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Review Article

The Role of PDZ in Cerebral Ischemia

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Abstract

Cerebral ischemia is a widespread disease and a leading cause of death and disability worldwide. Its complex origins and the mysterious mechanisms behind its development make it a formidable adversary in the field of medicine. PDZ proteins are part of the human proteome with multiple functions and have been identified as key mediators of cell signaling and synaptic transmission. Their interactions with PDZ-binding proteins underlie their role in the pathogenesis of a variety of diseases. In this paper, PDZ domains have been extensively studied, exploring their structural properties and functional roles in cells. This review highlights the importance of these domains in signal transduction pathways, which are essential for the normal function of the nervous system. It also highlights emerging evidence linking PDZ proteins to the regulation of angiogenesis in cerebrovascular diseases, a key process in the development of ischemic disease. In addition, we further discuss the potential of PDZ proteins in neuronal regeneration, an area that is expected to play a role in stroke development and subsequent rehabilitation. This review also discusses the link between PDZ proteins and excitatory synaptic transmission, further exploring the mechanisms involved in excitatory toxicity. By analyzing the complex relationship between PDZ proteins and their binding partner, this paper aims to reveal the molecular basis of cerebral ischemia. This suggests that a deeper understanding of these interactions could pave the way for innovative therapeutic interventions for stroke management. The review concludes by advocating continued research into PDZ proteins, recognizing their potential as building blocks for the development of new treatment and prevention strategies for stroke and related disorders.

Keywords

PDZ, Synaptic Transmission, NMDAR, nNOS, Ischemic Stroke

1. Introduction

Stroke is currently the second leading cause of death and permanent disability among individuals over the age of 60 globally [1]. With the progression of an aging population, the incidence of stroke is further increasing, which imposed a significant burden on both individuals and society. Ischemic stroke caused by severe stenosis or occlusion of the cerebral arteries is the most common type of stroke. Over the past 30 years, progress has been made in the treatment of ischemic

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stroke. To date, intravenous thrombolysis and mechanical thrombectomy remain the primary treatment methods for restoring cerebral blood flow after ischemia [2]. Therefore, there is an urgent need to further understand the mechanisms of ischemic brain injury to facilitate the development of neuroprotective drugs.

In all cells, proteins are the most crucial components. Protein-protein interactions (PPIs) are the most fundamental activities in the majority of cellular functions. PPIs constitute a major part of the cellular biochemical reaction network. These interactions are mediated by domains, which function to recognize and bind to specific sequences on other proteins.

The PDZ protein family is one of the largest protein families in the human proteome, with approximately 274 PDZ domains identified in 155 proteins [3]. PDZ domains are involved in a variety of cellular pathways, such as signal transduction, cell-cell junctions, cell polarity, adhesion, protein transport, and regulation of protein metabolism [4]. In the nervous system, PDZ domain proteins such as PSD-95 are involved in the formation and maintenance of synapses and are essential for neural function.

Therefore, this article reviews the structure and function of PDZ domains, as well as their relevance to signal transduction. By exploring the regulatory mechanisms of PDZ and its associated signaling pathways, the article reveals the significant role PDZ plays in the pathophysiological mechanisms of ischemic stroke. It primarily discusses the related roles of PDZ in ischemic stroke, such as participating in cell apoptosis [5], angiogenesis [6], improving the destruction of the blood-brain barrier [7], and promoting neuronal regeneration [8]. This contributes to a deeper understanding of the pathogenesis of ischemic stroke and provides potential therapeutic targets, offering new directions for the development of clinical drugs.

2. PDZ Domain Structure and Function

PDZ originates from the first three proteins in which these domains were identified: PSD-95 (Post-synaptic density protein of 95 kDa), Discs large and ZO-1 (Zonula occludens-1 protein). The PDZ domain is a small protein module containing approximately 80-110 amino acids [4], folded into a compact tertiary structure that includes two alpha helices (αA, αB) and six antiparallel beta strands (βA-F). These folding sheet structures are stabilized through hydrophobic interactions and hydrogen bond interactions [3].

The PDZ domain is known for its role in regulating neuronal synaptic signaling transmission and cell-cell junctions in most cell types, particularly in neurons. The function of PDZ domains lies in stabilizing the structure of the proteins themselves and linking proteins to each other to exert their functions [9, 10]. There are three main types of PDZ binding modes: C-terminal binding, N-terminal binding, and internal binding [11, 12]. PDZ proteins primarily interact with other proteins to form complexes through specific binding sites within their domains.
1) C-terminal binding: This is a common mode of interaction for PDZ proteins with most target proteins [13, 14]. The C-terminal alpha helix of the PDZ domain interacts with the C-terminal region of the target protein. In this binding mode, PDZ proteins regulate the function of the target protein by interacting with its C-terminal sequence, and through this interaction, they can form specific and stable protein complexes. This plays a key role in cellular signal transduction, cytoskeletal organization, and cell-cell interactions.

2) N-terminal binding: A minority of PDZ proteins can bind to the N-terminal region of target proteins through their N-terminal alpha helix. This mode of binding is less common but has been observed in some PDZ proteins [15]. Similar to C-terminal binding, N-terminal binding is also achieved through specific sequences and structural features. It may play a role in the processes of protein synthesis, folding, and degradation. N-terminal binding may involve the recognition of specific N-terminal modifications, such as phosphorylation or glycosylation, which can affect protein function and interactions [16].

3) Internal binding: Some PDZ proteins have the ability to interact with other proteins within their own structural domains. In internal binding, specific side chains on the PDZ domain interact with other proteins or molecules, thereby regulating the assembly and function of the complex. However, the binding of internal sequences to most PDZ domains is weak. Dvl binds to the internal PDZ motif of FZD and not the carboxyterminal site [17].

It is important to note that each PDZ binding mode relies on the complementarity of the sequence and structural features of the PDZ domain and the target protein. The specificity and stability of this interaction are crucial for ensuring proper signal transduction and cellular function.

3. Proteins with PDZ Domains Related to the Nervous System

PSD-95 (Postsynaptic density protein of 95 kDa)

PSD-95 is highly expressed in the adult mouse brain, with the highest expression levels in the hippocampus, cortex, and olfactory bulb. Membrane-associated guanylate kinases (MAGUKs) are major components of the postsynaptic density and play an important role in synaptic organization and plasticity [18, 19]. Most excitatory synapses are located on dendritic spines, which are dynamic structures that undergo morphological changes during synapse formation and plasticity. MAGUK proteins are involved in the trafficking of receptors and the assembly of key postsynaptic signaling complexes, utilizing their PDZ domains. As a result, they have been recognized as promising therapeutic targets for the management of neurological conditions, including stroke, chronic pain, and Alzheimer's disease. Among them, PSD-95 is the most abundant scaffold protein in PSD of excitatory neurons, containing three PDZ domains and a guanylate kinase domain. Its primary regulatory functions are attributed to

the three PDZ domains [20], with PDZ1 and PDZ2 binding to various membrane proteins, including NMDA receptor subunits, and PDZ3 interacting with the C-termini of receptors, ion channels, and enzymes to control synaptic signal transduction [21, 22]. PSD-95 is highly regulated by phosphorylation, with PKA phosphorylation within PDZ ligands weakening the binding of NLGN1 to PSD-95, thereby reducing its surface expression and decreasing NLGN1-dependent excitatory synaptic enhancement. Phosphorylation of S73 in PDZ1 selectively eliminates the binding to the GluN2A subunit of the NMDA receptor [23]. The PSD-95 family includes four members located at mammalian synapses: PSD-95/SAP90, SAP97, PSD-93/chapsyn-110, and SAP102. The main function of PSD-95 is to stabilize and anchor membrane protein complexes in synaptic membranes. In the case of AMPARs and NMDARs, it directly or indirectly binds these receptors to aggregate them into larger signaling complexes.

nNOS

Nitric oxide synthase (NOS) exists in three distinct isoforms, with neuronal NOS (nNOS) being the predominant supplier of nitric oxide (NO) within the central nervous system and predominantly found in neuronal cells. nNOS is a Ca2+-dependent constitutive synthase [24], whose activity is strictly regulated by changes in intracellular Ca2+ concentration mediated by the N-methyl-D-aspartate receptor (NMDAR). Notably, nNOS contains an N-terminal PDZ binding domain. The PDZ domain of nNOS can interact with proteins containing PDZ domains, affecting the subcellular localization and activity of nNOS in the brain [25]. NOS1 adaptor protein (NOS1AP) was first identified as a C-terminal PDZ ligand of BOS1, composed of its N-terminal phosphotyrosine-binding (PTB) domain and its C-terminal PDZ ligand sequence [26]. NOS1AP forms a NOS1-NOS1AP-Dexras complex through its PTB domain with Dexras and PDZ ligand with NOS1, promoting NOS1 activation and participating in the MAPK signaling cascade and NMDA/NO-induced neurotoxicity [27, 28]. NOS1AP regulates the Hippo signaling pathway, and through its PDZ binding sequence with NOS1, and PTB domain with synapsin I, it forms a ternary complex containing NOS1, NOS1AP, and synapsin I.

PICK1 (Protein interacting with kinase C1)

PICK is a membrane protein composed of an N-terminal PDZ domain and a C-terminal BAR domain, highly expressed in the brain and peripheral tissues. It is an intracellular transport protein that regulates various neuronal receptors/transporters and involves in the internalization of AMPA-type receptors located on the neuronal surface. The PDZ domain of PICK1 recognizes and binds to the intracellular PDZ binding motif of GluA2 C-terminus. The protein-protein interaction between PICK1 and GluA2 leads to the endocytosis of AMPA receptors away from the neuronal surface, thereby reducing synaptic transmission [29].

PDZ Scaffold Protein Lnx1/2

Lnx1/2 are expressed in both the cerebrum and cerebellum, with particularly extensive expression in neurons [30]. Lnx1/2 contains four PDZ domains, allowing it to interact with the C-terminal ends of a variety of proteins [31]. Lnx1 has been identified as being specifically expressed in the neurons of the hippocampal CA3 region. As a scaffold protein, Lnx1 engages with GluN2B via its first PDZ domain (PDZ1) and with the EphB2 receptor through its second PDZ domain (PDZ2). It can also form a complex known as Lnx1-NMDAR-EphB2 through these interactions, which are crucial for maintaining the stability and activity of GluN2B at the postsynaptic membrane. This complex is critical for the synaptic function and the development of social memory in the CA3 region's neurons [32]. Lnx2 may have a potential role in neurogenesis within the subventricular zone [SVZ]. The binding of LNX2 to Caspr4 necessitates the involvement of the second PDZ domain, suggesting that LNX2 might recognize different substrates through its distinct PDZ domains. Overexpression of LNX2 can rescue the deficits in neuronal differentiation that arise from the reduction of Caspr4 [33].

GRIP1 (Glutamate Receptor Interacting Protein)

Glutamate receptor interacting protein 1 (GRIP1), an AMPAR-binding protein shown to regulate the trafficking and synaptic targeting of AMPARs, is required for LTP and learning and memory [34]. GRIP1, with seven PDZ domains, directly interacts with the C-termini of GluA2 and GluA3 through its fourth and fifth PDZ domains, regulating the surface expression and synaptic stability of AMPARs [35, 36].

4. PDZ-Involved Signaling Pathways

PDZ proteins are implicated in numerous signaling pathways and play a widespread role in signal transduction within the nervous system. Signal transduction in the nervous system requires the transmission of signals between and within nerve cells. Within neurons, signals are transmitted through ion conduction across the cell membrane, occurring between electrically sensitive regions of the membrane. Between neurons, signal transduction is mediated by intracellular connections or synapses.

PDZ Proteins and Synaptic Development

Excitatory synapses, particularly their postsynaptic densities (PSDs), contain many PDZ proteins. PDZ proteins are crucial for the formation, function, and positioning of postsynaptic receptor complexes [37, 38]. PDZ proteins interact with receptors and ion channels at the postsynaptic membrane through their C-terminal sequences, participating in the formation and stabilization of postsynaptic receptor complexes. Proteins containing PDZ domains play a dual role in synaptic function: on one hand, they are important in the development and function of synapses, with scaffold proteins such as PSD-95 and other members of the MAGUK family stabilizing transmembrane proteins in the postsynaptic domain through PDZ interactions [39]; or like the postsynaptic adhesion molecule neurexin (NL2) itself, which is stabilized at synapses through PDZ ligands [40]. On the other hand,

synapses are asymmetric intercellular connections that allow the transmission of signals from the presynaptic neuron to the postsynaptic neuron [i.e., synaptic transmission], and PDZ-ligand interactions are essential for synaptic transmission. For example, PDZ proteins positively regulate the excitatory synaptic targeting of Slitrk2 and the formation and transmission of excitatory (but not inhibitory) synapses mediated by Slitrk2 [41]. Therefore, regulating the affinity between PDZ domains and their ligands may play a significant role in modulating synapses.

PDZ Proteins and Glutamate Signaling Pathway

PDZ proteins are intricately involved with the Glutamate signaling pathway. Glutamate serves as the primary excitatory neurotransmitter within the nervous system, conducting its signals through ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs) glutamate receptors. A variety of PDZ domain-containing proteins have the capacity to directly interact with the C-terminal sequences of glutamate receptors, particularly engaging with mGluRs to stabilize their positioning and modulate signal transduction. An example of this is the PDZ domain protein CAL, which can modulate mGluR activity, subsequently influencing downstream signaling pathways such as AKT, ERK1/2, and JNK [42]. Moreover, PDZ proteins participate in the internalization and recycling of glutamate receptors, thereby regulating their levels of expression and functionality.

PICK1, which includes an N-terminal PDZ domain, binds to mGluRs and impacts the endocytosis of AMPARs mediated by mGluRs [43]. These PDZ proteins also interact with signaling molecules and cytoskeletal elements, playing a role in the assembly and maintenance of the postsynaptic density. This function is essential for synaptic plasticity and the maturation of synaptic connections. Through these interactions, PDZ proteins contribute to the modulation of the strength and efficiency of synaptic transmission. Consequently, the interplay between PDZ proteins and the Glutamate signaling pathway is crucial for the proper functioning and adaptability of the nervous system. AMPA receptors (AMPARs) and NMDA receptors (NMDARs) are connected to various enzymatic signal pathways and regulators through PDZ proteins, including members of the PSD-95 family, PICK1, and ABP/GRIP [44]. AMPARs mediate rapid synaptic transmission, while NMDARs are crucial for activity-dependent plasticity and excitotoxicity in the nervous system. The C-termini of AMPAR's GluR2 and GluR3 subunits interact with GRIP (glutamate receptor interacting protein) and PICK's PDZ domain proteins, participating in the aggregation of AMPARs at excitatory synapses [45]. PICK1 plays a key role in regulating the intracellular trafficking of the AMPA GluA2 subunit, which is related to synaptic plasticity.

PDZ Proteins and GABA Receptor Signaling Pathway

PDZ proteins are an important class of domains closely related to GABA receptor signaling pathways in the nervous system. GABA (gamma-aminobutyric acid) receptors are the main inhibitory receptors in the nervous system, and their function and positioning are regulated by binding to PDZ proteins. Studies have shown that PDZ proteins can bind to the C-termini of GABA receptor subunits, forming complexes that affect receptor expression, stability, and signal transduction. For example, the PDZ protein Glycine receptor-associated protein (GlyR) interacts with the α and β subunits of the GABA-A receptor at the C-terminus, promoting the aggregation and localization of GABA receptors at the postsynaptic membrane, thus playing a key role in the transmission of inhibitory signals [46]. In addition, other PDZ proteins such as GAT1, with its C-terminal PDZ binding motif, primarily interact with syntenin-1's PDZ domain 1, regulating receptor expression and function [47].

Excitotoxicity

Most of the rapid excitatory synaptic transmission in the central nervous system of mammals is mediated by ionotropic glutamate receptors. PDZ proteins aggregate glutamate receptors at synapses with their corresponding signal transduction proteins, thereby affecting the release of neuronal glutamate and influencing the structural and functional aspects of neurons and synapses.

nNOS / PSD-95 / NMDAR

The signaling pathway coupled by scaffold proteins with PDZ, through which glutamate receptors are associated, represents a potential mechanism for mediating excitotoxicity. PSD-95 directly binds to the intracellular threonine/serine-X-valine-COOH [T/SXV] motif of the GluN2 subunit of NMDAR through its PDZ1 and PDZ2, and through its PDZ2, it binds to the N-terminus of nNOS, forming an NMDAR-PSD-95-nNOS ternary complex [21, 48]. The CK2 phosphorylation of GluN2B regulates the binding of NMDAR to PSD-95 and stabilizes it at synapses [49]. The key structural basis for the association between nNOS and PSD-95 is the internal salt bridge between Asp62 of the PDZ domain and Arg121 of the β-finger domain of nNOS [48]. The disruption of the salt bridge causes the β-finger to melt and prevents its interaction with PSD-95-PDZ2. Additionally, residues Leu107 to Phe111 on the β-finger of nNOS contribute to the conformational changes induced by their binding to PSD-95 PDZ2. Furthermore, studies have shown that cell-permeable peptides fused with the PDZ ligand motif or "ExF" motif of NOS1AP can inhibit the activation of p38MAPK and excitotoxic injury in rat cortical neurons and hippocampus induced by NMDA [50]. This ternary complex is central to the physiological functions of neurons, including plasticity, learning, or memory [51].

NMDAR-PSD93-SynGAP

In addition to PSD95, PSD93 is another postsynaptic density protein that specifically binds to the C-terminal tail of NMDAR. The deletion of PAD93 shows neuroprotection against ischemic brain injury. Significant improvements in neurologic deficits and reductions in neuronal death were found in PSD-93 knockout mice and PSD-93 deficient neurons in ischemic models, which is associated with the inhibition of Tyr-2 phosphorylation in NR1472B [52]. Moreover, it

has been shown that PSD-93 can directly interact with SynGAP, a GTPase activating protein used in the Ras [renin-angiotensin system] pathway, and exacerbate ischemic brain injury by regulating the degradation of ubiquitin and SynGAP. Additionally, the Tat-SynGAP interference peptide targeting the amino acid sequence of the binding site between SynGAP and PSD-93 is effective in mice.

MAGUK-NLGN1

NLGN mediates the formation of spines and synapses, and the interaction between MAGUK and NLGN is regulated by PDZ phosphorylation. Phosphorylation of the S839 residue weakens the binding of NLGN1 to PSD-95, thereby reducing its surface expression and the enhancement of NLGN1-dependent excitatory synapses [53]. Other members of the MAGUK family, such as SAP97, SAP102, and PSD-93, as well as the inverse direction (MAGI) family of MAGUK, such as S-SCAM, Magi1, and Magi3, also interact with NLGN1 through PDZ ligands [54-56].

5. PDZ and Ischemic Stroke

Stroke is a leading cause of death, disability, and dementia worldwide, with ischemic stroke accounting for 87% of cases [57]. When an ischemic stroke occurs, ischemia and hypoxia can act as signals triggering a series of multifactorial and multilink cascade reactions. During the process of brain injury, reduced blood perfusion leads to the formation of an irreversible damage core known as the infarct, surrounded by an ischemic penumbra where the function is impaired but metabolism remains active. However, the ischemic penumbra suffers from secondary neuronal death caused by excessive stimulation of N-methyl-D-aspartate type receptors [NMDARs] by glutamate and the subsequent excitotoxicity.

Excitotoxicity is the process by which excitatory amino acids produce neurodegenerative changes and is a primary mechanism of cell death in many acute central nervous system diseases, including stroke [58]. Glutamate toxicity is considered the initiator of excitotoxicity in stroke. When the brain is in a state of ischemia and hypoxia, metabolic disorders lead to the excessive release of glutamate from presynaptic terminals into the synaptic cleft. The released glutamate overactivates NMDARs on the postsynaptic membrane, leading to an increased influx of Ca2+ ions [59]. The Ca2+ influx from NMDARs activates nNOS, promoting the production of excessive nitric oxide (NO) in the synaptic structure, ultimately leading to excitotoxicity [60, 61]. The coupling between NMDAR and nNOS after brain ischemia is not a simple protein-protein interaction but rather a tight ternary complex formed by the PDZ domain of PSD-95 at excitatory synapses [62]. Stroke induces the translocation of nNOS from the cytoplasmic matrix to the cell membrane, promoting its binding to PSD-95 [25]. The NMDAR-dependent association of nNOS-PSD-95 is crucial for neuronal death in the acute phase of stroke [63]. The binding of the NMDAR/PSD-95/nNOS complex leads to activated phosphorylation through various mechanisms, including CaMKII-dependent and Src/Fyn kinase-dependent mechanisms. After brain ischemia, CaMKII-dependent phosphorylation differentially affects different NMDAR subtypes; Phosphorylation of PSD-95 at Ser73 by CaMKII causes the detachment of NR2A from PSD-95, while leaving the interaction between NR2B and PSD-95 intact, thus modulating the downstream death signaling pathways associated with NMDAR [64]. Similarly, brain ischemia and reperfusion increase PSD-95 phosphorylation through Src/Fyn kinase in rat hippocampal neurons, leading to NMDAR activation after ischemia. PSD-95 is essential for the tyrosine phosphorylation of NR2A mediated by Src/Fyn kinase after brain ischemia [65]. During the period of transient cerebral ischemia followed by reperfusion, PSD-95 engages with NR2A, facilitating its tyrosine phosphorylation. This interaction results in an elevated formation of the Fyn/NR2A/PSD-95 complex, which in turn enhances the functionality of NMDAR. The heightened NMDAR activity contributes to the death of ischemic neuronal cells [66, 67]. This may be related to ion channel failure and overload following NMDAR activation. After calcium elevation induced by NMDA, PSD-95 utilizes its unique molecular structure to recruit calcium-dependent nNOS from the cytoplasm to the membrane, mediating the production of the neurotoxic molecule NO, which triggers a series of downstream cellular death events [68]. By inhibiting NMDAR receptor activation and nNOS activity, it plays a key role in protecting neuronal cells from excitotoxic effects [69]. Ischemic boundary areas after cerebral ischemia/reperfusion [I/R] injury exhibit angiogenesis. Angiogenesis, including proliferation, migration and tube formation of internal secretions, can promote the recovery of neurological function after ischemic stroke. Hippo pathway is regulated by G protein-coupled receptor signal transduction, and its main downstream effectors are Yes-associated protein (YAP) and transcriptional coactivator (TAZ) with PDZ-binding motif [70].

Cerebral ischemia leads to impaired synaptic transmission. Cerebral ischemia can activate the mitogen-activated protein (MAP) kinase pathway and increase the level of tyrosine phosphorylation of proteins associated with PSD. SynGAP binds to the PDZ domain of PSD-95/SAP90 and co-immunoprecipitates with PSD95. After ischemia, the co-immunoprecipitation of SynGAP with PSD-95 is reduced, which may affect the connection of the NMDA receptor with downstream signaling pathways [71].

6. Inhibitors and Small Molecule Peptides Based on PDZ

TAT-NR2B9C

A peptide drug targeting PSD-95, the first peptide inhibitor NA-1 or Tat-NR2B9c, is created by fusing the 9 C-terminal residues of the GluN2B subunit with the 11 residues of the cell

membrane transduction facilitator Tat. It is developed to target and disrupt the interaction between PSD-95 and nNOS, minimizing the excitotoxicity caused by ischemic stroke, thereby providing neuroprotective effects in reducing infarct volume and improving neurobehavioral outcomes [72]. Tat-NR2B9c (NA-1) alleviates cell atrophy, nuclear pyosis, cytoplasmic vacuole change, extracellular space expansion, and tissue structure destruction in cortical infarct areas [73].

Cyclohexylethyl- [A/G]- [D/E]-X-V Peptides

N-Cyclohexylethyl- [A/G]- [D/E]-X-V Peptides blocked the interaction between nNOS and CAPON by competitive binding to the PDZ domain of nNOS. N-cyclohexylethyl-adav (Che-ADAV) has the strongest affinity for the nNOS PDZ domain, and in the rat model of MCAO, Che-ADAV significantly reduced the infarct volume, indicating that it can combat brain damage caused by ischemic stroke, indicating that it has a potential neuroprotective effect [74].

PTEN Peptide [AVLX-144]

AVLX-144 interacts with the PDZ binding motif of PTEN, preventing PTEN from binding to PDZ proteins such as MAGI-2 or MAST205, which are known to recruit PTEN to the cell membrane and stabilize its interaction with PIP3 [8]. Through this mechanism, AVLX-144 can increase the activity of PTEN, potentially having a positive impact on neuroprotection and neural repair. This peptide has increased neuronal survival rates in multiple stroke models and improved axonal regeneration after MCAO in adult rats [75].

7. Conclusion and Outlook

Based on the research summarized above, proteins containing PDZ domains are important components of the nervous system. They regulate the structure and function of neurons and synapses and interact with glutamate receptors to control excitatory synaptic transmission, leading to the occurrence of excitotoxicity. Excitotoxicity has always been a focus of research on ischemic stroke, and most existing neuroprotective drugs have limited effectiveness in treating ischemic stroke due to short half-lives, potential toxicity, poor distribution specificity, and poor penetration of the blood-brain barrier. Therefore, in the absence of more effective drugs for treating ischemic stroke, proteins containing PDZ domains have become potential targets for the development of small molecule inhibitors as therapeutic agents. By inhibiting protein-protein binding and blocking interactions, these inhibitors can reduce central nervous system damage or neuronal apoptosis and cell death, thereby alleviating the harmful effects within brain tissue after ischemic stroke.

Abbreviations

PPIs	Protein-Protein Interactions
PSD-95	Post-synaptic Density Protein of 95 kDa
ZO-1	Zonula Occludens-1 Protein
MAGUKs	Membrane-Associated Guanylate Kinases
NOS	Nitric Oxide Synthase
nNOS	Neuronal NOS
NOS1AP	NOS1 Adaptor Protein
PTB	N-terminal Phosphotyrosine-binding
GRIP1	Glutamate Receptor Interacting Protein 1
iGluRs	Ionotropic Glutamate Receptors
mGluRs	Metabotropic Glutamate Receptors
AMPARs	AMPA Receptors
NMDARs	NMDA Receptors
GRIP	Glutamate Receptor Interacting Protein
GABA	Gamma-Aminobutyric Acid
GlyR	Glycine Receptor-Associated Protein
NO	Nitric Oxide
YAP	Yes-associated Protein
TAZ	Transcriptional Coactivator
MAP	Mitogen-activated Protein
MCAO	Middle Cerebral Artery Obstruction

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Author Contributions

Yeting Chen: Writing – original draft
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Wenping Cao: Formal Analysis
Ye Cao: Conceptualization
Jianfeng Pu: Funding acquisition

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Conflicts of Interest

The authors declare no conflicts of interest.

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