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Molecular mechanisms of electropuncture in cerebrovascular protection during enhanced recovery after surgery period

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The core intent of enhanced recovery after surgery (ERAS) is to alleviate the perioperative stress response and postoperative complications through perioperative multimodal analgesia and intensive surgery. Previous studies have demonstrated that multiple molecular mechanisms function in improving ischemic stroke, reversing the process of ischemia reperfusion, relieving intracerebral hemorrhage and traumatic brain injury. Meanwhile, electroacupuncture (EA) has been validated with regard to its efficacy and safety in perioperative treatment, which has an important impact on rehabilitation research and ERAS development. Currently, studies have showed that EA provides a new approach for cerebrovascular protection by activating various molecular mechanisms. In this review, we display the recent progress of main molecular mechanisms of EA in ERAS from the perspectives of protecting cerebrovascular functions, in order to provide guidance for the clinical treatment.

KEYWORDS

enhanced recovery after surgery, electroacupuncture, cerebrovascular protection, molecular mechanism, traditional Chinese medicine

1. Introduction

Enhanced recovery after surgery (ERAS) was originally proposed by Kehlet and Wilmore in 2001 (1), aiming to reduce the perioperative stress response. ERAS minimizes the perioperative stress response, reduces patient pain and promotes early recovery of organ function through various medical modifications, thus prompting patients to rapidly return to a preoperative state (2). Furthermore, traditional Chinese medicine (TCM) has preliminary practice and experience with ERAS. According to TCM, acupoints are the specific parts of the meridians where qi and blood gather and come in and out of the body surface during acupuncture (3). Electroacupuncture (EA) is performed on the basis of traditional acupuncture, and is a combination of acupuncture and electric stimulation technology (4). EA can improve neuromuscular activity, analgesia, and immune regulation and protect the function of organs (5). In addition, EA pretreatment has been proposed as a novel method to protect cerebrovascular function in the regulation of various molecular mechanisms (6). In this review, we reviewed the evidence for the role of main molecular mechanisms of EA in the cerebrovascular protection of ERAS.

2. Promotion of cerebrovascular ischemia reperfusion injury and ischemic stroke

Stroke is the second leading cause of death worldwide and a main cause of disability, thereby endangering human health (7). The most effective treatments are thrombolysis and interventions, but both treatments have a limited time window. Therefore, there is an urgent need for an alternative treatment strategy for cerebrovascular ischemia reperfusion injury (CIRI), which may promote the recovery of neurological function and reduce the burden of stroke through multidirectional and comprehensive treatment with multiple targets. A number of studies have been conducted to examine acupoints most commonly used to treat ischemic stroke. The most commonly used acupoints for ischemic stroke include Baihui (GV20), ST36, Quchi (LI11), Shuigou (GV26), and Hegu (LI4) (8). Here, we investigated the evidence of autophagy and related molecular mechanisms of EA in the ischemic stroke of ERAS (Table 1).

2.1. Autophagy

Autophagy is a highly conserved lysosomal-dependent process that may be in-volved in maintaining cell homeostasis. Autophagy may sequester aged proteins and misfolded molecules for degradation by nonspecifically targeting protein aggregates. Several studies have demonstrated that a variety of interventions may ameliorate CIRI by modulating autophagy. Therefore, autophagy plays a crucial role in the regulation of cerebral ischemia.

2.1.1. The mammalian target of rapamycin (mTOR) pathway

mTOR is a protein with serine/threonine kinase activity that orchestrates anabolic and catabolic processes to maintain essential homeostasis. mTORC1 is the main regulator of autophagy, which may promote anabolism and inhibit catabolic processes by inhibiting autophagy. Autophagosome formation is

TABLE 1 Research information of electroacupuncture on cerebrovascular diseases during enhanced recovery after surgery period.

Author (References)	Species/model	Acupuncture points	Parameters of manipulation	Results/conclusion
Liu et al. (9)	Rats with MCAO	ST36, LI11	1–20 Hz, 0.2 mA, 30 min	LC3-II/LC3-I↓, ULK1↓, Atg13↓, Beclin1↓
Liu et al. (9)	Rats with CIRI	ST36, LI11	2–15 Hz, 1 mA, 30 min	LC3-II/LC3-I↓, ULK1↓, Atg13↓, Beclin1↓
Wang et al. (10)	Rats with IS	ST36, LI11	2 Hz, 1 mA, 30 min	CCAS3↓, LC3-II/LC3-I↓, Atg7↓, p-mTOR↓, p-Akt↓, P62↓, LAMP1↓
Cao et al. (11)	Rats with MCAO	GV26	4/20 Hz, 1–3 mA, 30 min	miR-34↓
Chen et al. (12)	Rats with MCAO	GV20	2–15 Hz, 1 mA, 30 min	LC3-II/LC3-I↓, p-mTOR↓, p-Akt↓, p62↓
Xu et al. (13)	Rats with MCAO	GV20, GV26	3.85/6.25 Hz, 0.8–1.0 mA, 30 min	SIRT1↑, Beclin1↑, LC3-II↑, hMOF↓, H4K16ac↓
Mei et al. (14)	Rats with CIRI	GV20, ST36, LI11	2/15 Hz, 1 mA, 30 min	LC3-II/LC3-I↓, Ac-FOXO1↓, Atg7↓, p62↑, SIRT1↑, FOXO1↑
Wei et al. (15)	Patients with middle cerebral artery occlusion	GV20	1 mA, 2–15 Hz, 30 min	p-ERK1/2↑, ϵPKC↑, GSK-3β↑
Lan et al. (16)	Patients with middle cerebral artery occlusion	LI11, ST36	0.01 mA, 1–20 Hz	TLR4↓, NF-κB p65↓, p-IκB↓, TNF-α↓, IL-1β↓ and IL-6↓
Feng et al. (17)	Patients with middle cerebral artery occlusion	GV20, GV24	1–20 Hz, 30 min	Bax↓, Fas↓
Wang et al. (18)	Patients with chronic constrictive injury	GB30, GB34	1 mA, 2–100 Hz, 30 min	SOCS-3↑, IL-6↓
Liu et al. (19)	Patients with Alzheimer's disease	GV20, BL23	15 min	SOCS-3↑, JAK2↓, STAT3↓
Gao et al. (20)	Patients with obesity	ST36, SP6	1–5 mA, 6/20 Hz, 15 min	SOCS-3↓, PPARγ↓
Jing et al. (21)	Patients with type 2 diabetes mellitus	ST36, ST44	1 mA, 2–15 Hz, 30 min	STAT3↑, PPARγ↓
Liu et al. (22)	Patients with experimental autoimmune encephalomyelitis	LU11, PC9, ST36	3.5 V, 1 Hz, 30 min	Th17↓, CD4 + T↓, IL-17↓
Wang et al. (23)	Patients with spared nerve injury	ST36, SP6	1–3 mA, 3 Hz, 30 min	α7nAChR↑, IL-10↑, p-JAK2↓, p-STAT3↓, IL-6↓, IL-1β↓
Zhang et al. (24)	Patients with cerebral palsy	Scalp surface	3.5 mA, 2–4 mV, 2 Hz, 20 min	Akt↑, p-Akt↑, neuronal apoptosis↓
Du et al. (25)	Patients with middle cerebral artery occlusion	GV20	1 mA, 2–15 Hz, 30 min	p-ERK1/2↑, ϵPKC↑, GSK-3β↑
Wu et al. (26)	Patients with middle cerebral artery occlusion	LI11, ST36; LU5, LI4, ST36, SP6	1 mA, 4–20 Hz, 30 min; 2 mA, 2–15 Hz, 20 min	caspase-3↓, Bim↓, ERK↑ and Bcl-2↑
Cheng et al. (27)	Patients with middle cerebral artery occlusion	GV20, GV16	2.7–3.0 mA, 5–25 Hz, 30 min	p38 MAPK/CREB/Bcl-xL/Bcl-2↑, cytosolic GFAP↓, mitochondrial Bax↓, caspase-3↓, astrocytes↓
Tao et al. (28)	Patients with middle cerebral artery occlusion	LI11, ST36	0.01 mA, 1–20 Hz	Notch↑, BDNF↑, GDNF↑, eNSCs↑
Zhao et al. (29)	Patients with middle cerebral artery occlusion	GV20	1 mA, 1–20 Hz/2–15 Hz, 30 min;	Notch 1↑, Notch 4↑, Jag1↑, Hes1↑, NICD↑, HIF-1α↑
Tu et al. (30)	Patients with chronic constrictive injury	ST36, GB34	1.5 mA, 2–100 Hz, 30 min	TrkB↓, microglia↓, BDNF↓
Zou et al. (31)	Rats with ICH	GV20, Gb7	30 min	Notch1↓, Hes1↓
Guan et al. (32)	Rats with ICH	GV20-GB7	4 Hz, 1 mA, 15 min	P53↓
Shi et al. (33)	Rats with CIRI	GV26	15 Hz, 1 mA, 5 min	Ki67↑

LAMP1, lysosomal-associated membrane protein 1; CCI, chronic constrictive injury; GDNF, glial cell-derived neurotrophic factor; Hes1, hairy and enhancer of split-1; HMGB1, high mobility group box 1; IKKβ, inhibitor kappa B kinase β; NICD, intracellular domain of Notch; p-IκB, phospho-inhibitor of nuclear factor kappa-B; TRIF6, toll-interleukin-1 receptor domain contain-ing adaptor inducing interferon-β 6; ϵPKC, protein kinase Cϵ.

regulated by the mTORC1 pathway and LC3-II (34). LC3-I is localized in the autophagosome membrane, and the number of autophagosomes is closely related to the ratio of LC3-II/LC3-I (35). Furthermore, the activation of autophagy in postischemic neurons occurs through the activation of Beclin1 and LC3 in the periinfarct cortex (35). Liu et al. (9) demonstrated that EA pretreatment may downregulate the LC3-II/LC3-I ratio and reduce the number of autolysosomes, lysosomes, and autophagosomes in ischemic paracortical areas. mTOR regulates autophagy in CIRI through two major pathways: the Akt-mTOR pathway and the adenosine 5′-monophosphate-activated protein kinase (AMPK)-mTOR pathway. The Akt-mTOR pathway is regulated by the phosphatidylinositol 3-kinase (PI3K) enzyme, and its downregulation may induce autophagy (36). Conversely, the increased adenosine monophosphate (AMP)/adenosine triphosphate (ATP) ratio and calcium influx caused by ischemic stress might enhance AMPK activity (37). Wang et al. (10) showed that the protective effect of EA at Quchi (LI11) and ST36 was related to the inhibition of neuronal autophagy and the activation of the PI3K-Akt signaling pathway. In this study, EA pretreatment after IS inhibited the expression levels of ischemia-activated LC3-II/LC3-I and Atg7 and increased the expression levels of ischemia-inhibited PI3K and phosphorylation of mTOR and Akt (10). In addition, since mTORC1 inactivates autophagy-inducing proteins [ULK1/2 and autophagy-related gene 13 (Atg13)], the reduction in mTORC1 activity may enhance the activation of ULK1, thereby promoting autophagic flux (38). Moreover, EA also decreased the expression of autophagosome membrane markers, such as ULK1 and Atg13. Liu et al. (9) showed that autophagy is mediated through the mTORC1-ULK complex-Beclin1 pathway, and EA may prevent IS by inhibiting autophagy. They demonstrated that stimulation of LI11 and ST36 improved neurological deficits and reduced infarct volume. After EA stimulation, the levels of LC3 II/I, ULK1, Atg13 and Beclin1 decreased, while the expression of mTORC1 increased in the peripheral cortex (9).

2.1.2. The hypoxia-inducible factor 1 (HIF-1) pathway and ROS

HIF-1 is a transcription factor that regulates adaptive responses to hypoxia. It has become a major focus of neuroscience research because it regulates postischemic pathological processes such as apoptosis, energy metabolism, and gene transcription. Recent studies have shown that HIF-1 is involved in the regulation of autophagy after IS (39). Activated HIF-1 promotes the expression of BINP under ischemic conditions. BCL2/adenovirus E1B 19 kd-interacting protein (BNIP)3/BNIP3l competes with Beclin1 and dissociates it from the Beclin1/Bcl-2 complex, thereby stimulating Beclin1 to participate in autophagosome formation (40). Lu et al. (41) demonstrated that hypoxic preconditioning (HPC) activates autophagy through the HIF-1/BNIP3/Beclin1 signaling pathway, which indicates that HIF-1 is involved in the activation of autophagy and is a potential therapeutic target. Furthermore, HIF-1 ex-pression is also involved in the upregulation of mitophagy by inhibiting the mTOR signaling pathway, although whether this effect is regulated by BNIP3

needs to be further verified (42). In addition, HIF-1 may activate autophagy by regulating the expression of p53 (43). Oxidative stress after CIRI leads to excessive reactive oxygen species (ROS) accumulation, which is related to the regulation of autophagy (44). ROS mediate autophagy mainly through intracellular transcriptional regulation (45). Elevated ROS increases p53 levels, which activates two autophagy modulators, Tp53-induced glycolysis and apoptosis regulator (TIGAR), and DNA damage-regulated autophagy modulator (DRAM) (46, 47). ROS also enhanced the transcription of Nrf2. Nrf2 promotes the expression of the autophagy-related protein P62 to mediate autophagy (48). ROS stimulate forkhead box O3 (FOXO3) expression by activating LC3 and BNIP3 to regulate autophagy (49). On the other hand, Atg4, which is responsible for autophagosome membrane elongation, has also been shown to be inhibited by ROS, thereby supporting autophagosome formation (50). Atg4 is involved in the formation of LC3-I by exposing the C-terminal residue of LC3, and LC3-I then com-bines with phosphate ethanolamine (PE) to form LC3-II. In addition, Atg4 is involved in LC3-II cleavage. Atg4 protease activity was inhibited by ROS oxidation. Inhibition of Atg4 promotes autophagy by reducing LC3-II cleavage (44, 51, 52).

2.1.3. Extra signaling pathways

Micro ribonucleic acid (MiRNA)s are small endogenous noncoding ribonucleic acid (RNA)s that control messenger RNA (mRNA) degradation and/or regulate protein translation by interacting with specific sites located in the 3′ or 5′-untranslated regions of target mRNAs. Studies have shown that the Wnt pathway may play an important role in EA pretreatment in CIRI. Cao et al. (11) showed that EA attenuated CIRI by inhibiting autophagy through activation of the miR-34/Wnt pathway. The results showed that miR-34 was significantly increased in the middle cerebral artery occlusion (MCAO) group, while EA pretreatment decreased the expression of miR-34. Wnt1 is a target of miR-34, so EA pretreatment after MCAO also alleviated autophagy in the MCAO group. Similarly, Chen et al. (12) found that EA pretreatment inhibited autophagy by inhibiting glycosynthase kinase (GSK)3β in the Wnt pathway, thereby inducing tolerance to CIRI. In addition, Xu et al. (13) showed that EA inhibited the H4K16ac process, promoted autophagy and attenuated CIRI. These findings suggest that modulation of histone H4 lysine 16 acetylation-mediated autophagy may be a key mechanism for EA in CIRI (13). Mei et al. (14) proposed that the neuroprotective mechanism of EA may be realized through the regulation of autophagy by the silent mating type information regulation 2 homolog-1 (SIRT1)-recombinant forkhead box protein O1 (FOXO1) signaling pathway. The experimental results showed that EA pretreatment decreased the LC3-II/LC3-I ratio, the levels of Ac-FoxO1 and Atg7, and the interaction between AcFOXO1 and Atg7 but in-creased the levels of P62, SIRT1 and FOXO1 (14). Wang et al. (53) found that EA could ameliorate mitochondrial damage induced by nitro/oxidative stress and reduce the ac-cumulation of damaged mitochondria through Pink1/Parkin-mediated mitophagy clearance, thereby protecting cells from neuronal injury in CIRI (53). In conclusion, the mechanism of

autophagy in the treatment of CIRI and ischemic stroke (IS) has not been clarified, and further studies are urgently needed.
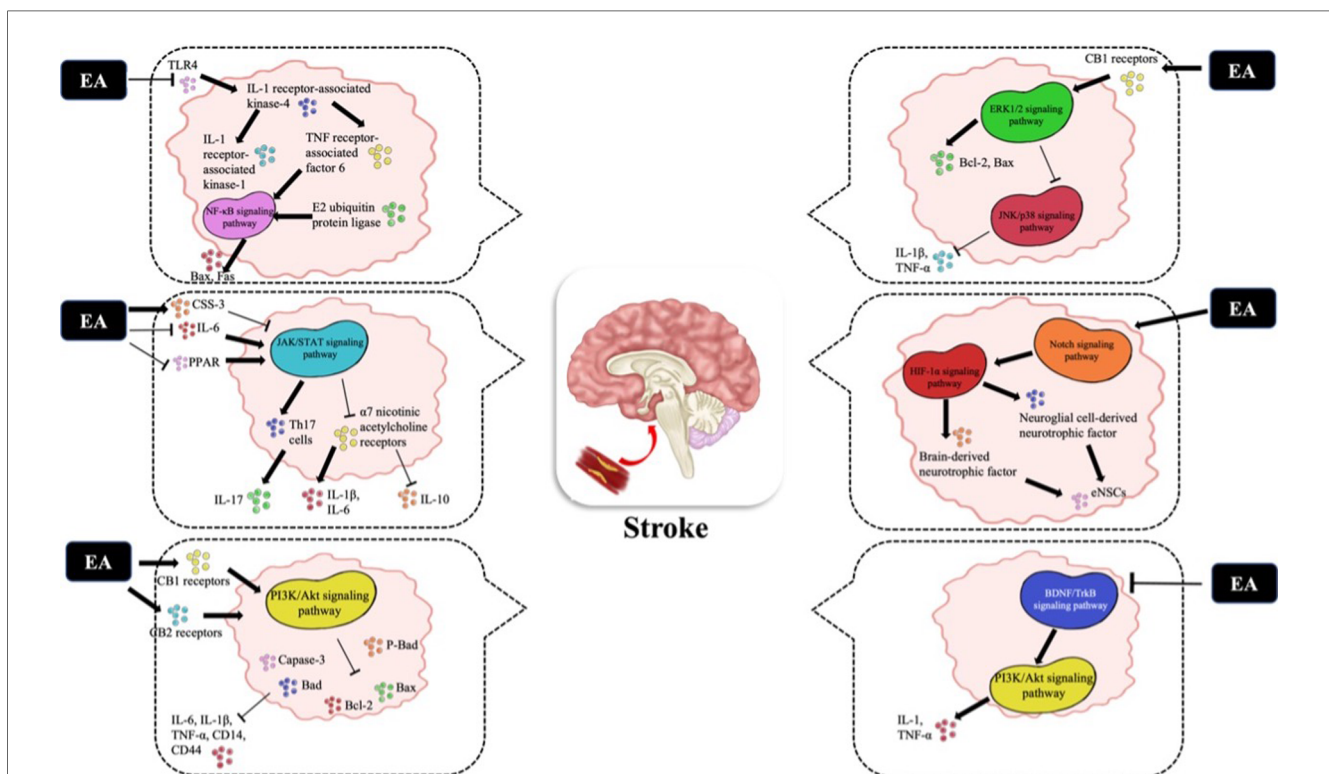
2.2. Related main molecular mechanisms

The pathological mechanism of CI/R is complex, and energy metabolism disorder, excitatory amino acid toxicity, inflammatory response and apoptosis are all involved in the pathophysiological process (54). In addition to autophagy, the cytokine-mediated inflammatory response plays a crucial role in pathological damage in CI/R (55). Therefore, early control of glial cell activation, reduction in leukocyte infiltration and release of inflammatory mediators and inhibition of the inflammatory response are essential to reduce the occurrence of stroke. In particular, the inflammatory cascade following acute cerebral infarction (ACI) is accompanied by the activation of many inflammatory cells and the release of inflammatory mediators, and signaling pathways are critical to these inflammatory cells. Therefore, it is of great significance to study the effect of EA on the inflammatory signaling pathway after ACI. Some studies have

shown that the signaling pathways of the inflammatory response after ACI mainly include Toll-IL-1 receptor (TLR)4/ nuclear factor kappa-B (NF-κB), Janus kinase (JAK)2/signal transducer and activator of transcription (STAT)3, phosphatidylinositol-3-hydroxykinase (PI3K)/Akt, extracellular regulated protein kinases (ERK)/Jun N-terminal kinase (JNK)/p38, Notch and brain-derived neurotrophic factor (BDNF)/tyrosine kinase receptor B (TrkB) (Figure 1). In addition, the brain protective mechanism of EA may be related to CE1R (15, 56).

2.2.1. TLR4/NF-κB

TLR is a pattern recognition receptor, and the signaling pathway is closely related to the precise regulation of the cell TLR domain adapter, in which TLR4 is closely related to inflammatory gene expression (57). After TLR4 activation, IL-1 receptor-associated kinase-4 activates other members of the IL-1 receptor-associated kinase family, including IL-1 receptor-associated kinase-1 and TNF receptor-associated factor 6. TNF receptor-associated factor 6 is then combined with E2 ubiquitin protein ligase to activate a complex containing transforming growth factor-β (TGF-β) activated kinase 1 and TGF-β-activated

FIGURE 1

The related molecular mechanisms by which EA promotes CIRI. (I) EA may upregulate the expression of the TLR4/NFκB signaling pathway and decrease the expression of Bax and Fas. (II) After EA stimulation, the JAK2/STAT3 signaling pathway is activated; (i) CSS-3 is upregulat-ed and plays an anti-inflammatory role; (ii) PPARγ expression is downregulated to play an an-ti-inflammatory role; (iii) Th17 cells and the α7 nicotinic acetylcholine receptor are inhibited to reduce brain damage. (III) EA activates the PI3K/Akt signaling pathway to decrease the expres-sion of Bad, p-BAD, Bcl2, Bax and Caspase-3. (IV) The ERK/JNK/P38 signaling pathway is acti-vated by EA to downregulate the expression of Bad, Bax and Caspase-3, which decreases the ex-pression of TNF-α and IL-1β. (V) After EA stimulation, the Notch signaling pathway and down-stream HIF-1α pathway are activated to reverse intracerebroventricular injury. (VI) EA can acti-vate the BDNF/TrkB signaling pathway to activate the downstream P13K/Akt pathway. EA, electropuncture; CI/R, cerebral ischemia/reperfusion; TLR, toll-like receptor; JAK/STAT, Janus ki-nase/signal transduction and transcriptional activator; CSS-3, cytokine signal suppressor protein 3; PPAR, peroxisome proliferator-activated receptor; ERK, extracellular regulated protein kinases; JNK, c-Jun N-terminal kinase; BDNF, brain-derived neurotrophic factor; TrkB, tyrosine kinase receptor B.

kinase 11. This complex activates the mitogen-activated protein kinase (MAPK) and NF-κB pathways (58). The results showed that EA significantly decreased the expression of TLR4, NF-κB and other key signaling molecules in the TLR4/NF-κB signaling pathway after ACI and inhibited the secretion of TNF-α and other inflammatory cytokines. Therefore, it is speculated that EA may mediate the TLR4/NF-κB signaling pathway to exert an anti-inflammatory effect after ACI (16). EA stimulation of GV20 and Shenting (GV24) inhibited the activation of NF-κB signaling and apoptosis of brain cells, decreased the expression of Bax and Fas, and improved learning ability and poststroke recognition ability (17). These studies suggest that EA in ACI can upregulate the expression of the TLR4/NFκB pathway and play a role in nutritional protection and inflammatory response limitation.

2.2.2. JAK/STAT signaling pathway

The JAK/STAT signaling pathway is an important pathway that regulates cellular inflammation and oxidative stress. Activated JAKs catalyze tyrosine phosphorylation, recruit STATs through the SH2 domain, and then increase gene transcription and ex-pression by forming homodimers and binding to corresponding target gene promoters (59). The JAK2/STAT3 pathway is most closely associated with central nervous system (CNS) diseases and is important in the regulation of microglial activation. After CI/R, the expression of JAK2, p-JAK2 and p-STAT3 is increased in the brain, especially in activated microglia and astrocytes, which may aggravate cerebral edema (60, 61). It has been demonstrated that downregulation of JAK2/STAT3 phosphorylation reduces the secretion of TNF-α and IL-1β in lipopolysaccharide-induced microglia (62). After EA stimulation of GV20, IL-1β activates JAK2/STAT3, which promotes phosphorylation of STAT3, levels of glial fibrillary acidic protein (GFAP) and vimentin as well as the release of inflammatory factors and adhesion molecules by binding to IL-1β receptors, resulting in T-cell immune responses (63). Overactivation of the JAK2/STAT3 pathway not only acts as an extramembrane signal of ischemia and hypoxia but also upregulates inflammatory factors and activates neuroglial cells, thus exacerbating the damage to brain tissues. Therefore, identifying downregulated targets for JAK2/STAT3 signaling may be a novel strategy for inhibiting neuroinflammation. Moreover, cytokine signal suppressor protein 3 (CSS-3) belongs to the suppressor of cytokine signaling (SOCS) family of cytokine signal suppressor proteins and is involved in the negative regulation of JAK2/STAT3 signaling. After EA, activation of neuroglial cells was inhibited, and expression of CSS-3 was upregulated, thus providing a negative regulation to JAK2/STAT3 signaling to yield an anti-inflammatory role (18). Another study found that IL-6-induced activation of JAK2/STAT3 signaling increased the expression of superoxide dismutase (SOD)2 target genes and is involved in antioxidant/anti-inflammatory responses (64). However, knocking out or blocking IL-6 signaling exacerbated ischemic injury (65). JAK2/STAT3 mRNA and protein levels were significantly upregulated following EA treatment of chronic cerebral hypoperfusion rats, suggesting that EA may inhibit inflammation by regulating IL-6. Furthermore, EA can regulate the release of microglial inflammatory factors by downregulating the expression of JAK2 and STAT3 in the cerebral

cortex JAK2/STAT3 signaling pathway, thereby alleviating chronic inflammatory injury (19, 66). In addition, peroxisome proliferator activated receptor (PPAR) is a ligand-dependent transcription factor in the nuclear hormone receptor family, including three subtypes: PPARα, PPARβ/δ and PPARγ (67). Recent studies have shown that PPARγ is closely related to the JAK2/STAT3 signaling pathway after CI/R. In obese rat models, EA inhibits PPARγ agonist-induced JAK2/STAT3 signal activation, downregulates CSS-3 and PPARγ expression, and increases leptin receptor and STAT3 levels, thereby reducing food intake and weight gain. Therefore, EA stimulation was speculated to have a benign regulatory effect on the overexpression of CSS-3 and PPARγ in obese rat models (20, 21). The effect of EA after CI/R on PPARγ-mediated receptors in the JAK2/STAT3 pathway is still unclear. Further studies are needed to determine how downstream protein and gene expression in the JAK2/STAT3 pathway is involved in pathological brain injury. Last but not least, experimental results showed that CD4+ T lymphocytes differentiated into Th17 cells regulated by JAK2/STAT3 with the induction of IL-6 (68). EA can significantly reduce inflammatory cell infiltration, downregulate CD4+ T lymphocyte expression, improve neurological function scores (69, 70), reduce the expression of Th17 cells and pathological changes in the brain, and effectively inhibit the secretion of the proinflammatory cytokine IL-17 in mice (22, 71). α7 nicotinic acetyl-choline receptors are widely distributed in the CNS. After activation, it regulates the phosphorylation of JAK2/STAT3 signaling pathway proteins and participates in inflammatory responses (72). EA stimulation activates α7 nicotinic acetylcholine receptors by inhibiting JAK2/STAT3 signaling and promotes the balance between the proinflammatory cytokines IL-1β and IL-6 and the anti-inflammatory cytokine IL-10 (23). Therefore, EA may affect various targets in the JAK2/STAT3 signaling pathway to inhibit inflammatory responses and reduce brain damage.

2.2.3. PI3K/Akt

The PI3K/Akt signaling pathway plays a role in regulating cell survival, proliferation, metabolism and cancer progression (73). Cannabinoid receptor (CB) 1 receptor mediates activation of the PI3K/Akt pathway and increases phosphorylation of glycogen synthase kinase 3β. Therefore, the activation of the PI3K/Akt signaling pathway may be related to neuroprotective properties (74). Increased expression of micro-glia/macrophages and the inflammatory cytokines IL-6, IL-1β, TNF-α, CD14, CD44 and inducible nitric oxide synthase were observed after cerebral ischemia (75). CI/R sig-nificantly increased the expression of Bad, p-BAD, Bcl-2 and Bax and the number of Caspase-3-positive cells in the PI3K/Akt signaling pathway. Similar to the CB1 receptor, the CB2 receptor also shows neuroprotective functions by activating the PI3K/Akt pathway in the MAPK cascade (76). After EA treatment, the expression levels of PI3K and p-Akt were significantly increased, while the expression levels of Bad, p-BAD, Bcl2, Bax and Caspase-3 were significantly decreased, indicating that EA may interfere with the expression of downstream apoptotic genes through the PI3K/Akt signaling pathway. Zhang et al. (24) combined TCM with modern medical theory, and scalp acupuncture was used to stimulate the corresponding motor cortex

projection area (GV20, etc.), and it was found that this therapy can inhibit the PI3K/Akt signaling pathway, reduce hip-pocampal neuron apoptosis, and promote functional recovery. The effect of EA on the PI3K/Akt signaling pathway may be mediated by CB receptors, which downregulate the expression of inflammatory cells.

2.2.4. ERK/JNK/p38

The MAPK family is an important signal regulating enzyme that connects cell membrane surface receptors and regulatory genes. Cellular responses to neuroprotection may involve the CB1 receptor and associated signal transduction elements, including ERK 1/2, JNK and p38, which are phosphorylated to activate and promote transcription factors to regulate cell survival, differentiation and apoptosis (77). It was reported that p38 mitogen-activated protein kinase (p38 MAPK) signaling not only promotes reactive astrocyte injury but also exacerbates progressive infarction in CI/R (78). Activation of the MAPK/ERK pathway promotes proliferation and differentiation of hippocampal endogenous neural stem cells (eNSCs) in rats and reduces neuronal apoptosis after CI (79). Another study found that activation of the MAPK/ERK signaling pathway exacerbates brain damage after CI/R, and this mechanism may be associated with activation of JNK/p38 (80, 81). The protective effects of EA may be associated with activation of the ERK1/2 pathway by the CB1 receptor, promotion of endogenous protein kinase Cε (εPKC)-mediated anti-apoptosis, and enhancement of glycogen synthase kinase 3β (15, 25). Liu et al. (82) demonstrated by dUTP gap terminal labeling and transmission electron microscopy that EA stimulation of GV20 and GV24 inhibited JNK and P38 activation, enhanced ERK1/2 activation and upregulated Bcl-2/Bax signaling pathway protein expression to promote apoptosis clearance. Studies have shown that EA may induce the ERK/JNK/P38 pathway to inhibit the upregulation of caspase-3, reverse the inhibition of ERK and Bcl-2, and exert an-ti-apoptotic and neuroprotective effects (26, 83). In addition, the ERK/p38 signaling pathway activates adenosine monophosphate response element binding protein after EA stimulation, which is a kind of selective nuclear transcription factor that regulates gene expression and nuclear translocation, is involved in cell survival, neurogenesis and neural plasticity, inhibits reactive astrocytes, and reduces TNF-α, IL-1β, and other downstream inflammatory factors (27).

2.2.5. Notch

In mammals, the Notch receptor is a highly conserved membrane-surface receptor that regulates neuronal cell development, including intracellular, transmembrane and extracellular segments. Notch 3, which is closely associated with stroke, was the first Notch gene to be identified. First, Notch 3 mutations are associated with subcortical infarction and autosomal dominant cerebral arteriopathy in leukoencephalopathy syndrome (84). In addition, Notch 1 is involved in microglia-mediated inflammation driven by NF-κB, and the use of γ-secretase inhibitors and Notch 1 antisense transgenic techniques may inhibit cerebral ischemia and reduce microglial toxicity in a synergistic manner (85). It was found that activation of eNSC CI/R in the spinal cord by the Notch signaling pathway induces differentiated astrocytes, amplifies the inflammatory cascade, inhibits eNSC diffusion and inhibits nerve repair. EA stimulation

may inhibit the expression of signaling pathways and proinflammatory cytokines, induce the proliferation and differentiation of eNSCs, inhibit the differentiation of eNSCs into as-trocytes and promote the recovery of damaged nerves (86). EA stimulation promoted the proliferation and differentiation of eNSCs into functional neurons and neuroglial cells. Tao et al. (28) found that EA of GV20 promoted the proliferation and differentiation of hippocampal eNSCs by promoting the secretion of brain-derived neurotrophic factor and neuroglial cell-derived neurotrophic factor through the Notch signaling pathway. After I/R, the level of hypoxia-induced factor-1α (HIF-1α) was significantly increased in the EA group. This neuroprotective effect was reversed by intracerebroventricular injection of a γ-secretase inhibitor and HIF-1α antagonist, suggesting that EA ischemic pretreatment may be induced by activating the Notch signaling pathway and downstream HIF-1α pathway (29).

2.2.6. BDNF/TrkB

BDNF is involved in synaptic connections and synaptic plasticity between nerve cells and is a neurotrophic factor for neuronal survival and growth (87). After stroke, activated microglia secrete more BDNF, which works by binding to the high-affinity receptor TrkB. Microglia-mediated BDNF-TrkB signaling pathway interactions play an important role in hyperalgesia after spinal cord injury. Downregulation of BDNF/TrkB signaling pathway protein expression is associated with neuronal apoptosis in the striatum. In the model of CI, inflammation is triggered by activation of microglia and astrocytes and upregulation of the BDNF/TrkB pathway in the hypothalamus and amygdala, accompanied by release of TNF-α. However, the mRNA and protein expression of BDNF and TrkB in the hippo-campus was opposite to that in the hypothalamus and amygdala and decreased after brain injury (88). Activation of the BDNF/TrkB signaling pathway may further promote neutrophil and microglia/macrophage infiltration and secretion of IL-1 and NF-κB (89). Proinflammatory cytokines in the CNS induce depression-like symptoms by activating the BDNF-TrkB pathway in the prefrontal cortex, hippocampus, and nucleus accumbens (90). EA of GV20 induces the BDNF/TrkB signaling pathway and reduces abnormal mechanical pain and hyperalgesia by mediating microglial activity and BDNF expression (30). EA increases serum BDNF secretion, activates the downstream P13K/Akt pathway, and has a neuroprotective effect on apoptosis (91). In addition, the application of the TrkB-specific inhibitor K252a inhibited the recovery of neural functions, suggesting that EA-induced upregulation of BDNF may be related to the activation of the BDNF/TrkB/p-Akt/p-ERK1/2 signaling pathway (91).

3. Blood−brain barrier and intracerebral hemorrhage

Vascular endothelial cells in the brain are closely connected by various connexins and interact with pericytes and astrocytes to form the blood brain barrier (BBB) system (92). Treatment options for CNS disorders are greatly limited by the BBB. EA may be used to induce an increase in BBB permeability, providing a potential

approach to deliver drugs from the systemic circulation to the brain (Table 1). Furthermore, intracerebral hemorrhage (ICH) is a cerebrovascular disease with a high mortality rate and usually results in impaired neurological function, which leads to long-term disability (93). Nontraumatic ICH results from cerebrovascular rupture and subsequent compression, and the pathophysiology is characterized by perihematoma ischemia, edema, apoptosis, and necrosis (94–96). Zou et al. (31) showed that inhibition of the Notch-Hes signaling pathway in the basal ganglia after ICH inhibited neuronal differentiation and maintained neural stem cell proliferation. In addition, Zhang et al. (97) found that EA pretreatment may be achieved by enhancing autophagic clearance of damaged mitochondria. The protective effect of autophagy during the reperfusion phase of IS may be attributed to the inhibition of mitophagy-related mitochondrial clearance and downstream apoptosis, as reflected by the decrease in cyclooxidase IV and translocase outer mitochondrial membrane 20 (TOMM20) and the increase in LC3-II/glyceraldehyde-3-phosphate dehydrogenase (GAPDH) after oxygen-glucose deprivation/reperfusion (97). Guan et al. (32) found that stimulation of GV20 with Qubin (GB7) could enhance mitophagy and thereby alleviate ICH. Therefore, EA (GV20-GB7) treatment may upregulate mitophagy and inhibit apoptosis after ICH.

4. Traumatic brain injury (TBI)

TBI is a common cerebrovascular disease. Due to direct/indirect violence to the head, the brain parenchyma is damaged, causing temporary/permanent loss of consciousness, memory loss, cognitive and neurological dysfunction, and a high disability/mortality rate (98, 99). Studies have demonstrated that EA is effective in the treatment of TBI (100). Moreover, a series of secondary neuroinflammatory reactions and neurological function loss caused by hemiplegia may be alleviated (Table 1). Gu et al. (101) showed that EA may inhibit the overactivation of autophagy in cortical neurons by regulating the activation of AMPK, mTOR and ULKl, downregulating AMPK and upregulating p-mTOR and p-ULK1, thereby improving the symptoms of TBI. Shi et al. (33) reported that EA could significantly improve the blood flow and oxygen uptake capacity in the damaged brain areas, promote the proliferation and differentiation of oligodendrocyte precursor cells, and improve the repair ability of neurons. He et al. (102) showed that p-AMPK induced autophagy and promoted cell apoptosis during TBI by inhibiting the activity of mTOR. Fan et al. (103) confirmed that when cells are in an abnormal state, activated AMPK may inhibit the activity of mTOR, leading to the dissociation of the mTOR-ULK1 complex and thereby activating autophagy.

5. Future directions and conclusions

The brain is the most sensitive organ to hypoxia. Cerebrovascular diseases seriously threaten human health. Above studies have shown that EA pretreatment may alleviate IS and its related symptoms and alleviate CIRI. Meanwhile, EA may relieve the symptoms of ICH and TBI. However, there are still defects in the design of EA-related experiments, and how to improve the design of experiments to avoid bias is also an urgent problem to be solved. Furthermore, EA may be used to treat a variety of diseases, but the disease spectrum is not clear, and the molecular mechanisms need to be further expanded. Additionally, perioperative EA affects the long-term health status of patients after surgery still needs to be further explored. This review mainly focus on the role of EA in the induction of molecular mechanisms in cerebrovascular protection to provide potential methods for further research. In the future, we believe that as the mechanism of EA is further revealed and clarified, the clinical application of EA during perioperative ERAS will be further expanded, and it will have brighter development prospects.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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