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Molecular Mechanisms of Synaptic Plasticity Impairment in Chronic Cerebral Hypoperfusion-Induced Vascular Cognitive Impairment and Advances in Traditional Chinese Medicine Interventions

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Abstract: ***Chronic cerebral hypoperfusion (CCH) is considered one of the major driving factors underlying vascular cognitive impairment (VCI), and CCH-induced impairment of synaptic plasticity constitutes an important pathological basis for cognitive decline. This review summarizes the molecular mechanisms underlying CCH-induced synaptic plasticity impairment and recent advances in traditional Chinese medicine (TCM) interventions. Current evidence suggests that CCH can suppress the BDNF/TrkB/CREB signaling axis, disrupt the PI3K/Akt/mTOR pathway, remodel the glutamatergic receptor system, and disturb calcium homeostasis, thereby initiating a vicious cycle in which neuroinflammation and synaptic dysfunction mutually reinforce each other. These pathological changes ultimately contribute to dendritic spine loss and impaired hippocampal long-term potentiation (LTP). Regarding TCM interventions, various herbal formulas and bioactive compounds have been shown to regulate these pathways through multiple targets, exerting synergistic neuroprotective effects by activating neurotrophic signaling, restoring synaptic protein synthesis, rebalancing central excitatory signaling, and remodeling the neurovascular microenvironment. Nevertheless, current research is still limited by insufficient clinical translation, inadequate target validation, heterogeneity among experimental models, and sex bias. Future studies should integrate biomarker-driven clinical trials, druggability assessment of therapeutic targets, and animal models that more closely reflect clinical conditions to facilitate precision TCM interventions for VCI.***

Keywords: Chronic cerebral hypoperfusion, Vascular cognitive impairment, Synaptic plasticity, Traditional Chinese medicine**.**

1. Introduction

Vascular cognitive impairment (VCI) is a common form of cognitive impairment second only to Alzheimer's disease (AD), and its disease burden continues to increase. Chronic cerebral hypoperfusion (CCH) is considered an important driving factor in the development and progression of VCI, while CCH-induced impairment of synaptic plasticity represents a major pathological basis for cognitive decline [1]. This impairment involves both structural plasticity deficits caused by dendritic spine loss and functional plasticity dysfunction characterized by impaired long-term potentiation (LTP), which together contribute to disturbances in learning and cognition [1-2]. Current evidence suggests that the molecular mechanisms underlying CCH-induced synaptic injury mainly involve dysregulation of BDNF/TrkB/CREB-mediated neurotrophic signaling, remodeling of the glutamate receptor system, and a vicious cycle between neuroinflammation and synaptic dysfunction [1]. Targeting these mechanisms, traditional Chinese medicine (TCM), characterized by its multicomponent, multitarget, and holistic regulatory properties, may ameliorate synaptic injury through the modulation of neurotrophic factors, the PI3K/Akt/mTOR pathway, glutamate receptors, and neuroinflammatory signaling [3]. However, current studies remain limited by insufficient mechanistic elucidation and inadequate clinical translation. Therefore, this review systematically summarizes the molecular mechanisms of CCH-induced synaptic plasticity impairment and recent advances in TCM interventions, with the aim of providing a theoretical basis for precision TCM-based treatment of VCI.

2. Pathological Characteristics and Significance of Synaptic Plasticity Impairment in Chronic Cerebral Hypoperfusion

CCH-mediated impairment of synaptic plasticity is characterized by pathological alterations in both structural and functional plasticity and represents one of the major pathological bases of cognitive decline in VCI. At the structural level, morphological studies have shown that dendritic spine density is significantly reduced in the hippocampal CA1 region of CCH model rats, accompanied by degenerative changes in synaptic ultrastructure and marked downregulation of the presynaptic markers synaptophysin (SYN) and growth-associated protein 43 (GAP43), as well as the postsynaptic density protein PSD95 [2-3,7]. Notably, no significant differences in the total expression levels of core synaptic proteins were observed between the model and sham-operated groups, suggesting that CCH-induced cognitive impairment may primarily arise from disruption of synaptic structural integrity rather than a global reduction in synaptic protein abundance, thereby further refining the pathological understanding of synaptic structural injury [5]. At the functional level, impairment of long-term potentiation (LTP) in the hippocampal CA3–CA1 pathway is a key feature of CCH-induced synaptic dysfunction. Electrophysiological

studies have shown that the field excitatory postsynaptic potential (fEPSP) slope in CCH model rats remains at only approximately 103% of baseline, indicating a marked impairment of long-term synaptic potentiation [6]. The underlying mechanisms are closely associated with reduced activity of the Neurogranin–CaM–CaMKII pathway and temporally dysregulated activation of neuroinflammatory signaling pathways [4-5]. From the perspective of disease progression, dynamic proteomic analyses indicate that remodeling of synaptic regulatory molecules can occur at an early stage after CCH induction, preceding irreversible neuronal apoptosis, suggesting that disruption of synaptic molecular homeostasis may represent an early event in CCH-related cognitive impairment and a potential therapeutic target [5]. Collectively, structural synaptic damage and functional suppression constitute important pathological bases of cognitive decline, and restoration of synaptic plasticity may therefore represent an important strategy for intervening in the progression of VCI.

3. Molecular Regulatory Mechanisms of Synaptic Plasticity Impairment

3.1 Dysfunction of the BDNF/TrkB/CREB Signaling Pathway

The BDNF/TrkB/CREB signaling axis is a key pathway involved in the regulation of hippocampal synaptic structural remodeling and functional homeostasis, and its suppression or dysregulation represents an important molecular mechanism underlying CCH-induced synaptic injury. Brain-derived neurotrophic factor (BDNF) is initially synthesized as the precursor proBDNF, which must undergo extracellular proteolytic cleavage to generate mature BDNF (mBDNF) before exerting neuroprotective effects. The S100A10/tPA plasminogen activation system promotes the conversion of proBDNF to mBDNF, while matrix metalloproteinase-9 (MMP-9) can directly cleave proBDNF; together, these mechanisms constitute a dual regulatory system governing proBDNF/mBDNF conversion [3,8]. Functionally, mBDNF preferentially binds to the TrkB receptor to activate protective signaling pathways that promote neuronal survival and synaptic remodeling, whereas uncleaved proBDNF exerts neurotoxic effects through the p75 neurotrophin receptor (p75NTR)/sortilin complex. The dynamic balance between these two forms contributes to the regulation of neuronal survival and synaptic function. Under CCH conditions, the hippocampal proBDNF/mBDNF ratio is abnormally elevated, accompanied by downregulation of the protective TrkB receptor and upregulation of the neurotoxic p75NTR receptor, thereby disrupting neurotrophic signaling homeostasis. Meanwhile, the phosphorylation levels of downstream Akt and CREB are significantly reduced, resulting in decreased expression of key synaptic proteins, including SYN, GAP43, and PSD95. These changes ultimately lead to reduced dendritic spine density and disruption of synaptic ultrastructure, thereby impairing structural synaptic plasticity [3]. In addition, CCH can induce abnormal accumulation of β-amyloid (Aβ) in brain tissue, while Aβ can further suppress CREB phosphorylation and reduce BDNF expression, forming a vicious cycle between Aβ accumulation and inhibition of the BDNF/TrkB pathway that continuously aggravates synaptic plasticity impairment and accelerates cognitive decline [9].

3.2 Dysregulation of the PI3K/Akt/mTOR Signaling Axis

The PI3K/Akt/mTOR signaling axis plays an important role in regulating synaptic protein synthesis, neuronal autophagic homeostasis, and the stability of the cerebral microenvironment. Evidence suggests that this pathway is suppressed under CCH conditions and may contribute to synaptic plasticity impairment through multiple mechanisms. Following inhibition of pathway activation, the levels of p-mTOR, p-p70S6K, and p-4EBP1 in the hippocampus are significantly reduced, whereas p-eEF2 levels are increased. These changes interfere with the synthesis and modification of synaptic structural proteins, resulting in reduced expression of key proteins such as PSD95 and synaptophysin, and ultimately leading to impaired LTP and disrupted synaptic transmission [10]. Meanwhile, weakened negative regulation of autophagy by the PI3K/Akt/mTOR pathway may result in excessive activation of autophagy-related proteins, including Beclin1 and LC3, thereby inducing excessive neuronal autophagy and further aggravating neurodegenerative damage and synaptic loss [11]. Several intervention studies have shown that restoration of this pathway can ameliorate CCH-induced synaptic injury. Ginkgo biloba extract EGb761 can reverse the suppression of mTOR phosphorylation, promote synaptic protein synthesis, and restore synaptic function [10]. Tongqiao Huashuan Granules can activate the PI3K/Akt/mTOR pathway while simultaneously suppressing excessive neuronal autophagy, thereby alleviating brain injury [11]. In addition, exercise-induced skeletal muscle-derived small extracellular vesicles (sEVs) can activate the mTOR pathway through miR-17/20a-5p-mediated suppression of DEPTOR, whereas rapamycin treatment or DEPTOR overexpression can completely abolish this protective effect [4]. Another study showed that activation of ChemR23 can enhance PI3K/Akt phosphorylation, activate the Nrf2 antioxidant pathway, and inhibit NLRP3 inflammasome-mediated pyroptosis, thereby indirectly preserving synaptic homeostasis [12]. Collectively, dysregulation of the PI3K/Akt/mTOR pathway represents an important mechanism of CCH-induced synaptic injury, and restoration of its activity may serve as a potential molecular strategy for the treatment of VCI.

3.3 Remodeling of the Glutamate Receptor System and Disruption of Calcium Signaling

Remodeling of the glutamate receptor system and disruption of intracellular calcium homeostasis are important molecular events involved in CCH-induced impairment of synaptic plasticity. Under physiological conditions, N-methyl-D-aspartate receptors (NMDARs), which are highly calcium-permeable ligand-gated ion channels, initiate hippocampal long-term potentiation (LTP) by precisely regulating Ca^{2+} influx and therefore serve as key molecular switches for maintaining synaptic plasticity [13]. Persistent hypoperfusion induced by CCH disrupts this regulatory system. Energy metabolism impairment increases presynaptic glutamate release while dysfunction of the astrocytic glutamate transporters GLT1 and GLAST reduces extracellular glutamate uptake, resulting in glutamate accumulation within the synaptic cleft. This phenomenon has been observed in a

mouse model of unilateral common carotid artery occlusion, in which cortical glutamate concentrations increased during the early ischemic phase and were accompanied by neuronal hyperexcitability [13-14]. Disruption of glutamate homeostasis leads to sustained overactivation of synaptic and extrasynaptic NMDARs, overcoming the voltage-dependent Mg^{2+} blockade and triggering diffuse Ca^{2+} influx. Consequently, localized calcium signaling is transformed into global intracellular calcium overload, thereby impairing synaptic transmission [13,16]. Meanwhile, tissue acidosis and glutamate accumulation reinforce each other, forming a positive feedback loop involving hypoperfusion, acidosis, and excitotoxicity that further aggravates cerebral injury [14].

Intracellular calcium overload is further exacerbated by decompensation of the intracellular calcium-buffering system. Excessive activation of postsynaptic NMDARs triggers calcium-induced calcium release (CICR) mediated by endoplasmic reticulum ryanodine receptors (RyRs) and inositol 1,4,5-trisphosphate receptors (IP3Rs), resulting in depletion of endoplasmic reticulum calcium stores. At the same time, dysfunction of the mitochondrial calcium uniporter (MCU) complex due to insufficient L-lactate supply impairs mitochondrial Ca^{2+} uptake and clearance, further aggravating intracellular calcium overload [13,16]. Ultrastructural studies have shown that mitochondrial-associated endoplasmic reticulum membranes (MAMs) are disrupted in the hippocampal CA1 region of CCH model rats, as evidenced by endoplasmic reticulum swelling, mitochondrial cristae fragmentation, and reduced organelle contact sites, accompanied by impaired ATP synthesis and increased reactive oxygen species production. Such MAM disruption not only weakens the mitochondrial buffering capacity for cytosolic Ca^{2+} but may also interfere with signaling communication between the endoplasmic reticulum and mitochondria [15]. In addition, abnormal activation of calcium-permeable AMPA receptors (Ca-AMPARs) lacking the GluA2 subunit provides an additional route for Ca^{2+} influx, thereby accelerating calcium overload-mediated synaptic loss and neuronal dysfunction [16].

Targeting these mechanisms, the partial NMDAR antagonist memantine has been shown in animal models to suppress early neuronal hyperexcitability after CCH and improve long-term cognitive function, whereas activation of cannabinoid receptor type 2 (CB2) can alleviate endoplasmic reticulum stress and restore MAM integrity, thereby ameliorating post-ischemic synaptic injury and providing potential therapeutic strategies for VCI [14-15].

3.4 Coupling Between Neuroinflammation and Synaptic Plasticity

Neuroinflammation is closely associated with synaptic plasticity impairment. CCH activates innate immune responses within the central nervous system and reshapes the functional phenotypes of glial cells, thereby abnormally regulating synaptic remodeling and establishing a vicious cycle in which inflammatory activation promotes synaptic injury, while synaptic damage further exacerbates inflammation. Microglia and astrocytes are key cellular mediators of this pathological process, and their functional phenotypes are highly dependent on the local inflammatory microenvironment [17-18]. Under CCH conditions, microglia may undergo phenotypic remodeling, with the pro-inflammatory M1 phenotype aggravating brain injury and the anti-inflammatory, reparative M2 phenotype alleviating ischemic damage and promoting tissue repair. The transmembrane receptor TREML2, an important regulator of microglial function, is upregulated following CCH and modulates the efficiency of myelin debris clearance through the TLR9 pathway. Moreover, Treml2 deficiency promotes microglial polarization toward the M2 phenotype and effectively alleviates CCH-induced demyelination [17]. In a bilateral common carotid artery occlusion model, astrocytes exhibit a shift toward a protective A2 phenotype, characterized by markedly increased S100a10 expression, no obvious activation of the pro-inflammatory complement component C3, and reduced Connexin 43 expression, thereby contributing to the regulation of the inflammatory microenvironment [19].

At the level of synaptic regulation, microglia physiologically participate in synaptic plasticity remodeling through phagocytic pruning. However, chronic inflammation induced by CCH may pathologically amplify this process, leading to excessive microglial engulfment of key synaptic proteins such as PSD-95, thereby reducing synaptic density and impairing structural synaptic plasticity [5]. Within the molecular regulatory network, circRNAs may regulate inflammation-related genes through competing endogenous RNA mechanisms. Gene Ontology and KEGG enrichment analyses have shown that differentially expressed genes are significantly enriched in immune and inflammatory pathways, suggesting that non-coding RNAs may participate in the coupled regulation of inflammation and synaptic injury [18]. Overall, neuroinflammation is closely linked to synaptic plasticity impairment through multiple mechanisms, including glial phenotypic remodeling, excessive synaptic pruning, and non-coding RNA regulation, thereby providing a theoretical basis for targeted anti-inflammatory and synaptoprotective interventions in VCI.

4. Advances in Traditional Chinese Medicine Interventions

4.1 Drugs Targeting the BDNF/TrkB/CREB Pathway

Activation of the BDNF/TrkB/CREB pathway is considered an important mechanism underlying the restoration of synaptic structure and function after CCH and represents a major therapeutic target of traditional Chinese medicine (TCM) for VCI. A variety of TCM-derived active compounds and herbal formulas have been reported to exert synaptoprotective effects by targeting this pathway. Among them, hexahydrocurcumin has been relatively well studied and has been shown to activate the BDNF/TrkB/CREB signaling axis in CCH models, upregulate key pre- and postsynaptic proteins, and simultaneously exert antioxidant effects and inhibit abnormal Aβ and pTau accumulation, making it a representative active compound targeting this pathway [21]. Epimedium flavonoids can upregulate BDNF and PI3K expression and increase the levels of p-Fyn, p-Akt, and p-CREB, suggesting that they may converge on CREB activation through the BDNF/Fyn and PI3K/Akt/CREB parallel signaling pathways. However, their regulatory effect

on the TrkB receptor has not yet been verified, and the classical TrkB-dependent mechanism requires further confirmation [24]. In addition, several TCM preparations have been reported to activate BDNF/TrkB signaling, although the involvement of downstream CREB remains unclear. Intranasal icariin can activate the BDNF/TrkB pathway, muscone can regulate the BDNF-TrkB-NP2 signaling axis, and total saponins from Panax notoginseng leaves can exert neuroprotective effects through the BDNF-TrkB-PI3K/Akt pathway [20,22-23]. Modified Kongsheng Zhenzhong Pill can activate the S100A10/tPA pathway, promote the conversion of proBDNF to mature mBDNF, and ameliorate synaptic injury, although whether this effect further activates the TrkB-CREB axis remains to be determined [3]. Overall, the evidence supporting regulation of the BDNF-TrkB-CREB pathway by hexahydrocurcumin is relatively robust, whereas most other TCM interventions appear to act through indirect activation or partial regulation of this signaling cascade. Further studies are therefore needed to systematically compare the regulatory effects of different TCM compounds and formulas on individual nodes within this pathway.

4.2 Drugs Targeting the PI3K/Akt/mTOR Pathway

The PI3K/Akt/mTOR pathway is involved throughout the processes of neuronal survival, apoptosis, autophagy, and synaptic protein synthesis, and represents an important signaling pathway through which TCM exerts multitarget effects against CCH-related cognitive impairment. A variety of TCM formulas and active compounds can act on different nodes of this pathway to exert multiple effects, including anti-inflammatory, anti-apoptotic, autophagy-regulating, and synaptoprotective actions.

Buqi Huoxue Tongnao Formula has been shown to significantly activate the PI3K/Akt pathway in a 2-vessel occlusion (2-VO)-induced CCH rat model, suppress the expression of inflammation- and apoptosis-related factors including IL-1β, TNF-α, cleaved caspase-3, and iNOS, and thereby exert anti-inflammatory, antioxidant, and anti-apoptotic effects while significantly improving learning and memory in model rats [25]. A combined preparation of astragaloside A, chlorogenic acid, and scutellarin (ACS) can upregulate p-PI3K, p-AKT, p-GSK3β, and the anti-apoptotic protein Bcl-2, while downregulating cytochrome c (Cyto-c), cleaved caspase-3, and the pro-apoptotic protein Bax, thereby reducing mitochondrial injury and neuronal apoptosis. Importantly, the PI3K-specific inhibitor LY294002 significantly reverses these protective effects, suggesting that the neuroprotective action of ACS is at least partly dependent on activation of the PI3K/Akt pathway [26].

With respect to mTOR-mediated autophagic dysregulation downstream of this pathway, Tongqiao Huashuan Granules (THg) can increase the expression of p-PI3K, p-AKT, and p-mTOR, inhibit Beclin1- and LC3-mediated excessive neuronal autophagy, ameliorate hippocampal neuronal injury, and improve cognitive function in VCI rats [11]. Ginkgo biloba extract EGb761 can reverse CCH-induced suppression of the mTOR pathway, effectively restore LTP, improve synaptic transmission efficiency and dendritic spine structure, and alleviate axonal demyelination, suggesting that remodeling of mTOR signaling plays an important role in its synaptoprotective effects [10]. Taken together, different TCM preparations can act on both upstream and downstream components of the PI3K/Akt/mTOR pathway and alleviate CCH-induced pathological injury through multiple mechanisms, providing substantial experimental evidence for TCM-based modulation of this signaling pathway.

4.3 Drugs Regulating Glutamate Receptors and Calcium Homeostasis

The imbalance between glutamatergic and GABAergic synaptic transmission, excessive activation of NMDA receptors, and intracellular calcium overload induced by CCH are important contributors to neuronal excitotoxicity and synaptic injury. A variety of TCM-derived active compounds can exert neuroprotective effects by regulating receptor balance and stabilizing calcium homeostasis. Dengzhan Shengmai Formula and its major active components can modulate the balance between excitatory and inhibitory synaptic signaling in the central nervous system. Among these components, 4,5-caffeoylquinic acid (4,5-CQA) and scutellarin can downregulate the NMDA receptor NR2B subunit while upregulating the GABAA receptor α1 subunit, thereby restoring the balance between glutamatergic and GABAergic synaptic transmission. In cellular experiments, 10 μM scutellarin blocked approximately 10% of NMDA NR1/NR2B currents, while both 4,5-CQA and scutellarin enhanced GABAA receptor activation in a concentration-dependent manner, thereby counteracting glutamate-mediated neuronal excitotoxicity. In addition, Dengzhan Shengmai Formula can regulate synaptic transport proteins such as vGluT1 and vIAAT and modulate postsynaptic membrane lipid metabolism, thereby stabilizing the synaptic microenvironment through multiple mechanisms [27]. Polygalasaponin F (PGSF) can concentration- dependently antagonize glutamate-induced injury in hippocampal neurons. It reduces intracellular Ca^{2+} overload by inhibiting excessive NMDA receptor activation and reversing the receptor subunit imbalance characterized by NR2A downregulation and NR2B upregulation. Meanwhile, PGSF upregulates p-CREB and BDNF expression, thereby synergistically promoting the restoration of synaptic plasticity and exerting multitarget neuroprotective effects [28]. Collectively, the active components of Dengzhan Shengmai Formula and PGSF may suppress glutamate excitotoxicity through complementary mechanisms involving receptor balance, restoration of calcium homeostasis, and activation of neurotrophic signaling, making them potential therapeutic agents for CCH-induced synaptic injury.

4.4 Drugs Targeting the Synaptic Microenvironment

Disruption of neurovascular unit homeostasis and deterioration of the synaptic microenvironment are important pathological features of CCH-related cognitive impairment. TCM interventions may restore synaptic microenvironmental homeostasis through multiple mechanisms, including direct repair of synaptic structures, regulation of glial cell function, suppression of inflammatory pyroptosis, promotion of angiogenesis, and enhancement of myelin repair. In terms of direct synaptic structural restoration, Modified Kongsheng Zhenzhong Pill can activate the S100A10/tPA pathway,

promote the maturation of proBDNF into mBDNF, reduce the potentially neurotoxic proBDNF/mBDNF ratio, markedly upregulate the expression of synaptic proteins including SYN, GAP43, and PSD95, and thereby ameliorate hippocampal synaptic structural damage [3]. Regarding modulation of the inflammatory microenvironment, Chuanzhi Tongluo Capsule can enhance the ChAT/α7nAChR-mediated cholinergic anti-inflammatory pathway, inhibit excessive activation of NF-κB signaling, alleviate hippocampal neuroinflammation, and indirectly preserve synaptic function [29].

A variety of naturally derived active compounds can remodel the cerebral microenvironment by targeting glial and vascular cells. Salidroside promotes microglial polarization toward the anti-inflammatory and reparative M2 phenotype, thereby reducing neuronal apoptosis [34]. Sinomenine regulates the release of microglia-derived exosomes enriched in miR-223-3p and suppresses the neuronal NLRP3-mediated pyroptotic pathway, consequently alleviating neuroinflammatory injury [31]. Puerarin activates the IL-10/STAT3/CD36 pathway, enhances the clearance of myelin debris, promotes white matter remyelination, and thereby improves the cerebral white matter microenvironment [32]. Farrerol inhibits NLRP3 inflammasome activation through the MAPK–NF-κB pathway and suppresses neuronal pyroptosis [30]. In addition, with respect to vascular regulation, panaxadiol activates the VEGF-A/p38 MAPK/Src pathway, promotes cerebral angiogenesis, and improves local cerebral blood flow, thereby helping to alleviate hypoperfusion-induced brain injury [33]. Taken together, these agents restore neurovascular unit function through multiple mechanisms and provide diverse TCM-based strategies for targeted remodeling of the synaptic microenvironment in VCI.

4.5 Multitarget Synergistic Regulation by TCM Formulas

The pathological progression of CCH-induced VCI involves multiple processes, including inflammation, oxidative stress, neuronal apoptosis, dysregulated autophagy, and impaired synaptic plasticity. Therefore, interventions targeting a single molecular pathway may be insufficient to comprehensively modify disease progression. Owing to their multicomponent, multitarget, and multipathway characteristics, TCM formulas and characteristic herb pairs can simultaneously modulate multiple pathological processes, integrating microenvironmental restoration with the recovery of synaptic function and thereby aligning well with the complex pathophysiological mechanisms of VCI [3,36].

Chuanzhi Tongluo Capsule acts in part through the cholinergic anti-inflammatory pathway. By upregulating hippocampal ChAT and α7nAChR expression and suppressing NF-κB-mediated inflammatory cascades, it improves learning and memory in CCH model mice. Meanwhile, the cholinergic pathway regulated by this formula is closely associated with synaptic development and plasticity restoration, thereby producing dual anti-inflammatory and synaptoprotective effects [29]. Buqi Huoxue Tongnao Formula suppresses the expression of inflammatory and apoptotic factors through activation of the PI3K/AKT pathway, thereby reducing secondary neuronal injury. It also upregulates the LXRα/CYP7A1 pathway to correct lipid metabolic disturbances, demonstrating a multipathway synergistic regulatory effect on the pathological progression of CCH [25]. The baicalin–geniposide herb pair targets the HIF-1α/EPO/NF-κB pathway by upregulating HIF-1α and EPOR expression, inhibiting NF-κB phosphorylation and the release of pro-inflammatory cytokines, and regulating microglial polarization, thereby alleviating inflammatory injury in brain tissue. It also ameliorates ischemia-related secondary renal injury, reflecting the holistic regulatory characteristics of TCM [35]. Huoluo Yinao Formula exerts dual regulatory effects on autophagy and oxidative-inflammatory signaling. By suppressing HSP90AA1 expression, it inhibits excessive neuronal autophagy, while simultaneously activating the PI3K/AKT/mTOR pathway, reducing oxidative and inflammatory mediators, enhancing antioxidant activity, alleviating oxidative-inflammatory neuronal injury, and improving cognitive dysfunction [36].

Modified Kongsheng Zhenzhong Pill is a representative TCM formula targeting synaptic plasticity. By activating the S100A10/tPA/BDNF pathway, it promotes BDNF maturation and activation, thereby significantly improving cognitive function in CCH model rats, repairing neuronal and synaptic structural damage in the hippocampal CA1 region, reversing dendritic spine loss, and upregulating the expression of key synaptic proteins. Moreover, in vitro gene-silencing experiments support this pathway as an important target underlying its synaptoprotective effects, providing relatively strong mechanistic evidence [3]. Overall, TCM formulas can counteract CCH-induced injury through two complementary modes: indirect regulation of the neural microenvironment and direct restoration of synaptic signaling pathways, thereby reflecting the holistic therapeutic advantages of TCM. However, current studies mainly focus on overall pharmacological effects and downstream pathway verification. The bioactive constituents reaching the systemic circulation, the specificity of core targets, and the precise molecular mechanisms of these formulas still require further investigation.

5. Current Limitations

Although considerable progress has been made in elucidating the molecular mechanisms of CCH-induced synaptic injury and the effects of TCM interventions, substantial challenges remain in translating basic research findings into precision clinical diagnosis and treatment. In terms of clinical translation and model design, interventions such as intermittent fasting, Modified Kongsheng Zhenzhong Pill, and Nurr1 agonists have so far been evaluated mainly in rodent models, with no clinical trials yet using synaptic plasticity-related molecular biomarkers, such as plasma BDNF and PSD95, or synaptic imaging indicators as primary endpoints. Moreover, BCAS-induced stenosis, stepwise BCCAO ligation, and permanent BCCAO models differ substantially in the degree of hypoperfusion and patterns of injury they produce, making it difficult to fully reproduce the marked heterogeneity of clinical VCI. Most studies have also used only male animals, which does not reflect the fact that VCI affects both sexes, and the lack of female data limits the generalizability of findings to female patients [2-3,5]. In addition, animal dosing regimens generally lack pharmacokinetic bridging to human exposure. Current clinical

management of cerebral small vessel disease (cSVD) still relies mainly on basic measures such as blood pressure control, while evidence supporting lipid-lowering therapy remains limited, and no treatment specifically targeting synaptic plasticity pathways has yet been validated [37]. Mechanistically, although animal studies have demonstrated the synaptic regulatory effects of pathways such as BDNF/TrkB and PI3K/Akt/mTOR, regulatory networks in the human brain are considerably more complex, and methods for evaluating target engagement within the brain remain insufficient. For example, although multiple circulating bioactive constituents of Modified Kongsheng Zhenzhong Pill have been identified, the interaction network between its core bioactive molecules and target proteins, as well as their in vivo metabolism, remains poorly defined, limiting biomarker-guided precision dose optimization [3]. Furthermore, important gaps remain in the understanding of the synaptic microenvironment. Although evidence supports a role for glial cell dysfunction in excessive synaptic pruning, the temporal dynamics and therapeutic window of complement-mediated synaptic injury under CCH remain unclear. Findings obtained with complement inhibitors in neurodegenerative diseases cannot be directly extrapolated to VCI, and other key mechanisms, including impaired astrocytic glutamate buffering, extracellular matrix remodeling, and the role of perivascular macrophages in synaptic regulation, require further investigation [5,37].

6. Summary and Perspectives

Current evidence indicates that CCH can impair synaptic protein synthesis and remodeling by suppressing the BDNF/TrkB/CREB and PI3K/Akt/mTOR signaling axes, while remodeling of the glutamate receptor system and disruption of intracellular calcium homeostasis can induce neuronal excitotoxicity. Meanwhile, CCH activates neuroinflammatory cascades, driving a vicious cycle in which neuroinflammation and synaptic injury mutually reinforce each other. These pathological processes ultimately lead to dendritic spine loss and impaired LTP, constituting an important pathological mechanism underlying cognitive decline in VCI. TCM formulas and their bioactive components can regulate these pathways through multitarget actions, restore synaptic structure and function, and thus show considerable therapeutic potential.

However, current research still has notable limitations in terms of the clinical relevance of experimental models, sex bias, depth of target validation, and clinical translation. Future studies may advance in three major directions. First, for precision target discovery, mass spectrometry, molecular docking, gene silencing, and inhibitor-based reverse validation should be integrated to elucidate the interaction networks between circulating bioactive constituents of TCM formulas and their target proteins, thereby identifying candidate targets with both blood-brain barrier permeability and favorable druggability. Second, at the level of multi-omics integration, spatial transcriptomics, single-cell proteomics, and metabolomics may be employed to dynamically characterize the hippocampal synaptic microenvironment and the interaction networks between glial cells and neurons, with the aim of identifying potential biomarkers for the early diagnosis and therapeutic evaluation of VCI. Third, for clinical translation, aging animal models that incorporate vascular risk factors and include both sexes should be established, and biomarker-guided clinical trials of TCM interventions targeting synaptic plasticity should be conducted. These efforts may facilitate individualized precision treatment and provide both theoretical and practical support for the integrated prevention and treatment of VCI using TCM and Western medicine.

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