Annals of Pharmacology and Pharmaceutics

Review Article
Published: 19 Mar, 2020

The Critical Role of Complexion in Central Nervous System

Lan-Chun Zhang[1], Jia Liu[1], Liu-Lin Xiong[2] and Ting-Hua Wang[1,2,]**

[1]Department of Animal Zoology, Kunming Medical University, China

[2]Department of Anesthesiology, West China Medical Center, China

Abstract

Complexins, as key presynaptic proteins in the progress of fast synchronous neurotransmitter release, play crucial roles in membrane fusion reactions and operate by associating with trimeric SNARE complexes. CPLX I/II act differentially influence on cognitive function of central nervous system disease, which exposed disruption of inhibitory synaptic terminals to trigger early cognitive impairment. Phenotype and preliminary application of CPLX1 knockout have been construction and application in animals. Although, CPLX1 located in presynaptic often forms SNARE complex to perform the physiological function, while, abnormal levels of CPLX1 appearances in neurodegenerative and psychiatric disorders could exhibit disrupted neurobehaviors. The critical role of CPLX1 in CNS is needed to widely recognize and utilize in neurodegenerative and psychiatric disorders.

Introduction

Complexin I (CPLX I) was small presynaptic protein consisting of 134 amino acids, which belongs to the highly conserved complexin protein family. In the central nervous system, CPLX I encoding protein together with synaptobrevin, syntaxes, snap 25 and other related proteins to form SNARE complex, which is involved in anchoring, preexcitation and fusion of axon-terminal vesicles [1]. Here, we summarized the critical role of cplx-1 in Central Nervous System (CNS).

Functions and Mechanisms of Complexin I

Complexins function with SNARE complexes

Complexins, as key proteins in the progress of fast synchronous neurotransmitter release, play crucial roles in membrane fusion reactions and operate by associating with trimeric SNARE complexes consisting of vesicle protein synaptobrevin, plasma membrane proteins Syntaxin, and SNAP-25. Accessory α-helix of CPLX I can displace VAMP2 locally in the complexin–SNARE quaternary complex. The regularity between accessory a-helix and N-terminal domain might determine the final outcome of the complexin function, either stimulatory or inhibitory, when the N-terminal region of CPLX I removed, the accessory α-helix could lead the SNARE complex weaker [2]. Complexins were activated at presynaptic nerve terminals to regulate spontaneous SNARE-mediated Synaptic Vesicle (SV) fusion machinery, and enhance stimulated neurotransmitter release [3-5]. Neurotransmitter release was triggered by complexin regulating spontaneous and activating Ca^{2+}, SNAREs and other synaptic proteins were mediated in the central nervous system to utilize Ca^{2+}-triggered synaptic vesicle fusion for neurotransmitter release into the synaptic cleft. Complexins binding with SNARE complex to stabilize and clamp in a highly fusogenic state, and provide a pool of readily releasable synaptic vesicles that lead to a quickly and synchronously in response to active and increase expression of in Ca^{2+} intra-synaptic [6]. In addition, CPLX I played a dual role in regulating spontaneous mini release and in activating Ca^{2+}-triggered fusion, its C-terminal domain localized to the highly curved membrane of synaptic vesicles is substantial for moderating spontaneous release [7]. In the single molecule fluorescence resonance energy transfer experiments, CPLX I was found to induce a subtle change at the membrane-proximal C-terminal, which may lead to activation of synchronous neurotransmitter and spontaneous release [8]. Moreover, CPLX I plays a critical role of recruiting Ca^{2+} channels to docked vesicles in synaptic transmission during development at the calyx of Held synapse [9].

CPLX I/II were crucially implicated in neuronal synaptic regulation

CPLX I/II were largely localized in presynaptic nerve terminals of mature mammalian neurons,

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***Correspondence:**

Ting-Hua Wang, Department of Anesthesiology, Institute of Neurological Disease, Translational Neuroscience Center, West China Medical Center, Sichuan University, Chengdu, China; E-mail: wangtinghua@vip.163.com

Liu-Lin Xiong, Department of Anesthesiology, Institute of Neurological Disease, Translational Neuroscience Center, West China Medical Center, Sichuan University, Chengdu, China; E-mail: Nil

Received Date: *21 Feb 2020*

Accepted Date: *16 Mar 2020*

Published Date: *19 Mar 2020*

Citation:

Zhang L-C, Liu J, Xiong L-L, Wang T-H. The Critical Role of Complexion in Central Nervous System. Ann Pharmacol Pharm. 2020; 5(3): 1182.

GABAergic and glutamatergic terminals, while, the expression and distribution were quite different. CPLX I/II regulated the exocytosis of the contents of SSVs, and LDCVs, in PC12 cells. Over expression of CPLX I could reduce hGH and ACh release from PC12 cells [10]. In schizophrenia, CPLX levels were reported to be decreased, with a lower CPLX I/II ratio using in situ hybridization and immunovant radiography, which may lead to effect in excitatory or inhibitory neurotransmission, and altered in schizophrenia [11]. CPLX II was a candidate in sperm and expression was increased, while, CPLX I exist in the acrosomal region of sperm and was essential to acrosomal exocytosis and normal fertility [12]. In addition, it has been reported CPLX I/II were expressed to inhibit AMPA receptor exocytosis by NMDA-induced spine remodeling and were the targets of MiR 135 [13].

CPLX I/II act differentially influence on cognitive function of Alzheimer's disease, which exposed disruption of inhibitory synaptic terminals, may trigger early cognitive impairment, while excitatory terminal disruption may contribute relatively more to later cognitive impairment [14]. Significant expression variations of CPLX I in Behcet's disease and Neuro-Behcet's Disease (NBD) patients revealed that CPLX I has a proinflammatory action [15]. Perinatal exposure to alcohol (PEA) leads to general developmental and specific neuropsychiatric disturbances. PEA reduces the expression of CPLX I/II in CA1, together with other hippocampal and cortical regions. Suppression of CPLX I/II exposits disturbed synaptic plasticity and corresponds to ethanol-induced deficits of learning and memory [16]. Main disturbed synaptic transmission contributes to the pathophysiology of mood disorders. Postmortem studies reported reduce of CPLX I/II depression. Antidepressants could induce the expression levels of CPLX I/II, which provides a further validation of the LH model and players a key role in the pathophysiology of depression and tentative targets of antidepressants [17]. *Via* modulating synthesis and clearance of neurotransmitters, a small portion of antidepressant drugs, affect differentially the expression of CPLX I/II in rat hippocampus, and CPLX I were regulated only in habenular nuclei by fluoxetine, whereas, CPLX II was significantly induced by desipramine and tranylcypromine, but not fluoxetine [18].

CPLX I improves the on-rate of synaptic vesicle docking imitates containing full-length synaptotagmin-1 and neuronal SNAREs by simultaneous interactions among membrane-mimicking vesicles containing full-length syntaxin-1A and SNAP-25A [19]. CPLX I mRNA levels related to SNAP25 or Rab3A mRNA levels, and down-regulation of expression may be correspond to haloperidol-induced depolarization barrier of mesocorticolimbic dopamine neurons [20]. CPLX I expression increased progressively across development lead to complexin levels increase during synaptic maturation in human DLPFC, and appear an increase in the inhibitive effect on synapses relative to that of excitatory synapses occurs during progress in cortical region [21]. CPLX I could be causative of Intellectual Disability (ID), migrating epilepsy and structural brain abnormalities [22]. Parkinson's Disease (PD) is a customary neurodegenerative proceeding in old ages. The most specific known prodromal stage of general PD, only blood CPLX I levels were altered in rapid eye movement sleep behavior disorder, which revealed CPLX I was a PD risk factor and provide functional insights into the role and regulation of blood SNCA levels [23].

Phenotype and preliminary application of CPLX I knockout in animals

CPLX1 modulated neurotransmitter release and marketed as an inhibitor of synapses, respectively. The gene knock-out of complexins from mammalian neurons reduces neurotransmitter release, and regulated complexin levels in synaptic transmission were revealed to the etiology or pathogenesis of psychiatric and neurological diseases, including schizophrenia, Huntington's Disease (HD), Parkinson's Disease (PD), Alzheimer's Disease (AD), Traumatic Brain Injury (TBI), Depression, Bipolar Disorder (BP) [6]. CPLX I Expression levels changes of CPLX I in α/β-synuclein double knockout mice, is respond to pathogenic gain-of-function mutations of α-synuclein [24]. CPLX I knockout mice (CPLX $I^{-/-}$) exhibited a profound ataxia that deficits their ability to perform co-ordinate motor tasks in social transmission but appear to be cognitively normal [25]. Adult CPLX I knockout (CPLX $I^{-/-}$) mice remain severely ataxic and show deficits in exploration and emotional reactivity. CPLX I-/- mice in infancy clearly manifest marked abnormalities in sensory and motor development found could lead to develop schizophrenia in later life [26]. However, CPLX I gene knockout with rats reduces abnormal histomorphology of the stomach and intestine and down regulated dendritic branching in spinal motor neurons, causing different phenotypes [27].

Discussion

Neurotransmitter release was triggered by trimeric SNARE complexes including complexins, and mediated in the central nervous system to utilize Ca^{2+}-triggered synaptic vesicle fusion for neurotransmitter release into the synaptic cleft. CPLX I play a crucial roles in the progress of fast synchronous neurotransmitter release, accessory a-helix and N-terminal of CPLX I can make SNARE complexes weaker to regulate spontaneous release and activate Ca^{2+}-triggered fusion. Moreover, the expression and distribution of CPLX I/II were obviously different in presynaptic nerve terminals of mature mammalian neurons, although CPLX II was still a candidate of CPLX I, but CPLX I exist in the acrosomal region of sperm and was essential to acrosomal exocytosis and normal fertility. CPLX I was familiar to neurotransmitter release and marketed as an inhibitor of synapses, respectively. Changes of CPLX I levels revealed to the etiology or pathogenesis of psychiatric and neurological diseases, including schizophrenia, Huntington's Disease (HD), Parkinson's Disease (PD), Alzheimer's Disease (AD), Traumatic Brain Injury (TBI), Depression, Bipolar Disorder (BP). Nowadays, phenotype and preliminary application were investigated in CPLX I gene knockout animals. These confirmed CPLX I may play potential valuable in CNS after injury or disease and may be considered as a target for drug administration.

Conclusion

Together, CPLX I as an important small molecule protein located in presynaptic often forms SNARE complex in the central nervous system to perform the physiological function, while, abnormal levels of CPLX I appearances in neurodegenerative and psychiatric disorders could exhibit disrupted neurobehaviors. CPLX I as presynaptic protein associated the anchoring, pre-excitation, and fusion of axonal end vesicles, may lead to synaptic transmission disorder with abnormal regulation and it plays an essential pathophysiological mechanisms and therapeutic targets of nervous system disease including Parkinson's disease, Alzheimer's disease,

autism, schizophrenia, major depressive illness and bipolar disorder. In the future, research is needed to more control CPLX I to improve neurodegenerative and psychiatric disorders.

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