Review Article

14-3-3 Proteins in Glutamatergic Synapses

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Received 15 September 2017; Revised 13 March 2018; Accepted 27 March 2018; Published 23 April 2018

Academic Editor: Zygmunt Galdzicki

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The 14-3-3 proteins are a family of proteins that are highly expressed in the brain and particularly enriched at synapses. Evidence accumulated in the last two decades has implicated 14-3-3 proteins as an important regulator of synaptic transmission and plasticity. Here, we will review previous and more recent research that has helped us understand the roles of 14-3-3 proteins at glutamatergic synapses. A key challenge for the future is to delineate the 14-3-3-dependent molecular pathways involved in regulating synaptic functions.

1. Introduction

14-3-3 refers to a family of homologous proteins that consist of seven genetic loci or isoforms (β, γ, ε, η, α, ζ, and τ) in vertebrates. The name 14-3-3 was given based on the fraction number and migration position on DEAE-cellulose chromatography and subsequent starch-gel electrophoresis during its initial biochemical purification process [1]. 14-3-3 proteins exist as homo- or heterodimers, in which each 14-3-3 monomer shares a similar helical structure and forms a conserved concave amphipathic groove that binds to target proteins via specific phosphoserine/phosphothreonine-containing motifs [2–7]. Through protein-protein interactions, 14-3-3 functions by altering the conformation, stability, subcellular localization, or activity of its binding partners. To date, 14-3-3 proteins have been shown to interact with hundreds of proteins and are implicated in the regulation of a multitude of cellular processes [8, 9].

14-3-3 proteins are highly expressed in the brain, comprising ~1% of its total soluble proteins. Thus, it comes to no surprise that 14-3-3 proteins are involved in a variety of neuronal processes, such as neurite outgrowth, neural differentiation, migration and survival, ion channel regulation, receptor trafficking, and neurotransmitter release [10–12]. In addition, 14-3-3 proteins are genetically linked to several neurological disorders, including neurodegenerative diseases (e.g., Parkinson’s, Alzheimer’s, and Creutzfeldt-Jakob diseases), neurodevelopmental diseases (e.g., Lissencephaly), and neuropsychiatric disorders (e.g., schizophrenia and bipolar disorder) [13–15], thus making them a potential therapeutic target [16, 17]. In recent years, a number of small molecule 14-3-3 modulators have been discovered that could be used to either stabilize or inhibit 14-3-3 protein-protein interactions [18, 19]. However, as 14-3-3 proteins are involved in diverse cellular processes, it is highly desirable to further characterize and develop compounds that have enhanced isoform specificity as well as can selectively modulate the 14-3-3 interaction with a critical target in a particular pathway.

14-3-3 proteins are generally found in the cytoplasmic compartment of eukaryotic cells. In mature neurons, however, certain 14-3-3 isoforms are particularly enriched at synapses, suggesting their potential involvement in synaptic neurotransmissions and plasticity. In this review, we will discuss the functional role of 14-3-3 proteins in the regulation of glutamatergic synapses.

2. Functions of 14-3-3 at the Presynaptic Site

Early evidence that 14-3-3 might regulate synaptic transmission and plasticity came from genetic and functional studies of the fruit fly Drosophila. The gene leonardo encodes 14-3-
Ca^{2+} in a central role in neurotransmitter release by mediating ionic depolarization, thus markedly impacting the channels undergo cumulative inactivation after a brief, repetitive depolarization, thus markedly impacting the fidelity of synaptic transmission and short-term synaptic plasticity [35, 36]. 14-3-3 modulates inactivation properties of CaV2.2 channels through its direct binding to the channel pore-forming α1 subunit. In cultured rat hippocampal neurons, inhibition of 14-3-3 proteins in presynaptic neurons augments short-term depression, likely through promoting the closed-state inactivation of CaV2.2 channels (Figure 1) [37]. As 14-3-3 binding can be regulated by specific phosphorylation of the α1 subunit, this regulatory protein complex may provide a potential mechanism for phosphorylation-dependent regulation of short-term synaptic plasticity.

3. Functions of 14-3-3 at the Postsynaptic Site

The role of 14-3-3 at the postsynaptic site emerged more recently from the studies of various 14-3-3 mouse models. One of them, the 14-3-3 functional knockout (FKO) mice, was generated by transgenic expression of difopein (dimeric fourteen-three-three peptide inhibitor) that antagonizes the binding of 14-3-3 proteins to their endogenous partners in an isoform-independent manner, thereby disrupting 14-3-3 functions [38–41]. Transgene expression is driven by the neuronal-specific Thy-1 promoter which produces variable expression patterns in the brains of different founder lines, making it possible to assess the behavioral and synaptic alterations associated with expression of the 14-3-3 inhibitor in certain brain regions [42, 43]. Inhibition of 14-3-3 proteins in the hippocampus impairs associative learning and memory behaviors and suppresses long-term potentiation (LTP) at hippocampal CA3-CA1 synapses of the 14-3-3 FKO mice [41]. Through comparative analyses of two different founder lines with distinct transgene expression patterns in the subregions of the hippocampus, it was further determined that postsynaptic inhibition of 14-3-3 proteins may contribute to the impairments in LTP and cognitive behaviors. These observations thus revealed a postsynaptic function for 14-3-3 proteins in regulating long-term synaptic plasticity in mouse hippocampus.

What might be the molecular targets of 14-3-3 proteins at the postsynaptic site of hippocampal synapses? In the 14-3-3 FKO mice, there is a significant reduction of the NMDA receptor-mediated synaptic currents in CA1 pyramidal neurons which express the 14-3-3 inhibitor. Consistently, the level of NMDA receptors (NMDARs), particularly GluN1 and GluN2A subunits, is selectively reduced in the postsynaptic density (PSD) fraction of 14-3-3 FKO mice that exhibit deficits in cognitive behaviors and hippocampal LTP [41]. Considering the critical role that NMDARs play in mediating LTP at hippocampal CA3-CA1 synapses [44], 14-3-3 proteins likely exert their effects on postsynaptic sites through the regulation of NMDA receptors, either directly or indirectly (Figure 2).

NMDARs are heterotetramers composed of two obligatory GluN1 subunits and two regulatory subunits derived from GluN (GluN2A-2D) and GluN3 subunits [45, 46]. 14-3-3 is known to promote surface expression of NMDA receptors in cerebellar neurons through its interaction with PKB-phosphorylated GluN2C subunits [47]. A more recent study also showed that inhibiting endogenous 14-3-3 proteins...
using difopein greatly attenuate GluN2C surface expression in cultured hippocampal neurons [48]. However, it remains to be determined whether 14-3-3 proteins directly interact with other subunits of NMDAR and have similar effects on their surface expression. Alternatively, 14-3-3 might indirectly regulate the PSD level of NMDARs by modulating other critical steps of NMDAR synaptic trafficking, such as dendritic transport and synaptic localization [45, 49]. Therefore, further studies are needed to better understand the exact mechanism underlying 14-3-3 proteins’ regulation of NMDA receptors. Interestingly, the synaptic level of certain 14-3-3 isoforms is reduced in GluN1 knockdown mice, but not by subchronic administration of an NMDAR antagonist in wild-type mice [50]. It raises a possibility that a reciprocal regulation between 14-3-3 and NMDARs may take place at the postsynaptic site.

14-3-3 proteins also modulate other glutamate receptors at the postsynaptic membrane. For example, 14-3-3 interacts with GluK2a, a subunit of the kainate receptor (KAR) that mediates postsynaptic transmission, synaptic plasticity, and neuronal excitability [51]. 14-3-3 binding slows desensitization kinetics of GluK2a-containing KARs. In 14-3-3 FKO mice, expression of the 14-3-3 inhibitor in CA3 neurons leads to a faster decay of KAR-EPSCs at hippocampal mossy fiber-CA3 synapses [52]. This study provides another potential mechanism by which 14-3-3 proteins regulate synaptic functions at the postsynaptic site.

In addition to modulating the level and biophysical properties of postsynaptic glutamate receptors, 14-3-3 functions by regulating synaptogenesis. In the 14-3-3 FKO mice, there is a reduction of both dendritic complexity and spine density in the cortical and hippocampal neurons where the 14-3-3 inhibitor is extensively expressed [53]. A similar reduction in dendritic spine density was observed in 14-3-3ζ-deficient mice in BALB/c background [54, 55]. On the contrary, over-expressing 14-3-3ζ in rat hippocampal neurons significantly increases spine density [56]. Collectively, studies on these animal models provide in vivo evidence for a significant role of 14-3-3 proteins in promoting the formation and maturation of dendritic spines.

While the molecular mechanism for 14-3-3 dependent regulation of synaptogenesis remains elusive, several in vitro studies have proposed 14-3-3 proteins as important regulators of cytoskeleton and actin dynamics, which are critical for controlling the shape, organization, and maintenance of dendritic spines in postsynaptic neurons [57, 58]. Earlier studies showed that 14-3-3ζ regulates actin dynamics through its direct interaction with phosphorylated coflin (p-cofilin) [57]. Cofilin is a major actin depolymerizing factor. Reduction of p-cofilin enhances

**Figure 1:** 14-3-3 regulates presynaptic short-term plasticity by modulating CaV2.2 channel properties. 14-3-3 binding reduces cumulative inactivation of CaV2.2 channels and sustains Ca²⁺ influx and neurotransmitter release (a). Inhibition of 14-3-3 accelerates CaV2.2 channel inactivation and enhances short-term synaptic depression (b).
the activity of coflin, promotes the turnover of actin filaments, and consequently destabilizes dendritic spines [55, 56]. Moreover, a different group identified coflin and its regulatory kinase LIM-kinase 1 (LIMK1) as binding partners of 14-3-3ζ and suggested that interactions with the C-terminal region of 14-3-3ζ inhibit the binding of coflin to F-actin [59]. However, a direct interaction between 14-3-3 and coflin/p-cof lin was challenged by a later study, in which Sudnitsyna et al. demonstrated that 14-3-3 only weakly interacts with coflin, and they suggested that 14-3-3 proteins most likely regulate actin dynamics through other regulatory kinases such as LIMK1 or slingshot 1L phosphatase (SSH) [60]. In fact, 14-3-3ζ has been shown to directly bind with phosphorylated SSH and lower its ability to bind F-actin [58]. More recently, Toyo-oka et al. showed that 14-3-3ε and 14-3-3ζ bind to δ-catenin and potentially regulate actin dynamics through δ-catenin [11, 61]. Catenin activates the Rho family of GTPase that results in the phosphorylation and activation of LIMK1. Loss of 14-3-3 proteins results in stabilization of δ-catenin through the ubiquitin-proteasome system, thereby decreasing LIMK1 activity and reducing p-cof lin level. Therefore, it is possible that 14-3-3 proteins may promote F-actin formation and spinogenesis by interacting with multiple elements in the regulatory pathways of the actin polymerization/depolymerization cycles (Figure 2).

4. Conclusion

The glutamatergic synapses mediate the majority of excitatory neurotransmission in the mammalian brain. Regulation of the property and connectivity of glutamatergic synapses represents a major mechanism for activity-dependent modification of synaptic strength and is critical for higher brain functions. 14-3-3 proteins have emerged as one of the important modulators at these synapses. It is particularly interesting that 14-3-3 binding and function are generally regulated by phosphorylation, which is a well-established molecular process underlying synaptic plasticity. Thus, 14-3-3 can potentially integrate multiple signaling pathways and plays a significant role in dynamic modification of glutamatergic synapses. As demonstrated by recent animal models, 14-3-3 deficiencies in rodent brain often result in the onset of abnormal behaviors, which might correspond to symptoms of neurological disorders.

Abbreviations

NMJ: Neuromuscular junction
EJCs: Excitatory junctional currents
EPSCs: Excitatory postsynaptic currents
PTP: Posttetanic potentiation
LTP: Long-term potentiation
difopein: Dimeric fourteen-three-three peptide inhibitor
The authors declare no conflicts of interest.

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