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REVIEW ARTICLE

H_2S-mediated inhibition of RhoA/ROCK pathway and noncoding RNAs in ischemic stroke

Weizhuo Lu[2] · Jiyue Wen[1]

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Abstract

Ischemic stroke is one of major causes of disability. In the pathological process of ischemic stroke, the up-regulation of Ras homolog gene family, member A (RhoA) and its downstream effector, Ras homolog gene family (Rho)-associated coiled coil-containing kinase (ROCK), contribute to the neuroinflammation, blood-brain barrier (BBB) dysfunction, neuronal apoptosis, axon growth inhibition and astrogliosis. Accumulating evidences have revealed that hydrogen sulphide (H_2S) could reduce brain injury in animal model of ischemic stroke via inhibiting the RhoA/ROCK pathway. Recently, noncoding RNAs (ncRNAs) such as circular RNAs (circRNAs), long noncoding RNAs (lncRNAs) and microRNAs (miRNAs) have attracted much attention because of their essential role in adjusting gene expression both in physiological and pathological conditions. Numerous studies have uncovered the role of RhoA/ROCK pathway and ncRNAs in ischemic stroke. In this review, we focused on the role of H_2S, RhoA/ROCK pathway and ncRNAs in ischemic stroke and aimed to reveal new strategies for preventing and treating this devastating disease.

Keywords H_2S · RhoA/ROCK pathway · miRNA · circRNA · lncRNA · Ischemic stroke

Introduction

Hydrogen sulphide (H_2S) is the third gaseous molecule, along with carbon monoxide (CO) and nitric oxide (NO) (Wu et al. 2015). Endogenous H_2S is one of widely distributed gaseous neurotransmitters and mainly synthesized by cystathionine-β-synthase (CBS), cystathionine-γ lyase (CSE) and 3-mercaptopyruvate (3-MST) (Wen et al. 2019). Numerous studies have revealed that H_2S mediates the variously biological effects in different ways such as inducing long-term potentiation (LTP), maintaining calcium homeostasis, inhibiting oxidative stress and regulating the neural signals under physiological condition (Kimura 2013). In addition to its biological effects, H_2S also increases intracellular calcium concentration and promotes the cyclic adenosine monophosphate (cAMP) production, as well as activates ATP-dependent potassium channels (Zhang and Bian 2014). Besides, H_2S is also related to the pathological process of the central diseases such as stroke, subarachnoid hemorrhage (SAH) and Alzheimer's disease, etc. (Gong et al. 2011).We have revealed that endogenous H_2S protects against the cerebral ischemia/reperfusion (I/R) injury via inhibiting RhoA/ROCK pathway (Wen et al. 2018, 2019).

Non-coding RNAs (ncRNAs) make up about 98–99% of RNAs generated from all mammalian genomes (Arraiano 2021). Although ncRNAs do not have the potential to be translated to proteins, they could function as vital regulatory molecules via actively interacting with nucleic acids or other molecules on almost all cellular processes in normal development and the pathological process of various diseases, containing ischemic stroke (Al Mamun et al. 2020). In addition, one ncRNA can directly interact with one or more target molecules within variously cellular signalling pathways such as RhoA/ROCK pathway, which make the regulation network mediated by ncRNAs be even more complicated (Sun et al. 2022). This review outlines the role of H_2S, Rho/ROCK pathway and ncRNAs in ischemic stroke, which has been reported recently.

✉ Jiyue Wen
wenjiyue139@aliyun.com

[1] Department of Pharmacology, School of Basic Medical Sciences, Anhui Medical University, Hefei, China

[2] Medical Branch, Hefei Technology College, Hefei, China

H_2S-mediated anti-neuroinflammation via inhibiting the RhoA/ROCK pathway in ischemic stroke

Until now, mechanical thrombectomy and intravenous thrombolysis have been widely used to treat ischemic stroke. Nevertheless, such treatments are often limited due to potential bleeding risks, narrow time window and limited eligibility criteria (Collaborators 2017). Hence, new treatment for stroke is urgently needed. The pathological process of cerebral ischemic injury includes inflammatory response, excitatory amino acid toxicity, oxidative stress, peroxidation, brain edema, free radical production, neuronal apoptosis and death (Zhu et al. 2015). Among all the damage elements, neuroinflammation is receiving increasing attention. Although inflammation and immune responses following cerebral ischemic insult contribute to isolating the injured region, an exaggerated inflammatory response could aggravate the ischemic injury (Magnus et al. 2012). Lively S et al. have found that inflammation and immune responses are crucial factors involved in the onset and progression of ischemic stroke (Lively et al. 2016).

H_2S inhibits the neuroinflammation

As one of neuromodulatory and neuroprotective molecules, H_2S can freely cross the cell membrane, thereby regulates various intracellular signaling processes in vivo (Zhang and Bian 2014), for instance, H_2S acts as an endogenous neuromodulator modulating Ca^{2+} levels in astrocytes, neurons, and microglia (Donertas Ayaz and Zubcevic 2020). Besides, CBS-produced H_2S has inhibitory effects on glia-mediated neuroinflammation, thereby exerts neuroprotective effect against cerebral ischemia injury (Zhang et al. 2017). Furthermore, beneficial effects of exogenous H_2S donors on glia-mediated neuroinflammation have also been found in various neurodegenerative conditions (Lee et al. 2016). In our previous study, we have found that supplement with H_2S could inhibit the cerebral I/R-induced release of inflammatory factors such as IL-6 and TNF-α (Ding et al. 2022).

H_2S-mediated anti-neuroinflammation via inhibiting RhoA/ROCK pathway

RhoA/ROCK pathway, widely expressed in neurons and astrocytes, is involved in the pathological process of ischemic stroke (Lu et al. 2021). Rho is active when bound to GTP while becoming inactive when bound to GDP based on the guanine exchange factors. Activated Rho-GTP activates its downstream effector, ROCK, which includes ROCK1 and ROCK2 isoforms and belongs to a serine/threonine kinases family. ROCK1 transcript is prominently expressed in non-neuronal tissues, while ROCK2 is present more abundantly in the brain and skeletal muscles (Lu et al. 2021). Besides, ROCK1 and ROCK2 can be respectively activated by caspase-3 and granzyme B via the cleavage of inhibitory C-terminal domain (Sladojevic et al. 2017).

Activated ROCK then phosphorylates its downstream effectors, including ezrin/radixin/moesin (ERM), myosin light chain (MLC), adducin, LIM kinase, collapsin response mediator protein 2 (CRMP2), and so on. As a consequence, ROCK regulates cytoskeletal rearrangement via affecting stress fiber formation, focal adhesion, smooth muscle contraction, growth cone collapse, actin filament stabilization, and actin network assembly (Amano et al. 2010). Furthermore, inhibition of ROCK could obviously lower the stress fiber formation and reduce the focal adhesion in astrocytes induced by Thy-1 (CD90), a glycosylphosphatidylinositol-anchored protein. These findings indicated the importance of the Rho/ROCK pathway in the process of neuron-glia communication (Avalos et al. 2004).

In addition, stroke-induced ROCK activation contributes to the deterioration of brain injury in the acute phase via stimulating neuronal inflammation (Laufs and Liao 1998). Inhibition of ROCK activity could mitigate the neutrophil accumulation in the ischemic area and decrease the ischemic-induced infarct volume (Satoh et al. 1999, 2001). Moreover, ROCK activation in the resident macrophages and microglias leads to the secretion of pro-inflammatory cytokine (Jin et al. 2010). ROCK inhibitor Fasudil has been found to reduce hippocampal injury by suppressing pro-inflammatory cytokine secretion from the microglial cells (Ding et al. 2010). In our previous study, we have found that CSE-derived H_2S promotes neural functional recovery after cerebral I/R injury in mice via inhibiting the RhoA/ROCK pathway (Zhang et al. 2021). Combined with the above description, we conclude that H_2S-mediated inhibition of the neuroinflammation following cerebral I/R is via inhibiting the RhoA/ROCK pathway (Fig. 1).

H_2S-mediated anti-neuroinflammation and astrocytes

Astrocytes, abundant glial cells in central nervous system (CNS), have emerged as vital regulators in health such as keeping the ionic homeostasis, as well as controlling normal neurotransmission, neurotransmitter reuptake and recycling (Abeysinghe et al. 2016). Interaction between astrocytes and endothelial cells in neurovascular unit (NVU) is crucial to adjusting BBB under both normal and pathological conditions (Abbott et al. 2006). Astrocytes could connect with neurons and blood vessels through astrocytic endfeet. During the pathological process of ischemic stroke, astrocytes

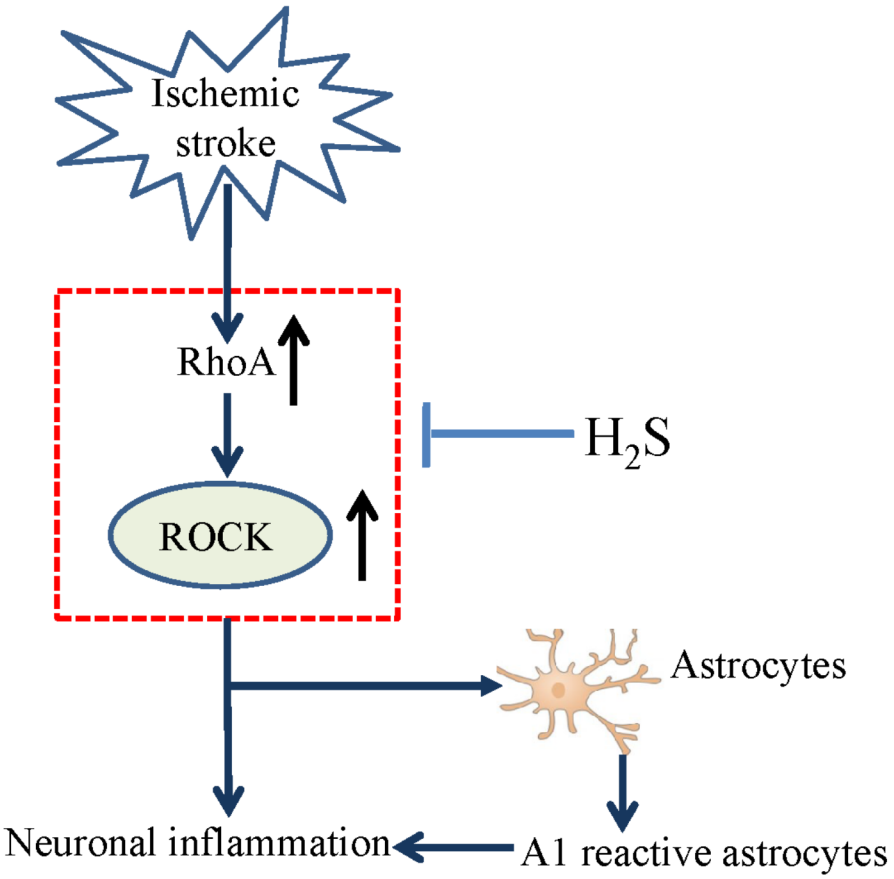

Fig. 1 Relationship between RhoA/ROCK pathway and H_2S in ischemic stroke
ROCK: Rho kinase

play multifaceted roles in the context of CNS inflammation induced by cerebral ischemia (Linnerbauer et al. 2020).

Immediately after cerebral ischemia, activation of astrocytes will happen for the oxidative stress. The activated astrocytes release excessive amounts of proinflammatory mediators, such as TNF-α, IL-6 and IL-1β, which are directly deleterious to neighboring neurons (Liu et al. 2020b; Wang et al. 2017). With the further research on distinct roles of astrocyte on neuronal injury, two distinct subtypes of reactive astrocytes, named as "A1" and "A2", have been termed by Liddelow et al. (Liddelow et al. 2017), which is widely accepted by increasing researches (Escartin et al. 2021). Ischemia and neuroinflammatory stimuli respectively induce the formation of A2 and A1 reactive astrocytes. A1 reactive astrocytes were induced by C1q, IL-1α and TNF-α secreted by activated microglia during neuroinflammation after ischemic stroke, and contribute to the death of neurons and oligodendrocytes. By contrast, the formation of A2 reactive astrocytes was induced by cerebral ischemia and A2 astrocytes were postulated as neuroprotective subtype via up-regulating neurotrophic factors (Liddelow et al. 2017). Besides, A2 astrocytes were found to promote the expression of anti-inflammatory cytokine transforming growth factor β (Wang et al. 2021c). Furthermore, A2 astrocytes obtain the capacity to phagocytize and clear myelin debris following cerebral ischemia, the accumulating myelin debris can exacerbate the inflammatory response (Jiang et al. 2021b). Therefore, promoting the formation of A2 astrocytes is a potential therapeutic strategy for inhibition of neuroinflammation and promotion of neuronal recovery after ischemic stroke (Guo et al. 2021).

Ischemic injury could induce the morphological change of astrocytes via activation of RhoA/ROCK pathway, which is complied with the retractation of astrocytic endfeet, thereby leading to the breakdown of neurovascular coupling, as well as formation of reactive astrogliosis (Abeysinghe et al. 2016; LeComte et al. 2015). We previously have found that H_2S could not only restrain the proliferation of reactive astrocytes induced by cerebral I/R but also promote the transformation of reactive astrocytes from A1 type to A2 type in mice hippocampal tissues (Ding et al. 2022). In addition, we have revealed that H_2S-mediated transformation of astrocytes from "A1" to "A2" is related to inhibition of RhoA/ROCK pathway (Fig. 1).

The relationship between H_2S-mediated inhibition of RhoA/ROCK pathway and ncRNAs in ischemic stroke

What is ncRNA and its contribution to ischemic stroke

Noncoding RNAs (ncRNAs) constitute the majority of the human transcribed genome, they initially were considered as junk. NcRNAs started to gain more and more attention for they were considered as key regulatory factors in cellular and biological processes, ranging from gene expression to genome remodeling in the early 21st century (Jae and Dimmeler 2020). Besides, the ncRNAs have been recognized as important contributors to both disorder and cellular homeostasis in CNS (Deng et al. 2022; Zhang et al. 2022). The group of ncRNAs contain microRNA (miRNA), circular RNA (circRNA), long noncoding RNA (lncRNA), and so on (DeOcesano-Pereira et al. 2020).

MiRNA

MiRNAs, consisting of 20–22 nucleotides, adjust gene expression via interacting with the 30-untranslated region (UTR) of the target mRNAs (Mirzaei et al. 2018). Primary RNA (pri-RNA) of miRNA, transcribed from genomic DNA, contains at least one hairpin loop and some long loops with several thousand base pairs. This hairpin loop of pri-RNA is cleaved by the endonuclease Drosha to generate precursor miRNA (pre-miRNA) (Basyuk et al. 2003; Han et al. 2004; Lee et al. 2002), which is transported by the intervention of exportin-5 from the nucleus to the cytoplasm. In the cytoplasm, pre-miRNAs are cleaved to form a duplex of mature miRNA strands (Chendrimada et al. 2005; Hutvagner et al. 2001; Lau et al. 2001). Mature miRNAs control various cellular functions such as neuronal development, proliferation, metabolism and differentiation, and synaptic plasticity (Bartel 2004). Previous studies have shown that miRNAs participated in pathological process of stroke via affecting the neuroinflammation, apoptosis, oxidative stress and vascular endothelial damage (Bam et al. 2018; Khoshnam et al. 2017).

MiRNAs mediate post-transcriptional gene regulation by controlling the mRNA translation into protein (O'Brien et al. 2018), thereby involve in multiple cellular functions such as injured tissue repair, neuronal development, remodeling different neuronal activities in ischemic stroke (Khoshnam et al. 2017). MiRNAs and their target genes exert a key inhibitory effect on the cerebral I/R-induced neuroinflammation, which make miRNAs as potential therapeutic targets in ischemic stroke (Khoshnam et al. 2017). Lots of miRNAs participate in controlling target genes expression of ischemic stroke risk factors. For instance, single nucleotide polymorphisms (SNPs) within the binding site of miRNA could affect miRNA-induced genetic repression, which is called miR-SNP. Mu-En Liu et al. have found that miR-SNP rs3735590 at the paraoxonase 1 (PON1) gene is associated with an elevated risk for ischemic stroke because it could affect genetic expression (Liu et al. 2013).

Afterwards, increasing circulatory miRNAs such as PC-3p-57,664, miR-211-5p, PC-5p-12,969 and miR-122-5p were successively identified as biomarkers for early diagnosis of ischemic stroke because of their up-regulation in human ischemic stroke serum samples (Vijayan et al. 2018). Furthermore, accumulated researches have revealed that miRNAs are related to neurogenesis, angiogenesis and neuroprotection after ischemic stroke (Bulygin et al. 2020). Therefore, miRNAs have recently been used as potential biomarkers for early diagnosis and prognosis, and used as a therapeutic target for ischemic stroke.

Circular RNAs

CircRNAs, containing multiple exons or a single exon, are mainly expressed from known protein coding genes, and generally locate in the cytoplasm (Memczak et al. 2013). Despite the generally lower expression than their linear counterparts, many circRNAs are the predominant transcripts. Besides, competition between back splicing and canonical splicing is likelihood to exist for the majority of loci that produce circRNAs (Hansen et al. 2013). It is well known that circRNAs are enriched in the nervous system, and affect neuronal migration and axon growth (Ostolaza et al. 2020). Besides, circRNAs interact with human RNA binding proteins and take part in neuronal development under physiological status and participate in the pathogenesis of neurological diseases. CircRNAs protect the dysfunction of BBB, and inhibit the neuroinflammation and apoptosis following cerebrovascular diseases (Wang et al. 2020c). Thus, circRNAs are gaining interest as a possible biomarker for their several functions in the onset and progression of ischemic stroke. Therefore, understanding the role of circRNAs on the ischemic stroke process will provide us new biomarkers for the diagnosis and prognosis of ischemic stroke.

CircRNAs were initially known as viroids in 1976. Subsequently, circRNAs were detected in many species such as unicellular prokaryotes, eukaryotes and mammals (Huang et al. 2020). Further researches have revealed that circRNAs could act as protein scaffolds or miRNA sponges and could be translated into polypeptides (Wang et al. 2018b). Notably, circRNAs are revealed to adjust the target genes expression at the post-transcriptional level through antagonizing the activity of miRNA through a sponge-like mechanism

(Granados-Riveron and Aquino-Jarquin 2016). CircRNAs could act as competitive endogenous RNAs (ceRNAs), which contains harbors miRNA response elements (MREs) and can compete for miRNA binding.

Moreover, circRNAs have the same selective transcribed sequences which can capture the corresponding linear mRNAs and may exert specific roles via influencing the combination of other RNAs. CircRNAs affect the miRNA expression through micro-adjustment, for example, circRNAs perturb miRNA function via competing with miRNA combination, and then, blocking the posttranslational repression of target-coding RNA species and adjusting the expression levels of target genes (Rybak-Wolf et al. 2015). The combination ability of circRNAs with miRNAs is 10 times higher than other known transcriptions (Chen et al. 2015). Furthermore, circRNAs serve as a natural miRNA sponges those bind with corresponding miRNAs and then restrain the activity of them, thus regulating target genes (Shao and Chen 2016).

LncRNAs

LncRNAs, comprising more than 200 nucleotides, regulate gene expression via various mechanisms (Mercer et al. 2009) at transcriptional, epigenetic, post-transcriptional and chromatin remodeling levels (Bali and Kuner 2014). LncRNAs can activate or inhibit target genes expression by directly binding to the recruiting transcription factors or the target genes (Li et al. 2018b). LncRNAs exert the spatiotemporal regulation for cell type-specific genes expression and physiological functions via regulating the transcription at multiple levels (Li et al. 2022b). Thus, not surprisingly, lncRNAs have been shown to adjust the neural differentiation and specification, and maintain the cell identity. Furthermore, dysregulation of lncRNA function has been found to be involved in multiple neurological diseases such as ischemic stroke (Bao et al. 2018).

LncRNAs are associated with inflammation, cell apoptosis, angiogenesis and cell death in ischemic stroke (Wang et al. 2020a, b; Xiang et al. 2020; Zhang and Zhang 2020). Thus, lncRNAs are emerging as a new therapeutic target of ischemic stroke (Bao et al. 2018). X-inactive specific transcript (XIST) RNA is one of lncRNAs, which regulates X chromosome inactivation in mammals (Chen et al. 2017). During the late stage after the onset of ischemic stroke, LncRNA XIST exhibits increased expression, and the lncRNA XIST level in sera of ischemic stroke patients was obviously negatively correlated with the severity of neurological impairments. Therefore, lncRNA XIST has been regarded as a therapeutic target for stroke patients and been considered as a potential biomarker for the prognosis of ischemic stroke (Wang et al. 2021a). Silencing lncRNA XIST markedly impairs the angiogenesis and exacerbates cerebral vascular injury (Wang et al. 2021a).

What's the relationship between H_2S-mediated inhibition of RhoA/ROCK pathway and ncRNAs

MiRNA

Endogenous H_2S mediates biological effects in a variety of ways in plenty of disease models. Controlling H_2S content exerts a protective role on the cerebral ischemia, making it becomes a therapeutic candidate for cerebrovascular diseases. In CNS of mammals, H_2S is mainly produced by CBS (Renga 2011), which is expressed in radial glial/astrocyte cell lines. The up-regulation of CBS expression in active astrocytes promotes the recovery of injured neurons, suggesting that CBS-produced H_2S, mainly from astrocytes, plays important roles in a variety neuronal damages induce by I/R and oxidative stress (Campagnoli et al. 1971; Kimura et al. 2010). At present, accumulating literature reports have revealed a close relationship between miRNA and H_2S, uncovered that H_2S is involved in different pathophysiological processes via up-regulating the expression of miRNAs such as miR-393, miR-396 and miR-398 (Liu et al. 2011). Using miScript microRNA (miRNA) polymerase chain reaction array-based screening, Jyotirmaya et al. have identified miR-218 as a particular miRNA, and found that H_2S could up-regulate the expression of miR-218 and then protect endothelial cells against ethanol-induced permeability (Behera et al. 2021).

Despite the diverse target genes of miRNAs associated with ischemic stroke, RhoA/ROCK pathway related with miRNAs was only wildly reported in ischemic stroke in recent years (Kimura et al. 2021). Jiang et al. have revealed that RhoA was a direct target of miR-190 by using cerebral I/R model and found that the overexpression of miR-190 ameliorates the brain damage and apoptosis via down-regulation of RhoA/ROCK pathway (Jiang et al. 2021a). Using model of traumatic brain injury, Lilja Meissner have found that MiR-190 is down-regulated after cerebral injury (Meissner et al. 2016). Besides, RhoA/ROCK pathway is up-regulated in mice brain tissues after cerebral I/R (Ding et al. 2022). These findings confirmed that MiR-190 may be used as a biomarker for diagnosis of cerebral injury and a therapeutic target of ischemic stroke.

Along with decreased miR-431 expression, Han et al. have observed a significant increment of RhoA expression in rat middle cerebral artery occlusion

(MCAO)/R model, suggesting that RhoA was the potential target gene of miR-431. They revealed the neuroprotective effects of miR-431 and concluded that miR-431 inhibited apoptosis and promoted proliferation by negatively

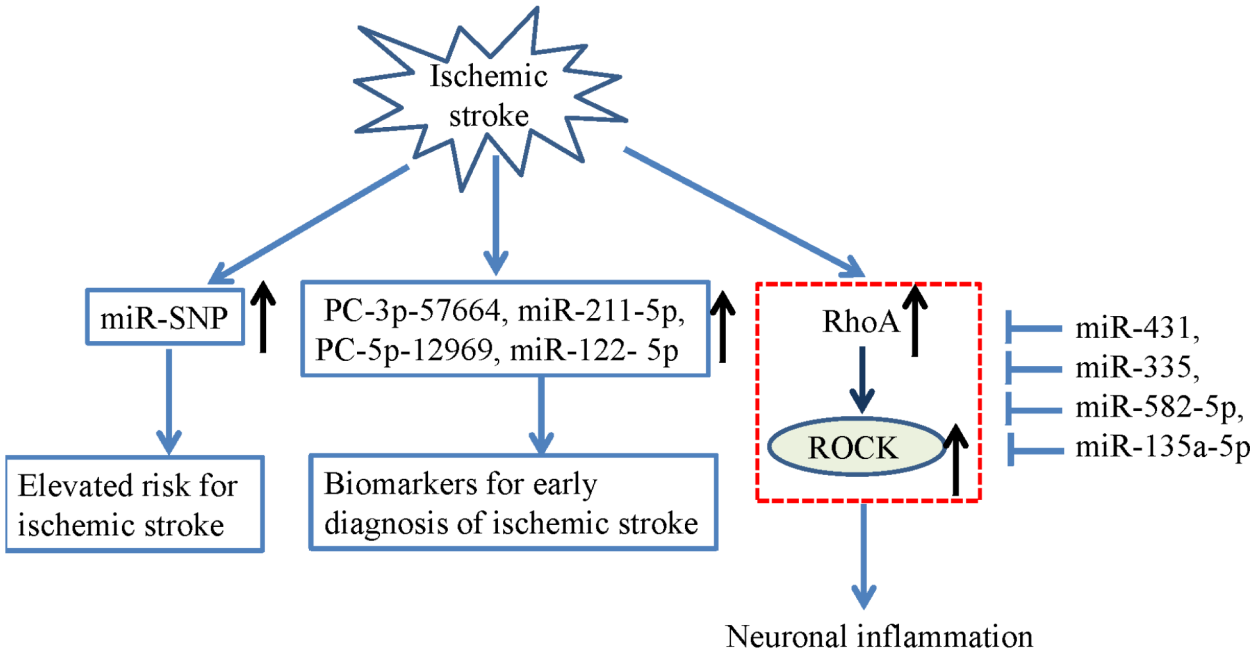

Fig. 2 Relationship between RhoA/ROCK pathway and miRNA in ischemic stroke

regulating the RhoA/ROCK pathway (Han et al. 2018). The relationship between anti-apoptotic effect of miR-335 and the RhoA/ROCK pathway has been revealed by Si et al. They have found that miR-335 promotes the formation of stress granules (SGs) by inhibiting the ROCK2 expression (Si et al. 2019). SGs generates in the cytoplasm when eukaryotic cells suffer from stress such as heat shock, acute energy starvation and endoplasmic reticulum stress (Gutierrez-Beltran et al. 2015). The formation of SGs protects the mRNA and proteins against misfolding and degradation, which enhances cellular resistance to apoptosis (Sampuda et al. 2017). Stein ES et al. have found that miR-582-5p expression decreases after cerebral I/R, while the expression of RhoA and ROCK2 increases. The over-expression of miR-582 alleviates the neuronal apoptosis via inhibiting the up-regulation of RhoA/ROCK pathway (Olson et al. 2004; Stein et al. 2015).

MiR-135, one of miRNAs, has been shown to be involved in regulation of cell regeneration and differentiation (Xie et al. 2016). Liu et al have found that miR-135a-5p is involved in the regulation of ROCK2 expression by targeting the 3'-UTR of ROCK2 mRNA to inhibit its protein translation in a mouse model for Parkinson's disease (Liu et al. 2016). They have revealed that H_2S could inhibit the up-regulation of ROCK2 expression in brain tissues but not affect the mRNA of ROCK2. Furthermore, the research demonstrated that miR-135a-5p mediated the inhibitory effect of H_2S on ROCK2 expression. In a word, some miRNAs could inhibit the up-regulation of RhoA/ROCK pathway after ischemic stroke (Fig. 2). Combined with the previous description that H_2S could up-regulate the expression of miRNAs such as miR-393, miR-396 and miR-398 [56], we speculate that H_2S-mediated inhibition of RhoA/ROCK pathway maybe related to up-regulation of miRNAs expression, which needs further exploration.

Circular RNAs

As aforementioned, circRNAs are shown to play a key role in regulating genes expression through the circRNA-miRNA-mRNA pathway via acting as miRNA sponges (Liu et al. 2017). Zhao et al. have found that circRNAs play a vital role in cerebral ischemia. They have revealed that knockdown of circRNA_0072309 can accelerate the cell apoptosis following ischemic stroke and demonstrated that the role of circRNA is via sponge miR-100 (Zhao et al. 2020). Silencing circRNA cZNF292 alleviates oxygen-glucose deprivation/reperfusion (OGD/R)-induced injury of rat neural stem cells by upregulating miR-22 (Cao et al. 2020). Furthermore, Circ_002664 has been found to participate in neuronal apoptosis following OGD/R via directly targeting miR-182–5p/Herpud1 pathway (Liu et al. 2020a). All of these studies illustrated the relationship between miRNA and circRNAs (Fig. 3).

Although there is no finding about the relationship between circRNA and RhoA/ROCK pathway in the

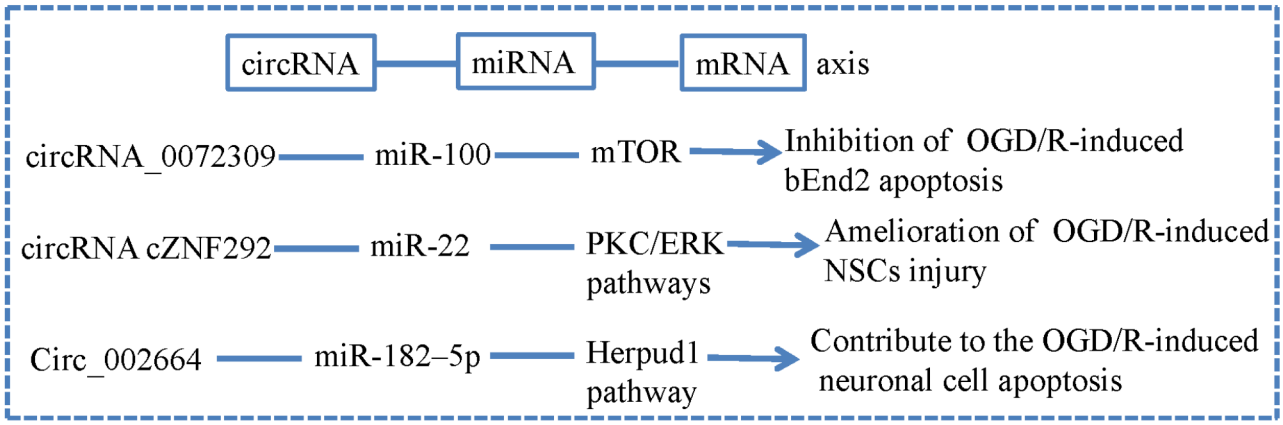

Fig. 3 Relationship between circRNA pathway and miRNA in ischemic stroke

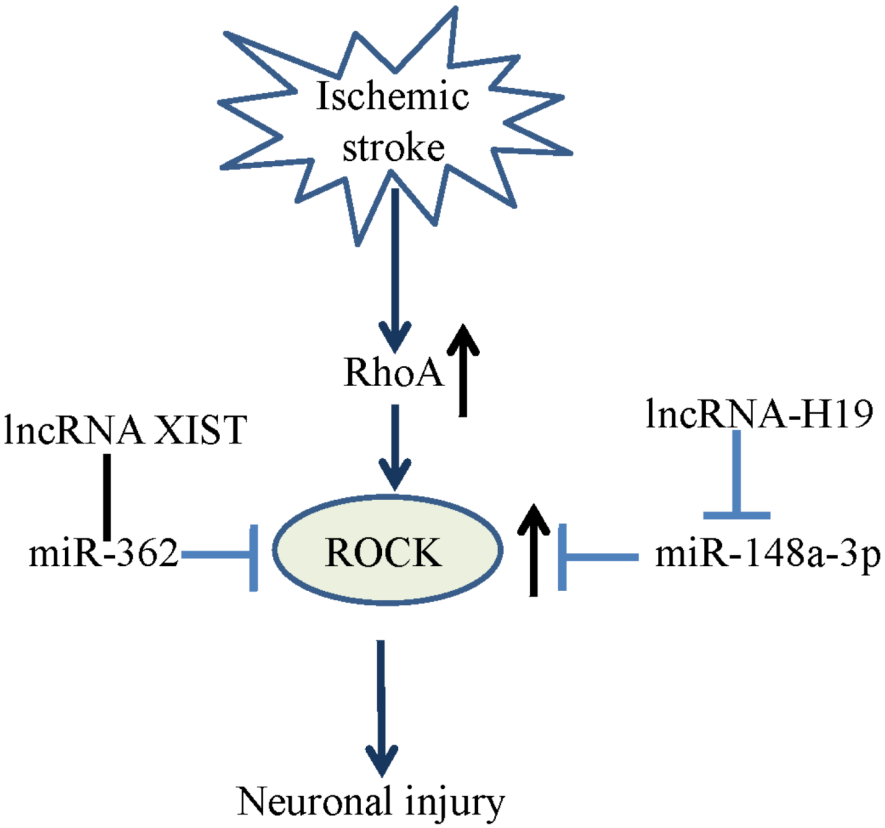

Fig. 4 Relationship among lncRNA, miRNA and RhoA/ROCK pathway in ischemic stroke

ischemic stroke, circNRIP1, one of circRNAs, has been demonstrated to enhance ROCK1 expression in gastric cancer cells, thereby promoting carcinogenesis. Overexpression of miR-182 could significantly inhibit the luciferase activity of ROCK1-expressing MGC-803 in AGS cancer cells (Liang and Li 2020). ROCK1 has been founded to be upregulated in miR-584-3p inhibitor-transfected SCLC cells. FLI1 exonic circRNA (FECR) silencing results in a reduction of ROCK in small cell lung cancer cells (Li et al. 2019). In addition, the researchers have found that FECR reduces the inhibitory effects of miR-584-3p on ROCK1 expression by sponging the miRNA away from its target (Li et al. 2019). Furthermore, in melanoma cells, ROCK1 was directly targeted by miR-431-5p. Circ0001591 could antagonize the miR-431-5p-mediated targeting of ROCK1 (Yin et al. 2021). Circ_101141, an oncogenic circRNA has been

found to block miR-1297-mediated inhibition of ROCK1 expression (Zhang et al. 2020).

LncRNAs

Previous studies have revealed that lncRNAs interact functionally with various miRNA molecules via competitively binding with miRNAs, thereby resulting in miRNA degradation (Siddeek et al. 2014). This interaction has been found in ischemic stroke (Yan et al. 2017). Among the predicted potential XIST targeting miRNAs, Liu et al. have found that XIST directly interacts with miR-362-5p on breast cancer cell malignant behaviors, they have revealed that miR-362-5p mediates the regulatory effects of XIST overexpression (Liu et al. 2021). MiR-362 acts as a target of lncRNAs in regulation of the development of tumors (Wei et al. 2020). However, the studies on the functional role of miR-362 in ischemic stroke are still rarely.

In the acute phase of stroke, ROCK activation leads to the deterioration of cerebral injury by stimulating neuroinflammation (Laufs and Liao 1998). Inhibition of ROCK reduces neutrophil accumulation in the ischemic region and lessened the infarct volume (Satoh et al. 2001). Wang et al. have found that ROCK2 is the candidate target of miR-362 using the TargetScan database. Using the cerebral I/R model, Wang et al. have revealed the relationship among XIST, miR-362, and ROCK2. They found that knockdown of miR-362 or over-expression of ROCK2 attenuates the effect of XIST down-regulation on OGD/R-induced neuronal impairment and inflammation injury. These findings revealed that knockdown of XIST ameliorates the ischemic stroke injury through regulation of miR-362/ROCK2 axis (Wang et al. 2021b). Using bioinformatic software combined with sequence complementation analysis, Zeng et al. have demonstrated that miR-148a-3p is an inhibitory target of lncRNA-H19. They found that miR-148a-3p is a located downstream of lncRNA-H19 that regulates cerebral ischemic processes. Besides, the researchers have revealed that miR-148a-3p directly targets the 3′UTR of ROCK2 in N2a cells and inhibits the expression of ROCK2 at both mRNA and protein levels in N2a cells. As a result, lncRNA-H19 promotes the OGD/R-induced oxidative stress by down-regulating miR-148a-3p to increase ROCK2 expression (Zeng et al. 2019).

LncRNA/miR-376a/CBS/H_2S axis

H_2S, an uprising gasotransmitter, is associated with stoke regulation. H_2S exerts imperious role in maintaining homeostasis of cerebrovascular function under physiological condition. Not surprisingly, reduction of H_2S level is related to endothelial dysfunction and pathological process of ischemic stroke (Narne et al. 2019). Cerebrovascular protection of H_2S was validated by the promotion of vascular remodeling and regeneration induced by supplement with H_2S (Nath et al. 2019). CBS is the main synthase for H_2S production in the brain, enhancement of CBS-produced H_2S concentration alleviates brain injury and exerts inhibitory effect on the inflammatory responses following mimicking ischemia stroke of mice (Zhang et al. 2017).

Bioinformatics predictions indicate the direct interaction between H_2S synthase CBS and miR-376a, which is closely related to the occurrence and development of stroke (van Kralingen et al. 2019). Moreover, risk factors of ischemic stroke such as apoptosis, oxidative stress, inflammation and excitotoxity are all found to be regulated by miRNAs (Li et al. 2018a). Thus, the hypothesis is worthy discussing to explore whether miRNA can regulate the pathological process of stroke through CBS/H_2S pathway.

Recent studies have indicated that lncRNA can act as competing endogenous RNAs and interact with and immobilize miRNA via conserved sequences, protecting their target genes (Zhang et al. 2016). Abnormal expression of lncRNA is also related to the occurrence of many diseases such as cerebral ischemic stroke (Yu et al. 2019). Besides, lncRNA SNHG1 can alleviate oxygen-glucose deprivation (OGD) injury of brain microvascular endothelial cells, which confirms that lncRNAs exert a key role in the pathogenesis of stroke (Yang and Zi 2019). Bioinformatics analysis have further revealed that the targeting effect of SNHG1 is via inhibiting miR-376a (Meng et al. 2021).

Using OGD model of human cerebral microvascular endothelial cell line (HCMIEC/D3), Li et al. sought to explore whether lncRNA SNHG1 can ameliorate OGD injury of HCMIEC/D3 through CBS/H_2S pathway through targeting miR-376a. They have found that SNHG1 and CBS expression at RNA level in HCMEC/D3 cells is downregulated while miR-376a is upregulated, inhibition of miR-376a blocks the apoptosis and inflammation in HCMEC/D3 cells under OGD conditions. In addition, the researchers have revealed that miR-376a exacerbates apoptosis and inflammation in OGD-induced HCMEC/D3 cells via inhibiting CBS/H_2S production. While the researchers also have found that overexpression of lncRNA SNHG1 reduces the apoptosis and inflammation in OGD-induced HCMEC/D3 via inhibiting miR-376a and up-regulating CBS/H_2S production (Lv et al. 2021).

The challenges of H_2S and RhoA/ROCK pathway-based therapies for ischemic stroke

H_2S

Although H_2S has specific neuroprotection on the cerebral ischemic injury, several issues hinder the clinical translation of H_2S-based therapies from the bench. First, we know very little about the effect of endogenous H_2S in pathological process of stroke. Second, the neuroprotective mechanisms underlying the therapeutic effects of H_2S is not complete clear. Besides, it is not clear whether the therapeutic mechanisms of H_2S can be isolated from its toxic mechanisms. Until now, research mainly use the gene knockout of H_2S synthases or the inhibitors of them to investigate the effect of endogenous H_2S in pathological process of stroke. No clear conclusion has been obtained based on these studies (Jia et al. 2019). Third, present research almost exclusively focuses on the acute neuroprotection of H_2S against cerebral ischemia. It is of great importance to examine the effect of H_2S on long-term stroke outcomes.

ROCK inhibitors

In view of the evidence of increased ROCK activity in pathological conditions of ischemic stroke, it is of great importance to determine the precise effect of ROCK in ischemic stroke and stroke recovery by using ROCK inhibitors. Y-27,632 is a selective and highly potent inhibitor of ROCK. It binds intracellularly to the catalytic site of ROCK (both ROCK1 and 2), thereby inhibits its kinase activity. Y-27,632 has been shown to inhibit ROCK kinase activity in neurons, smooth muscle cells and epithelial cells (Gong and Yang 2014). Y-27,632 has been used in treating spinal cord injury, for it is known to promote neurite outgrowth and axonal regeneration in neurons (Wang et al. 2018a).

But for the important limitation of the nonselective mechanism of ROCK inhibitor and for the use of ROCK inhibitors which inhibit other serine-threonine kinases such as PKC and PKA at higher concentrations, Fasudil is the only ROCK inhibitor approved for human use in China and Japan to treat and prevent cerebral ischemia, and subarachnoid hemorrhage-induced vasospasm (Sladojevic et al. 2017). KD025 (formerly SLx2119), a selective ROCK2 inhibitor, also has neuroprotective effect and can improve the mice outcome after focal cerebral ischemia in a dose-dependent manner by improving collateral cortical blood flow. Interestingly, KD025 has been shown to be safe when compared with nonselective ROCK inhibitors in aged, diabetic, or female (Lee et al. 2014).

The challenges of ncRNA-based therapies for ischemic stroke

MiRNA

MiRNAs, enriched in brain, can regulate the expression of potentially deleterious genes in post-transcriptional manner after ischemic stroke, thereby might be potential targets. However, all the mechanisms of cerebral I/R injury are simultaneously present during ischemic stroke and it is not easy to isolate these events from each other. Neuroprotective effect of miRNAs is interlinked with inhibition of neuroinflammation (Alhadidi et al. 2022), oxidative stress damage (Zhai et al. 2022) and neurons loss, as well as promotion of neuronal recovery (Zhou and Qiao 2022). Overexpression of the miRNAs such as miR-216a (Tian et al. 2018) and miRNA-589 (Ma et al. 2020) exerts neuroprotection and improves the outcome after cerebral I/R. While some other miRNAs such as microRNA-153 (Yan et al. 2020) impair the presynaptic plasticity and injure the neurological function after cerebral I/R. Therefore, "reversing" the expression of the miRNAs (overexpression or inhibiting an overexpressed miRNA) improves the outcome and studied parameters. These findings could mean that a miRNA-centered therapeutic approach could be beneficial. It is very likely that this strategy in a clinical setting is insufficient. Further study is needed to evaluate the exact roles of miRNAs in cerebral I/R injuries and to assess the most favorable candidates as treatment options.

CircRNA

Based on mouse model subjected to transient MCAO, Mehta et al. have found that there are 283 circular RNAs altered compared with sham control by using circular RNA microarrays and real-time PCR (Mehta et al. 2017). Bai et al. have found that circRNA DLGAP4 (circDLGAP4) is increased both in the plasma of ischemic stroke patients including 13 females and 13 males and in mice plasma of stroke model. Besides, they have revealed that circDLGAP4 serves as a microRNA-143 sponge. More importantly, the research revealed that overexpression of circDLGAP4 could obviously reduce infarct area and decrease neurological deficits in mouse stroke model following transient MCAO. These data indicated that circDLGAP4 provide a novel therapeutic target for treatment of cerebral ischemic diseases (Bai et al. 2018).

LncRNA

The potential diagnostic and therapeutic roles of lncRNAs have been made in ischemic stroke. Nevertheless, there is

still several challenges in the way of lncRNA-based translational research for ischemic stroke. For example, more sensitive methods for RNA detection should be established due to the lncRNAs expression is relatively low in comparison to the levels of mRNAs and proteins in the circulation system. In addition, there is still a significant challenge that the targeted lncRNAs deliver into the CNS of stroke patients. The carry ability of viral vectors, non-viral vectors, nanoparticles, exosomes, chemically modified antisense oligonucleotides, and liposomes to carry lncRNA-based drugs into the cerebral infarction area should be evaluated (Bar et al. 2016; Li et al. 2022a).

Conclusion

Cerebral ischemia-induced upregulation of RhoA/ROCK pathway is deeply involved in the pathological process of ischemic stroke in various ways such as neuroinflammation. Growing evidences have revealed that both exogenous and endogenous H_2S could ameliorate cerebral I/R-induced brain injury via inhibiting of the RhoA/ROCK pathway. Here, we introduced the inhibitory effect of H_2S on the neuroinflammation after ischemic stroke via inhibiting the RhoA/ROCK pathway, and discussed the relationship among H_2S, Rho/ROCK pathway and ncRNAs in ischemic stroke. Besides, we also discussed the challenges of RhoA/ROCK pathway, as well as ncRNA-based therapies for ischemic stroke. Furthermore, as mentioned in this review, circRNAs, miRNA and lncRNA, have been proposed as valuable biomarkers for diagnosing ischemic stroke. Therefore, endogenous H_2S, Rho/ROCK pathway and ncRNAs are worthy of further exploration as therapeutic targets for ischemic stroke.

Authors' contribution WZL had the main idea of the article; WZL was a major contributor in writing the manuscript; JYW organized the sequence of the whole manuscript, and thoroughly revised the manuscript.

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Data Availability Data sharing is not applicable to this review article as no new data of our own were created.

Declarations

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

Conflict of interest All authors declare that there is no conflict of interest.

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