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Research Progress of Synaptic Plasticity in Post-Stroke Spasticity: The CCR5/CREB Axis and Traditional Chinese Medicine Interventions

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ABSTRACT

Post-stroke spasticity (PSS) is one of the most disabling sequelae of stroke, yet its treatment remains largely symptomatic. Botulinum toxin, oral antispastic agents and rehabilitation reduce tone without addressing the circuit-level process that generates it. Over the past decade PSS has been reconceptualised: rather than a passive consequence of corticospinal destruction, it is increasingly understood as the behavioural expression of maladaptive reorganisation, in which loss of corticoreticulospinal inhibition and excessive reticulospinal drive converge on hyperexcitable spinal motoneurons. Synaptic plasticity, both functional and structural, is the cellular substrate of that reorganisation. This review first summarises the forms, molecular effectors and measurement strategies of synaptic plasticity in the post-stroke brain, and then argues that the therapeutic objective in PSS is not to maximise plasticity but to restore excitation–inhibition balance within the corticoreticulospinal system. Particular attention is given to the C-C chemokine receptor 5 (CCR5)/cAMP response element-binding protein (CREB) axis, an emerging brake on use-dependent plasticity that couples neuroinflammation to structural remodelling through ERK1/2, Homer1 and PSD-95. Finally, traditional Chinese medicine (TCM) interventions built on the classical principle that contracture should be attributed to blood deficiency are reviewed alongside the pharmacological strategies discussed above, and the experimental agenda required to test whether restoring CCR5/CREB balance is a viable therapeutic strategy is outlined.

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1. Introduction

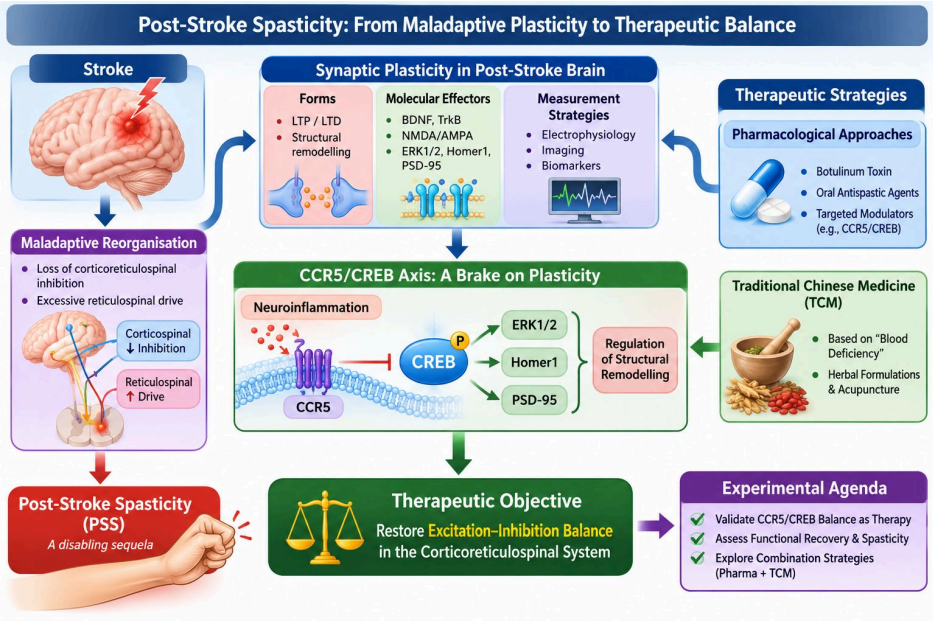
Stroke is the leading cause of death and acquired adult disability in China, and its burden continues to rise as the population ages [1,2]. Reperfusion therapy has improved survival, but a large proportion of survivors carry residual neurological deficits, among which motor impairment is the most common and the most costly. Spasticity — a velocity-dependent increase in muscle tone resulting from hyperexcitability of the stretch reflex — develops in a substantial minority of patients, and when it appears it multiplies the direct cost of care and independently predicts poor functional outcome [3,4].

Conventional management rests on three pillars: rehabilitation, oral antispastic agents such as baclofen and tizanidine, and focal chemodenervation with botulinum toxin. Each is useful and each is limited. Oral agents act on the spinal cord and brainstem indiscriminately, producing sedation and weakness; botulinum toxin is effective for focal patterns but requires repeated injection and does not alter the underlying central process; rehabilitation is dose-limited by reimbursement and by the patient's endurance [5,6]. None of these approaches is directed at the mechanism that produces and maintains the increased tone.

That mechanism is now described in terms of network reorganisation rather than simple loss. The corticoreticulospinal tract (CRT) comprises a lateral, inhibitory component arising from the contralateral motor cortex and relaying in the pontomedullary reticular formation, and a medial, excitatory component arising from the ipsilateral premotor cortex and projecting directly to the cord [7,8]. After a lesion of the corticospinal and corticoreticular pathways the balance tips: the lateral CRT loses cortical facilitation, the medial CRT is released from inhibition, and reticulospinal drive to spinal motoneurons increases [6,9]. The result is a stretch reflex that fires too readily and a limb that resists passive movement.

Crucially, this rebalancing is not fixed at the moment of infarction. It is built over weeks by synaptic plasticity, the same process that underlies recovery when it is adaptive and disability when it is not [9,10]. This dual character is the conceptual thread of the present review. Most reviews of plasticity after stroke are organised around recovery, and spasticity, when mentioned at all, appears as a complication rather than as a plasticity phenotype in its own right. We take the opposite starting point. If PSS is maladaptive plasticity, the relevant question becomes what constrains plasticity within the CRT circuit and whether that constraint can be adjusted. The review therefore summarises the forms and molecular machinery of synaptic plasticity relevant to the post-stroke motor system, examines the CRT-based pathophysiology of PSS through this lens, develops the case for the CCR5/CREB axis as a plasticity brake that is both mechanistically coherent and pharmacologically tractable, and reviews TCM interventions that target this axis.

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Graphical Abstract.

2. Synaptic Plasticity After Stroke: Forms, Effectors and Measures

2.1. Functional plasticity: LTP, LTD and the excitation–inhibition balance

Synaptic plasticity refers to the capacity of synaptic efficacy to change as a function of activity. Its best-characterised forms are long-term potentiation (LTP), the persistent strengthening of transmission after high-frequency stimulation, and long-term depression (LTD), the converse weakening after low-frequency stimulation [11,12]. LTP and LTD are not opposites to be maximised and minimised respectively; they are the two directions of a single homeostatic dial, and the computational function of a circuit depends on their balance rather than on the absolute magnitude of either.

After focal ischaemia both directions are perturbed. Within hours to days, neurons in the structurally intact but functionally silent penumbra show altered synaptic efficacy, and over the following weeks a window of heightened plasticity opens in peri-infarct cortex, coinciding with the phase of fastest behavioural gain [10,13]. Whether that window is exploited adaptively depends on what the circuit is asked to do during it. This is why the timing of rehabilitation matters, and equally why maladaptive patterns can consolidate: the same critical period that permits restitution of function can also entrench pathological coupling between cortex, reticular formation and cord.

A second layer of control is homeostatic. Synapses scale their strength to keep neuronal firing within a functional range, so that a sustained fall in activity produces compensatory up-regulation of transmitter release, receptor number and ultimately synapse number [14]. After stroke the initial depression of activity in and around the lesion triggers this compensation, which restores activity levels but does not distinguish between circuits that should be restored and circuits that should not. In the CRT, homeostatic compensation of the medial component is precisely the wrong response: it restores excitability at the cost of tone. This reframes spasticity from a failure of inhibition into a success of the wrong kind of plasticity.

2.2. Structural plasticity: the postsynaptic density, spines and the synaptic cleft

Functional change is consolidated by structural change. Structural plasticity encompasses the number and morphology of dendritic spines, the size and thickness of the postsynaptic density (PSD), the width of the synaptic cleft, and the formation and maturation of new synapses [15]. These are not cosmetic correlates. The PSD is a phase-separated condensate of scaffold proteins, receptors and signalling enzymes whose assembly state determines transmission efficiency [16,17], and the cleft width sets the dwell time of neurotransmitter and therefore the fidelity of transmission.

In the post-stroke cortex these parameters move in a characteristic direction: peri-infarct tissue shows reduced PSD length and thickness, widened clefts and fewer mature spines, and interventions that improve motor outcome tend to reverse these changes [18]. This makes synaptic ultrastructure an unusually direct readout, because it reports the net outcome of all molecular signals acting on the compartment without requiring the investigator to know in advance which pathway matters. Quantitative transmission electron microscopy of PSD length, thickness and cleft width has therefore become a standard endpoint in post-stroke plasticity research.

2.3. Molecular effectors: ERK1/2, Homer1, PSD-95 and the CREB–BDNF loop

Three postsynaptic proteins recur across studies of post-stroke structural plasticity. Extracellular signal-regulated kinase 1/2 (ERK1/2) is the convergence point for neurotransmitter and neurotrophin signals travelling to the nucleus; its activation is necessary for brain-derived neurotrophic factor (BDNF) to increase spine density, and it phosphorylates transcription factors that drive the synthesis of plasticity-related proteins required for spine stabilisation [19,20]. Homer1 exists as constitutively expressed long isoforms that scaffold group I metabotropic glutamate receptors to downstream effectors, and an activity-induced short isoform that acts as a dominant-negative brake on the same complexes; the balance between them sets spine morphology and PSD stability [21]. PSD-95 is the principal scaffolding protein of the excitatory PSD, required for AMPA receptor anchoring and for the structural integrity of the spine head [22].

These effectors are bound together by the CREB–BDNF loop. cAMP response element-binding protein (CREB) is a nuclear transcription factor whose phosphorylation recruits co-activators and drives transcription of target genes bearing cAMP response elements, among them BDNF [23,24]. Calcium influx activates CREB, CREB drives BDNF transcription, BDNF acts on TrkB to engage ERK1/2 and CaMKII, and the resulting plasticity feeds back on the circuit that produced it. In cortex this loop is not merely permissive for recovery but required for it: mice lacking CREB fail to reorganise cortical representations and to recover function after stroke [25]. The loop is therefore the natural place to look for an explanation of why some post-stroke circuits recover and others become spastic.

A fourth element is the trafficking of glutamate receptors themselves. CaMKII phosphorylates AMPA receptor subunits and their auxiliary proteins to increase the number of functional receptors at the synapse during LTP, and the resulting change in the amplitude of excitatory currents is the proximate cause of the strengthened response [12]. Receptor trafficking is also the point at which plasticity of opposite sign competes, since the same synapse may be potentiated or depressed depending on the pattern of calcium entry, and the scaffold proteins described above determine which outcome dominates [22]. For the CRT this matters because the balance between excitatory and inhibitory drive at the motoneuron is set largely by the number and subunit composition of postsynaptic receptors, not only by the amount of transmitter released.

2.4. How plasticity is measured

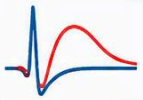
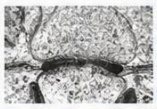
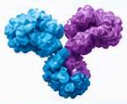
Because plasticity is defined operationally, the choice of measure determines the conclusion, and the available measures operate at different levels

(Table 1). Electrophysiological recording of LTP and LTD remains the gold standard for function, but it is difficult to apply to a pathway that spans cortex, brainstem and cord. Structural endpoints describe the machinery of plasticity rather than its efficacy. Behavioural proxies fill the gap at the circuit level. For the CRT specifically, prepulse inhibition (PPI) of the acoustic startle reflex has emerged as a practical index: the startle circuit runs through the cochlear nucleus and caudal pontine reticular nucleus to spinal motoneurons via the medial CRT, so that reduced PPI indicates increased reticulospinal excitability [26]. In patients, transcranial magnetic stimulation combined with startle acoustic stimulation can probe the same pathway directly [8].

A limitation that runs through the literature is that these measures are rarely combined. Studies report either ultrastructure, or protein abundance, or behaviour, seldom all three in the same animals, and almost never with electrophysiology. The result is a field rich in correlations and poor in causal chains.

Table 1. Measures of synaptic plasticity in post-stroke spasticity

From molecular machinery to clinical tone: what each measure captures and where it falls short.

Measure	Level	What it reflects	Main limitation
 **LTP/LTD from slice recording**	Synaptic function	Direction and magnitude of activity-dependent efficacy change	Not feasible for the corticoreticulospinal tract; ex *vivo*
 **PSD length, thickness, cleft width (TEM)**	Ultrastructure	Structural substrate of transmission; net outcome of all molecular inputs	Static snapshot; sampling bias; labour-intensive
 **PSD-95, Homer1, ERK1/2 (WB/IF)**	Molecular	Machinery of postsynaptic assembly and plasticity signalling	Abundance does not equal efficacy; antibody variability
 **Spine density and morphology**	Structural	Synapse number and maturity	Requires Golgi or two-photon imaging; density is not function
 **Prepulse inhibition of startle**	Circuit	Reticulospinal excitability and sensorimotor gating	Indirect; influenced by hearing, anxiety and arousal
 **Modified Ashworth Scale**	Clinical	Resistance to passive movement (tone)	Conflates neural and mechanical components; modest reliability

Abbreviations: *ERK1/2, extracellular signal-regulated kinases 1/2; IF, immunofluorescence; LTD, long-term depression; LTP, long-term potentiation; PSD, postsynaptic density; TEM, transmission electron microscopy; WB, western blotting.*

3. Spasticity as Maladaptive Plasticity of the Corticoreticulospinal System

3.1. The CRT disinhibition model

The classical account of spasticity centred on the stretch reflex arc: loss of descending inhibition, increased fusimotor drive and hyperexcitability of the alpha motoneuron. That account explains why tone rises, but not why it rises in a characteristic distribution, why it evolves over weeks rather than appearing immediately, or why it coexists with apparently excessive voluntary activation of the same muscles. The CRT model addresses all three [5,6].

In the intact nervous system the lateral CRT carries an inhibitory signal from the contralateral motor cortex through the pontomedullary reticular formation to the cord, while the medial CRT carries an excitatory signal from the ipsilateral premotor cortex directly to axial and proximal motoneurons. The two are held in balance, and that balance is what allows a limb to be moved without being fought by its own antagonists. A lesion of the corticospinal tract and of the corticoreticular projections removes facilitation of the lateral, inhibitory limb; the medial, excitatory limb is left unopposed and over time becomes hyperactive [7,9]. The spinal motoneuron, deprived of descending inhibition and bombarded with reticulospinal drive, responds to stretch with a reflex gain no longer appropriate to the task.

Two features of this model matter for the present argument. First, the excitatory limb does not merely lose a competitor; it actively grows. Increases in reticulospinal drive after stroke are documented in humans using startle-based transcranial magnetic stimulation paradigms, and they correlate with the severity of spasticity rather than with the size of the lesion [8]. Growth of a pathway is a plasticity phenomenon, requiring axonal sprouting, synapse formation and strengthening. Second, the change is distributed: cortex, reticular formation and cord all participate, which is why therapies aimed at a single node produce partial and temporary benefit.

Clinically, the model fits the observed phenomenology. Spasticity appears in antigravity muscles — elbow and wrist flexors, hip adductors, knee extensors, ankle plantarflexors — which is the distribution expected from an unopposed medial reticulospinal projection rather than from a uniform loss of inhibition [4]. It emerges over weeks, in parallel with the process of reorganisation described above, and it is frequently accompanied by co-contraction and by a loss of independent joint control, both of which indicate disordered descending command rather than a purely segmental mechanism [5]. The practical importance of this account is that it identifies the target of therapy as the reorganisation process itself rather than the final common pathway, and it explains why treatments directed at the motoneuron, however effective in the short term, do not alter the natural history of the condition.

Animal modelling follows the same logic. Middle cerebral artery occlusion in the rat reproduces the cortical lesion and, when combined with repeated assessment of resistance to passive movement, produces a preparation in which the molecular, structural and circuit-level consequences of the lesion can be examined together. The limitations of such models are considerable — lesion topography in the rat differs from that in humans, and tone in a quadruped is not directly comparable to tone in a biped — but they remain the only setting in which mechanism can be manipulated and outcome measured in the same animal.

3.2. Why "more plasticity" is the wrong therapeutic goal

If spasticity is maladaptive plasticity, the intuitive corollary is to inhibit plasticity in the CRT. That is equally wrong. The medial CRT is not a pathological pathway but a normal one released from control, and the same pathway contributes to the recovery of postural and proximal motor function in

patients whose corticospinal tract is destroyed [7,10]. Abolishing its plasticity would abolish recovery along with tone.

The correct objective is therefore not the magnitude of plasticity but its distribution: to permit or restore plasticity in the inhibitory limb and in spared cortical representations, while restraining the runaway potentiation of the excitatory limb. Framed in the language of section 2, the aim is to move the excitation–inhibition set point of the CRT rather than to raise or lower the gain of the system as a whole. This distinction has practical consequences. Interventions that globally enhance plasticity, such as exercise, enriched environment and non-invasive stimulation, are likely to help when applied to a circuit that is under-active and to fail, or to do harm, when applied to one that is over-active. It also predicts that the same molecule may be therapeutic in one phase and counterproductive in another, which is what has been observed for plasticity-promoting drugs in stroke recovery trials [10].

3.3. The temporal structure of the window

Plasticity after stroke is not uniformly distributed in time. In rodent models, peri-infarct cortex passes through a period of heightened structural and functional plasticity in the first month, followed by a decline; in humans the equivalent window is measured in weeks to a few months and is modulated by age, lesion location and rehabilitation dose [13]. Two clinical observations follow. The first is that spasticity typically emerges as this window closes, suggesting that the maladaptive consolidation of reticulospinal drive occurs during the very period in which adaptive reorganisation is possible. The second is that intervention delayed until spasticity is established acts on a consolidated circuit, which is a different and harder problem than preventing its consolidation.

This has an under-appreciated implication for trial design. If a candidate therapy acts by restraining maladaptive plasticity, its effect size will be largest when given early, and a trial that enrols only chronic patients may underestimate it. Conversely, a therapy that promotes structural repair may show its effect only later. Stratifying by time since stroke is therefore not a methodological nicety but a consequence of the biology.

4. The CCR5/CREB Axis as a Plasticity Brake

4.1. CCR5 beyond chemotaxis

C-C chemokine receptor 5 (CCR5) is a seven-transmembrane G protein-coupled receptor best known as a co-receptor for HIV entry and as the target of maraviroc. Its ligand CCL5 is produced by activated T cells, platelets and glia, and the CCL5–CCR5 axis is a canonical driver of leukocyte recruitment [27]. In the central nervous system, however, CCR5 is expressed by neurons as well as microglia, and its function there is not primarily immune.

The first indication that CCR5 might restrain neuronal repair came from work on HIV-associated neurocognitive disorder, in which cognitive impairment persists despite viral suppression and has been linked to chemokine receptor signalling in the brain. Subsequent studies associated CCR5 activation with impaired learning and memory and with microglial activation, and the unifying observation is that CCR5 signalling opposes the structural changes that underlie learning: it reduces spine density, limits axonal sprouting and biases neurons towards a growth-inhibited state [27].

Which cell type matters is not a trivial question. In the injured brain CCR5 is expressed on microglia, astrocytes and neurons, and the three populations are engaged by different ligands and produce different consequences. Microglial CCR5 contributes to the inflammatory cascade that strips synapses and amplifies injury; neuronal CCR5, by contrast, appears to act cell-autonomously, suppressing the transcriptional programme that would otherwise rebuild the dendritic arbour [28]. The distinction matters therapeutically, because a systemically administered antagonist will engage all three populations, and the net behavioural effect will depend on which one predominates in the circuit of interest. For a disorder of cortical reorganisation the neuronal pool is the more plausible target; for a disorder in which inflammation is the driving force, the glial pool may matter more. No study has yet separated these contributions in PSS.

4.2. CCR5 as a therapeutic target for recovery

The decisive experiment was reported by Joy and colleagues, who showed in mouse models of stroke and traumatic brain injury that CCR5 expression rises in neurons after injury, that deleting or pharmacologically blocking CCR5 improves recovery, and that the mechanism involves enhanced CREB signalling, preserved dendritic spines and increased axonal sprouting in peri-infarct cortex [28]. Importantly, the effect was obtained with delayed administration of a small-molecule antagonist, which is the clinically relevant scenario. A subsequent medicinal-chemistry effort produced a novel CCR5 antagonist with improved brain penetration that promoted neural repair after stroke in mice [29].

These findings establish CCR5 as one of the few molecular brakes on post-stroke plasticity that is both causally implicated and druggable. They do not, however, address spasticity. The behavioural endpoints in these studies were sensorimotor and cognitive rather than tone, and the circuits examined were cortical rather than corticoreticular. Whether the same brake operates in the CRT is an open question, and a clinically important one, because a therapy that enhances cortical plasticity while leaving reticulospinal drive unchecked could improve voluntary movement and worsen spasticity simultaneously.

4.3. How CCR5 restrains CREB

The mechanistic link between CCR5 and plasticity runs through CREB. In a model of intracerebral haemorrhage, CCR5 activation drove neuronal pyroptosis through a CCR5/PKA/CREB pathway, with CCR5 ligation reducing CREB phosphorylation and thereby removing the transcriptional drive required for BDNF expression and synaptic maintenance [30]. The same logic applies after ischaemia: CCR5 up-regulation lowers CREB activity, CREB-dependent transcription of BDNF and other plasticity genes falls, and the structural consequences follow [23,25].

This is a coherent design. CREB sits at the centre of the CREB–BDNF–ERK loop described above, so a signal that tonically suppresses CREB will suppress the entire loop, and it will do so without regard to which circuit is using it. That is precisely the behaviour required of a global brake on use-dependent plasticity, and precisely why releasing it indiscriminately is dangerous.

4.4. Downstream effectors: ERK1/2, Homer1 and PSD-95

If CCR5 suppresses CREB, the predicted downstream signature is a coordinated reduction in the proteins that build and stabilise the PSD. ERK1/2 activity falls when CREB signalling is low, and ERK1/2 is required for BDNF-induced spine density increases and for the transcription of plasticity-related proteins [19,20]. Homer1 shifts towards its dominant-negative short isoform when activity-dependent transcription fails, destabilising receptor complexes [21]. PSD-95, whose expression is partly CREB-dependent, falls, and with it the anchoring of AMPA receptors at the synapse [22].

The functional consequence is measurable at the level of the synapse. Reduced PSD-95 and Homer1 predict shorter, thinner PSDs and fewer mature spines; a widened cleft follows from the loss of trans-synaptic adhesion; and the net effect is a synapse that transmits less reliably. In the post-stroke motor cortex this appears as impaired representation of movement. In the CRT it may appear as the loss of the inhibitory limb's capacity to compete — in other words, as spasticity.

4.5. Neuroinflammation as the upstream input

CCR5 is not activated in a vacuum. Its ligand CCL5 is released by reactive microglia and astrocytes, and the post-stroke inflammatory cascade is a well-documented suppressor of plasticity: tumour necrosis factor-α and interleukin-1β reduce synaptic protein expression, activated microglia strip synapses, and the resulting loss of connections contributes to the failure of recovery in aged animals [31]. Age is the strongest clinical predictor of poor recovery, and part of that effect is plausibly mediated by this axis, since older brains have lower basal BDNF and more reactive glia.

Placing CCR5 at the junction of inflammation and plasticity is therefore not a coincidence of signalling but a functional design: the immune system holds a brake on structural reorganisation, presumably to limit the cost of unchecked rewiring in the presence of damage. The pathological consequence is that a self-limiting repair process becomes a self-perpetuating one when inflammation does not resolve.

5. Traditional Chinese Medicine Interventions Targeting Synaptic Plasticity

5.1. The classical principle: contracture should be attributed to blood deficiency

Chinese medicine has no term for post-stroke spasticity, but the clinical picture of flexed, rigid, slow-to-release limbs after a stroke was recorded under *jiji* (contracture), *juluan* (spasm), *piangu* (hemiplegia) and *ban shen bu sui* (half-body paralysis). The earliest accounts attributed contracture to wind and cold invading the channels: the *Zhubing Yuanhou Lun* held that when the channels and network vessels are deficient, wind pathogen injures the sinews, causing the four limbs to contract and to be unable to flex or ex-

tend, and the formularies of the Tang and Song treated the condition with warming, wind-dispelling combinations of Ephedra, Saposhnikovia, Angelica pubescens and Aconitum.

That consensus shifted once clinicians noticed that chronic contracture coexists with muscle wasting and weakness rather than with signs of excess. Cheng Wuji, commenting on the *Shanghan Lun*, put the relationship plainly: when the yin pulse is weak, blood is deficient, and blood deficiency produces contracture of the sinews. Sun Yikui generalised it in the sixteenth century into the maxim that to treat wind one should first treat the blood, since when the blood moves the wind extinguishes itself. The decisive formulation, however, is Zhang Jiebin's in the *Jingyue Quanshu*: when qi is without blood the disease is one of pulling and contracture, and therefore for contracture of the sinews one should hold the absence of blood responsible. Zhang paired the diagnosis with a treatment — the San Yin, Da Ying and Xiao Ying decoctions, all built on blood-enriching drugs — and later authors extended the principle to combine blood enrichment with wind-extinguishing, channel-freeing and qi-tonifying strategies [32,33].

The modern reading is that the basic pattern of PSS is liver yin and blood deficiency, stasis obstructing the brain collaterals, and malnourishment of the sinews — a root deficiency with branch excess. Two features of this formulation are worth noting for a mechanistic audience. First, it is a statement about tissue nutrition rather than about an offending pathogen, which maps onto the modern emphasis on the trophic and metabolic support of peri-infarct tissue. Second, it predicts that the appropriate intervention is restorative and slow-acting rather than suppressant, which is consistent with clinical experience and inconsistent with the logic of antispastic drugs that simply reduce excitability.

Later practitioners did not read the principle as an instruction to enrich blood and nothing else. Four strategies were derived from it and are still used in combination: blood enrichment with sinew softening as the base strategy, represented by the Si Wu, San Yin, Da Ying and Xiao Ying decoctions; yin enrichment with wind extinguishing when deficiency heat and internal wind coexist, typically with Paeonia, Uncaria and Gastrodia; blood enrichment with collateral unblocking in prolonged cases in which stasis has become prominent, with Salvia, Spatholobus, Persica and Pheretima; and qi supplementation to engender blood when the deficiency is dual and blood enrichment alone has failed, with Astragalus, Ginseng and Atractylodes. The organising idea is that the root is always the failure of nourishment, while wind, phlegm, stasis and heat are branch phenomena that modify the presentation without displacing the root.

5.2. Formulae reported to modulate post-stroke synaptic plasticity

A number of classical formulae have been examined in post-stroke models, and they differ in composition, in the pattern they are intended to address and in the model in which they have been tested. What unites them is that the endpoint in each case is structural rather than purely behavioural: the reported effects are on synaptic protein expression, on spine or PSD morphology, or on the ultrastructure of the synapse.

Buyang Huanwu Decoction, the canonical formula for qi deficiency and blood stasis after stroke, improved synaptic plasticity in ischaemic rats by activating cAMP/PKA/CREB signalling, with increased p-CREB and downstream BDNF, synaptotagmin 1, synapsin 1 and PSD-95 [34]. Jiawei Buyang Huanwu Decoction shifted microglial polarisation from the pro-inflammatory M1 to the reparative M2 phenotype and improved hippocampal synaptic plasticity in a model of post-stroke depression, which is of interest because it connects the formula's effect to the inflammatory input to the plasticity machinery described in section 4 [35]. Shaoyao Gancao Decoction improved hippocampal synaptic ultrastructure and plasticity-related protein expression in a spasticity model, particularly when combined with electroacupuncture [36]. Baishao Luoshi Decoction, a two-drug formula of Radix Paeoniae Alba and Caulis Trachelospermi, reduced spasticity and attenuated neuronal and synaptic injury in middle cerebral artery occlusion rats through the BDNF/TrKB–KCC2 pathway [37]; the interest of this result lies in KCC2, the potassium-chloride cotransporter that sets the chloride gradient and therefore the polarity of GABAergic inhibition at the motoneuron.

A methodological caveat applies to all of these studies. The preparations differ — whole decoctions, standardised granules, and in some cases single constituents — and dose translation from the clinical decoction to the rodent is rarely reported in enough detail to be reproduced. Where quality control is described at all, it is usually limited to one or two marker constituents determined by high-performance liquid chromatography, which establishes identity but not the composition of the fraction that was actually administered. Comparisons between formulae should therefore be read as comparisons of research programmes rather than of pharmacological agents.

The convergence on CREB is the common thread. Most of these formulae are composed of blood-invigorating and yin-enriching drugs, and the pathways they engage — cAMP/PKA, PI3K/AKT, MEK/ERK — are the same pathways through which CREB is phosphorylated. A systematic review of Chinese herbal drugs in post-stroke cognitive impairment reached the same conclusion from a different literature, identifying synaptic plasticity as the common mechanistic denominator across otherwise unrelated formulae [38]. Whether the convergence reflects a shared pharmacophore or simply the fact that CREB is a hub through which most plasticity-promoting signals pass is unknown, and distinguishing the two would require comparative pharmacology that has not been done.

5.3. Acupuncture and electroacupuncture

Acupuncture has a larger evidence base in post-stroke rehabilitation than any other TCM modality, and a growing mechanistic literature connects it to synaptic plasticity. Electroacupuncture improved depressive behaviour and hippocampal plasticity in post-stroke mice by inhibiting JNK signalling, with restored synaptic protein expression and reduced neuroinflammation [39]. In spasticity specifically, electroacupuncture combined with Jiawei Shaoyao Gancao Decoction improved plasticity-related protein expression and normalised synaptic ultrastructure in spastic rats [36].

The methodological weakness of this literature is consistent: small samples, single-centre designs, heterogeneous acupoint selection and almost no blinding. The mechanistic weakness is more interesting, in that most studies measure hippocampal rather than cortical or reticulospinal plasticity, which is a poor match to a motor disorder. Whether the clinical effect of acupuncture on spasticity is mediated by cortical plasticity, segmental modulation or simply the afferent barrage of needling remains unresolved.

5.4. Rehabilitation and neuromodulation as co-interventions

Rehabilitation is the substrate on which any plasticity-directed therapy must act, because activity is what selects among competing circuits. Task-specific training, constraint-induced movement therapy and aerobic exercise all increase BDNF, promote spine remodelling and raise plasticity-related protein expression in animal models and in patients [40]. Repetitive transcranial magnetic stimulation increased synaptic density, active zone length and PSD thickness while narrowing the cleft in ischaemic rats [18]. Reviews of this field converge on the conclusion that the effect of any single modality is modest and that combination, timed to the critical period, is where the gains are.

For the present argument the practical implication is that a plasticity-directed pharmacological or herbal intervention should be evaluated as an adjunct to rehabilitation rather than in isolation. A therapy that releases a brake on plasticity without providing the activity that directs it may produce reorganisation that is neither adaptive nor predictable.

6. Current Issues and Future Research Directions

6.1. From enhancing plasticity to restoring balance

The central claim of this review is that PSS is best understood as the consolidation of an inappropriate pattern of plasticity in the corticoreticulospinal system (Figure 1), and that the therapeutic objective is therefore to redistribute plasticity rather than to increase it. This reframing generates predictions that differ from those of the conventional recovery framework. It predicts that global plasticity enhancers will have phase-dependent and circuit-dependent effects, beneficial early and in under-active circuits, neutral or harmful late and in over-active ones. It predicts that the most useful molecular targets will be brakes rather than accelerators, since a brake can be released selectively in time and space whereas an accelerator cannot easily be confined. And it predicts that combination therapy, releasing the brake while supplying the activity that directs reorganisation, will outperform either alone.

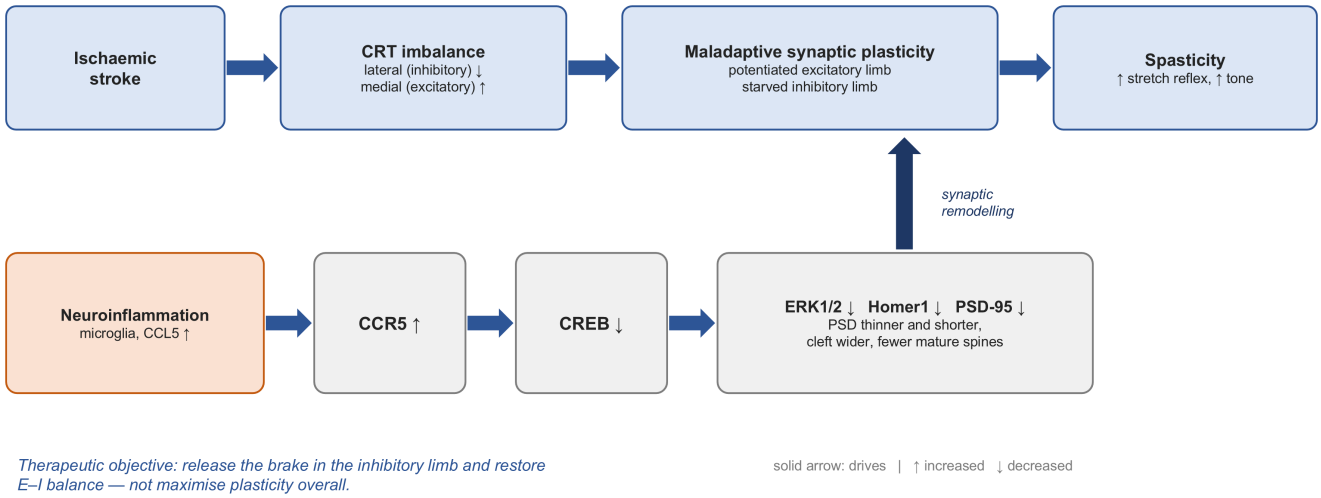


Figure 1. Synaptic plasticity and the CCR5/CREB brake in post-stroke spasticity. Upper tier: the clinical chain from ischaemic lesion to spasticity, in which maladaptive plasticity consolidates the imbalance between the inhibitory lateral and the excitatory medial corticoreticulospinal tract. Lower tier: post-stroke neuroinflammation raises neuronal CCR5, which suppresses CREB-dependent transcription of ERK1/2, Homer1 and PSD-95, thinning and shortening the postsynaptic density and widening the synaptic cleft.

6.2. Gaps in the evidence

Four gaps stand between the current evidence and a defensible causal model.

First, there is no direct electrophysiological evidence. Neither the human nor the rodent literature has demonstrated that the molecular changes described here alter LTP or LTD at corticoreticulospinal synapses, because those synapses are difficult to access. Paired recording in reticular formation slices after cortical lesion, or in vivo recording from reticulospinal neurons during reflex testing, would begin to close the gap. Without such data, synaptic plasticity in PSS remains an inference from protein abundance and ultrastructure.

Second, the circuit mapping is incomplete. Most of the literature examines motor cortex, whereas the CRT is a three-node pathway and the reticular formation is where the excitatory and inhibitory limbs actually compete. Whether CCR5/CREB signalling operates there as it does in cortex is unknown, and technically tractable with pathway-specific viral tracing.

Third, the causal chain from molecule to behaviour has not been closed in either direction. Upstream, the endogenous ligand driving CCR5 after stroke — CCL5 from microglia, from platelets or from neurons themselves — has not been identified in PSS models. Downstream, the link between cortical CREB activity and reticulospinal excitability is correlative. Chemogenetic manipulation of CREB in defined cortical projection neurons, combined with PPI and reflex testing, would test whether the relationship is causal or merely parallel.

Fourth, the TCM literature is fragmented in a way that prevents synthesis. Studies differ in formula composition and dose, in the model used to produce spasticity, in the timing of intervention relative to the lesion, and in which plasticity marker is reported. Two studies of the same formula may therefore be mutually uninformative even when both report a positive result. Standardising the model, the dosing period and a core set of outcome measures across laboratories would do more for the field than any single additional mechanism paper.

6.3. The CCR5 antagonist question and the place of herbal formulae

If CCR5 is the brake, a CCR5 antagonist should release it. Maraviroc is approved, moderately brain-penetrant and has been used clinically for years, which makes repurposing attractive. Two considerations argue for caution. The first is immunological: CCR5 blockade impairs leukocyte recruitment, and chronic administration in a population that is already infection-prone carries real risk. The second is that the available animal data tested sensorimotor and cognitive outcomes rather than tone, and the two can move in opposite directions [28,29].

This is where a herbal formula may have an advantage worth stating precisely. A crude extract is a multi-component mixture with modest affinity at any single target; it is unlikely to produce complete receptor blockade and may modulate a pathway at several points simultaneously. Whether that is an advantage, in the sense of being buffered and safer, or a disadvantage, in the sense of being unquantifiable and irreproducible, depends entirely on how well the chemistry is characterised. For most of the formulae discussed above the pharmacology is known only at the level of a few marker constituents, and the hypothesis that any of them acts on CCR5/CREB is currently supported by the direction of their reported effects rather than by binding data.

6.4. Optimising trial design

Translating any of this into patients requires trials designed around the biology rather than around convenience. Three modifications would help. Patients should be stratified by time since stroke, because the mechanism is expected to be time-dependent. Outcome assessment should include an objective circuit measure in addition to the modified Ashworth Scale; startle-based transcranial magnetic stimulation assessment of reticulospinal excitability is feasible and has been validated in stroke patients [8]. Rehabilitation dose should be controlled rather than left to usual care, since activity is the selector that determines whether released plasticity becomes adaptive.

7. Conclusion

Spasticity after stroke is not simply the absence of descending inhibition. It is the product of a reorganisation in which the excitatory limb of the corticoreticulospinal tract is potentiated while the inhibitory limb is starved of support, a plasticity that succeeds at the level of the synapse and fails at the level of the limb. Synaptic plasticity is therefore both the mechanism of the disorder and the target of its treatment, but the relevant therapeutic variable is the balance between potentiation and depression rather than the amount of either.

The CCR5/CREB axis is an attractive handle on that balance. It is induced by injury, it suppresses CREB-dependent structural plasticity through ERK1/2, Homer1 and PSD-95, it is expressed in neurons as well as glia, and it is pharmacologically accessible. Its role in the corticoreticulospinal circuit specifically remains to be established, and the evidence that traditional formulae act through it is suggestive rather than demonstrative. What can be said with more confidence is that the classical principle that contracture should be attributed to blood deficiency anticipated, in its own vocabulary, the modern insight that the spastic limb is a malnourished and badly rewired circuit rather than an overactive one, and that the therapeutic traditions built on that principle deserve to be tested with tools that would allow the claim to fail.

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