LIMK1 in Spine Regulation

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The LIM-domain-containing protein kinases (LIMK1 and LIMK2) are key regulators of the actin cytoskeleton by affecting the actin-binding protein, cofilin. Additionally, LIMK1 is implicated in the regulation of gene expression through its interaction with the cAMP-response element-binding protein (CREB). Accumulating evidence indicates that LIMKs are critically involved in brain function and dysfunction.

Keywords: LIMK ; actin ; long-term potentiation ; long-term depression ; memory ; brain disorders

1. Introduction

Long-term modifications in the efficacy of signal transmission at excitatory synapses, such as long-term potentiation (LTP) and long-term depression (LTD), are considered to be the major cellular mechanisms that contribute to the plasticity of neuronal circuits underlying learning and memory [1][2][3][4][5][6]. One of the key mechanisms for LTP and LTD involves postsynaptic modifications, including changes in the size and number of dendritic spines, as well as synaptic trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-type glutamate receptors (AMPARs), the principal mediators of excitatory synaptic transmission [7][8][9][10][11][12][13][14][15][16]. In the mammalian central nervous system, most excitatory synapses are located on small dendritic protrusions called dendritic spines, which represent the major postsynaptic component of these synapses [17][18]. Although dendritic spines can be found in various shapes and can alter their morphology during development and synaptic plasticity, mushroom spines with a narrow, short neck and a large distinguishable round head represent the major form of mature spines [19][20]. In addition to mushroom spines, spines may also exhibit other shapes, such as thin spines which lack a clear distinction between the head and neck and stubby spines, with no distinguishable neck. Thin spines represent young, immature spines that are more likely to undergo structural changes [17][18][19]. Dendritic filopodia are protrusions that are believed to actively search for presynaptic partners to initiate neuronal connections during synaptogenesis and are considered precursors of dendritic spines [21][22]. The unique shape of the mature dendritic spine (e.g., large head and narrow neck) is thought to be critical for compartmentalizing local electrical and chemical signals within the spine and restricts diffusion of synaptic molecules out of the spines [20][23][24][25][26][27]. Spine changes, including spine enlargement and shrinkage, are closely associated with LTP, LTD, and memory formation [10][13][20][28][29]. Dendritic spines possess a dense structure called the postsynaptic density (PSD), which is enriched with various synaptic molecules, including AMPARs and associated proteins, allowing for the conversion of electrical signals at synapse into biochemical responses to maintain basal synaptic transmission and promote synaptic plasticity [11][17][24][30][31][32][33]. Since the actin cytoskeleton is the major structural component of dendritic spines, many studies have shown that actin reorganization plays a central role in spine formation, maintenance, and dynamic changes under both basal conditions and activity-dependent neural plasticity [31][32][34][35][36][37][38][39][40]. There are two distinct pools of actin filaments within the spine [41], including a stable and dynamic pool. The stable pool is typically located at the base of the spine head and is important for the stability of the spine neck. Conversely, the dynamic pool, localized at the tip of the spine and can generate an expansive force by actin polymerization to mediate activity-dependent enlargement of the spine [28]. As key regulators of the actin cytoskeleton, LIM-domain kinase proteins (LIMKs) play a critical role in synaptic development and plasticity. In addition, studies suggest that LIMK1 may regulate synaptic plasticity and memory by actin-independent mechanisms. Abnormalities in LIMK1 signaling have been reported in multiple neurological and mental disorders (**Table 1**).

Table 1. Summary of key studies on LIMK1.

Experimental Model and Procedure	Spine Properties	Synaptic Function	Behaviour, Learning, and Memory	Mechanism
Meng et al., 2002 LIMK1 KO mice; cultured neurons; slices	-Reduced mature spines -Increased immature spines	-Enhanced mEPSC frequency and LTP	-Increased locomotor activity -Enhanced cued fear response	-Impaired basal and activity-induced change of p-cofilin -Abnormal actin
George et al., 2015 Rats; cultured neurons; LIMK1 knockdown	-Impaired spine density and plasticity -Rescued by LIMK1 overexpression	N/A	N/A	-Palmitoylation and spine translocation of LIMK1
Meng et al., 2004 LIMK2 KO; LIMK1 and LIMK2 DK mice; slices	N/A	-Enhanced basal synaptic transmission and LTP in LIMK1/LIMK2 DK mice	N/A	-Impaired p-cofilin in LIMK1/LIMK2 DK mice
Meng et al., 2005 PAK3 KO mice; cultured neurons; slices	Normal dendritic/spine morphology	-Normal E-LTP -Impaired L-LTP	N/A	-Normal basal level of p-cofilin -Impaired basal level of pCREB
Asrar et al., 2009 PAK1 KO mice; cultured neurons; slices	-Normal synaptic/spine structures	-Normal LTD -Impaired LTP	N/A	-Impaired activity-induced change of p-cofilin -Abnormal actin
Boda et al., 2004 Mice; cultured slices; PAK3 knockdown	-Increased immature spines	N/A	N/A	N/A
Wang et al., 2018 PAK2 KO mice; slices	-Reduced spine and synapse density	N/A	N/A	-Impaired basal levels of p-cofilin and pLIMK1
Hayashi et al., 2004 Transgenic DN PAK; slices	-Reduced spine density and increased spine size	N/A	N/A	N/A
Tashiro et al., 2004 Mice; cultured slices; inhibition of ROCK	-Reduced spine density -Increased spine length	N/A	N/A	N/A

Experimental Model and Procedure	Spine Properties	Synaptic Function	Behaviour, Learning, and Memory	Mechanism
Zhou et al., 2009 ROCK2 KO mice; slices	-Reduced synaptic density -Increased spine length	-Impaired basal synaptic transmission -Impaired LTP -Normal LTD	N/A	-Impaired basal level of p-cofilin -Normal activity-induced change of p-cofilin
Shi et al., 2009 Mice; cultured neurons; cofilin S3A and S3D expression	-Increased immature spines by cofilin S3A	N/A	N/A	N/A
Rust et al., 2010 Conditional n-cofilin KO mice; slices	-Increased spine density, length, and width	-Impaired L-LTP -LTD resistance	-Impaired spatial and fear learning and memory	N/A
Wolf et al., 2015 Conditional ADF/cofilin DK mice; slices	-Reduced synapse/spine density -Increased spine size	-Impaired PPF -Faster synaptic depression	N/A	-Increased F/G-actin ratio -Impaired synaptic actin dynamics
Todorovski et al., 2015 LIMK1 KO mice; slices	N/A	-Impaired L-LTP, rescued by PKA activator	-Impaired spatial and contextual fear LTM -Rescued by PKA activator	-Normal basal pCREB -Impaired activity-induced change in pCREB
Huang et al., 2011 PAK1/PAK3 DK mice; slices	-Reduced spine density -Increased spine size	-Enhanced basal synaptic transmission -Impaired LTP -Impaired LTD	-Increased locomotor activity and anxiety -Impaired spatial and fear memory	N/A
Lunardi et al., 2018 Rats; LIMK1 inhibitor	N/A	N/A	-Impaired contextual fear memory	N/A
Wang et al., 2013 Rats; cofilin peptides (S3 and pS3)	N/A	N/A	-Cofilin S3 and pS3 enhanced and impaired memory extinction, respectively	N/A
Pennucci et al., 2019 Rac1/Rac3 and Rac3 DK mice; cultured neurons	-Reduced dendritic spines -Increased filipodia	N/A	N/A	N/A

Experimental Model and Procedure	Spine Properties	Synaptic Function	Behaviour, Learning, and Memory	Mechanism
McNair et al., 2010 RhoB KO mice	-Reduced spine density -Increased spine size	-Reduced E-LTP -Normal L-LTP	N/A	-Impaired level of pLIMK1
Henderson et al., 2019 hAPP mice; cultured neurons; Aβ42 treatment	-Reduced spine density -Rescued by LIMK1 inhibitor	-Increased excitability -Rescued by LIMK1 inhibitor	N/A	-ROCK2-LIMK1-dependent mechanism
Heredia et al., 2006 Mice cultured neurons; human tissue	-Neuronal degeneration -Rescued by LIMK1 inhibitor	N/A	N/A	-Increased pLIMK1 level
Woo et al., 2015 Transgenic APP/PS1 mice; cultured neurons	-Synapse loss -Rescued by cofilin inhibitor	-Impaired LTP -Rescued by cofilin inhibitor	-Impaired fear memory -Rescued by cofilin inhibitor	-Increased cofilin dephosphorylation by Aβ42 oligomers
Hou et al., 2012 STZ-model Rats	-Synapse loss -Rescued by ROCK inhibitor	N/A	-Impaired learning and memory -Rescued by ROCK inhibitor	-Increased level of p-LIMK2 and p-cofilin
Segura-Puimedon et al., 2014 WBS mice	-Reduced spine density	-Impaired LTP	-Enhanced sociability and visuospatial deficits	N/A
Hoogenraad et al., 2002 Clip2 KO mice	N/A	-Impaired LTP	-Impaired contextual fear memory	N/A
Fujiwara et al., 2006 HPC-1/syntaxin 1A KO mice	N/A	-Impaired LTP	-Impaired fear LTM	N/A
Gory-Fauré et al., 2021 MAP6 KO mice	-Reduced spine density -Rescued by LIMK1 inhibitor	-Impaired LTP -Rescued by LIMK1 inhibitor	N/A	N/A

[42][43][44][45]. In addition to ... e N-terminus [46][47]. LIM domains can bind to the C-terminal kinase domain and negatively regulate kinase activity [48]. The LIM and PDZ domains also likely affect LIMK function through protein–protein interactions [49]. LIMKs consist of two members, LIMK1 and LIMK2. Both are expressed in multiple tissues in mammals, with LIMK1 being the most abundant in neuronal tissues [42][50]. Studies have shown that LIMK1 is highly expressed within the hippocampus, a brain region critical for learning and memory [51]. Thus, LIMK1 has been the focus of multiple studies in the context of learning and memory. LIMKs are key ... actin reorganization [52][53][54][55][56] ... is important to note ... necessarily lead to the activation of LIMKs. The Rho GTPases regulate LIMKs activity through Rho kinases (ROCKs) and p-21 activated kinases (PAKs) [52][54][57][58]. Both ROCKs and PAKs can directly phosphorylate LIMKs at Thr 508/Thr 505 and increase their kinase activity. In addition to ROCKs and PAKs, protein kinase A (PKA) can also phosphorylate LIMK1 at Ser 323/596 and facilitate its kinase activity [59]. On the other hand, slingshot protein phosphatase (SSH) can directly dephosphorylate LIMKs at Thr 508 and reduce their kinase activity [60]. In addition to kinase activity, the protein level of ... nslation [61] and E3 ... [62] ... actin-depolymerizing ... [63][64] ... actin filaments, thus ... [65][66] ... entified transcription ... tein (CREB) [67] and Nurr1 [68]. In the case of CREB, which regulates the expression of numerous cyclic-AMP responsive genes by binding to the gene promoter cAMP-response elements, it was shown that the activation of LIMK1 by basic fibroblast growth factor in immortalized hippocampal progenitor cells led to increased CREB phosphorylation and CREB-responsive promoter activity [67]. Nurr1 is an orphan member of the nuclear receptor family that regulates gene transcription via hormone response elements [69]. Purification of Nurr1-binding proteins from immortalized mesencephalic neurons identified LIMK1 as a binding partner, and further analysis revealed that LIMK1 phosphorylated Nurr1 and reduced its transcriptional activity [68]. Therefore, although cofilin is the best characterized LIMK substrate, there are multiple pathways by which LIMKs exert their effects in neurons. This will be further discussed in later sections.

Experimental Model and Procedure	Spine Properties	Synaptic Function	Behaviour, Learning, and Memory	Mechanism
Pyronneau et al., 2017	-Increased immature spine density -Rescued by PAK inhibitor	-Reduced mEPSC frequency -Rescued by PAK inhibitor	-Impaired sensory processing -Rescued by PAK inhibitor	-Increased Rac1-PAK1-LIMK1-cofilin signaling -Rescued by PAK inhibitor
Emr1 KO mice				

g and colleagues in 2002, who generated global LIMK1 knockout (KO) mice by homologous recombination. Although these mice showed no changes in the gross anatomy of the CNS, including the hippocampus and cortex, where LIMK1 is highly expressed, LIMK1 KO neurons showed abnormalities in dendritic spines and the actin cytoskeleton [70]. LIMK1 KO hippocampal and cortical neurons had longer, thinner immature spines compared to wild type (e.g., 70–80% of KO spines had a head/neck ratio less than 2, whereas 70–80% of wild type spines had a ratio greater than 2). In addition, the amount of actin filaments in the spine head of LIMK1 KO neurons were reduced and not significantly greater than those of adjacent dendritic areas, as opposed to wild-type neurons where actin filaments were highly enriched in the spines [70]. These data suggest that LIMK1 is critical for the assembly of actin filaments within spines and that abnormalities in the actin cytoskeleton underlie the abnormal spine morphology in LIMK1 KO mice. This conclusion was supported by changes in the activity of cofilin in LIMK1 KO mice, where both basal and activity-dependent cofilin phosphorylation were reduced [70]. Consistent with the genetic study, recent studies using shRNA knockdown showed that LIMK1, specifically LIMK1 palmitoylation at Cys 7/8, plays an important role in actin turnover and spine regulation [71]. In this study, impairment in spine actin turnover was detected immediately following LIMK1 knockdown in hippocampal neurons. In addition, the chronic loss of LIMK1 resulted in spine elimination and reduced spine density by approximately 40%. Reintroduction of wild-type LIMK1, but not a palmitoylation-deficient mutant, rescued both actin turnover and spine density [71]. Although no changes in spine density were detected in LIMK1 KO mice, it is possible that compensatory mechanisms may have occurred in these mice. As discussed earlier, although LIMK1 and LIMK2 have different expression patterns and subcellular localization, they show significant structural and functional similarities, including protein domain organization and their ability to regulate actin dynamics through cofilin [44][72]. Indeed, it has been shown that LIMK1 and LIMK2 double KO mice had more severe deficits in cofilin phosphorylation and synaptic function than LIMK1 and LIMK2 single KO mice, suggesting that LIMK2 may be able to compensate for the loss of LIMK1 [73]. Further studies are needed to investigate this possibility.

In addition to its role in basal spine properties, LIMK1 is also required for the activity-dependent changes in dendritic spines [71]. The knockdown of LIMK1 induced by the focal activation of glutamate receptors using 2-photon (2P) uncaging of glutamate reduced dendritic spine enlargement by 20% [28][71][74]. LIMK1 palmitoylation was also shown to be required for this spine enlargement [71]. How LIMK1 regulates these spine changes during synaptic plasticity remains unknown; however, studies have suggested that the cofilin-dependent actin reorganization may play a key role. It has been shown that following glutamate uncaging, cofilin underwent spine translocation and this process appears to be regulated by cofilin phosphorylation [75][76]. Spine accumulation of cofilin and its subsequent effect on local actin filaments may reduce the density of membrane-proximal actin and triggers new membrane protrusions as shown in other systems [77]. Similarly, the activation of glutamate receptors has been shown to induce accumulation and stabilization of LIMK1 to the juxtamembrane of the dendritic spines through a palmitoylation-dependent mechanism [71].

Other evidence supporting the role of LIMK1 in spine regulation comes from manipulations of its upstream regulators, including PAKs, ROCKs, RhoA, and Rac1. For example, although PAK1 or PAK3 single KO mice showed no structural deficits in spines or synapses [78][79], PAK1/3 double KO mice featured longer, thinner spines similar to the ones detected in LIMK1 KO [70][80]. Similarly, studies using antisense and RNA interference to inhibit PAK3 activity revealed abnormalities in dendritic spines, with increased levels of filipodia-like protrusions by approximately 500% and immature spines in rat organotypic slice culture by more than 100% [81]. In addition, PAK2 heterozygous mice had a 30% reduction in spine density that was associated with reduced LIMK1 and cofilin phosphorylation as well as impaired actin polymerization in the cortex and the hippocampus [82]. Cortical neurons in the dominant-negative PAK1 transgenic mice exhibited approximately 20% fewer spines and an increase in the proportion of larger synapses [83] These data suggest that PAKs regulate dendritic spines through LIMK1-dependent mechanisms. Another LIMK1 activator, ROCK2, can also regulate dendritic spines through LIMK1 and cofilin. In one study, using cultured mouse hippocampal slices, neurons treated with the ROCK inhibitors Y-27632 were found to have longer spines (spine length increased by 50%), similar to spines detected in LIMK1 KO neurons [84]. ROCK2 KO mice had reduced synaptic density (by 30%), increased spine length (by 40%), and filipodia-like protrusions, and these spine abnormalities were associated with altered spine actin filaments and reduced cofilin phosphorylation [85].

Numerous studies have shown that the downstream effector of LIMKs, cofilin, is involved in both basal spine properties and spine plasticity [86]. For example, overexpression of a constitutively inactive form of cofilin in hippocampal cultures led to the formation of more mature spines and elevated spine density, whereas overexpression of a constitutively active form of cofilin induced the formation of immature spines [87]. In cofilin conditional KO mice, hippocampal neurons showed a small increase in synapse density (10%) and spine size (20%) [88], and these changes were more pronounced in actin-

depolymerization factor (ADF) and cofilin-1 double KO mice [89]. Therefore, the PAK/ROCK-LIMK1-cofilin signaling pathway may represent a key mechanism to regulate basal spine properties and activity-dependent spine plasticity. It is important to note that the results from the manipulations of LIMK1 upstream and downstream regulators only provided indirect evidence that suggests the involvement of LIMK1 in spine regulation. Further studies, such as LIMK1 rescue experiments, are needed to determine whether the effects of these proteins are mediated by LIMK1.

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