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Review

Caveolin-1 and MLRs: A potential target for neuronal growth and neuroplasticity after ischemic stroke

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Abstract

Ischemic stroke is a leading cause of morbidity and mortality worldwide. Thrombolytic therapy, the only established treatment to reduce the neurological deficits caused by ischemic stroke, is limited by time window and potential complications. Therefore, it is necessary to develop new therapeutic strategies to improve neuronal growth and neurological function following ischemic stroke. Membrane lipid rafts (MLRs) are crucial structures for neuron survival and growth signaling pathways. Caveolin-1 (Cav-1), the main scaffold protein present in MLRs, targets many neural growth proteins and promotes growth of neurons and dendrites. Targeting Cav-1 may be a promising therapeutic strategy to enhance neuroplasticity after cerebral ischemia. This review addresses the role of Cav-1 and MLRs in neuronal growth after ischemic stroke, with an emphasis on the mechanisms by which Cav-1/MLRs modulate neuroplasticity via related receptors, signaling pathways, and gene expression. We further discuss how Cav-1/MLRs may be exploited as a potential therapeutic target to restore neuroplasticity after ischemic stroke. Finally, several representative pharmacological agents known to enhance neuroplasticity are discussed in this review.

Key words: Caveolin-1, membrane lipid raft, ischemic stroke, neuronal growth, neuroplasticity, non-coding RNA.

1. Introduction

Ischemic stroke is a common nervous system disease associated with high rates of disability and mortality. Ischemic stroke results from disruption of blood supply, resulting in hypoxic necrosis of brain tissue, and manifestation of corresponding neurological deficits [1]. The most effective treatment for acute ischemic stroke is intravenous administration of recombinant tissue plasminogen activator (rt-PA) within 3-4.5 hours after stroke to induce thrombolysis. However, less than 5% of patients are able to receive thrombolytic therapy within the critical time window because they do not meet the criteria for thrombolysis. In addition, owing to increased risk of hemorrhagic transformation, clinical application of thrombolytic therapy is limited [2]. There is currently no therapeutic strategy to improve stroke-related deficits. Recent studies have focused on identification of effective neuroprotectants and nerve repair drugs to protect brain tissue and promote neuronal growth and neuroplasticity following ischemic stroke.

This review will highlight the role of Cav-1 and MLRs in neuronal growth following ischemic stroke, with an emphasis on the mechanisms by which Cav-1/MLRs modulate neuroplasticity via related receptors, signaling pathways, and genes. Potential clinical applications will also be discussed.

2. Cav-1 and MLRs in neuronal growth and neuroplasticity after ischemic stroke

Recent studies have shown that new neurons are born during cerebral ischemia, and the underlying mechanisms of neuroplasticity may provide a basis for pharmacological enhancement of treatment of ischemic stroke [3]. Neuroplasticity includes structural and functional plasticity [4]. Structural plasticity is characterized by changes in neurite length, dendritic spine density, and synapse number. Functional

plasticity is characterized by changes in synaptic transmission efficiency [5]. Neuroplasticity involves angiogenesis, nerve regeneration, and synaptogenesis [6], which includes proliferation, migration, and differentiation of neural stem cells (NSCs) to mature neurons [7]. Neurotrophins (NTs) such as nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), and neurotrophic factors NT3, NT4 and NT5 are important promoters of neuroplasticity [8]. Neurotrophins exert physiological effects through specific binding to receptors on cell membranes (including Trk-A, Trk-B, Trk-C, etc.). Neurotrophin binding to receptors occurs in discontinuous regions of neuronal cell membranes called membrane lipid rafts (MLR), which are crucial structures for neuronal survival and function of growth signaling pathways [9]. Furthermore, MLRs are crucial to development, stability, and maintenance of synapses [10].

MLRs are rich in cholesterol, sphingomyelin, and scaffold proteins. In addition, caveolin, a scaffolding and cholesterol-binding protein, is enriched in MLRs. Caveolin is a structural component of caveolae, which are components of lipid rafts, and are highly ordered microdomains located in the plasma membrane [11]. The caveolin family has three members in mammals: caveolin-1 (Cav-1), caveolin-2 (Cav-2), and caveolin-3 (Cav-3). Cav-1 is expressed ubiquitously, but at different levels in different tissues. Caveolin-2 is co-expressed with Cav-1, and Cav-3 is expressed predominantly in muscle cells, such as skeletal, smooth, and cardiac myocytes [12]. In the brain, Cav-1 and Cav-2 are primarily expressed in endothelial cells and neurons, and Cav-3 is expressed in astrocytes [13]. Caveolin-2 may not be essential for caveolae formation, as caveolae formation is not affected in Cav-2-knockout mice [14].

Neurite and dendrite outgrowth consists of protrusion, engorgement, and consolidation. Membrane lipid rafts are located at the leading edge of neuronal growth cones, providing an essential plasma membrane platform to establish cellular polarity and to compartmentalize pro-growth signaling components [15]. Caveolin-1 is the main cholesterol binding protein in MLRs, and is important in many cellular functions [16]. In addition, Cav-1 is a target protein for many neuronal growth-promoting proteins expressed in MLRs, which promote growth of neurons and dendrites [17]. In addition, Cav-1 is a regulator of membrane cholesterol, and is directly involved in synthesis and transport of intracellular cholesterol, which is important for maintenance of cholesterol homeostasis and formation of MLRs [18]. A recent study showed that Cav-1 regulates N-cadherin and L1CAM trafficking independent of caveolae, resulting in immature neurite pruning and early neuronal maturation [19]. Many neurodegeneration studies have shown that neuron-targeted overexpression of Cav-1 increased MLR formation, pro-growth receptor localization to MLRs, myelination, and long-term potentiation, resulting in neuronal development and regeneration [20-23]. Furthermore, synapsin-driven overexpression of Cav-1 was shown to preserve and restore NT-receptors expression and localization to MLRs, resulting in delayed progression of ALS in a mouse model [24]. These studies suggested that Cav-1 and MLRs may be potential therapeutic targets to promote neuroplasticity in neurological disorders. Caveolin-1 may be a key factor in maintenance of MLRs and neuroplasticity after ischemic stroke.

3. Role of receptors associated with Cav-1 and MLRs in neuronal growth and neuroplasticity after ischemic stroke

Following ischemic stroke, disruption of pro-survival and pro-growth signaling pathways limits neuroplasticity and subsequent recovery. Several receptors associated with Cav-1 and MLRs are crucial to neuroplasticity, and may be potential therapeutic targets to improve functional recovery after ischemic stroke.

3.1. Src family kinases

The Src family kinases (SFKs) are non-receptor tyrosine kinases involved in signal transduction that modulates cell morphology, adhesion, migration, invasion, proliferation, differentiation, and survival [25]. Caveolin was discovered as a phosphorylation target of the kinase encoded by Rous sarcoma virus, v-Src kinase, which was the first tyrosine kinase to be identified [26]. Phosphorylation of caveolin at Tyr14 (pY14-Cav1) inhibits Src through recruitment of C-terminal Src kinase [27]. In mouse embryonic fibroblasts (MEFs), Cav-1 knockout increased the activation of Src, resulting in morphological changes and inhibition or polarization and directed motility [28]. In addition, aggregation of Cav-1 and MLR has been show to activate the proto-oncogene tyrosine protein kinase Src (c-Src) to induce gastric cancer cell migration [29]. Src has also been shown to modulate neuronal growth and oligodendrocyte maturation [30]. Another study showed that Cav-1 activated Src and enhanced N-methyl-D-aspartate receptor (NMDAR) localization on MLRs, resulting in protection against hypoxia in cultured neonatal rat neurons [31]. Based on these findings, modulation of Src and Cav-1 may provide a novel approach to promote neuronal growth after ischemic stroke.

3.2. Tropomyosin-related kinase receptors

Neurotrophins are a family of growth factors that mediate development and survival of neurons and glial cells. Furthermore, NTs are essential effectors of neuroplasticity [32]. Many signals elicited by neurotrophins (NGF, BDNF, and NT3,4) require binding to the tropomyosin-related kinase (Trk) receptor family (TrkA, TrkB, and TrkC) to activate downstream signaling pathways [33], and the combination process was performed in MLRs [21]. Limitation of functional recovery following stroke is primarily a consequence of downregulation of pro-growth and pro-survival signaling through pathways such as the TrkB signaling pathway [34]. Therefore, interventions that upregulate pro-growth and pro-survival signaling pathways may improve functional outcomes. A previous study showed that Cav-1 may exert protective effects against ischemia/reperfusion injury [35]. For example, neuron-targeted Cav-1 (Syn-Cav1) overexpression concentrated TrkB receptors in MLRs, resulting in enhanced dendritic growth and arborization of primary neurons in mice [22]. Conversely, another study showed that overexpression of Cav-1 in PC12 cells blocked NGF-mediated TrkA autophosphorylation, resulting in inhibition of neurite outgrowth [36]. Thus, Cav-1 may act through TrkB to promote nerve regeneration after ischemic stroke.

3.3. N-methyl-D-aspartate receptors

N-methyl-D-aspartate (NMDA) receptors, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropion ic acid (AMPA) receptors, and kainate receptors are the three classes of ionotropic glutamate receptors (iGluRs). These receptors are critical to neuronal development and synaptic plasticity [37]. NMDA receptors located in MLRs as a component of the neurotransmitter and neurotrophic receptors [22]. Cav-1 has been shown to regulate neuroplasticity and long-term plastic changes related to NMDAR2B, resulting in modulation of chronic pain [38]. Furthermore, Cav-1 overexpression has been shown to enhance MLR formation and enrichment of NMDAR2B in MLRs, resulting in improved motor function and preservation of memory in mice subjected to brain trauma [23]. In addition, a study showed that siRNA-mediated knockdown of Cav-1 disrupted NMDA2A-mediated signaling and attenuated neuroprotection following oxygen and glucose deprivation [31]. These findings demonstrate the potential beneficial effects of Cav-1/NMDAR on neuroplasticity.

3.4. G-protein coupled receptors

G-protein coupled receptors (GPCRs) are a large family of transmembrane signaling receptors that bind to extracellular molecules to produce intracellular signals [39]. Pro-growth signaling in neurons has been shown to occur following activation of a number of synaptic receptors, including GPCRs [40]. Studies have shown a close relationship between GPCRs and caveolin, with caveolin-rich domains organized proximal to GPCR signaling components in both the sarcolemmal and intracellular regions in rat heart [41]. Inactive Gα subunits are concentrated in caveolae and associate with the caveolin scaffolding domain (CSD). Upon activation, Gα subunits dissociate from caveolae [42]. Caveolin-1 and MLRs have been shown to modulate estrogen GPCR signaling in the nervous system [43]. Interestingly, Cav-1-mediated NMDA receptor activation may be coordinated by the Gαq subunit, resulting in modulation of pro-growth pathways in oxygen-glucose-deprived (OGD) neurons [31]. These findings suggest an important role for GPCRs alone or in combination with other receptors in Cav-1-mediated neuroplasticity.

3.5. Other receptors related to neuronal growth and neuroplasticity

Modulation of neuroplasticity by Cav-1 may depend on several mechanisms, including angiogenesis. The role of vascular endothelial growth factor (VEGF) in angiogenesis following ischemia has been established [44]. Caveolin-1 has been shown to colocalize with VEGF receptor 2 (VEGFR2), resulting in increased VEFGR2 autophosphorylation and activation of downstream angiogenic signaling in prostate cancer and in endothelial cells [45]. Studies have shown that treadmill exercise promoted NSC proliferation, migration, and neuronal differentiation, and improved neurological recovery via Cav-1/VEGF signaling after ischemic injury [46, 47]. In addition, fibroblast growth factor (FGF) has also been shown to exert protective effects against brain ischemia. Caveolin-1 was shown to interact with FGF receptor 1 (FGFR1) to regulate FGF-2-induced angiogenesis in ovine placental artery endothelial cells [48].

Cellular prion protein (PrP^c), a ubiquitous glycoprotein expressed strongly in neurons, acts as a cell-surface receptor and plays an important role in regulation of neuronal differentiation and neurite growth [49]. MLRs are critical to conformational changes in PrP^c that promote signal transduction and neurite outgrowth [50]. Pantera et al. demonstrated that PrP^c-mediated neuritogenesis and cell differentiation occurred through increased phosphorylation of Cav-1 in PC12 cells [51]. Bone

morphogenetic proteins (BMPs), members of the growth factor β (TGF β) family, are important in osteogenesis and neuroplasticity. The BMP receptors BRIa and BRII have been shown to colocalize with Cav-1 [52]. Colocalization of BMPRII with Cav-1 has been shown to regulate downstream signaling in vascular smooth muscle cells [53], resulting in stem cell differentiation [54]. The prorenin receptor ATP6AP2 may also affect neuroplasticity. Gα proteins can crosslink ATP6AP2 to caveolin where a switch from Gαi to Gαq was necessary to induce neuronal differentiation of adipose-derived mesenchymal stem cells (MSCs) [55]. Caveolin-1 is necessary for glucocorticoid receptor (GRs)-mediated proliferation of neural progenitor cells (NPCs) [56].

4. Signaling pathways mediated by Cav-1 and MLRs in neuronal growth and neuroplasticity after ischemic stroke

Several classical signaling pathways participate in neuronal growth and neuroplasticity. Caveolin-1 has been shown to directly or indirectly regulate signaling by concentrating signal transducers within distinct membrane regions [57]. Recent studies have focused on increasing understanding of intracellular signaling pathways linked to neuroplasticity. Elucidation of signaling mechanisms involving Cav-1 will aid in identification of new therapeutic targets.

4.1. PI3k/Akt signaling pathway

The phosphatidylinositol-3-kinase (PI3K) pathway is a well-characterized pathway that regulates endogenous neuroplasticity in response to ischemia [58]. Studies have shown that activation of the PI3K pathway promotes brain cell survival, resulting in reduced cell death after stroke [59, 60]. PI3K activates many different downstream effectors, such as Akt (via phosphorylation), which promotes growth, translation, and cell-cycle regulation [61]. Caveolin-1 has been shown to interact with the PI3k/Akt pathway. For example, previous studies showed that Cav-1 enhanced PI3k/Akt signaling, resulting in human MSC osteogenesis [62], alleviated the effects of ischemia-reperfusion injury in the diabetic myocardium [63], and increased morphine-induced neuroplasticity [57]. Another study showed that angiotensin II-induced remodeling of cerebral pial arterioles occurred via the Cav-1/Akt pathway [64]. Caveolin-1 overexpression has been shown to augment phosphorylation of Akt and to enhance dendritic growth in response to ischemic injury [31]. In contrast, other studies have shown that endothelial cell-specific expression of Cav-1 inhibited the Akt-endothelial nitric oxide synthase (eNOS) pathway and impaired microvascular angiogenesis [65], and Cav-1 decreased Akt and Stat3 phosphorylation, resulting in inhibition of neuronal differentiation of NPCs [66]. Therefore, determination of whether Cav-1 inhibits or activates the PI3k/Akt pathway requires further investigation.

4.2. MAPK/ERK signaling pathway

Extracellular signal-regulated kinase (ERK) is a member of the mitogen-activated protein kinase (MAPK) family, which transduces signals from the cell membrane to the nucleus to promote cell proliferation, migration, differentiation, and death [67]. A previous report suggested that Cav-1 can act as a negative regulator of the Ras-p42/44 ERK pathway in a variety of cell types [68]. Furthermore, Cav-1 has been shown to downregulate matrix metalloproteinase-1(MMP-1) expression via inhibition of ERK1/2/Ets1 signaling [69]. In contrast, a study showed that insulin-activated ERK translocation to the nuclear envelope was Cav-2-dependent [70]. Glial cell line-derived neurotrophic factor (GDNF) stimulation induced upregulation of caveolin and ERK expression in neurons, resulting in increased ERK signaling. GDNF-induced increases in ERK signaling were blocked by inhibition of caveolin [71]. In primary astrocytes exposed to OGD, overexpression of Cav-1 and increased phospho-ERK attenuated OGD-induced cell apoptosis [72]. Caveolin-1 expression was shown to be critical for nitric oxide-mediated angiogenesis through augmentation of ERK phosphorylation [73]. Furthermore, Cav-1 overexpression enhanced dendritic growth partly due to increased ERK phosphorylation in ischemic injury [31]. Li et al. showed biphasic regulation of Cav-1 gene expression through the MAPK/ERK signaling pathways following fluoxetine treatment in astrocytes [74]. Further characterization of the interactions between Cav-1 and the MAPK/ERK signaling pathways is needed.

4.3. NF-κB signaling pathway

Nuclear factor-kappa B (NF-κB) is a transcription factor comprised of p50, RelA/p65, c-Rel, RelB, and p52 subunits that can regulate growth and elaboration of neural processes, and protect neurons against ischemia-induced neurodegeneration [75]. NF-κB was shown to restore neuronal growth and differentiation through NMDAR, NGF, and NGFR signaling in hippocampus of degenerative brain [76]. One study showed that NF-κB regulated dendritic spine and synapse density in the hippocampus using a $p65^{-/-}$ model, which provided a structural basis for facilitation of learning and memory [77]. Caveolin-1

can facilitate activation of NF-κB through multiple pathways. For example, β-carotene induced downregulation of Cav-1, resulting in modulation of the Akt/NF-κB pathway to induce apoptosis in human esophageal squamous cell carcinoma [78]. Furthermore, Cav-1 was shown to regulate the inflammatory response through the STAT3/NF-κB pathway in mice with pseudomonas aeruginosa infection [79]. In addition, Cav-1 responded to inflammation through the cPLA2/p38/NF-κB [80] and eNOS/NO/NF-κB [81] pathways. Further study is needed to determine the mechanisms by which Cav-1 promotes neuroplasticity following cerebral ischemia through the NF-κB pathway.

4.4. Sonic hedgehog signaling pathway

The sonic hedgehog (Shh) signaling pathway mediates neuroprotection and neuroplasticity in various types of neurons in the central nervous system [82]. Sonic hedgehog signaling was shown to stimulate neurite outgrowth in astrocytes treated with cyclopamine [83]. Similarly, amygdala neuronal growth was promoted by Shh signaling to form long-term memories [84] and to eliminate fear memories [85]. Another study showed that Shh signaling stimulated NPC proliferation following ischemic stroke [86]. The Shh pathway may have mediated this proliferative effect through cerebrolysin-enhanced neuroplasticity [87]. Several treatment agents have been shown to enhance neuroplasticity via the Shh pathway following ischemia, such as salvianolic acid [88] and resveratrol [89]. Studies have shown that Shh was enriched in MLRs and was activated by Cav-1 during endocytosis [90] and other Shh-related biological and pathological process [91]. Another study found that Shh was associated with Cav-1 in the Golgi apparatus to form protein complexes which were transported to MLRs [92]. These data suggest that Cav-1 and MLRs may be important factors in Shh signaling-induced neuroplasticity following ischemic stroke.

4.5. cAMP signaling pathways

Cyclic adenosine monophosphate (cAMP) signaling in the brain has been shown to mediate numerous neural processes including development, synaptic plasticity, learning and memory, and motor function in response to neurodegeneration [93]. The cAMP-PKA pathway was shown to regulate synaptic plasticity in medium spiny neurons (MSNs) of the striatum [94] and to activate protein kinase A and p190B RhoGAP, resulting in neurite outgrowth in PC12 cells [95]. In addition, Cav-1 may stimulate cAMP/PKA pathway-dependent lipolysis via autocrine production of PGI2 [96]. Caveolin-1 knockout decreased cAMP levels and PKA phosphorylation, resulting in exacerbation of cardiac dysfunction and reduced survival time of mice subjected to myocardial infarction [97]. Furthermore, NMDA receptors, GPC receptors, the PI3K/Akt pathway, and the ERK pathway have been shown to enhance cAMP formation to promote neuronal growth and synaptic plasticity [98]. Head et al. showed that Cav-1 stimulated cAMP formation through activation of these signaling pathways to enhance dendritic growth [22].

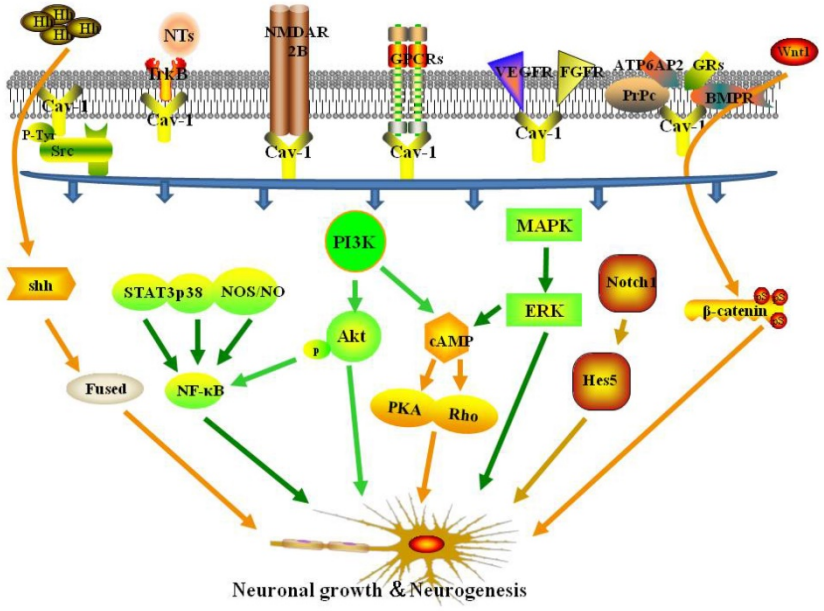

Fig.1 Cav-1- and MLR-associated receptors and signaling pathways in neuronal growth and neuroplasticity following ischemic stroke.

4.6. Other signaling pathways

The Notch and Wnt/β-catenin pathways have been shown to play important roles in regulation of neuroplasticity following cerebral ischemia [99]. Studies have shown that Notch signaling is a pivotal control mechanisms of NSCs, and NSCs express Notch receptors and the canonical Notch target, hairy enhancer of split 5 (Hes5) [100]. Notch1 signaling has been shown to modulate subventricular zone (SVZ) neuroplasticity in aged brains under normal and ischemic conditions [101]. Furthermore, Caveolin-1 has been shown to promote ovarian cancer chemoresistance through Notch-1/Akt pathway-mediated inhibition of apoptosis [102]. A study showed that Cav-1-containing MLRs coordinated the Notch1 and β1-integrin signaling pathways in NSCs [103]. Moreover, Cav-1 has been shown to regulate neural differentiation of bone MSCs to neurons [104], and NPCs to astrocytes [105], through modulation of Notch signaling. In contrast, a study showed that Cav-1 inhibited the Wnt/β-catenin pathway, resulting in reduced dorsal organizer formation in zebrafish [106] and reduced mammary stem cell number [107]. Li et al. demonstrated that Cav-1 inhibited differentiation of NSCs/NPCs into oligodendrocytes through modulation of β-catenin expression [108].

5. Non-coding RNAs regulate Cav-1 in neuronal growth and neuroplasticity after ischemic stroke

In addition to the classical non-coding RNAs (ncRNAs), transfer RNA (tRNA) and ribosomal RNA (rRNA), additional families of ncRNAs such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), small nuclear RNAs (snRNA), small nucleolar RNAs (snoRNA), and piwi-interacting RNAs (piRNAs) [109] have been investigated in ischemic stroke.

5.1. MicroRNAs

MicroRNAs (miRNAs) are a family of short non-coding RNA molecules that play important roles in gene expression via mRNA destabilization and translational repression [110]. Some miRNAs have been shown to regulate normal physiological activity and response to ischemic injury [111]. Recent studies have indicated that a number of miRNAs may be involved in regulation of neuroplasticity induced by cerebral ischemia [112]. For example, miR-210 was upregulated in OGD PC12 cells and suppressed apoptosis by inhibiting caspase activity [113], and miR-210 overexpression increased the number of NPCs in the ischemic mouse brain [114]. Furthermore, overexpression of the miR17-92 cluster enhanced stroke-induced NPC proliferation [115].

MiR-124, the most abundant microRNA in the adult brain, positively modulated differentiation of SVZ stem cells to neurons [116], a process that has been extensively investigated in neuroplasticity. MiR-124 has been shown to promote neuronal growth and neuroplasticity in various physiological processes, such as synaptic plasticity and memory formation [117]. Following focal cerebral ischemia, miR-124 promoted neuronal differentiation and modulated microglia polarization [118]. Interestingly, miR-124 has been linked to caveolae under many conditions. One study showed that MiR-124 regulated the expression of flotillin-2 and Cav-1 during acrosome biogenesis [119]. Another study indicated that miR-124 directly bound to Cav-1 mRNA and decreased Cav-1 expression at both the mRNA and protein levels [120]. Furthermore, miR-124 attenuated apoptosis by regulating the Cav-1/PI3K/Akt/GSK3β pathway in Alzheimer's disease [121], and promoted stroke-induced neuroplasticity by targeting the Notch signaling pathway [122].

The role of MiR-199 in ischemia-induced neuroplasticity has been studied extensively. A study showed that downregulation of miR-199a mediated neuroprotective effects in brain ischemic tolerance [123]. Similarly, sequestration of MiR-199a by lncRNA-Map2k4 promoted FGF-1 expression and neuronal proliferation in spinal cord injury [124]. Conversely, Bao et al. found that miR-199a-5p protected the spinal cord against ischemia/reperfusion-induced injury [125]. Moreover, miR-199a and miR-199b were shown to modulate endocytosis by controlling the expression Cav-1, and miR-199a-5p and miR-199b-5p overexpression markedly inhibited Cav-1 expression [126]. Furthermore, a study showed that miR-199a-5p downregulated Cav-1 in porcine preadipocyte proliferation and differentiation [127]. Thus, miR-199a may act as a negative regulator of Cav-1 in neuroplasticity following ischemic stroke.

Studies have also indicated that other miRNAs may regulate caveolin and other signaling pathways involved in neuroplasticity. MiR-22 was reported to protect neurons against cerebral ischemia/reperfusion injury [128], and to induce protective effects against cardiac infarction through Cav-3/eNOS signaling [129]. MiR-132 was shown to enhance dendritic morphogenesis, synaptic integration, and neuronal survival, and to improve outcomes of transplant therapies in olfactory bulb neurons [130]. Moreover, miR-132-3p activated the PTEN/PI3K/PKB/Src/Cav-1 signaling pathway to promote transcellular transport in glioma endothelial

cells [131]. Transfer of MiR-133 to neural cells contributed to neurite outgrowth in rats subjected to middle cerebral artery occlusion (MCAO) [132]. In contrast, MiR-133 overexpression suppressed Cav-1-mediated tumor cell proliferation, migration, and invasion [133]. MiR-138 attenuated PC12 cell proliferation following hypoxia and reoxygenation [134]. Downregulation of miR-138 promoted MLR formation via upregulation of Flot-1, Flot-2, and Cav-1 [135]. MiR-192 also suppressed cell proliferation through downregulation of Cav-1 [136]. Further studies to characterize the interactions between miRNAs and Cav-1 are needed.

5.2. Long non-coding RNAs

Long non-coding RNAs (lncRNAs) are defined as transcripts longer than 200 nucleotides without an open reading frame. More than half of lncRNAs are expressed in the central nervous system, and they play key roles in brain development and function [137]. A previous study showed that of 8,314 lncRNAs analyzed, the expression levels of 443 were significantly altered at 3, 6, and 12 hours after ischemia in rats [138]. Ayana et al. identified 222 lncRNAs specifically expressed in the subventricular and subgranular zones (SVZ/SGZ), and 54 of these lncRNAs were significantly up-regulated in neurogenesis zones [139]. Recent studies have demonstrated that lncRNAs such as NBAT-1 [140], FMR4 [141], PnKy [142], Gm15577 [143], and NONHSAT073641 [144] play important roles in neuronal growth and neuroplasticity. Several lncRNAs have been shown to activate signaling pathways related to neuroplasticity. For example, Malat1 promoted neuronal differentiation through activation of the ERK/MAPK signalling pathway in N2a cells [145]. Furthermore, LncND mediated regulation of Notch signaling to enhance NPC growth [146]. Interestingly, the lncRNA HOTAIR promoted ischemic infarction through regulation of NOX2 expression in a rat model [147], and Cav-1 promoted proliferation, migration, and invasion through HOTAIR in lung cancer cells [148]. Further studies to characterize interactions between Cav-1 and lncRNAs in neuroplasticity after stroke are needed.

6. Agents that modulate neuronal growth and neuroplasticity through Cav-1 following ischemic stroke

6.1. Valproic acid

Valproic acid (VPA), a classical anticonvulsive and antimanic agent, has been shown to promote neuronal regeneration in primary rat cortical neurons following hypoxia-reoxygenation via increased BDNF expression and activation [149]. Furthermore, VPA enhanced neuronal differentiation of NSCs through the PI3K/Akt/mTOR signaling pathway [150], and increased the expression of miR-210-3p, miR-29a-5p, and miR-674-5p [151]. Studies have shown that VPA inhibited glycogen synthase kinase-3β (GSK3β) [152], and reduced GSK3β expression in response to VPA increased neuronal growth in the adult dentate gyrus (DG) in a rodent mood disorder model [153]. Furthermore, a study showed that inhibition of GSK3β increased pituitary adenylate cyclase-activating polypeptide (PACAP)-induced neuritogenesis through activation of Rap1 in a Cav-1-dependent manner in PC12 cells [154]. These findings indicated that valproate may modulate multiple signaling targets related associated with Cav-1 to improve neuroplasticity after cerebral ischemic injury, suggesting the potential for further translational research.

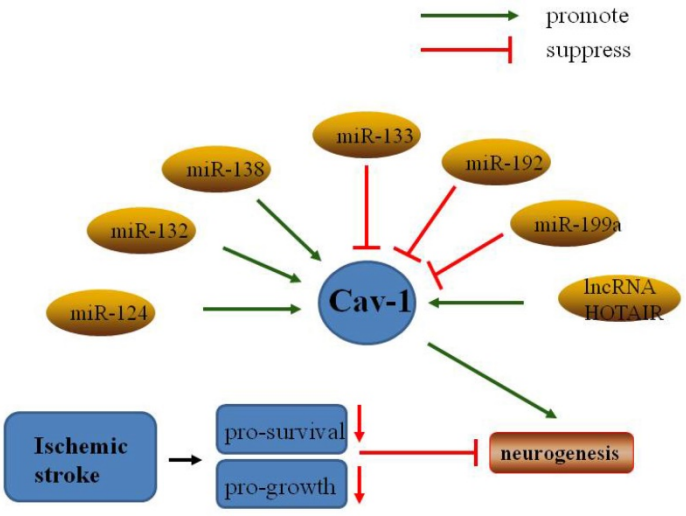

Fig.2 Non-coding RNAs regulate Cav-1 in neuronal growth and neuroplasticity after ischemic stroke.

6.2. Resveratrol

Resveratrol (3,5,4′-trihydroxy-trans-stilbene; RSV) is a phenol and phytoalexin found in grapes, red berries, and nuts [155]. RSV has been shown to enhance hippocampal plasticity through activation of the histone deacetylase enzyme sirtuin 1 (SIRT1) and AMP-activated kinase (AMPK), resulting in neurite outgrowth [156]. Recent studies have shown that RSV exerted protective effects against several neurological diseases including epilepsy [157], Alzheimer's disease [158], and age-related degeneration [159]. Furthermore, a study showed that RSV increased proliferation of NSCs and neurite outgrowth via the Shh signaling pathway following OGD/reoxygenation injury *in vitro* [89]. Neurological recovery induced by RSV was attributed to angioneurogenesis rather than neuroprotection [160]. Resveratrol may increase phosphorylation of Cav-1, c-Src, and eNOS in endothelial cells [161], and Cav-1 was shown to enhance RSV transport in HepG2 cells[162]. Another study showed that RSV promoted neovascularization and Cav-1 interaction with angiogenic molecules in hypercholesterolemic rats [163]. Peng et al. showed the effects of RSV on high glucose diet-induced vascular hyperpermeability through Cav-1/eNOS regulation [164]. These findings suggest that RSV may be a good drug candidate to induce neuroplasticity after stroke.

6.3. Sildenafil

Sildenafil (Viagra®) is an inhibitor of phosphodiesterase-5, and is used to treat erectile dysfunction [165]. Studies have shown that sildenafil may reduce neuronal apoptosis, and increase angiogenesis and cerebral blood flow, resulting in functional recovery after ischemic stroke [166]. Studies showed that sildenafil enhanced neuroplasticity through activation of the PI3-K/Akt/GSK-3 [167] and MAPK/ERK [168] signaling pathways in NSCs. Moreover, increased neuronal growth induced by sildenafil was also observed in NSCs in the SVZ [169] and the DG [170] after ischemic stroke. Studies have shown that sildenafil may restore Cav-1 expression to protect cavernous tissue following pelvic nerve injury [171], and may increase the expression of Cav-1 in dorsal nerve tissues of aged rats [172]. Further investigation of the neuroprotective effects of sildenafil in stroke is needed.

6.4. Other agents

Other agents may also target Cav-1 to enhance neuronal growth and neuroplasticity following ischemic stroke. Tanshinone I was shown to promote neuronal growth by increasing the expression of Wnt-3, p-GSK-3β, and β-catenin in mouse DG [173]. Another study showed that tanshinone IIA promoted neuronal differentiation via activation of Cav-1 and the MAPK42/44/BDNF/NGF signaling pathway [174]. Xu et al. demonstrated that a recombinant human IgM, rHIgM12, promoted axonal outgrowth through binding to MLR domains [175]. The hypoglycemic drug rosiglitazone was reported to up-regulate Cav-1 expression and activate Src, EGFR, and the MAPK/ERK pathways [176], and to exert neuroprotective effects against acute brain injury [177].

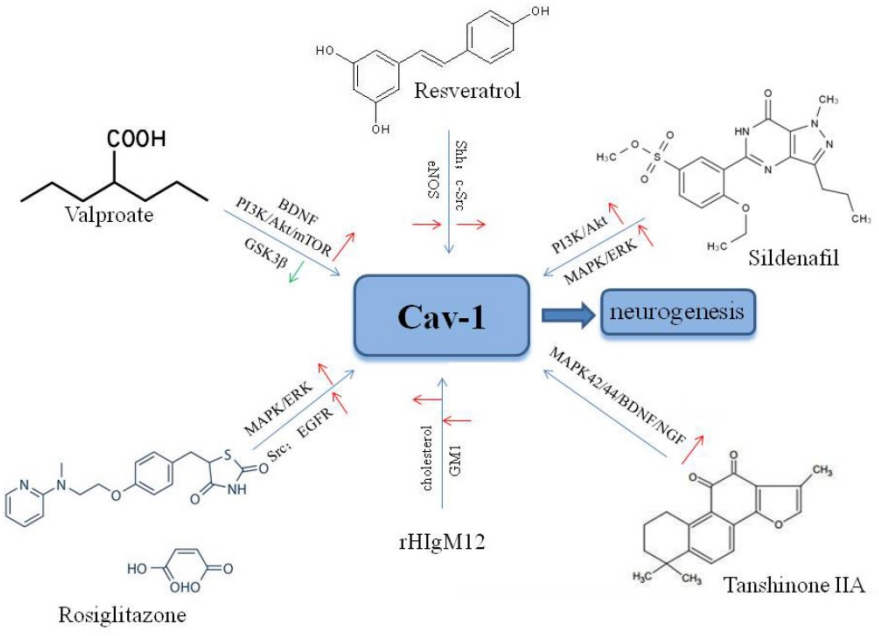

Fig.3 Agents targeting Cav-1 for neuronal growth and neuroplasticity after ischemic stroke.

7. Future perspectives

The effects of neuronal growth and neuroplasticity following stroke have received increased attention in recent years. Expansion of current studies might result in novel therapeutic options to restore neurological functions in patients that suffered strokes. Recent studies have shown that Cav-1 and MLRs are involved in regulation of neuronal growth and neuroplasticity after ischemic stroke. Many of these studies suggested that Cav-1 may be a promising molecular target to improve neuroplasticity. This review discussed the receptors, signaling pathways, genes, and treatment agents involved in Cav-1-mediated neuroprotection. Although more studies are needed to evaluate the efficacy and safety of the agents discussed in this manuscript, these agents should be evaluated further as treatment options to improve neuroplasticity following ischemic stroke. Further characterization of the roles of Cav-1 and MLRs in neuronal growth and neuroplasticity may provide for novel Cav-1/MLR-based therapies to treat cerebral ischemia. Additional studies are needed to determine whether findings in cells and rats can be translated to clinical applications in humans.

Acknowledgements

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Competing Interests

The authors have declared that no competing interest exists.

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