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Feasibility of recent peptide therapy for ischemic stroke: a comprehensive exploration

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ABSTRACT

Ischemic stroke is a prominent cause of disability and mortality worldwide, currently no drug therapy is helpful for post-stroke symptoms; thus, there is a need to develop effective treatment strategies. Peptide medication development has advanced significantly in the recent years and due to its potential to modulate key molecular pathways involved in stroke pathophysiology. This review provides an overview of recent advances in peptide therapy for stroke. These peptides can exert neuroprotective effects by inhibiting excitotoxicity, oxidative stress, and apoptosis, while also promoting neuronal survival and synaptic plasticity. Furthermore, artificial intelligence (AI) with deep learning holds a promising technique in peptide generation by enabling the design of novel peptides with specific binding site of a protein, this may accelerate drug discovery processes through predictive modeling and high-throughput analysis. Overall, peptide therapy holds great potential for improving stroke outcomes and represents a promising avenue for the development of novel stroke treatments.

1. Introduction

The traditional stroke treatments, such as thrombolytics (tPA) and mechanical thrombectomy, focus on restoring blood flow, while peptide therapies offer potential solutions for minimizing brain damage and enhancing recovery.[1] However, most peptide-based drugs are not specifically designed to target post-stroke symptoms but rather involve repurposing existing drugs to evaluate their effects on stroke outcomes.[2]

As research into disease-protein associations advances,[3] the interactions and binding pockets of protein may be suitable for mitigating diseases. Peptides showed a potential of interfering with specific protein-protein interactions, revealing the strategy in disease treatment. Additionally, generative AI can design high-precision peptide/protein structures that bind to specific protein targets,[4,5] addressing challenges in specificity and stability. Protein binder design has the potential to revolutionize the way we manage and treat various diseases by providing personalized and targeted treatments.

Furthermore, macrocyclic peptides showed potent biological activities in metabolic stability, target-binding affinity, and cell permeability than traditional peptide therapies.[6,7] Macrocyclic peptides possess unique structural features compared with linear peptides, including enhanced metabolic stability and improved binding affinity to specific protein targets. These characteristics allow them to modulate interactions that are often considered “undruggable” by small molecules. Furthermore, some macrocyclic peptides have demonstrated the ability to penetrate the blood–brain barrier (BBB), making them attractive therapeutic candidates for neurological diseases.[8] Among the six peptide drugs approved in 2023, three are macrocyclic peptides, including Rezafungin,[9] Motixafortide,[10] and Zilucoplan.[11] These highlighted the growing significance of macrocyclic peptides in therapeutic applications. The future of drug discovery, driven by machine learning and the advancement of macrocyclic peptides, is accelerating drug design while enabling the development of multi-target therapies that address complex diseases by targeting multiple pathways and unlocking more targets,[12] thereby expanding the potential for innovative treatments.

Here, we present the potential peptide-based therapies that are currently being explored for the treatment of ischemic stroke. These peptides have shown promising effect in various preclinical and clinical

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studies due to their neuroprotective, anti-inflammatory, and regenerative properties. In this review of peptide therapy for ischemic stroke, we delve into its multifaceted nature, highlighting its mechanisms of action, potential applications, and the evolving landscape of research and clinical implementation (Fig. 1, Table 1).

2. Method

2.1. Review criteria

References for this review were identified by searches of SciSpace, ResearchRabbit, and references from relevant articles. The search terms "Peptide therapy", "Ischemic stroke", "Cerebral ischemia-reperfusion" were used. The final reference list was generated on the basis of relevance to the topics covered in this review.

2.2. De novo peptide generating

De novo peptide design was complete by the use of RFdiffusion. Predicted structures are validated with AlphaFold3 to confirm folding. The basic safety and functional properties of this peptide was first confirmed through online predictive tools, AllerTOP v2.01, BBPpredict, ProtParam.

3. Result

3.1. Peptide therapy for treating inflammation

Li et al. described the correlations of inflammatory score, including different ratio of immune cells, and hemorrhagic transformation.[13]

3.1.1. Toll-like receptors (TLRs)

Microglial healing peptide 1 (MHP1) strongly suppresses TLR2 and TLR4 induced inflammation in microglia/macrophages (Mi/MΦ)[14] (Fig. 2A). Furthermore, a modified MHP1 with N-terminal acetylation and C-terminal amidation (MHP1-AcN) did not impair the thrombolytic effect of tPA and suppresses tPA-induced hemorrhagic transformation.[15] Fang et al. design a synthetic peptide, Tat cold-inducible RNA-binding protein (Tat-CIRP), which inhibits myeloid differentiation factor 2 (MD2) and serves as a neuro-protectant[16] (Fig. 2A). In rhesus monkeys, Tat-CIRP lowers brain infarct volume and improves long-term neurological outcomes. Furthermore, they found that Tat-CIRP can prevent the MD2-Sam68 interaction in neurons after ischemic stroke.

3.1.2. High-mobility group box 1 (HMGB1)

HMGB1 is a DNA-binding protein in the nucleus and has two opposite activities by its A and B box. B box of HMGB1 can activate inflammatory responses as DAMP via TLRs during cell death.[17,18] In contrast, A box of HMGB1 blocks inflammatory responses through the inhibition of TLR signals.[19] Goto et al. developed a recombinant HMGB1 fragment, Redasemtide (Fig. 2A), using the A box domain to promote tissue repair in a rat model of myocardial infarction.[20] It is now undergoing Phase II trial to evaluate its effectiveness in treating acute ischemic stroke (ClinicalTrials.gov, NCT05953480).

3.1.3. IκB kinase β (IKKβ)

In MCAO model rats, new peptide (NP1) successfully lowers cerebral infarct volume and alleviates neurological impairment via increasing

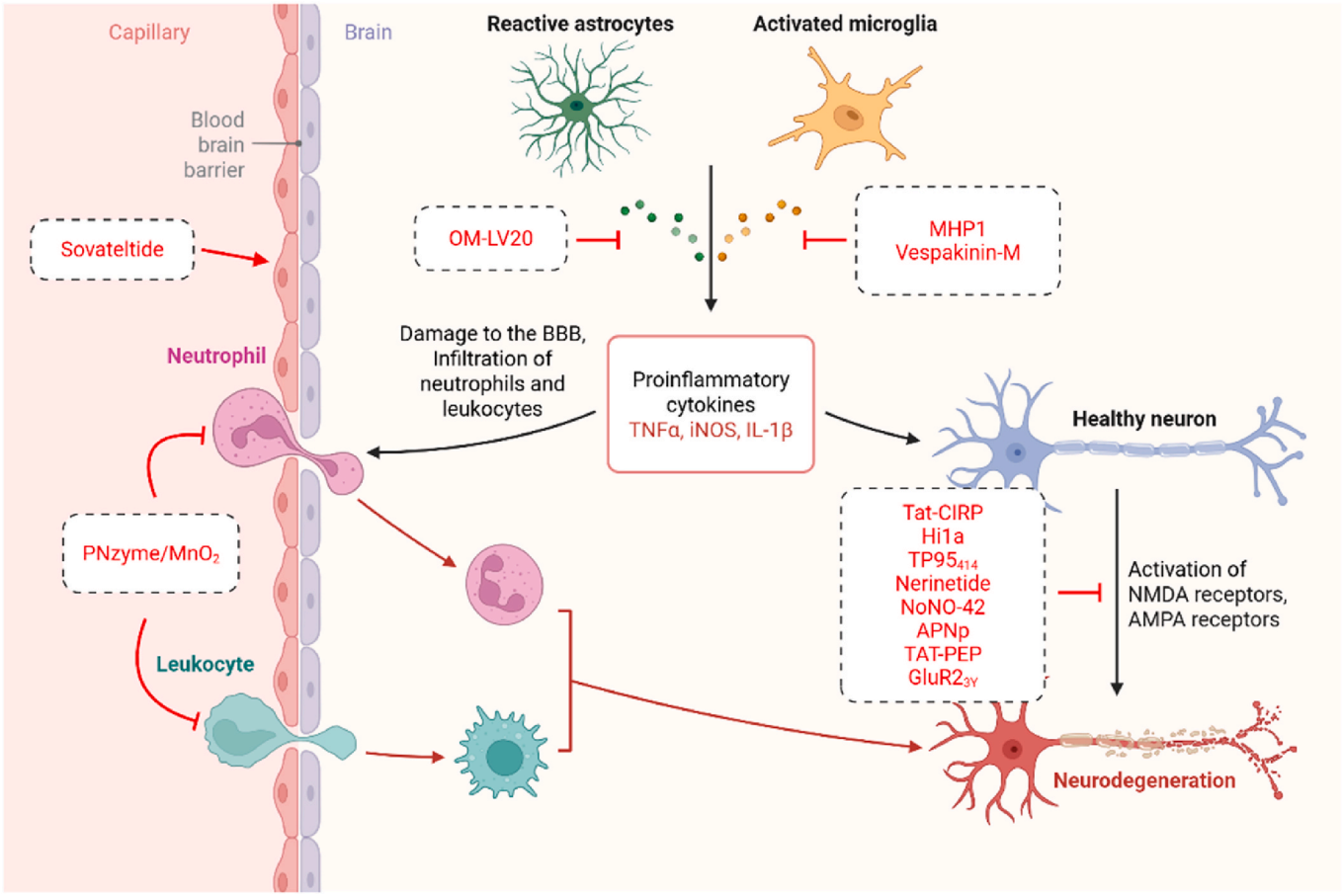

Fig. 1. Role of different cell types in ischemic stroke and the target cells of peptide therapies. Peptide therapies are designed to target neurons, glial cells, endothelial cells, and immune cells to reduce injury and promote recovery.

Table 1
Advantages and disadvantages of peptide therapy in clinical trials.

Types	Advantages	Disadvantages	Name (ClinicalTrials.gov)	Target	Routes of administration
Anti-inflammation	Anti-inflammatory drugs demonstrate neuroprotective effects in preclinical models of ischemic stroke.	Neuroinflammation in ischemic stroke has been characterized as a double-edged sword, playing both detrimental and beneficial roles depending on the context and timing.	Redasemtide (NCT05953480) Talfirastide (NCT06135103)	TLR signals ACE2/ Ang-(1–7)/ MasR	Intravenous
Neuroprotectant	Current standard treatments effectively restore cerebral blood flow but have limited impact on cellular injury. Neuroprotective agents can be used in combination to offer a multi-targeted therapeutic approach, integrating reperfusion with cellular protection.	Despite reaching the clinical trial stage, many neuroprotective agents have failed to demonstrate efficacy in clinical trials.	Nerinetide (NCT04462536) NoNO-42 (NCT06403267) BXOS110 (NCT06403267) AVLX-144 (NCT04689035) NVG-291 (NCT05965700)	PSD-95 PTPσ	Intravenous Intravenous Intravenous Intravenous Subcutaneous
Endothelial function	Sovateltide has shown promise in promoting neurogenesis, angiogenesis, and restoring endothelial function following ischemic stroke.	The endothelin system has been shown to play biphasic roles during various phases of stroke progression	Sovateltide (NCT05955326)	ETB receptor	Intravenous
Other mechanism	Preclinical studies suggest neuroprotective mechanisms of semaglutide through anti-inflammatory and antioxidative pathways. MT1002 targets both GP IIb/IIIa and thrombin, offering comprehensive antithrombotic protection. MK-0616 is administered orally, which enhances patient convenience and treatment adherence.	While semaglutide is primarily available as a subcutaneous injection, the oral formulation exhibits limited bioavailability and necessitates administration under fasting conditions, which may hinder its applicability during the acute phase of ischemic stroke.	Semaglutide (NCT05630586) MT1002 (NCT06533358) MK-0616 (NCT06492291)	GLP-1 receptor GPIIb/IIIa PCSK9	Subcutaneous Intravenous Oral

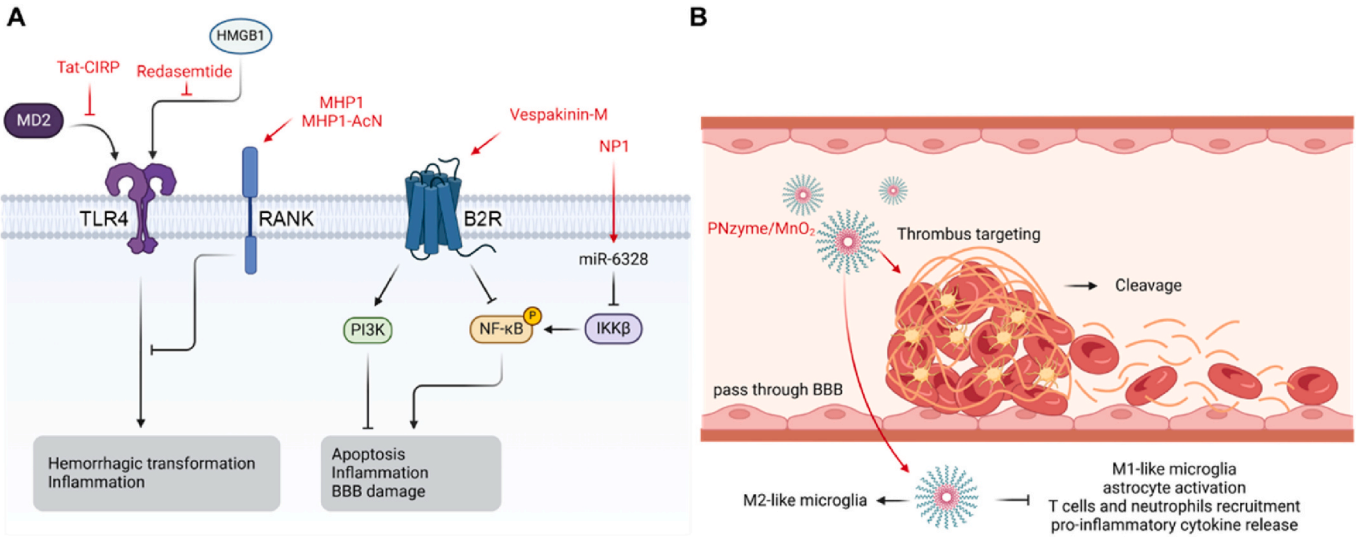

Fig. 2. Mechanisms for neuroinflammation with peptide therapies.
(A) Tat-CIRP inhibited interaction of MD2 and TLR4; therefore, preventing hyperactivation of immune response. Redasemitide could regenerate damaged tissue and reduce inflammation caused by ischemic events. MHP1 and MHP1-AcN inhibited immune response through RANKL/RANK signaling. NP1 activated miR-6328, thereby inhibiting IKKβ/NF-κB signaling. Vespakinin-M reduced inflammation and apoptosis by activating PI3K/AKT and suppressing the NF-κB signaling cascade via the B2R. **(B)** PNzyme/MnO_2 illustrated thrombolytic activity, and enhances M2-like microglia and suppressive pro-inflammatory cells.

miR-6328[21] (Fig. 2A). The reduction of IKKβ inhibits the activation of NF-κB pathway and effectively inhibits inflammation.

3.1.4. B2R

Vespakinin-M, a natural peptide derived from wasp venom, attenuates nerve damage, reducing infarct size, maintaining BBB integrity, and inhibiting oxidative stress and microglial inflammatory responses.[22] Vespakinin-M therapy lowered neuroinflammation and apoptosis through PI3K/AKT activation and suppression of the NF-κB signaling pathway via bradykinin B2 receptor (B2R) (Fig. 2A).

3.1.5. Multiple mechanisms affecting immune cells

Wang et al. described a new peptide-templated manganese dioxide nanozyme (PNzyme/MnO_2) that combines the ability of nanozymes to scavenge ROS with the functional peptide-templated nanozyme binding to fibrin in the thrombus[23] (Fig. 2B). Furthermore, mice treated with PNzyme/MnO_2 demonstrated a rise in M2-like microglia, and a decrease in M1-like microglia. Also, it suppresses astrocyte activation, T cells and neutrophils recruitment, and pro-inflammatory cytokine release. Another peptide, OPNpt7R, showed to upregulate anti-inflammatory cytokines, contributing to the resolution of inflammation in the

post-ischemic brain in MCAO animals.[24]

3.1.6. Programmed death-ligand 1 (PD-L1)/programmed cell death protein 1 (PD-1)

More recently, recombinant PD-L1 has been shown to reduce cerebral edema and reprogram monocytes to Ly6C^{lo}, CX3CR1^{hi}, CD43^{hi} phenotype, promoting tissue repair after stroke.[25] Given these advantages, BMSpep-57,[26] a potent and competitive macrocyclic peptide inhibitor of PD-1/PD-L1, warrants further investigation in preclinical trials to evaluate its therapeutic potential.

3.2. Peptide therapy for treating acidosis

With pH values of 6.03 ± 0.36 and 6.53 ± 0.24, respectively, the infarct core and peri-infarct inner rim were both consistently acidic,[27] demonstrating lactic acid poisoning. In the mammalian brain, the acid-sensitive ion channel 1a (ASIC1a) is the most important acid sensor,[28] which is thought to contribute to intracellular Ca^{2+} flux and a key mediator of acidosis-induced neuronal damage after ischemic stroke.[29–31] Hi1a, a disulfide-rich spider venom peptide, is highly neuroprotective in a focal model of ischemic stroke[28] (Fig. 3).

3.3. Peptide therapy for treating elevated intracellular calcium levels

During stroke, the disruption of calcium homeostasis results in elevated intracellular calcium levels, triggering cell death.[32] High levels of calcium activate enzymes that break down cellular components, disrupting the mitochondrial membrane potential.[33,34] Under ischemic conditions, glutamate is released from neurons and further activates N-methyl-D-aspartate receptors (NMDARs)[35] and α-amino-3--hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs).[36]

3.3.1. NMDARs

Postsynaptic density-95 (PSD-95) is an important scaffolding protein that interacts with NMDARs and neuronal nitric oxide synthase (nNOS) through protein-protein interactions.[37] Superoxide anion and NO interact to form peroxynitrite ($ONOO^-$), resulting in DNA damage, protein oxidation, lipid peroxidation, and cell apoptosis.[34]

Sara Ayuso-Dolado et al. designed $TP95_{414}$ targeting to interfere with the calpain substrate, PSD-95, in excitotoxic overprocessing stroke therapeutics[38] (Fig. 4). $TP95_{414}$ acts to preserve PSD-95 levels, neuronal viability and morphology in chronic excitotoxicity, and reduce ischemia-induced neuronal damage.

Furthermore, disrupting the NMDARs-PSD-95-nNOS complex suppresses NO production and protects neurons from excitotoxicity. Cationic arginine-rich peptides (CARPs), including nerinetide (Fig. 4), R18,[39] CN-105[40], PTD4,[41] etc., are an expanding class of compounds with neuroprotective properties, reduction of oxidative stress, and inhibition of proteolytic enzymes.[42] A Phase III trial of a novel drug candidate nerinetide (ESCAPE-NA1, Tat-NR2B9c) in acute ischemic stroke (AIS) was completed in 2020 (ClinicalTrials.gov, NCT02930018).[43] 1105 patients were randomly assigned (549:556) to receive a single intravenous dose of nerinetide or placebo. The modified Rankin Scale (mRS) score at 90 days was performed in both groups (adjusted risk ratio 1·04, 95 % CI 0·96-1·14; $P = 0·35$). The results showed that nerinetide did not improve the proportion of patients with favorable clinical outcomes after endovascular thrombectomy compared with patients who received placebo. A Phase III study of nerinetide in acute ischemic stroke patients undergoing endovascular thrombectomy excluding thrombolysis, has been completed (ClinicalTrials.gov, NCT04462536).[44] Furthermore, NoNO-42 builds on the first-generation PSD-95 inhibitor, nerinetide, focusing on acute ischemic stroke patients selected for thrombolysis with or without endovascular thrombectomy (ClinicalTrials.gov, NCT06403267). BXOS110 Injection in the Treatment of Acute Ischaemic Stroke trial (BEST, ClinicalTrials.gov, NCT06322394), BXOS110 injection showed up to a ninefold likelihood for achieving mRS score of 0–2 at 90 days. AVLX-144 is a dimeric ligand with high affinity for PSD-95[45] (Fig. 4), with a 1000-fold increase in affinity compared to the monomeric peptide nerinetide.[46] During the Phase I study, AVLX-144 demonstrated no noteworthy safety concerns related to the treatment (ClinicalTrials.gov, NCT04689035).[47]

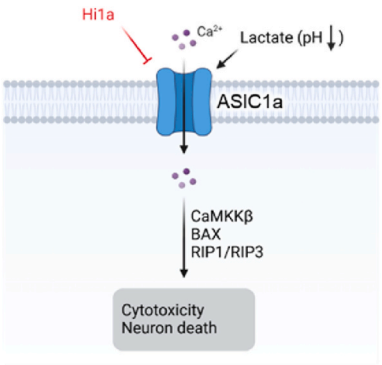

Fig. 3. Mechanism for acidosis with peptide therapy. Hi1a prevented the flux of Ca^{2+} by inhibiting ASIC1a.

3.3.2. AMPARs

Sharma et al. exhibited that sequential treatment of perampanel and aniracetam improved neurobehavioral outcome and infarct damage in ischemic reperfusion injury Wistar rats.[36] Furthermore, AMPARs activation on endothelial cells contributes to vascular permeability, leading to brain edema and hemorrhagic transformation.[48,49] Wang et al. showed the effect of $GluR2_{3Y}$ peptide in inhibiting cell apoptosis inducing by NMDA triggering of AMPARs endocytosis[50] (Fig. 4), demonstrating the AMPARs endocytic pathway may be novel therapeutic targets for neuroprotective agents.

3.4. Peptide therapy for treating mitochondrial dysfunction

In ischemic stroke, the balance between mitophagy and mitochondrial damage shifts result in the accumulation of dysfunctional mitochondria.[51] Furthermore, calcium overload, excitotoxicity, and inflammation contribute to neuronal cell death and further amplifies the ischemic injury[52,53] by promoting mitochondrial permeability transition pore (mPTP) opening and mitochondrial membrane depolarization.[51]

3.4.1. Drp1

Wu et al. found that adiponectin peptide (APNp) has the ability to control dynein-related protein 1 (Drp1)-mediated mitochondrial fission, which helps to reduce astrocyte-derived inflammation[54] (Fig. 5A). In intracerebral hemorrhage (ICH) animals, APNp therapy enhanced neurological function, lowered brain edema, reduced neuronal apoptosis, and alleviated BBB disruption.[54] Furthermore, APNp reduced Smad3 phosphorylation and nuclear translocation following ICH in diabetic mice.[55]

3.4.2. mPTP

MTP-131 (Elamipretide, Bendavia™), a mitochondria-targeting peptide, protected human brain microvascular endothelial cells from damage caused by oxygen/glucose deprivation (OGD)[56–59] (Fig. 5B). Furthermore, MTP-131 protected neural mitochondrial functions against toxic in several models.[60] Also, potential beneficial effects of CARPs on ischemic brain mitochondria after stroke have also been shown.[61]

3.5. Peptide therapy for other mechanisms of ischemic stroke

3.5.1. GLP-1

The LEADER trial with liraglutide[62] and the SUSTAIN-6 trial with

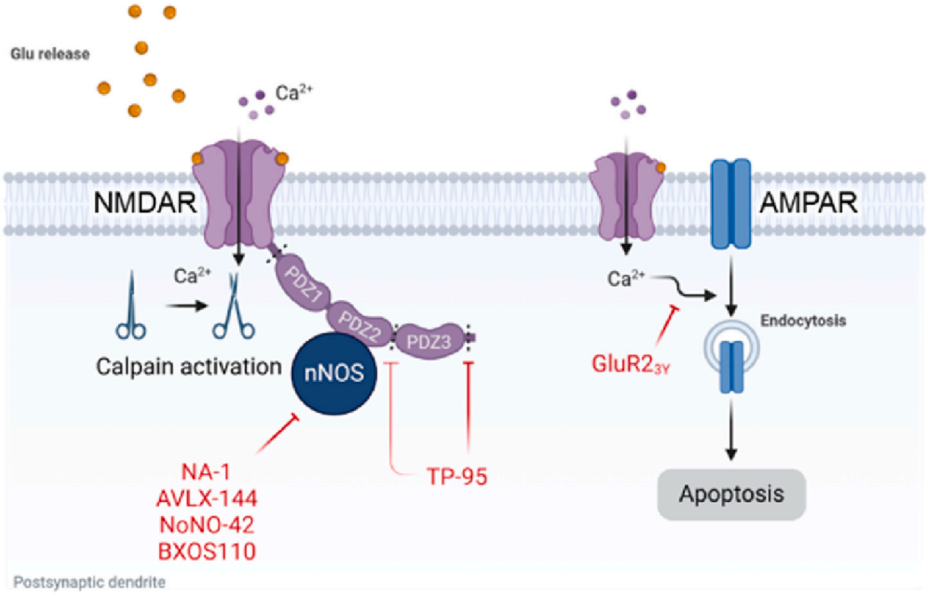

Fig. 4. Mechanisms for intracellular calcium levels with peptide therapies. Excess glutamate release leads to hyperactivation of NMDARs during ischemic stroke, and the regulation of NMDARs on AMPAR trafficking, influencing cell apoptosis, and neurodegeneration. $TP95_{414}$, nerinetide, NoNO-42, BXOS110, and AVLX-144 blocked the progress of PSD-95. $GluR2_{3Y}$ inhibited NMDAR-triggered signaling cascades, thereby blocking AMPAR endocytosis.

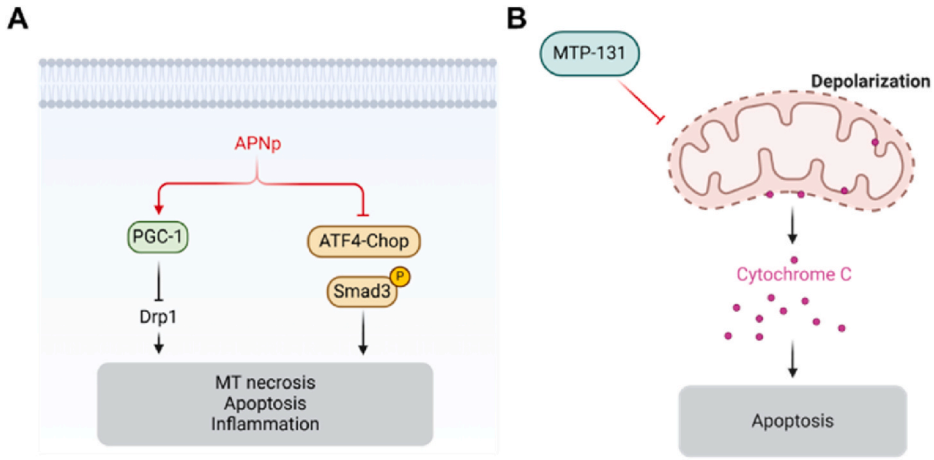

Fig. 5. Mechanisms for mitochondrial dysfunction with peptide therapies.
(A) APNp increases PGC-1/Drp1 signaling while decreasing inflammation and apoptosis brought on by ATF4-CHOP and Smad3 phosphorylation. **(B)** MTP-131 restored ATP synthesis, and prevented cell apoptosis.

semaglutide[63] have demonstrated significant reductions in major cardiovascular (CV) events with these glucagon-like peptide-1 (GLP-1) receptor agonists. Yang et al. reviewed the preclinical data demonstrating the impressive neuroprotective efficacy of both GLP-1 and GLP-1 receptor agonists in stroke,[64] with notable benefits observed in individuals with type 2 diabetes.[65] The ASSET trial is now ongoing for the investigation of semaglutide and ischemic stroke (ClinicalTrials.gov, NCT05630586).

3.5.2. ETA and ETB

Endothelin receptors come in two different varieties: endothelin A receptor (ETA) and endothelin B receptor (ETB). ETA receptors mediate a potent and long-lasting vasoconstriction in the cerebral circulation.[30] ETB receptor is involved in the regulation of blood vessel constriction and dilation by promoting the release of NO and prostacyclin.[66] Treatment with sovateltide (IRL-1620, PMZ-1620), an ETB receptors agonist, improves neurologic outcomes in acute ischemic stroke[67,68] (Fig. 6A). In the sovateltide and saline groups, 60 and 40 % of patients improved by 2 points on the mRS, respectively ($p = 0.0519$; odds ratio [OR] 5.25) (ClinicalTrials.gov, NCT04046484).[69] Additionally, 158 patients with cerebral ischemic stroke participated in a Phase III trial, which showed a notable improvement over standard care (ClinicalTrials.gov, NCT04047563).[70,71] A Phase IV clinical study is currently ongoing to evaluate the safety and efficacy of sovateltide treatment and the standard of care in patients with acute ischemic stroke (ClinicalTrials.gov, NCT05955326).

3.5.3. ACE2/Ang-1-7/MasR

The Angiotensin converting enzyme 2, Angiotensin-(1–7), Mas receptor (ACE2/Ang-(1–7)/MasR)[72] axis plays a crucial neuroprotective role in ischemic stroke by counterbalancing the harmful effects of the ACE/Ang II/Angiotensin II receptor type I (AT1R) axis in the renin-angiotensin system (RAS).[73] Ang-(1–7) reduces neuroinflammation by inhibiting pro-inflammatory cytokines and immune cell activation.[74] Talfirastide (TXA-127) (Fig. 6B), a naturally occurring peptide Ang-(1–7), is currently undergoing a Phase II trial for patients

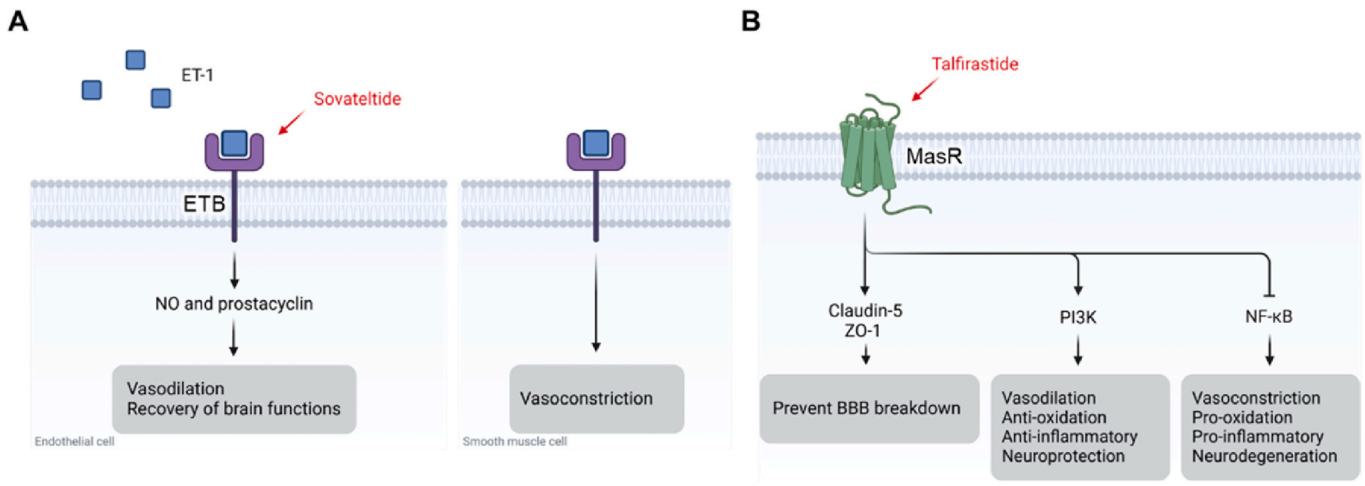

Fig. 6. Mechanisms for other pathways with peptide therapies. Other mechanisms of peptide therapy. **(A)** Sovateltide improved neurologic outcomes in acute ischemic stroke through NO and prostacyclin. **(B)** Talfirastide, a synthetic angiotensin-(1–7) analog, enhanced BBB integrity while exhibiting vasodilatory and anti-inflammatory properties.

6–24 months post ischemic stroke (ClinicalTrials.gov, NCT06135103).

3.5.4. GPIIb/IIIa

Xu et al. demonstrated that the administration of GPIIb/IIIa antagonists within 24–96 h of ischemic stroke onset significantly improve functional prognosis of patients with acute ischemic stroke not receiving endovascular therapy.[75] MT1002 is a novel synthetic peptide with both functions of thrombin inhibitor and GPIIb/IIIa antagonist in Phase II trial for patients with acute coronary syndrome undergoing PCI (ClinicalTrials.gov, NCT06533358).

3.5.5. PTPσ

Protein Tyrosine Phosphatase-Sigma (PTPσ) has been found to inhibit neuronal regeneration,[76] axon growth, and synaptic plasticity through its binding to chondroitin sulfate proteoglycans (CSPGs).[77] After ischemic stroke, glial scar formation leads to the accumulation of CSPGs,[77,78] which inhibit neuronal repair and plasticity or severely restrain potential neuroplasticity of the lesion perimeter.[79] Luo et al. found that the receptor modulatory peptide (NVG-291) showed to enhance the migration of newly born neuroblasts in post stroke model,[79] and a Phase 1b/2a clinical trial of NVG-291 for spinal cord injury is currently recruiting (ClinicalTrials.gov, NCT05965700).

3.5.6. Nrf2

Nuclear factor erythroid 2-related factor 2 (Nrf2) plays a key cellular antioxidant in cellular defense against oxidative stress and inflammation.[80] Liu et al. identified a novel neuroprotective peptide, OL-FS13, from *Odorrana livida*.[81] Animal behavioral and histological abnormalities were considerably reduced by OL-FS13, and cells in the OGD treatment demonstrated neuroprotective action. Similarly, a study explored into the neuroprotective effects and astrocytes-protective benefits of the amphibian-derived short peptide, OM-LV20,[82] in ischemia/reperfusion rats.[83]

3.5.7. BDNF/TrkB

BDNF is known to support neuronal survival, promote neurogenesis, and enhance synaptic plasticity,[84] making it a key target for developing treatments for stroke and other neurodegenerative conditions. GSB-106, a dimeric dipeptide mimetic of BDNF loop 4, has been shown to activate tropomyosin receptor kinase B (TrkB) and downstream signaling pathways, including PI3K/AKT, MAPK/extracellular signal-regulated kinase (ERK), and phospholipase C gamma 1 (PLC-γ1), which play key roles in neuroprotection and neuroregeneration.[85] OM-LV20 increased the expression of BDNF and TrkB.[86]

3.5.8. PirB

Furthermore, Zhao et al. created a transactivator of transcription-paired immunoglobulin-like receptor B (PirB) extracellular peptide (TAT-PEP) that can alter ROS formation by blocking connections between myelin-associated inhibitory proteins and PirB.[87] TAT-PEP can affect the expression of cleaved caspase 3, Bax, and Bcl-2 to reduce cerebral ischemia-reperfusion injury.

3.5.9. PCSK9

MK-0616, an oral macrocyclic peptide proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor,[88] has been evaluated for the treatment of adults with hypercholesterolemia and is currently in a Phase III clinical trial (ClinicalTrials.gov, NCT06492291).

3.5.10. Multiple mechanisms

Cerebrolysin is a mixture of low-molecular-weight peptides and amino acids derived from porcine brain, which has potential neuroprotective properties. The CEREHETIS trial demonstrated that early administration of Cerebrolysin alongside reperfusion therapy significantly reduced the rate of symptomatic hemorrhagic transformation (odds ratio: 0.248; 95 % CI: 0.072–0.851; $p = 0.019$) and mitigated early neurological deficits.[89] However, controversy remains regarding the effectiveness of Cerebrolysin in ischemic stroke patients. Zhang et al. reported that Cerebrolysin provided little benefit for patients with AIS.[90] Ziganshina et al. suggested that Cerebrolysin likely do not reduce all-cause mortality in acute ischemic stroke.[91] Additionally, Cerebrolysin does not significantly impact the total number of serious adverse events but may be associated with an increased risk of non-fatal serious adverse events.

4. New field in peptide/protein generation

AI can rapidly produce high-affinity protein binder candidates on a computational platform, markedly decreasing initial development expenses and duration, enhancing screening efficiency, and circumventing the intricate and expensive procedures of screening, optimization, and large-scale production in conventional peptide development. Currently, the most common methods for producing antibodies rely on the use of animals.[92] Similarly, the traditional development of peptide or protein-based drugs to treat diseases requires extensive experimentation and provides limited control over the properties of the resulting binding molecules. The rapid growth of available crystal structures in the PDB database (https://www.rcsb.org/), combined with advances in deep learning, has significantly enhanced the accuracy and addressed key

challenges in de novo peptide/protein design.[93] By combining protein structural data and deep learning, RFdiffusion bridges the gap between computational prediction and practical protein engineering.[4,94] Furthermore, AI-guided generation of macrocyclic drugs, leveraging computational protein design tools, is rapidly advancing.[95] The combination of AI and wet lab data generation is both complementary and synergistic, with the integration of these approaches expected to accelerate and enhance the outcomes of drug discovery innovation. Consequently, the optimal approach at this juncture may involve employing AI technology to swiftly find candidates in the preliminary phase, followed by thorough verification and optimization via conventional experimental approaches to attain a balance between cost-effectiveness and product quality.

While AI has become a powerful tool in drug discovery, its effectiveness remains fundamentally dependent on human-defined parameters. The identification and selection of appropriate therapeutic targets require domain expertise, biological insight, and contextual understanding that AI alone cannot fully replicate. Thus, human intervention is essential in guiding AI systems toward biologically meaningful objectives. For example, the endocytosis-triggering binding proteins (EndoTags) developed by Huang et al. to induce target protein degradation[96] could potentially facilitate the degradation of specific membrane proteins implicated in conditions such as hyperlipidemia or hypertension. Additionally, current literature indicates that no peptide drugs for the treatment of ischemic stroke have yet been developed using these emerging approaches. Although these methods have not been applied to ischemic stroke, existing studies demonstrate their therapeutic potential in innovative peptide discovery and development. Thus, this review may provide a valuable reference for the identification and prioritization of therapeutic targets in ischemic stroke (Fig. 7, and Table 2). Furthermore, collaboration with molecular dynamics simulations can further enhance the investigation of drug development potential.[97]

Next, we explored the use of RFdiffusion[4] to generate peptide (MDPVIQAAIAAR) capable of binding to example protein, ACE2 (Fig. 7). Before proceeding to laboratory experiments, simple in silico validations can streamline the development process. Here, to ensure the safety and potential clinical applicability of the designed peptides, we then conducted using AllerTOP v2.01 to evaluate the allergenicity prediction.[100] The designed peptides showed probable non-allergens based on auto cross covariance (ACC) transformation of protein sequences. Confirmation through BBPpredict helps to analysis the penetration of BBB.[101] Additionally, ProtParam showed that the estimated half-life is 30 h in vitro, ensuring the stability of the designed peptides.[102] The online tools simplify the early evaluation process by providing rapid and cost-effective assessments of peptide safety, stability, and therapeutic potential, thereby facilitating the selection of promising candidates for further experimental validation.

5. Discussion and perspectives

Peptide therapy has emerged as a promising and innovative approach in the field of medicine, offering a range of therapeutic possibilities across various medical conditions. Herein, we summarize several studies that have engineered peptides targeting specific mechanisms in an attempt to influence mortality and recovery in post-stroke conditions across both human and mouse studies. Given that ischemic stroke induces a cascade of mechanisms, combination therapy is a reasonable approach to enhance the effectiveness of tPA.[103] In this context, peptide drugs play a crucial role by targeting specific mechanisms to enhance therapeutic outcomes, and promote neuroprotection to preserve neuronal integrity and reduce neurodegeneration for improving long-term recovery and functional outcomes after stroke.

Additionally, a number of mechanisms, including as PKCβ and MMP-9,[104,105] influence BBB functioning and could be targets for peptide therapy exploitation. However, the selection and optimization of peptides targeting different pathways can be challenging, as the interactions and synergistic effects among the peptides need to be carefully considered, which may affect their individual efficacy or introduce unforeseen side effects. Moreover, tailoring combination peptide therapy to each patient's specific needs and characteristics can be challenging and may require personalized approaches, such as biomarker-based patient stratification.[106] Individual differences in peptide-induced immune responses may eventually result in therapeutic efficacy.[107,108]

Peptide drugs leverage their specificity and targeted effects, minimizing off-target interactions and reducing the likelihood of adverse reactions,[109] thereby enhancing the overall safety profile of the treatment. However, due to the lack of stability provided by secondary or tertiary structures, peptides are rapidly degraded by peptidases in blood, necessitating some alterations to stabilize them. For example, the

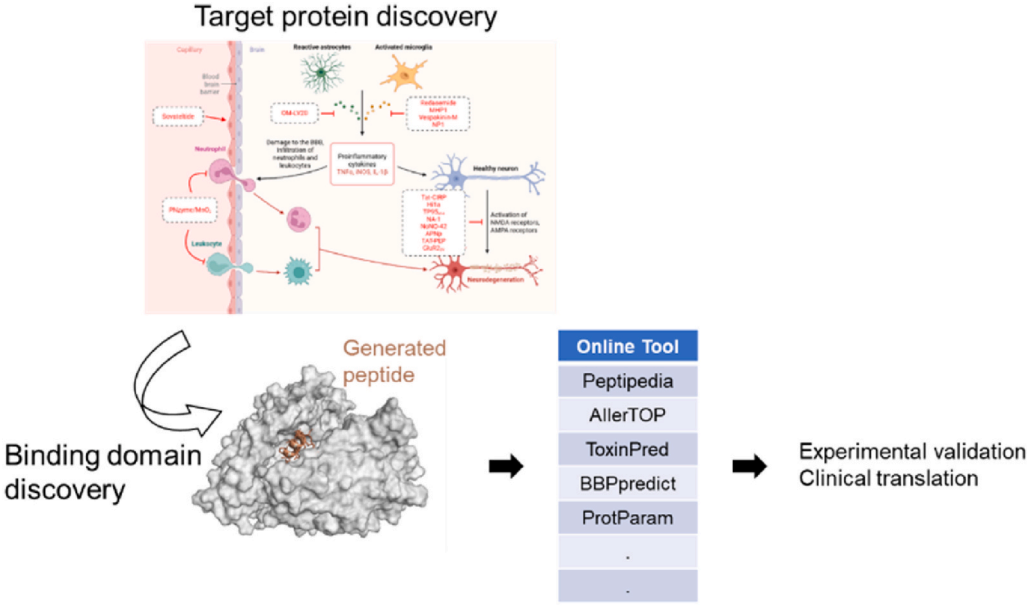

Fig. 7. *De novo* generation of peptides and their simple confirmation prior to experiments. *De novo* peptide design allows custom creation of therapeutic sequences, and their basic safety and functional properties can be confirmed through online predictive tools before experimental testing.

Table 2
Different scenarios of stroke and its peptide therapy.

Mechanism	Peptide	Target	Experimental model	Cell type	Effects/Key findings	Reference
Inflammation	MHP1	RANKL/RANK	C57BL/6 mice	Mouse microglial cell line, mouse monocyte cell line, and human monocyte cell line	TLR4	14
	MHP1-AcN	RANKL/RANK	BALB/c mice	Mouse microglial cell line	TLR4	15
	Tat-CIRP	MD2/TLR4	C57BL/6, MD2$^{-/-}$, TLR4$^{-/-}$ mice, and rhesus monkey	Mouse cortical neurons	N/A	16
	NP1	miR-6328	Sprague–Dawley rats	Rat pheochromocytoma cell line	IKKβ/NF-κB	21
	Vespakinin-M	B2R	C57BL/6J mice	Mouse microglial cell line, mouse neuronal cell line	PI3K/AKT, IκBα/NF-κB	22
	PNzyme/MnO_2	N/A	C57BL/6 mice	Human neuroblastoma cell line, mouse brain endothelial cell line, mouse monocyte cell line	SOD/CAT	23
	OPNpt7R	N/A	Sprague-Dawley rats	Rat primary microglia	Arginase 1, IL-10, IL-4, and CD36	24
	Tat-NTS	Annexin-A1	C57BL/6 mice, Cx3cr1-Cre mice	Mouse microglial cell	NF-κB	98
Acidosis	Hi1a	ASIC1a	Rats	Rat cortical neuron/astrocyte, E. coli BL21 cells, Human Embryonic Kidney 293 cell line	N/A	28
Intracellular Calcium Levels	$TP95_{414}$	PSD-95	Balb/cOlaHsd mice	Rat cortical neuron	NMDAR/PSD-95/nNOS/NO	38
	$GluR2_{3Y}$	AMPA receptor	N/A	Hippocampal Neurons	AMPA receptor endocytosis	50
Mitochondria	APNp	PGC-1α/ATF4-Chop/Smad3	C57BL/6J mice, db/db mice	Mouse neurons	Drp1	55
Other Mechanisms	Eptifibatide	GPIIb/IIIa	N/A	N/A	N/A	Clinical drug
	OL-FS13	Nrf2	Rats	Rat pheochromocytoma cell line	HO-1	81
	OM-LV20	PAC1R/JNK/TPH1	Sprague–Dawley rats	Rat astrocyte cell line	Tryptophan hydroxylase 1	82
	GSB-106	TrkB	Outbred rats	Mouse hippocampal cell line	PI3K/AKT, MAPK/ERK, and PLC-γ1	85,99
	TAT-PEP	PirB	Sprague–Dawley rats	Rat cortical neurons	cleaved caspase 3, Bax, and Bcl-2	87

ACE2: angiotensin converting enzyme 2; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxalone propionic acid; APNp: adiponectin peptide; ASIC1a: acid-sensing ion channel-1a; ATF4-Chop: activating transcription factor 4-CCAAT-enhancer-binding protein homologous protein; B2R: bradykinin B2 receptors; CAT: catalase; ERK: extracellular signal-regulated kinase; GPIIb/IIIa: glycoprotein IIb/IIIa; HO-1: heme oxygenase-1; IκBα: NF-kappaB inhibitor alpha; IKKβ: inhibitor of nuclear factor kappa-B kinase subunit beta; IL: interleukin; MAPK: mitogen-activated protein kinase; MasR: Mas receptor; MD2: myeloid differentiation protein 2; MHP1: microglial healing peptide 1; MHP1-AcN: MHP1-N-terminal acetylation and C-terminal amidation; mPTP: mitochondrial permeability transition pore; NF-κB: nuclear factor kappa B; NMDAR: N-methyl-D-aspartate receptor; nNOS: neuronal nitric oxide synthase; NO: nitric oxide; NP1: new peptide; Nrf2: nuclear factor erythroid 2-related factor 2; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PirB: immunoglobulin-like receptor B; PI3K: phosphoinositide 3-kinases; PLC-γ1: phospholipase C gamma 1; PNzyme/MnO2: peptide-templated manganese dioxide nanozyme; PSD-95: postsynaptic density protein 95; RANK: receptor activator of nuclear factor κB; RANKL: receptor activator of nuclear factor κB ligand; SOD: superoxide dismutase; Tat-CIRP: tat cold-inducible RNA-binding protein; TAT-PEP: transactivator of transcription-PirB extracellular peptide; TLR4: toll like receptor 4; TrkB: tropomyosin receptor kinase B.

half-life of nerinetide appears to be short. After IV injection, t_{max} is expected to be 10 min.[110] The stabilization of these peptides may increase by adding hydrogen bonds, van der Waals forces, and intramolecular hydrophobic interactions.[111,112] A new class of peptide therapeutics, macrocyclic peptides, are changing the field. PepExplainer, a computational tool developed by Zhai et al. deciphering amino acid substructures, translating macrocyclic peptides into detailed molecular graphs.[113]

Peptide-based drug delivery systems, such as exosomes, lipid nanoparticles, and dendrimers represent a novel and potential therapeutic approach for peptide degradation.[114–116] Howell et al. developed a non-immunogenic protein drug carrier elastin-like polypeptide (ELP) from human tropoelastin that stabilizes fused peptide therapies in the systemic circulation.[117] Peptide-based drug delivery systems can encapsulate multiple peptides and enable controlled release at the desired site. Additionally, many potential therapies that show promise in animal studies fail to provide the benefits in human clinical trials, highlighting the limitations of animal models in predicting human responses accurately.[118,119]

Neurodegeneration is a critical consequence of ischemic stroke, resulting in the loss of neuronal function and structure, and is closely linked to long-term cognitive and motor impairments in patients.[120] Additionally, targeting inflammatory signaling pathways has emerged as a promising therapeutic approach for treating neurodegenerative conditions[121,122] (Fig. 1); thus, addressing neuroinflammation in a comprehensive manner is also essential for effective neuroprotection and improved recovery outcomes in stroke.

6. Conclusion

Peptide therapy is a promising approach for treating stroke, offering potential benefits due to its ability to target specific molecular pathways involved in the condition. Additionally, the development of protein/peptide binders or macrocyclic peptides has opened new avenues for therapeutic intervention. These binders can be designed to block harmful interactions or stabilize beneficial ones, complementing peptide-based strategies. However, further research is needed to validate the therapeutic effects of peptide therapy and protein binders in stroke treatment, ensuring their safety, efficacy, and long-term benefits.

CRediT authorship contribution statement

Kuo-Feng Tseng: Writing – review & editing, Writing – original draft, Methodology. **Kuo-Wei Tseng:** Writing – original draft, Methodology. **Hsien-Yin Liao:** Writing – review & editing, Methodology. **Pei-Hsien Chen:** Writing – review & editing, Writing – original draft, Supervision.

Ethical standards

The manuscript does not contain clinical studies or patient data.

Statements and declarations

The authors declare no conflict of interest.

Disclosures

None.

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