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Review

LRP1 in Ischemic Stroke: From CNS Homeostasis to Ischemic Injury and Repair

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Abstract

Ischemic stroke is a leading cause of mortality and long-term disability worldwide, with complex pathophysiological mechanisms and limited therapeutic options. The identification of key molecular targets that can effectively modulate the multifaceted pathological and reparative processes underlying ischemic stroke is urgently needed. Low-density lipoprotein receptor-related protein 1 (LRP1) is a multifunctional receptor widely expressed in the central nervous system (CNS), where it regulates lipid and bioenergetic metabolism, preserves blood–brain barrier (BBB) function, modulates synaptic signaling, and supports neural stem/progenitor cell homeostasis. During cerebral ischemia, LRP1 undergoes a stage-dependent functional shift. In the acute phase, LRP1 promotes BBB disruption, tissue-type plasminogen activator (tPA)-associated hemorrhagic transformation, and early neuroinflammation, while also conferring neuroprotection by restraining inflammasome-mediated inflammatory responses and facilitating astrocyte-to-neuron mitochondrial transfer. In the recovery phase, LRP1 is involved in white matter injury and remodeling, including demyelination, remyelination, and white matter restoration. These effects are highly cell type–specific, reflecting distinct functions of LRP1 in endothelial cells, astrocytes, microglia, neutrophils, and oligodendrocyte-lineage cells. This context-dependent complexity underscores the need for a systematic review of the role of LRP1 in stroke. Here, we summarize the structural features and physiological functions of LRP1 in the CNS, discuss its roles and underlying mechanisms in ischemic stroke, and highlight the therapeutic potential and challenges of LRP1-targeted strategies for stroke intervention.

Keywords: low-density lipoprotein receptor-related protein 1; ischemic stroke; neurovascular homeostasis; blood–brain barrier; hemorrhagic transformation; neuroinflammation; white matter remodeling; neuroprotection

1. Introduction

Ischemic stroke, caused by the abrupt interruption of cerebral blood flow, remains a leading cause of mortality and long-term disability worldwide [1,2]. Although reperfusion therapies, including intravenous thrombolysis with tissue-type plasminogen activator (tPA) and endovascular thrombectomy, have substantially improved clinical outcomes, their clinical utility remains constrained by narrow therapeutic windows, incomplete recanalization, and the risk of hemorrhagic transformation (HT) and ischemia–reperfusion injury [3]. Thus, effective treatment of ischemic stroke remains a major clinical challenge. The pathophysiology of ischemic stroke is highly dynamic and involves multiple interrelated mechanisms that evolve over time. In the acute phase, cerebral ischemia rapidly induces energy failure and ionic imbalance, leading to excitotoxicity, oxidative stress, blood–brain barrier (BBB) disruption, and neuroinflammation [4,5,6]. During the subacute and chronic phases, sustained neuroinflammation coexists and interacts with endogenous repair responses, including neurogenesis, axonal sprouting, white matter remodeling, angiogenesis, and neurovascular unit (NVU) remodeling [7,8,9]. These interconnected processes ultimately influence infarct evolution, tissue remodeling, and functional recovery. Given this complexity, there is an urgent need to identify key molecular targets that can more effectively modulate the multifaceted pathological and reparative processes underlying ischemic stroke.

Low-density lipoprotein receptor-related protein 1 (LRP1), also known as CD91, is a type I transmembrane receptor widely expressed in the central nervous system (CNS) and peripheral tissues [10]. Although originally characterized as a lipoprotein-scavenging receptor, LRP1 is now recognized as a multifunctional receptor that not only mediates ligand clearance but also participates in intracellular signaling transduction and scaffold-dependent organization of membrane-associated protein complexes [11,12,13]. Through these properties, LRP1 contributes to the maintenance of lipid and energy homeostasis, synaptic function, BBB integrity, and neurovascular homeostasis in the CNS [10,14,15,16]. Clinical studies have shown that genetic variants of LRP1 may increase the risk of ischemic

stroke [17]. Accumulating preclinical evidence further indicates that LRP1 is involved in several key aspects of stroke pathophysiology, such as BBB dysfunction, HT after thrombolytic therapy, neuronal damage, neuroinflammation, white matter injury, and metabolic reprogramming [18,19,20,21,22,23]. However, most existing studies have focused on the roles of LRP1 in other neurological disorders, particularly Alzheimer's disease (AD), whereas evidence regarding its role in ischemic stroke remains fragmented and has not yet been systematically summarized. Moreover, the effects of LRP1 may vary across cell types, disease stages, ligand interactions, and signaling pathways, reflecting the differential engagement of its receptor functions and suggesting complex, context-dependent roles in stroke. A comprehensive review of the current evidence is therefore timely and necessary.

In this review, we summarize the structural features of LRP1 and its roles in the CNS under physiological conditions, highlight its emerging roles in the pathogenesis and recovery of ischemic stroke, and discuss the underlying molecular mechanisms and potential therapeutic strategies (Fig. 1). We also address current limitations and unresolved questions, with the aim of providing a foundation for future basic and translational research on LRP1 in ischemic stroke.

2. Biosynthesis, Structure, and Post-translational Modifications of LRP1

LRP1 is encoded by a gene located on human chromosome 12q13–14 and is synthesized as a large precursor that undergoes tightly regulated maturation before reaching the cell surface [24]. In the endoplasmic reticulum, the nascent LRP1 precursor associates with receptor-associated protein (RAP), a dedicated molecular chaperone that promotes proper folding and assembly while preventing premature ligand engagement [25]. The RAP-LRP1 complex is subsequently trafficked to the Golgi apparatus, where RAP dissociates, and the precursor undergoes proteolytic cleavage by furin, yielding two noncovalently associated subunits: a large extracellular α-chain and a smaller transmembrane β-chain [26,27]. This maturation process is a prerequisite for the broad ligand-binding capacity and signaling competence that characterize LRP1 in the CNS.

The extracellular α-chain of LRP1 is organized into four ligand-binding clusters (I-IV) comprising 2, 8, 10, and 11 complement-type repeats, respectively [28]. Clusters II and IV are the principal ligand-binding regions, interacting with diverse ligands such as apolipoprotein E (apoE), tPA, and α2-macroglobulin (α2M), whereas cluster I shows little or no ligand-binding activity and cluster III has relatively fewer reported ligand interactions [29]. The representative LRP1 ligands, their binding regions, and the associated cellular functions are summarized in Table 1 (Ref. [11,14,29,30,31,32,33,34,35,36,37,38,39,40]). The β-chain, in turn, provides a transmembrane anchor and a motif-rich cytoplasmic tail that couples extracellular ligand engagement to intracellular trafficking and signal transduction [27]. Specifically, two dileucine motifs, two NPxY motifs, and a YXXL motif serve as docking/recognition elements for adaptor proteins, thereby coordinating clathrin-dependent endocytosis, endosomal sorting, and signal propagation [27,41]. This domain organization thus allows LRP1 to serve dual roles: as an endocytic receptor that clears extracellular ligands and as a mediator that organizes intracellular signaling complexes, both of which are involved in ischemic stroke pathobiology. Meanwhile, LRP1 function is dynamically regulated by a range of post-translational modifications, including phosphorylation, glycosylation, ubiquitination, and proteolytic processing. These modifications exert distinct effects, as summarized in Table 2 (Ref. [13,33,42,43,44,45,46,47,48,49,50]). By modulating LRP1 downstream signaling, cell-surface availability, and ligand-binding capacity, these post-translational modifications provide mechanistically diverse targets for ischemic stroke therapeutic intervention.

Notably, the domain architecture of LRP1 also defines pharmacologically actionable interfaces that have been exploited as experimental tools and potential therapeutic entry points. RAP is among the best-characterized inhibitors of the LRP1 extracellular domain and is commonly used to broadly block ligand binding via competitive mechanisms, thereby suppressing LRP1-mediated ligand-induced signaling [51]. More selective interference is achieved through mouse anti-LRP1 antibodies 11H4 and 11E2. 11H4 targets the β-chain to attenuate downstream signaling [52,53], whereas 11E2 targets the extracellular ligand-binding domain to selectively block the tPA-LRP1 interaction without affecting other LRP1 ligands or related receptors [54]. In addition to antibody-based approaches, several mimetic peptides have been developed to target the extracellular domain of LRP1. SP16 is a short peptide that activates LRP1 by mimicking the LRP1-binding portion of endogenous serine protease inhibitors and has been evaluated in a Phase I first-in-human clinical trial [55,56]. COG1410, an apoE-mimetic peptide derived from the apoE receptor-binding region, engages the apoE-binding site on LRP1 and activates LRP1-dependent neuroprotective signaling [57]. Hence, interventions targeting extracellular ligand-binding clusters and the intracellular motif-dependent adaptor network provide a practical basis for dissecting LRP1 biology and for designing strategies to therapeutically modulate LRP1 pathways in CNS diseases.

3. Roles of LRP1 in the CNS Under Physiological Conditions

As a broadly expressed multifunctional receptor across multiple cell types of the NVU, LRP1 coordinates several homeostatic programs essential for normal brain function, including lipid and energy metabolism, BBB maintenance, synaptic regulation, and neural

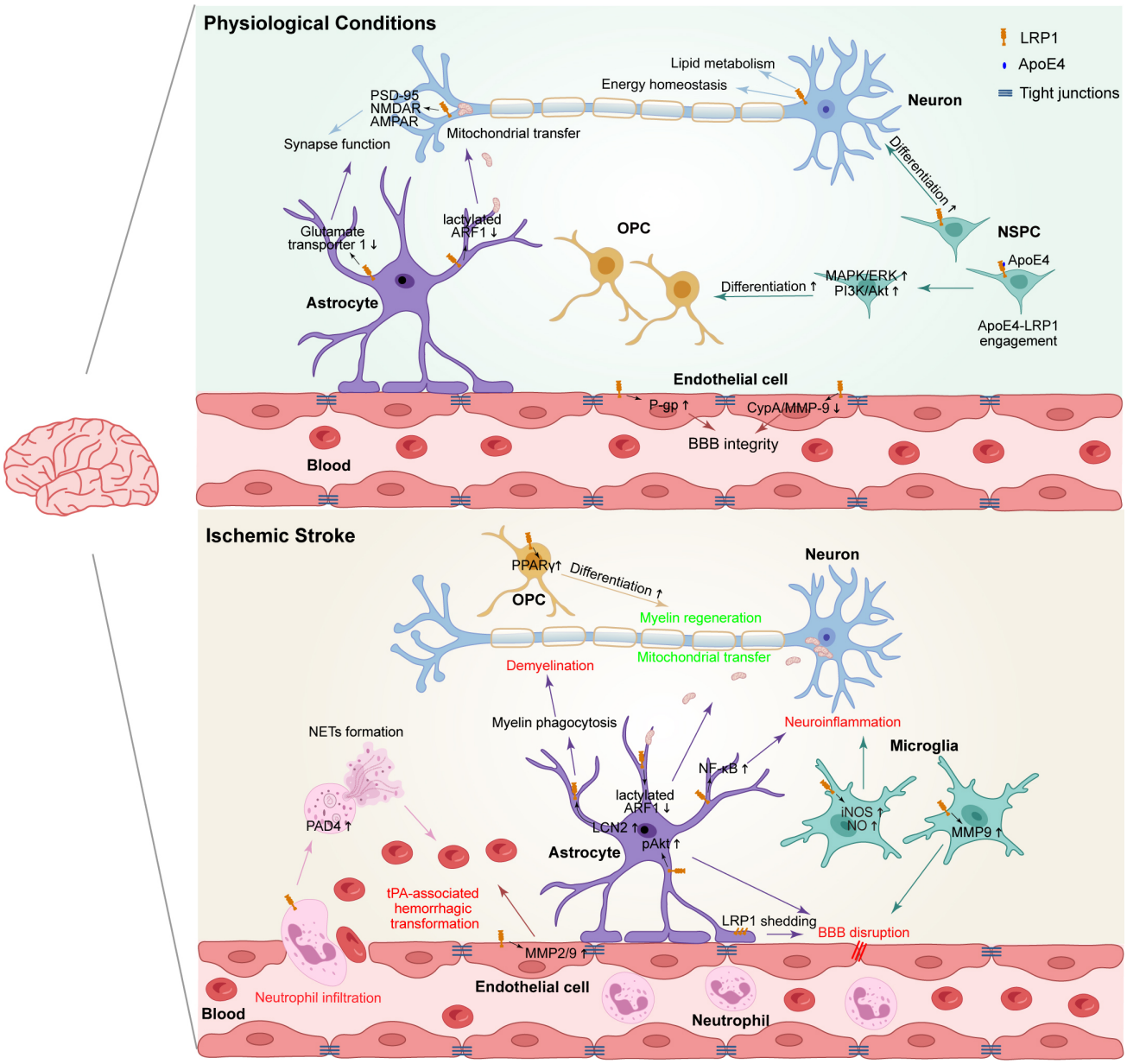

Fig. 1. Roles of LRP1 in CNS homeostasis and ischemic stroke. Under physiological conditions, LRP1 maintains lipid/energy metabolism, synaptic function, BBB integrity, mitochondrial transfer, and NSPC differentiation. After ischemia, LRP1 contributes to BBB disruption, tPA-associated hemorrhagic transformation, neuroinflammation, and demyelination, while also supporting mitochondrial transfer and myelin regeneration. Red, detrimental processes; Green, protective/reparative processes. Akt, protein kinase B; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ApoE, apolipoprotein E; ARF1, ADP-ribosylation factor 1; BBB, blood–brain barrier; CNS, central nervous system; CypA, cyclophilin A; ERK, extracellular signal-regulated kinase; iNOS, inducible nitric oxide synthase; LCN2, lipocalin-2; LRP1, low-density lipoprotein receptor-related protein 1; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NET, neutrophil extracellular trap; NF-κB, nuclear factor-κB; NMDAR, N-methyl-D-aspartate receptor; NO, nitric oxide; NSPC, neural stem/progenitor cell; OPC, oligodendrocyte precursor cell; PAD4, peptidylarginine deiminase 4; P-gp, P-glycoprotein; PI3K, phosphatidylinositol 3-kinase; PPARγ, peroxisome proliferator-activated receptor γ; PSD-95, postsynaptic density protein 95; tPA, tissue-type plasminogen activator. Created with Adobe Illustrator.

stem/progenitor cell (NSPC) dynamics. These processes collectively sustain the structural integrity, metabolic balance, and functional homeostasis of the CNS. Notably, each of these processes is markedly perturbed during cerebral ischemia, raising the possibility that LRP1 contributes to stroke pathobiology, at least in part through disruption or maladaptive engagement of its physiological functions.

Table 1. Representative ligands of LRP1 in the CNS and their cellular functions.

Ligand category	Representative ligands	Binding sites [30,31]	Functions	References
Lipoprotein metabolism	ApoE	Cluster II, III, IV	Lipoprotein metabolism and transport; OPC differentiation	[31,32,33]
Proteases and their inhibitors	tPA	Cluster II, IV	Fibrinolysis; Regulation of synaptic plasticity	[11,34,35]
	PAI-1	Cluster II, IV	Regulation of tPA activity	[35,36]
	α2M	Cluster II, IV	Regulation of NMDAR-mediated Ca^{2+} influx	[37]
	MMP9	Cluster II, IV	Extracellular matrix degradation; BBB disruption	[36,38]
Chaperone	RAP	Cluster II, III, IV	Inhibition of ligand binding to LRP1	[34]
Proteins involved in AD	Amyloid precursor protein	Cluster II	Amyloid β peptide generation	[39]
	Amyloid β peptide	Cluster II, IV	Main component of amyloid plaques in AD	[29]
Other ligands	Leptin	Unknown	Regulation of energy balance and neuronal function	[14]
	MAG	Cluster II, IV	Myelination regulation	[40]
	MBP	Unknown	Myelin sheath formation	[31]

MAG, myelin-associated glycoprotein; MBP, myelin basic protein; PAI-1, plasminogen activator inhibitor-1.

3.1 LRP1 in Lipid Metabolism and Energy Regulation

Lipids are among the most abundant biomolecules in the brain and are present in virtually all cellular compartments, where they regulate energy metabolism, synaptic plasticity, and neuronal viability [58]. As a lipoprotein receptor, LRP1 plays a pivotal role in CNS lipid homeostasis. Liu and colleagues [59] reported that neuron-specific deletion of *Lrp1* disrupted lipid homeostasis in the brain. This disturbance was characterized by reduced levels of multiple lipid species, including cholesterol, triglycerides, sulfatides, and galactosylceramides. Consistently, shRNA-mediated knockdown of *Lrp1* in neurons significantly reduced neuronal cholesterol content after incubation with astrocyte-conditioned medium, supporting a role for LRP1 in neuronal lipid transport [59]. Together, these findings highlight the essential role of LRP1 in supporting the neuronal lipid supply and maintaining lipid balance in the brain.

Zhou et al. [22] showed that LRP1 regulates astrocytic glycolysis, as *Lrp1* silencing enhanced glycolysis relative to oxidative phosphorylation, evidenced by increased intracellular glucose, glycolytic intermediates, lactate, and several tricarboxylic acid cycle metabolites, together with elevated oxygen consumption rate (OCR), extracellular acidification rate (ECAR), and ECAR/OCR ratio. Mechanistically, *Lrp1* deficiency promoted the membrane localization of glucose transporter-1, thereby increasing glucose uptake and activating the mitogen-activated protein kinase (MAPK)-c-MYC pathway, which in turn increased glycolysis and lactate production; these effects were attenuated by inhibition of MAPK activity with U0126. These findings identify LRP1 as a suppressor of glycolysis in astrocytes. Moreover, the authors found that knockdown of *Lrp1* in astrocytes markedly reduced the abundance and bioenergetic function of extracellular mitochondria in astrocyte-conditioned medium, thereby limiting astrocyte-to-neuron mitochondrial transfer and reducing neuronal OCR and adenosine triphosphate production, effects associated with increased lactate production driven by enhanced glycolysis [22]. *Ldha/b* (two isoforms of lactate dehydrogenase [LDH]) depletion abolished the inhibitory effects of *Lrp1* knockdown, whereas *Ldha/b* overexpression mimicked these effects. These findings were further validated in astrocyte-specific *Lrp1* knockdown mice, in which increased brain glucose uptake and lactate levels were accompanied by reduced astrocyte-derived mitochondria in the cerebrospinal fluid (CSF) and decreased transfer of astrocytic mitochondria to neurons compared with those in control mice [22]. Together, these findings indicate that astrocytic LRP1 facilitates mitochondrial transfer to neurons by restraining glycolysis-driven lactate production. Moreover, elevated lactate levels following *Lrp1* knockdown increased global lysine lactylation in astrocytes, as determined by lactylproteomics, identifying the vesicle-trafficking protein ADP-ribosylation factor 1 (ARF1) as a key LRP1 effector [22]. *Lrp1* depletion-induced hyperlactylation promoted ARF1 activation and lactylation, suppressing mitochondrial release, the effect that was phenocopied by the lactylation-mimetic K73Q mutant; conversely, the nonlactylatable K73R mutant inhibited ARF1 activity and enhanced mitochondrial release. In astrocyte-specific Lrp1 knockdown mice, ARF1 K73R increased, whereas ARF1 K73Q decreased, astrocyte-derived mitochondria in the CSF and neurons. These findings reveal that ARF1 lactylation induced by LRP1 knockdown

Table 2. Post-translational modifications of LRP1.

Modification types	Regulatory molecules	Modification sites/regions	Biological functions	Disease context	References
Phosphorylation	PDGFBB	Tyrosine 63 of NPxY motif (β-chain)	Recruitment of adaptor protein Shc to the second NPxY motif	None	[13,42]
	tPA	Tyrosine 4507 of NPxY motif (β-chain)	Activation of LRP1-dependent PI3K/Akt signaling, suppression of hepatic stellate cell activation marker expression, and promotion of fibrosis resolution	Liver cirrhosis	[43]
	PKA	Serine 76 of cytoplasmic tail (β-chain)	Increase in the initial endocytosis rate of LRP and enhancement of the efficiency of ligand delivery for degradation	None	[44]
Ubiquitination	LIM domain-only protein 7	Lysine 45 of β-chain	Enhancement of LRP1 degradation via the proteasome, suppression of phagocytosis, and promotion of tumor progression	Colon cancer; Melanoma	[45]
	Oxidized LDL	Unknown	Enhancing LRP1 internalization and downregulation, impairing macrophage efferocytosis and exacerbating atherosclerosis	Atherosclerosis	[46]
	Checkpoint protein with FHA and RING finger domains	Unknown	Destabilization of LRP1 and enhancement of atherosclerosis progression	Atherosclerosis	[47]
Glycosylation	GalNAc-T11	Thr residues of LA linker motif (α-chain)	O-glycosylation-mediated enhancement of LDL and VLDL binding and uptake	None	[48]
	None	None	Upregulation of LewisX glycosylated LRP1 in NSPCs of the developing spinal cord and cortex	None	[33]
Proteolytic processing	tPA	Extracellular domain of β-chain	Shedding of LRP1's extracellular domain, increase in BBB permeability, and formation of perivascular edema	Ischemic stroke	[49]
	γ-secretase	Transmembrane domain of β-chain	Enhancement of LRP1 intracellular domain translocation to the nucleus and increase in apoptotic cell death	Ischemic stroke	[50]

LDL, low-density lipoprotein; PDGFBB, platelet-derived growth factor BB; PKA, protein kinase A; VLDL, very-low-density lipoprotein.

suppresses astrocytic mitochondrial release and transfer, a mechanism with critical neuroprotective implications in ischemic stroke, as elaborated in subsequent sections.

Additionally, LRP1 participates in signaling pathways that maintain systemic energy balance. Liu et al. [14] showed that LRP1 interacts with leptin and the leptin receptor complex to facilitate downstream signaling. Hypothalamic neuronal LRP1 deletion (via Cre lentiviral delivery) reduced the interaction between the leptin receptor and its key effector janus kinase 2, thereby impairing Stat3 phosphorylation and disrupting leptin signaling. Functionally, knockdown of neuronal LRP1 led to increased food intake and reduced energy expenditure, culminating in obesity, elevated circulating free fatty acids, hypertriglyceridemia, insulin resistance, and impaired glucose tolerance. These studies suggest that neuronal LRP1 functions not only in regulating central lipid and glucose metabolism but also as a molecular link between central metabolic signaling and whole-body energy homeostasis.

3.2 LRP1 in the Maintenance of BBB Integrity

The BBB is a highly selective interface that preserves CNS homeostasis by restricting the entry of potentially harmful peripheral factors and tightly regulating molecu-

lar exchange between blood and brain parenchyma [60]. Its integrity is maintained through coordinated interactions among endothelial cells, pericytes, and astrocytes [61,62]. As the principal cellular component of the BBB [61], brain endothelial cells are central to barrier function, and endothelial LRP1 has emerged as an important regulator of BBB physiology.

Nikolakopoulou et al. [63] demonstrated that endothelium-specific *Lrp1* knockout (*Lrp1*$^{lox/lox}$; Tie2-Cre) results in BBB breakdown. Mechanistically, LRP1 deletion activated the cyclophilin A (CypA)/matrix metalloproteinase (MMP)9 pathway, promoting the degradation of tight-junction proteins (zonula occludens 1, occludin, and claudin-5) and collagen IV, thereby compromising barrier integrity. These findings support a protective role for endothelial LRP1 in restraining CypA/MMP9 pathway activation and preserving BBB structure. Storck et al. [64] further refined this view using an inducible, brain endothelium-targeted model (*Lrp1*$^{lox/lox}$; Slco1c1-CreER^{T2} mice), minimizing potential developmental confounds associated with Tie2-Cre lines. Following tamoxifen-induced *Lrp1* deletion in adult endothelium, mice exhibited downregulation of tight-junction protein expression and a marked reduction in P-glycoprotein (P-gp) expression. P-gp is a key endothelial efflux transporter that limits the entry of xenobiotics and facilitates the clearance of potentially toxic substrates from the brain; therefore, reduced P-gp can increase BBB permeability and impair efflux capacity, promoting the accumulation of harmful molecules [65]. Collectively, these studies suggest that endothelial LRP1 regulates BBB function through at least two distinct routes: preserving paracellular barrier properties via tight-junction maintenance and modulating transcellular transport and efflux capacity by regulating transporters such as P-gp. Additionally, the BBB is a multicellular, integrated structure, and LRP1 is also expressed in astrocytes and pericytes. Thus, the extent to which nonendothelial LRP1 contributes to physiological BBB regulation remains to be clarified.

3.3 LRP1 in Synaptic Function and Plasticity

Synapses are specialized structures that enable communication between neurons or between neurons and other cells [66]. As a pleiotropic modulator of synaptic function, LRP1 maintains synaptic homeostasis by regulating stability, plasticity, and transmission through its coordinated influence on signaling pathways, metabolic support, and receptor trafficking. Early evidence linking LRP1 to synaptic plasticity came from Zhuo et al. [34], who showed that the interaction of tPA and LRP1 is required for late-phase long-term potentiation (L-LTP) in the hippocampus. In hippocampal slices, tPA binding to LRP1 increased the magnitude of L-LTP, whereas blockade of LRP1 with RAP markedly inhibited synaptic potentiation. RAP abolished the potentiating effect of exogenous tPA in slices from tPA knockout mice. Mechanistically, tPA-LRP1 engagement activated the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) pathway, which is required for L-LTP maintenance, suggesting that the tPA-LRP1-dependent enhancement of synaptic plasticity might be related to cAMP/PKA signaling.

LRP1 supports synaptic integrity via metabolic regulation [59]. In forebrain neuron-specific *Lrp1* deletion models, disrupted lipid homeostasis was accompanied by memory impairment; progressive, age-dependent dendritic spine degeneration; loss of synaptic proteins (e.g., synaptophysin and postsynaptic density protein 95 [PSD-95]); and selective reductions in the glutamate receptor subunits (N-methyl-D-aspartate receptor 1 [NMDAR1] and glutamate receptor 1 [GluR1]). Notably, cholesterol supplementation partially restored NMDAR1 but not GluR1 expression in *Lrp1*-knockdown neurons, suggesting that LRP1 maintains the levels of these glutamate receptor subunits through both cholesterol-dependent and cholesterol-independent mechanisms.

Meanwhile, LRP1 influences postsynaptic organization and receptor signaling. May et al. [67] reported that LRP1 coimmunoprecipitates with NMDA receptor subunits (NR2A/NR2B) and PSD-95, findings that are consistent with a postsynaptic localization and a scaffolding role in postsynaptic organization. NMDA stimulation reduced the co-immunoprecipitation of PSD-95 with LRP1, suggesting that LRP1 interaction with PSD-95 is dynamically regulated by NMDA receptor activity. Moreover, Syn Cre-LRP1$^{lox/lox}$ mice exhibited hyperactivity, gait abnormalities, and tremors despite largely preserved gross brain morphology and neuromuscular junction architecture, suggesting that LRP1 is involved in neurotransmission rather than overt structural pathology. Nakajima et al. [68] further showed that LRP1 depletion in primary neurons impaired NMDA receptor-dependent intracellular signaling after NMDA treatment, as evidenced by reduced levels of basal phosphorylated cAMP-response element-binding protein and decreased transcription of NMDA-responsive genes. In agreement with the role of LRP1 in NMDA receptor-coupled signaling, Bacskai et al. [37] showed that activation of LRP1 by a ligand (activated α2M) induced a rapid increase in neuronal intracellular Ca^{2+}, which was blocked by the NMDAR antagonist MK-801 as well as by RAP, supporting a model in which ligand engagement of LRP promotes NMDAR-dependent Ca^{2+} entry. Similarly, LRP1 depletion impaired α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)-mediated Ca^{2+} influx [15]. These studies indicate that LRP1 participates in postsynaptic scaffold remodeling and glutamate receptor-dependent intracellular signaling, thereby supporting excitatory synaptic transmission and plasticity.

LRP1 also regulates the trafficking of glutamate receptor subunits. Maier et al. [69] demonstrated that mutation of the LRP1 NPxY2 motif reduced the internalization of NR1/NR2B NMDAR subunits, resulting in their accu-

mulation on the neuronal surface, which may consequently affect synaptic function. Furthermore, Gan et al. [15] found that *Lrp1* knockdown in primary neurons selectively accelerated the turnover and internalization of AMPAR subunit GluA1 but not GluA2/3, as evidenced by a faster decrease in GluA1 levels following cycloheximide (a protein synthesis inhibitor) treatment and reduced surface expression of GluA1 relative to total GluA1 in the cell lysate. Moreover, depletion of LRP1 decreased the phosphorylation of GluA1 at Ser845 and Ser831, which affected the trafficking of GluA1 to synapses and disturbed the stability of GluA1. Together, these findings suggest that LRP1 may maintain synaptic transmission by regulating the trafficking, surface distribution, and stability of specific NMDAR and AMPAR subunits.

More recently, Romeo et al. [70] extended the synaptic roles of LRP1 to glia-neuron interactions. Astrocyte-specific *Lrp1* deletion increased the number of glutamate transporter 1-positive astrocytes, suggesting that altered glutamate handling has potential consequences for synaptic transmission efficiency. Depletion of astrocytic *Lrp1* was also associated with reduced hippocampal neuronal activity and abnormalities in synaptic organization, including increased presynaptic formation. These results support the view that LRP1 contributes to the regulation of the tripartite synapse through astrocyte–neuron crosstalk.

3.4 LRP1 in NSPC Proliferation and Differentiation

NSPCs are multipotent cells capable of self-renewal and differentiation into neurons, oligodendrocytes, and astrocytes [71]. Accumulating evidence indicates that LRP1 regulates NSPC homeostasis, with roles in proliferation, survival, and lineage specification.

Compared with control NSPCs, *Lrp1*-knockout NSPCs derived from the cortex and spinal cord exhibited reduced BrdU incorporation and an increased proportion of active caspase-3-positive cells, indicating impaired proliferation and increased apoptosis. These findings suggest that LRP1 supports the expansion and survival of the NSPC pool [33]. LRP1 exerts lineage-dependent effects during differentiation. Lrp1 deletion negatively affected multiple stages of oligodendroglial development *in vitro*, reducing both early platelet-derived growth factor (PDGF) receptor α-positive progenitors and mature myelin basic protein (MBP)-positive oligodendrocytes [33]. Neuronal differentiation was similarly impaired, with fewer βIII-tubulin-positive neurons derived from both cortical and spinal cord NSPCs. In contrast, *Lrp1* deficiency increased the generation of glial fibrillary acidic protein-positive astrocytes, suggesting that LRP1 biases differentiation toward neuronal and oligodendroglial lineages while restraining astrocytic differentiation [33]. Mechanistically, LRP1 may regulate NSPC differentiation via ligand-dependent signaling rather than via its role in cholesterol uptake. Although cholesterol can promote oligodendrocyte differentiation, *Lrp1* deletion did not markedly alter cholesterol uptake or total cholesterol levels in NSPCs, likely reflecting compensation by other members of the low-density lipoprotein (LDL) receptor family [33]. In contrast, ApoE4 stimulation increased oligodendrocyte production by ~50% in wild-type NSPCs, but this effect was absent in *Lrp1*-deficient NSPCs. ApoE4-LRP1 engagement directly activates downstream MAPK/extracellular signal-regulated kinase (ERK) and PI3K/Akt (phosphatidylinositol 3-kinase/protein kinase B) signaling pathways, thereby driving oligodendroglial lineage progression [33]. These findings highlight the critical importance of ligand-dependent LRP1 activation, particularly by ApoE4, in regulating the fate of NSPCs toward oligodendrocytes.

In addition, through screening of LewisX glycoproteins, Hennen et al. [16] identified LRP1 as a LewisX-modified carrier protein on NSPCs. LewisX is a surface antigen linked to stem cell proliferation, migration, and stemness. However, blocking LewisX glycans with the LewisX-epitope-blocking mAb 487 LewisX did not significantly alter oligodendroglial differentiation, suggesting that the effects of LRP1 on oligodendroglial lineage specification are largely independent of LewisX glycosylation. However, whether LewisX modification influences the proliferative activity of LRP1 in NSPCs remains unknown.

4. LRP1 in Ischemic Stroke

The functional profile of LRP1 is more complex in ischemic stroke than it is under physiological conditions. Current evidence suggests that, particularly in the acute phase, ischemic stress tends to shift LRP1-associated signaling toward pathways that amplify neurovascular dysfunction and inflammatory injury. Moreover, LRP1 is not exclusively detrimental, as it may also contribute to selected protective/reparative responses depending on cell type and disease stage [72,73]. This complexity is reflected across the major pathological processes of ischemic stroke.

4.1 LRP1 in Ischemic Stroke-Induced BBB Disruption

BBB disruption is a hallmark of ischemic stroke and a major contributor to brain injury [74]. Under physiological conditions, LRP1 supports BBB integrity by regulating tight junction stability and transporter function [63,64]. However, during the acute phase of ischemic stroke, LRP1 undergoes a functional shift and becomes a detrimental facilitator of BBB breakdown [75,76]. Polavarapu et al. [49] found that the extracellular domain of LRP was shed from perivascular astrocytes and deposited in the basement membrane following middle cerebral artery occlusion (MCAO), whereas the intracellular C-terminal fragment remained within the astrocytic intracellular compartment. These changes are closely associated with the detachment of astrocytic end-feet from the basement membrane, increased BBB permeability, and perivascular edema for-

mation. Using $tPA^{-/-}$ mice, the authors further demonstrated that these effects are dependent on tPA/LRP1 interactions [49]. Importantly, pharmacological blockade of LRP1 with RAP or anti-LRP antibodies reduced ectodomain shedding, preserved BBB structural integrity, and improved locomotor activity after MCAO.

Extending these findings, the same group further investigated whether the intracellular domain of LRP1 also contributes to BBB disruption by transducing tPA-dependent signals. In a transient MCAO (tMCAO) mouse model, they demonstrated that tPA-LRP1 signaling contributes to BBB breakdown by inducing Akt phosphorylation in perivascular astrocytes [77]. Notably, this effect is independent of plasminogen, as plasminogen-deficient mice showed a comparable ischemia-induced increase in Akt phosphorylation to that of wild-type animals [77]. Instead, the regulation of Akt is LRP1-dependent and cell-type specific. tPA enhanced Akt phosphorylation in perivascular astrocytes but reduced pAkt levels in neurons, and both effects were inhibited by RAP. Co-immunoprecipitation further revealed that pAkt interacted with the intracellular domain of LRP1 in perivascular astrocytes in a tPA-dependent manner, an effect blocked by RAP. Moreover, pharmacological inhibition of Akt phosphorylation reduced BBB leakage and attenuated edema after ischemic stroke, linking astrocytic LRP1-pAkt signaling to BBB permeability. Collectively, these findings suggest that LRP1 exerts cell type-specific, bidirectional regulation of Akt signaling after ischemia, promoting deleterious Akt activation in perivascular astrocytes while suppressing Akt phosphorylation in neurons. Although opposite at the signaling level, both effects may converge toward a detrimental ischemic outcome by aggravating BBB disruption and limiting neuronal survival signaling.

Subsequent studies extended this concept by demonstrating an additional contribution of microglial LRP1 to BBB breakdown. Zhang et al. [38] showed that microglial LRP1 functions as a signaling receptor that links ischemia-associated tPA activity to BBB disruption. They found that oxygen-glucose deprivation (OGD) increased MMP9 expression in wild-type and plasminogen-deficient microglia but not in *tPA*- or *Lrp1*-deficient microglia, confirming a plasminogen-independent pathway requiring tPA and LRP1. Exogenous tPA increased the expression of MMP9 mRNA in tPA-deficient microglia but not in LRP1-deficient microglia. These findings indicated that tPA induces microglial MMP9 expression through LRP1-mediated signaling, independently of plasminogen. Consistent with these *in vitro* observations, MCAO increased MMP9 expression and activity in wild-type mice, whereas both responses were markedly attenuated in tPA-deficient and microglial *Lrp1*-deficient mice. Importantly, LRP1 deficiency reduced Evans blue extravasation and preserved claudin-5 levels, further supporting a role for microglial LRP1 in BBB damage during ischemia.

Taken together, the current evidence indicates that LRP1 promotes BBB disruption after ischemic stroke through coordinated, cell-specific mechanisms in both astrocytes and microglia. In perivascular astrocytes, tPA-driven LRP1 signaling contributes to barrier failure through extracellular ectodomain shedding associated with end-foot detachment as well as intracellular Akt activation, whereas in microglia, LRP1 mediates the tPA-dependent induction of MMP9, thereby facilitating extracellular matrix degradation and tight junction loss. These convergent actions position LRP1 as an important regulator of BBB dysfunction in ischemic stroke.

4.2 LRP1 in HT After Thrombolytic Therapy

Given the established role of LRP1 in ischemia-induced BBB disruption [38,49,77], exogenous tPA administered during thrombolysis may further engage LRP1-dependent pathways, thereby amplifying neurovascular injury and promoting HT. In addition to the mechanisms described above, recent studies have identified distinct LRP1-dependent pathways involved in tPA-associated HT. Wang et al. [78] demonstrated that neutrophil LRP1 may contribute to tPA-associated HT by facilitating neutrophil-driven vascular injury. In a photothrombotic MCAO model, tPA increased LRP1 expression in the ischemic cortex together with neutrophil infiltration and neutrophil extracellular trap (NET) formation. Pharmacological inhibition of LRP1 with RAP reduced myeloperoxidase activity and the expression of neutrophil-associated citrullinated histone H3 [79], indicating the suppression of neutrophil recruitment and NET formation. In isolated neutrophils, RAP further attenuated the tPA-induced upregulation of the expression of peptidylarginine deiminase 4 (PAD4), a key enzyme required for NET formation [80], thereby placing LRP1 upstream of PAD4-dependent NET formation. Consistent with these findings, NET inhibition preserved cerebrovascular integrity, reduced cerebral hemorrhage, and improved neurological outcomes. Taken together, these findings suggest that neutrophil LRP1 participates in tPA-induced NET formation, which may constitute a mechanism underlying the contribution of LRP1 to tPA-associated HT.

Xie et al. [19] identified asparagine endopeptidase, a lysosomal cysteine protease, as a regulator of endothelial LRP1 in the context of tPA-induced hemorrhagic injury. In human umbilical vein endothelial cells, tPA treatment induced the upregulation of asparagine endopeptidase, LRP1, MMP2, and MMP9 expression after OGD, whereas the inhibition of asparagine endopeptidase with 7,8-dihydroxyflavone (7,8-DHF) reversed these molecular changes. Similar upregulation was observed *in vivo* after MCAO/reperfusion with tPA administration, while genetic deletion of asparagine endopeptidase abolished the activation of LRP1, MMP2, and MMP9 and markedly attenuated severe HT, as reflected by reduced hematoma formation,

hemoglobin extravasation, and cerebral edema. These findings suggest that endothelial LRP1 may act downstream of asparagine endopeptidase to exacerbate tPA-induced HT by promoting MMP2 and MMP9 activation after acute ischemic stroke.

Collectively, these studies suggest that LRP1 is an important contributor to tPA-associated HT through distinct cell-specific mechanisms. Targeting these LRP1-related pathways may therefore help preserve the reperfusion benefits of tPA while reducing its hemorrhagic risk.

4.3 LRP1 in Neuroinflammation After Ischemic Stroke

Neuroinflammation is a major contributor to stroke-induced brain injury [81]. Recent studies have indicated that LRP1 is closely involved in this process. More specifically, depending on the cellular context and downstream pathway engaged, LRP1 can either activate inflammatory signaling or restrain inflammasome-driven injury.

Zhang et al. [21] showed that in a permanent MCAO (pMCAO) mice model, upregulated LRP1 expression increased the levels of phosphorylated p65, inducible nitric oxide synthase (iNOS) mRNA, and nitric oxide (NO) production, indicating the activation of the nuclear factor (NF)-κB inflammatory pathway and increased postischemic inflammation. These changes were attenuated in tPA-deficient mice or by RAP, suggesting that LRP1 mediates tPA-dependent inflammatory signaling. Moreover, RAP reduced ischemic lesion volume at 48 hours after pMCAO, suggesting that LRP1 contributes to ischemic injury. *In vitro*, OGD selectively upregulated LRP1 and iNOS mRNA in astrocytes but not in neurons, and this induction was suppressed by RAP or the tPA inhibitor neuroserpin. Together, these findings suggest that LRP1 may function as a mediator of a detrimental, astrocyte-associated inflammatory cascade after stroke. The pro-inflammatory role of LRP1 is further supported by microglial evidence [82]. At 24 hours after tMCAO in mice, microglia-specific LRP1 deficiency reduced ischemia-induced microglial activation, iNOS mRNA expression, nitrotyrosine accumulation, and ischemic lesion volume, indicating that microglial LRP1 promotes iNOS-related nitrosative inflammatory responses after ischemic stroke.

However, on the basis of findings from a mouse bilateral common carotid artery occlusion (BCCAO) model, Yang et al. [57] demonstrated that LRP1 can exert anti-inflammatory effects. They showed that activation of LRP1 with COG1410 alleviated ischemia injury by promoting an anti-inflammatory (M2) microglial phenotype and inhibiting thioredoxin-interacting protein (TXNIP)/nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) signaling at 72 hours after BCCAO. Specifically, COG1410 shifted microglia from a pro-inflammatory (M1) phenotype toward an M2 phenotype, as indicated by reduced iNOS (a marker of M1) and increased arginase-1 (a marker of M2) [83] levels in microglia. LRP1 activation also reduced brain edema, improved hippocampal CA1 histopathology, and enhanced short- and long-term neurological and cognitive outcomes. These protective effects were associated with suppression of the TXNIP/NLRP3 pathway, as evidenced by decreased TXNIP, NLRP3, cleaved caspase-1, interleukin-1β, and interleukin-18 expression. Importantly, TXNIP overexpression reversed the protective effects of COG1410, suggesting that LRP1-mediated neuroprotection depends, at least in part, on inhibition of the TXNIP/NLRP3 pathway. In addition, COG1410 attenuated oxidative stress and neuronal apoptosis, supporting the integrated anti-inflammatory, antioxidant, and antiapoptotic roles of LRP1 after cerebral ischemia. The divergent effects of RAP and COG1410 may arise from their binding to distinct LRP1 domains. RAP broadly antagonizes extracellular ligand binding, whereas COG1410, an apoE-mimetic peptide, may preferentially activate apoE-related protective signaling. These findings highlight the need to selectively target pathogenic LRP1-ligand interactions while preserving beneficial LRP1-mediated functions.

4.4 LRP1 in Mitochondrial Transport and Lactate Metabolism

Mitochondrial transfer is impaired after ischemic stroke, contributing to neuronal metabolic failure and injury [84]. As neurons are highly dependent on mitochondrial energy production, mechanisms that preserve mitochondrial function are critical for recovery after ischemic injury [85]. As discussed above, under physiological conditions, astrocytic LRP1 supports mitochondrial release and astrocyte-to-neuron mitochondrial transfer by restraining glycolysis-driven lactate production.

Zhou et al. [22] further extended this physiological mechanism to ischemic stroke and showed that, during acute ischemic injury, knockdown of astrocytic LRP1 suppresses mitochondrial transfer and thereby aggravates neuronal damage, which is associated with lactate-induced ARF1 lactylation. Co-culture of OGD-treated neurons with control astrocytes or astrocyte-derived extracellular mitochondria alleviated neuronal injury, as evidenced by improved neuronal viability and mitochondrial function, whereas co-culture with *Lrp1*-knockdown astrocytes significantly diminished these protective effects, underscoring the requirement of astrocytic LRP1 for this neuroprotective effect. In tMCAO models, astrocyte-specific *Lrp1* knockdown increased brain lactate levels, reduced astrocyte-derived mitochondrial transfer to neurons, and aggravated I/R injury, leading to larger infarcts, impaired neuronal mitochondrial function, and worsened neurological deficits. Mitochondrial supplementation rescued these phenotypes, whereas lactate administration mimicked them. Inhibiting LDH with (R)-GNE-140, a selective inhibitor of LDHA/B, or knocking down *Ldha/b* alleviated the effects of *Lrp1* deficiency. These findings confirm that astrocytic LRP1 pre-

serves protective mitochondrial transfer by limiting LDH-dependent lactate production. Meanwhile, ARF1-K73R, which prevents lactylation, restored mitochondrial transfer and reduced ischemic injury, whereas lactylation-mimetic ARF1-K73Q worsened injury, suggesting that LRP1 deficiency suppresses astrocytic mitochondrial release through lactate-driven ARF1-K73 lactylation. Importantly, CSF lactate levels were elevated in ischemic stroke patients and tended to correlate positively with infarct volume but negatively with the number of astrocytic and neuronal mitochondria. This clinical association is consistent with a potential role for LRP1/lactate-regulated mitochondrial transfer in human ischemic injury.

Overall, the results of this study highlight astrocyte–neuron interactions as an active protective mechanism during acute ischemic injury, in which astrocytes support vulnerable neurons through mitochondrial transfer. In this process, astrocytic LRP1 appears to be a key mediator that facilitates mitochondrial support and preserves neuronal viability, identifying it as a potential neuroprotective target.

4.5 LRP1 in Demyelination and Myelin Regeneration After Ischemic Stroke

White matter injury after ischemic stroke causes persistent neurological dysfunction through secondary demyelination and myelin debris accumulation, whereas its repair relies on coordinated debris clearance, oligodendrocyte precursor cell (OPC) differentiation, and remyelination [86,87,88]. Emerging evidence indicates that LRP1 participates in these processes in a highly cell type-dependent manner.

Wan et al. [23] demonstrated that LRP1 acts as a critical downstream effector of lipocalin-2 (LCN2) in astrocyte-mediated myelin phagocytosis after distal MCAO (dMCAO). In the demyelinating corpus callosum, reactive astrocytes showed elevated levels of cytosolic LCN2, which served as an upstream trigger for myelin phagocytosis. LCN2 colocalized with and interacted with LRP1 in reactive astrocytes, as confirmed by reciprocal co-immunoprecipitation. This interaction was further enhanced after dMCAO *in vivo* and after lipopolysaccharides (LPS) stimulation *in vitro*. Accordingly, LRP1/p38 MAPK signaling was activated, with increased LRP1, phosphorylated LRP1, and phosphorylated p38 levels, suggesting enhanced myelin phagocytic activity. Notably, *Lrp1* knockdown suppressed the signaling activation without altering LCN2 or complement component 3d (a pro-inflammatory astrocytic marker) levels, suggesting that LRP1 acts downstream of LCN2 rather than controlling the activation of inflammation in astrocytes. Functionally, *Lrp1* knockdown markedly decreased the proportion of phagocytic astrocytes, the number of astrocytes engulfing myelin debris, and the amount of internalized myelin. These phenotypes directly indicate impaired myelin uptake by astrocytes. Similar inhibitory effects were observed in primary astrocytes under LPS stimulation and in $Lcn2^{-/-}$ astrocytes with restored cytosolic LCN2 levels, further confirming that LRP1 is required for LCN2-driven myelin uptake. Importantly, LRP1 knockdown preserved MBP and myelin-associated glycoprotein (MAG), increased the myelinated area and myelin sheath thickness without altering axonal degeneration at 7 days after dMCAO. These findings indicate that cytosolic LCN2-LRP1 signaling selectively drives astrocyte-mediated myelin phagocytosis and demyelination rather than axonal degeneration.

Recently, Wang et al. [89] described a distinct role for LRP1 in preserving white matter integrity during the post-stroke recovery phase. They found that agomelatine markedly upregulated LRP1 expression in oligodendrocyte-lineage cells, particularly in OPCs. This upregulation was accompanied by enhanced OPC differentiation, as indicated by elevated MBP expression and increased numbers of MBP-positive oligodendrocytes. Knockdown of LRP1 reduced MBP expression and largely reversed the pro-differentiating effect of agomelatine, demonstrating that LRP1 is required for agomelatine-induced OPC differentiation. Mechanistically, agomelatine promoted OPC differentiation and myelination by activating LRP1-peroxisome proliferator-activated receptor γ (PPARγ) signaling, a pathway essential for oligodendrocyte development [90]. This finding is supported by the agomelatine-induced increase in the LRP1-PPARγ interaction, accompanied by increased PPARγ expression and activation, whereas the PPARγ inhibitor GW9662 reversed the pro-differentiating effect of agomelatine. Therefore, in contrast to astrocytic LRP1, oligodendroglial LRP1 appears to function as a pro-differentiation signal that supports oligodendrocyte maturation and may facilitate white matter repair following stroke. However, this study still lacks rigorous validation in animal models, particularly through cell-specific and pathological stage-specific interventions *in vivo*. This limitation underscores the need for precise, context-dependent modulation of LRP1 to better evaluate its therapeutic potential and facilitate clinical translation.

5. Therapeutic Perspectives and Clinical Translation of LRP1

Although accumulating evidence implicates LRP1 in multiple pathological processes of cerebral ischemic injury, translating LRP1-targeted strategies into effective therapies remains challenging. A central obstacle is the dual roles of LRP1, which can exert both beneficial and detrimental effects even within the same phase of ischemic injury. For example, in the acute phase, LRP1 promotes BBB disruption through the tPA-MMP9 axis, yet concurrently exerts neuroprotective effects by attenuating oxidative stress and neuronal apoptosis via apoE-mimetic peptide binding. In the recovery phase, LCN2-LRP1 signaling drives astrocyte-mediated myelin phagocytosis and demyelination, whereas oligodendroglial LRP1-PPARγ signaling facilitates oligo-

dendrocyte maturation, contributing to white matter repair and axonal regeneration. These divergent effects are collectively governed by differential ligand engagement and the selective activation of distinct downstream signaling cascades. Accordingly, future drug development should prioritize stage-dependent, ligand- and pathway-specific modulation of LRP1, with particular attention to extracellular ligand-binding clusters (clusters II and IV) and to post-translational modifications that govern ligand binding and downstream signaling, thereby suppressing detrimental effects while preserving beneficial ones and improving the precision and translational potential of LRP1-targeted therapies.

At present, the primary LRP1-targeting agents in cerebral ischemia models include RAP and COG1410. RAP is the most widely used pharmacological tool for LRP1 blockade and exhibits favorable BBB permeability. Current studies investigating RAP in cerebral ischemia have demonstrated robust protective effects following systemic administration. However, as a protein-based inhibitor, its potential immunogenicity and limited stability may hinder future clinical translation. Interestingly, COG1410, despite acting as an LRP1 agonist, does not elicit effects opposite to those of RAP. Instead, by selectively engaging the apoE-binding site of LRP1, COG1410 activates apoE-related protective signaling pathways, thereby exerting anti-inflammatory and neuroprotective effects. Nevertheless, its clinical translation remains limited by poor plasma stability and moderate anti-inflammatory efficacy. Moreover, both agents face a shared translational consideration, as the ubiquitous expression of LRP1 across CNS and periphery may lead to considerable off-target effects upon systemic modulation. To address these translational limitations, targeted delivery and optimized peptide strategies from other CNS disease models offer valuable insights. In glioma, computer-aided design has miniaturized RAP into RAP12, a short peptide with reduced immunogenicity, as well as enhanced BBB penetration, stability, tumor cell targeting, and anti-tumor activity [91]. In AD, COG1410-containing hybrid peptides have been engineered to target BBB pericytes by incorporating high-affinity targeting peptides, thereby improving cell specificity, therapeutic efficacy, and stability [92]. These advances suggest that therapeutic modulation of LRP1 in ischemic stroke may benefit from emerging strategies, including cell type-specific high-affinity peptides, functional short peptides derived from existing LRP1 modulators, nanomedicine-based delivery platforms, and alternative administration routes such as intranasal delivery.

In addition to serving as a direct therapeutic target, LRP1 may also be exploited for CNS drug delivery, given its high expression at the BBB and involvement in receptor-mediated transport. LRP1 has been used as a targeting receptor for carnosine-loaded functionalized polymersomes, increasing brain carnosine accumulation and enhancing its neuroprotective effects [93]. In the future, LRP1-based delivery systems may help improve the intracerebral concentration and therapeutic efficacy of ischemia-related drugs while reducing the required dosage and systemic adverse effects.

6. Limitations and Future Directions

As summarized above, most current studies on LRP1 in ischemic stroke have employed commonly used ischemic models (pMCAO, tMCAO, BCCAO, and dMCAO). While these models provide valuable mechanistic insights, they cannot fully recapitulate the heterogeneity and complexity of human ischemic stroke. Further studies should incorporate clinically relevant models of aging, vascular risk factors, and metabolic comorbidities to better evaluate LRP1-targeted interventions.

Meanwhile, the cell-specific roles of LRP1 after ischemic stroke remain incompletely defined. Current evidence indicates that LRP1 is involved in BBB disruption, HT after thrombolytic therapy, neuroinflammation, neuronal injury, metabolic remodeling, white matter injury, and remyelination. However, the extent to which these effects are mediated by LRP1 in specific cell types remains insufficiently defined. Whether endothelial and pericyte LRP1 directly contribute to BBB disruption after ischemic stroke remains to be clarified. The precise mechanisms through which astrocytic LRP1 regulates post-stroke inflammation are also incompletely understood. Whether microglial LRP1 participates in the processes of white matter injury and post-stroke repair requires further investigation. Therefore, cell-specific knockout, knockdown, and overexpression strategies are essential for distinguishing beneficial from detrimental LRP1 activity across NVU populations. Additionally, peripheral inflammatory cells warrant investigation, as LRP1-induced neutrophil infiltration and NET formation promote HT following thrombolytic therapy, yet their role in broader LRP1-mediated inflammatory responses remains unclear.

A further critical question concerns the functional transition of LRP1 from physiological homeostasis to pathological or reparative states under ischemic conditions. Research has focused predominantly on the acute phase, leaving the role of LRP1 in subacute and chronic recovery largely unexplored. Synaptic plasticity and neural NSPC homeostasis, both of which are mediated by LRP1 under physiological conditions, are essential for long-term neurological recovery. Therefore, future studies should determine whether LRP1 orchestrates these reparative mechanisms after ischemia.

7. Conclusions

In summary, LRP1 plays a pivotal yet paradoxical role in ischemic stroke pathophysiology, either exacerbating ischemic injury or promoting neuroprotection and repair. Its effects are highly context-dependent and vary according to

cell type, disease stage, ligand interactions, and signaling pathways. Therefore, achieving successful clinical translation of LRP1-targeted therapies will necessitate precision intervention strategies that selectively suppress detrimental signaling while preserving its beneficial functions, thereby opening new avenues for stage- and cell-specific intervention in ischemic stroke.

Abbreviations

AD, Alzheimer's disease; Akt, protein kinase B; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; apoE, apolipoprotein E; ARF1, ADP-ribosylation factor 1; BBB, blood–brain barrier; BCCAO, bilateral common carotid artery occlusion; cAMP, cyclic adenosine monophosphate; CNS, central nervous system; CSF, cerebrospinal fluid; CypA, cyclophilin A; dMCAO, distal MCAO; ECAR, extracellular acidification rate; ERK, extracellular signal-regulated kinase; GluR1, glutamate receptor 1; HT, hemorrhagic transformation; iNOS, inducible nitric oxide synthase; LCN2, lipocalin-2; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; L-LTP, late-phase long-term potentiation; LPS, lipopolysaccharides; LRP1, low-density lipoprotein receptor-related protein 1; MAG, myelin-associated glycoprotein; MAPK, mitogen-activated protein kinase; MBP, myelin basic protein; MCAO, middle cerebral artery occlusion; MMP, matrix metalloproteinase; NET, neutrophil extracellular trap; NF-κB, nuclear factor-κB; NLRP3, nucleotide-binding oligomerization domain-like receptor protein 3; NMDAR1, N-methyl-D-aspartate receptor 1; NO, nitric oxide; NSPC, neural stem/progenitor cell; NVU, neurovascular unit; OCR, oxygen consumption rate; OGD, oxygen-glucose deprivation; OPC, oligodendrocyte precursor cell; PAD4, peptidylarginine deiminase 4; PDGF, platelet-derived growth factor; P-gp, P-glycoprotein; PI3K, phosphatidylinositol 3-kinase; PAI-1, plasminogen activator inhibitor-1; PKA, protein kinase A; pMCAO, permanent MCAO; PPARγ, peroxisome proliferator-activated receptor γ; PSD-95, postsynaptic density protein 95; RAP, receptor-associated protein; tMCAO, transient MCAO; tPA, tissue-type plasminogen activator; TXNIP, thioredoxin-interacting protein; VLDL, very-low-density lipoprotein; α2M, α2-macroglobulin.

Author Contributions

YJZ and JQJ performed the literature search and wrote the manuscript. YJZ and ZYW prepared the figures and revised the manuscript. YYF and JHG contributed to conception and manuscript editing, scientific and English revision, and supervision of the work. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest. Yan-Ying Fan is serving as one of the Editorial Board members of this journal. We declare that Yan-Ying Fan had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Changjong Moon.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used Consensus AI tool in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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