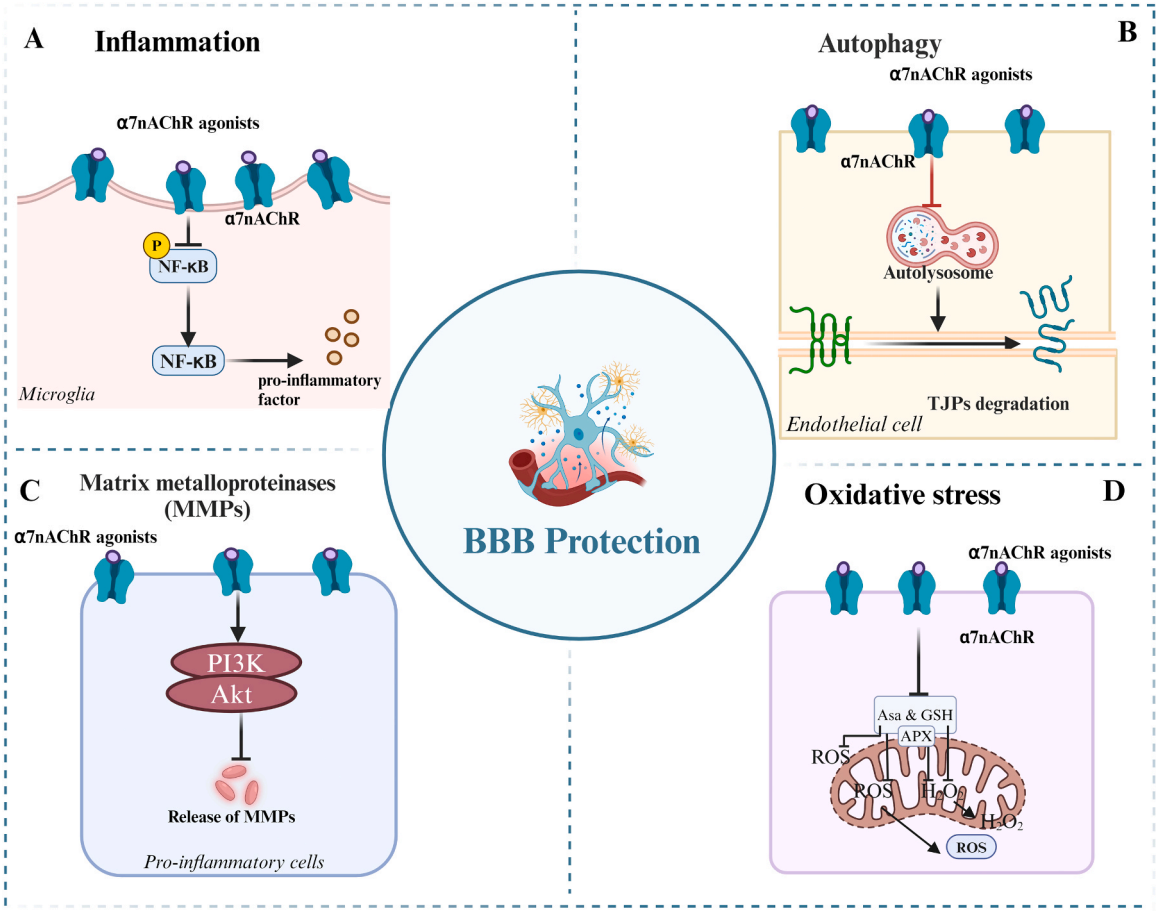

Fig. 2. Mechanisms of activation of α7nAchR for BBB protection after stroke. (A) Activation of α7nAchR inhibits NF-κB nuclear translocation and release of inflammatory factors, and blocks microglia-induced inflammation. (B) α7nAChR agonists protect BBB integrity by affecting autophagy-mediated degradation of tight junction proteins (TJPs). (C) Activation of α7nAchR promotes phosphorylation of PI3K and Akt and inhibits the release of MMPs. (D) α7nAChR agonists inhibit oxidative stress by reducing oxygen radical production through inhibition of NADPH oxidase.

OGD was found to increase cell permeability with occludin degradation and activation of autophagic pathways in brain endothelial cells, and claudin-5 in brain ECs was degraded by activation of autophagy-lysosome [107]. Furthermore, increased autophagy accounts for BBB damage after brain ischemia in diabetic mice [108], and post-stroke hyperglycemia during early reperfusion increases BBB permeability by affecting autophagy-mediated ZO-1 reduction and redistribution [109].

Rapamycin and lithium carbonate are and s respectively. Lithium carbonate, an mTOR-independent autophagy inducer can attenuate, while inhibiting autophagy by 3-MA promotes BMECs apoptosis. In addition, rapamycin, mTOR-dependent autophagy inducer, and lithium carbonate pretreatment can significantly reverse OGD/R-induced ZO-1 decrease, promote the redistribution of ZO-1, and reduce BBB damage and edema in the ischemic hemisphere of the rat [110]. Silencing histone deacetylase 9-mediated autophagy in the ischemic hemisphere leads to BBB protection after I/R [111] and promoting autophagy by miRNA regulation protects ECs from OGD/R-induced injury [112]. In addition, there were upregulated autophagy and BBB disruption in p50−/− mice, and they can be reversed by autophagic inhibition, suggesting that autophagy makes a critical contribution to ischemic neuronal and vascular damage by regulating NF-κB[113]. Furthermore, 3-MA elicits a significant loss of the protective effect of heat shock protein B8 (HSPB8) against I/R-induced BBB damage and TJPs loss and HSPB8 over-expression prevents BBB disruption by promoting autophagic flux after cerebral I/R injury [114].

3.2.6. *Oxidative stress*

Oxidative stress is thought to be a common pathway resulting in BBB injury[115]. Superoxide and other ROS can upregulate BBB permeability in a time- and concentration-dependent manner[116]. Short-term oxidative stress induces redistribution and loss of occludin and claudin-5 [117]. Importantly, oxidative stress plays a key role in BBB damage after ischemic stroke[118].

4. Nicotine's effect on BBB damage after stroke

Nicotine is the main component of cigarette smoke[119] and it is thought that much of the toxic effects of smoking are due to a variety of gas-phase constituents and tar rather than nicotine [120]. Interestingly, nicotine can decrease cigarette (tar and nitric oxide)-produced toxicity to endothelial cells in BBB [121] and if the tar component is similar, there is a negative correlation between the nicotine content and BBB damage [121]. Of note, compared to the dose of 100 ng/ml of nicotine content in the plasma of long-term smokers, only when the dose is more than 1 μg/ml, nicotine can affect cell viability [121]. Additionally, treatment endothelial cells with nicotine can cause a protein kinase C-dependent upregulation of mRNA and protein of plasminogen activator inhibitor-1 (PAI-1), an endogenous inhibitor of tPA [122].

Nicotine can protect BBB from disruption by various stimuli. For instance, treatment with nicotine can alleviate saturated-fat feeding-induced BBB damage in mice [123]. Moreover, chronic nicotine pretreatment can reduce the BBB damage from nicotine-induced seizures in the rat [124]. Furthermore, chronic low-dose nicotine treatment can

promote functional recovery after focal ischemia in rats [125]. Our recent study reported that treatment with nicotine at a dose of 4.5 mg/kg for two weeks significantly ameliorated BBB disruption after AIS by modulating pdlim5 in endothelial cells [126]. However, it has also been reported that chronic nicotine treatment (1–4 weeks) at a dose of (2–4.5 mg/kg) before ischemic stroke appears to increase vulnerability to stroke injury by i) decreasing the induction of glucose transporter 1 (GLT-1) [127]; ii) worsening transient focal cerebral ischemia exposure-induced brain injury [128,129]; iii) increasing BBB permeability to [14 C]-sucrose, likely associated with changes in ZO-1 distribution and claudin-3 reduction [130]. Moreover, nicotine pretreatment seems to increase edema after 24 h permanent MCAO in female mice [131] and nicotine exposure along with oral contraceptive treatment exacerbates hypoperfusion after ischemic stroke in female rats [132]. Therefore, nicotine is a double-edged sword. It can offer some benefits, but it also comes with significant risks. Careful consideration is needed before using nicotine or nicotine-derived products [133].

5. Nicotinic acetylcholine receptor (nAChR) and BBB protection after stroke

5.1. Receptor type, distribution, and neurological function

nAChR, a member of the ligand-gated ion channel superfamily, is a pentamer composed of 12 different subunits. Multiple combinations of these subtypes give nAChR different pharmacological and physiological properties. It is expressed in both peripheral and central nervous systems. In the CNS, the most distributed subtypes are α4β2 nAChR and α7nAChR, which are mainly expressed on the surface of neurons and glial cells [133]. As the second most abundant receptor in the nervous system, the α7nAChR has multiple biological roles in cognitive function, neuron survival and neurodegeneration [134].

In neurons, nAChR can participate in many physiological and pathophysiological processes. In particular, the α7nAChR subtype has a high permeability to calcium ions, suggesting its regulatory role in intracellular signal transduction and release of neurotransmitters, which are implicated in various nervous system diseases. The loss of cholinergic neurons and the decrease of acetylcholine production in the PFC can lead to schizophrenia-associated working memory deficits [135]. Previous studies have shown that nicotine can enhance long-term potentiation [136] fear memory[137] and working memory[138,139]. In the mouse model of Alzheimer's disease, inhibiting the action of α7nAChR can cause inflammation and increase the accumulation of amyloid proteins [140]. In Parkinson's disease, the α7nAChR plays a protective role in the dyskinesia caused by dopamine reduction [141]. Moreover, nicotine and other nAChR agonists have been shown to upregulate the expression of nAChRs and alleviate glutamate-induced neurotoxicity to cortical neurons by acting α7 nAChRs [142].

5.2. Effect of activation of the nACh receptor on BBB protection after stroke

Activation of α7nAChR has been shown to alleviate I/R-induced BBB damage [6,7]. For example, PHA543613, a selective agonist of α7nAChR, can decrease endothelial cell permeability and increase claudin-5 and occludin expression levels after 24 hours of exposure. In contrast, 5-iodo-A-85380, a selective agonist of α4β2 nAChR does not affect endothelial cell permeability or TJP expression, suggesting that selective activation of α7 nAChR has a specific role in upregulating BBB properties by increasing claudin-5 and occludin expression[143]. Treatment with α7 nAChR agonist PHA 568487 can have a protective effect on BBB integrity after cerebral ischemia by inhibiting neuroinflammation [144], and treatment with PHA-543613 can maintain BBB integrity after ICH[12].

5.3. nAChR and anti-inflammation

The α7nAChR is a target for the regulation of the innate immune system. Primarily expressed on the surface of peripheral macrophages, α7nAChR is also found in neurons, astrocytes, microglia, and endothelial cells within the CNS [13]. Our understanding of the cholinergic anti-inflammatory pathway has grown steadily. It works by activating nAChRs on immune cells, leading to reduced cytokine release[5]. α7nAChR can regulate the innate immune and inflammatory responses by regulating the release of inflammatory cytokines and chemokines [145,146]. α7nAChR agonists act as anti-inflammatory agents by inhibiting the release of TNF-α and IL-1β, and by suppressing the activation of the NF-κB signaling pathway [147]. PNU-282987, a selective agonist of α7nAchR can reduce microglial-mediated inflammation by preventing nuclear translocation of NF-κB and upregulating the expression of IL-10 [148]. Periphery α7nAChR activation reduces the production of macrophage inflammatory factors, which in turn inhibits the progress of inflammation [149–151].

In vivo imaging of α7nAChR could be a novel method to monitor neuroinflammation after cerebral ischemia [152]. α7nAChR agonist GTS-21 can reduce the activation of microglia, reduce the expression of TNF-α, IL-1β and IL-6, and reduce neuron death after mouse cerebral ischemia [153]. Administration of an α7nAChR agonist can reduce neuroinflammation and oxidative stress, thereby reducing brain damage [8,154]. Moreover, activating α7 nAChR can alleviate neuroinflammation, and decrease neuron injury and functional impairment of sensorimotor and memory of mice with Tibia fracture shortly before stroke [155].

Activation of α7nAChR can achieve anti-inflammatory and antioxidant effects through nuclear factor erythroid-2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway in microglia [156]. The α7 nAChR agonist can also reduce the production of oxygen free radicals by inhibiting NADPH oxidase, NF-kB/iNOS-induced NO, and then OGD-induced damage[157]. α7nAChR activation by PNU282987 could alleviate cognitive impairment by decreasing neuroinflammation and oxidative stress in D-galactose-produced aging model mice via modulating Nrf2/HO-1 [158]. In addition, genistein-3′-sodium sulfonate, a derivative of genistein, can significantly reduce IL-1β and M1 polarization of microglia cells, alleviate expression of α7nAChR, and ameliorate NF-κB activation in the penumbra of ischemic hemisphere [159]. Therefore, the α7nAChR could be a potential target for anti-inflammation.

5.4. Effect of the nACh receptor activation on autophagy

α7nAChR signaling is reported to be regulated by prion protein (PrPC) expression, and α7nAChR upregulation might be associated with autophagic signaling that prevents PrPc-mediated neurotoxicity[160]. In addition, activation of α7nAChR by PNU-282987 can dramatically enhance the LC3-II/I ratio as well as Beclin expression[161]. Moreover, activating α7nAChR with the agonist PNU282987 can increase monocyte/microglia autophagy, which can suppress neuroinflammation [162], thus exerting a palliative effect in experimental autoimmune encephalomyelitis[162]. Furthermore, α7nAChR deficit can worsen the severity of inflammatory bowel disease, whereas activation of α7nAChR can increase autophagy and suppress inflammatory factors in bone marrow-derived macrophages via LPS/dextran sulfate sodium stimulation[163]. Low-dose nicotine appears to promote autophagy and accelerate autophagic flux in neonatal mouse cardiomyocytes (NMCMs), as well as inhibit apoptosis in NMCMs, whereas high-dose nicotine seems to inhibit autophagy and promote apoptosis[164].

5.5. Side effects of α7nAChR agonists and potential strategies to reduce the side effects

Despite promising properties, the α7nAChR agonist has not shown

successful clinical translation [165]. For instance, several α7nAChR agonists, such as EVP-6124 and GTS-21, were tested in clinical trials for schizophrenia-related cognitive deficits but failed to gain marketing approval due to cardiotoxic side effects [165].

The cardiotoxic side effects observed with some selective α7nAChR agonists, such as QT prolongation, ventricular tachycardia, and other cardiac adverse events, are a significant challenge in the development of these compounds as therapeutics. The famous selective α7nAChR agonist PNU-282987 is reported to possess significant human *ether-a-go-go* (hERG) potassium channel activity [166], which encodes the pore-forming subunit of the rapidly activating delayed rectifier potassium channel (IKr), an important component of cardiac repolarization [167]. Even other selective α7nAChR agonists like PHA-543613 and PHA568487, have demonstrated good hERG safety profiles, yet they were still reported to cause adverse cardiovascular events in phase I clinical trials. These cardiovascular findings included symptomatic non-sustained ventricular tachycardia and premature ventricular contractions in healthy volunteers [168]. Further, the α7nAChR agonist CP-810, which has a low affinity for hERG and high affinity for α7nAChR, had its clinical trial discontinued due to the occurrence of non-sustained ventricular tachycardia [169]. The cardiotoxic side effects observed with these selective α7nAChR agonists, despite their apparent hERG safety, highlight the complexity of the underlying mechanisms.

The α7nAChR subunit has been reported to be present in sympathetic and parasympathetic neurons innervating the heart, as well as in fibroblasts, and cardiomyocytes. Interestingly, α7nAChR plays a role in regulating calcium balance and cardiac repolarization, α7 nAChR knockout mice have been shown to exhibit a prolonged QT interval [170]. This regulation of cardiac electrophysiology by α7nAChR is further complicated by the receptor's unique properties that α7nAChRs are rapidly and deeply desensitized, a process whereby continuous agonist-mediated receptor stimulation results in receptor inactivation, by repeated administrations of agonists. In the continuous presence of agonists, α7nAChR-mediated currents can be completely inhibited by desensitization and/or agonist-mediated open channel block [171]. Therefore, we presume that agonists-mediated α7nAChR inactivation and the resulting imbalance in calcium regulation may be another contributing factor driving the adverse cardiovascular events associated with selective α7nAChR agonists.

One approach being explored to mitigate the cardiotoxic side effects of α7nAChR agonists is optimizing the dosing and pharmacokinetic profile of α7nAChR agonists to minimize exposure to concentrations that trigger hERG channel inhibition and cardiac electrophysiological disturbances. In addition, a possible approach along these lines could be to combine lower doses of an α7nAChR agonist with a positive allosteric modulator (PAM), which does not directly activate α7 nAChR but instead enhances neurotransmitter activation.

6. Possible mechanisms and potential strategy

6.1. Melatonin

Melatonin can attenuate lipopolysaccharide-induced neuroinflammation and α7nAchR mRNA downregulation in astrocytoma cells of rats [172]. Melatonin also can reduce NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome activation by increasing α7 nAChR-mediated autophagic flux[173]. Activation of the α7nAChR reduces macrophage inflammatory cytokine production and inhibits the progression of inflammation [149–151].

Recently melatonin has been shown to promote neuroprotection by activating α7nAChR/ Nrf2/HO-1[174]. Melatonin protects against ischemic cerebral infarction by up-regulating the α7nAChR in the hippocampus [92]. Melatonin regulates the autophagic flux via upregulation of α7nAchR and α7nAchR inactivation can inhibit melatonin-induced autophagic activation and beneficial effect against prion-produced mitochondrial damage[175]. Modulation of α7nAChR by melatonin alleviates I/R-compromised integrity of BBB through inhibiting HMGB1-mediated microglia activation and CREB-regulated transcriptional coactivator 1 (CRTC1)-mediated neuron loss, which could be ameliorated by MLA (selective α7nAChR antagonist) [176]. In addition, the inactivation of α7nAChR by α-Bgt (a selective α7nAChR antagonist) or MLA appears to inhibit melatonin-induced protective effects [92,175].

6.2. Electroacupuncture treatment

Electroacupuncture pretreatment can alleviate ischemia-induced brain injury by inhibiting HMGB1 release via α7nAChR activation in rats [177] and inhibition of NLRP3 inflammasome in stroke rats [178]. Electroacupuncture also can reduce α7nAChR downregulation and attenuate brain injury by inhibiting neuroinflammation via α7nAChR activation in a rat model of asphyxial cardiac arrest [179]. These findings suggest that α7nAChR-mediated cholinergic anti-inflammatory pathway and NLRP3 inflammasome in neurons might be potential targets in electroacupuncture-produced neuroprotective effect after cerebral ischemia stroke.

6.3. Vagus nerve stimulation (VNS), echinacoside, and pulsed electromagnetic fields

VNS can modulate inflammatory responses and metabolism through the action of acetylcholine. For example, pretreatment with GTS-21, an α7nAChR agonist, can improve disordered glucose metabolism and glutathione reduction[180]. In addition, VNS can alleviate inflammatory responses in peripheral tissues and improve neurological function by elevating the hippocampal expression of α7nAChR in continuous-stress animals. Treatment with α7nAChR antagonist can upregulate TNF-α and IL-1 expression, inhibit VNS-produced anti-inflammatory effects [181].

The significant VNS-mediated reduction of neutrophil numbers in peritoneal exudates requires the α7nAChR subunit [182] and the anti-inflammatory signal of the vagus nerve is mediated by α7nAchR [183]. For example, VNS alleviated cerebral I/R injury in rats by inhibiting pyroptosis via α7nAchR [184] and α7nAChR mediates VNS-induced neuroprotection in acute permanent cerebral ischemia by α7nAchR/JAK2 pathway [185]. In addition, transcutaneous auricular vagus nerve stimulation (ta-VNS) treatment can upregulate the expression of α7nAchR in the cortex of the ischemic hemisphere. Strikingly, α7nAchR is a potential target for ta-VNS-mediated neuroprotective effect during the chronic phase of ischemic stroke [186].

Echinacoside (ECH) can significantly alleviate brain injury and ameliorate neurological deficits and brain edema in rats. In addition, administration of ECH can lead to increased α7nAChR expression, ACh content, and enhanced autophagy in MCAO rats[187]. Furthermore, pulsed electromagnetic fields are reported to have anti-inflammatory effects after cerebral ischemia by regulating α7nAChR/STAT3 signaling in astrocytes [188].

6.4. Positive allosteric modulation (PAM)

PAM of α7nAChRs offers a promising approach to enhance endogenous cholinergic signaling in a controlled manner within brain regions critical for learning and memory. This strategy has the potential to overcome limitations associated with current clinical-stage α7nAChR agonists, such as selectivity issues and the development of tolerance. As a result, α7nAChR PAMs represent a novel and potentially more effective therapeutic avenue for targeting this ion channel in neurological disorders. LL-00066471, a novel PAM of α7nAChR, is reported to ameliorate cognitive and sensorimotor gating deficits in animal models [189]. PNU-120596, a PAM of α7nAChR appears to amend neuroinflammatory and motor dysfunction correlated with the associated PD

dysfunction [190]. Of note, the duration of treatment seems to affect the efficacy of PAM after focal ischemia in rats [191] and a combination of short treatment duration and prolonged treatment duration may be required to maximize the therapeutic effects of PNU120596, reduce relapses, and ensure sustained therapeutic efficacy after AIS.

7. Conclusion

BBB integrity is critical in preventing vasogenic edema and hemorrhagic transformation following tPA thrombolytic therapy and thrombectomy for AIS. Developing strategies to protect the BBB is an urgent clinical challenge. The α7nAChR has shown promise as a therapeutic target due to its potential to mediate anti-inflammation and autophagy. Further research is needed to explore the possibility of activating α7nAChR to reduce BBB damage after stroke.

Authors' contributions

YG, WL, WD, PG drafted the manuscript, WD drafted the figures. CG and XJ revised the manuscript. All authors agreed on the final draft.

Ethical statement

This review article does not contain any studies with human participants or animals performed by any of the authors.

CRediT authorship contribution statement

Panpan Geng: Writing – review & editing, Writing – original draft. **Wencao Liu:** Writing – review & editing, Writing – original draft, Conceptualization. **Chun Guo:** Writing – review & editing. **Fengying Gao:** Writing – original draft. **Weihong Du:** Writing – original draft, Software. **Xinchun Jin:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Data availability

No data was used for the research described in the article.

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