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Review Article

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Spinal Stargazin-Mediated Cross-Talk of AMPA/NMDA Receptors in Chronic Pain

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Introduction

Chronic pain resulting from a variety of health conditions is the primary reason people seek medical care; yet current therapies either are inadequate or cause intolerable side effects [1-8]. Understanding cellular and molecular processes that lead to the initiation and maintenance of chronic pain will provide substantial promise for the development of more effective and specific pain therapies. Chronic pain is an expression of neuronal plasticity. One component of the plasticity is that the afferent input generated by injury and intense noxious stimuli triggers an increased excitability of nociceptive neurons in the spinal cord. Glutamate is the principal excitatory amino acid neurotransmitter within the mammalian nervous system. As such, it is involved in synaptic transmission within the spinal cord, including the processing of nociceptive information [9]. It has been established that *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and metabotropic glutamate receptors play different roles in spinal cord nociceptive processing [10-13]. Considerable evidence has demonstrated that the development of spinal hyperexcitability and persistent pain involves activation of NMDA and AMPA receptors and that NMDA receptor or AMPA receptor blockade has an antinociceptive effect on chronic pain [14-25].

Stargazin (STG), also named γ-2, is a 36-kDa transmembrane protein with structural similarity to the γ subunit of skeletal muscle voltage-gated calcium channels and is encoded by *Cacng2*, a gene discovered in 1998 [26]. STG is the first transmembrane protein known to associate with AMPA receptors and regulate their synaptic targeting and recycling, specifically by delivering them to the surface membrane of postsynaptic neurons [27-31]. The synaptic clustering of AMPA receptors relies on interaction of the cytoplasmic tail of STG with a PDZ domain from the postsynaptic density protein PSD-95 [32]. Furthermore, several laboratories have demonstrated that STG directly modulates AMPA receptor function by influencing AMPA receptor channel activities and properties [33-37]. In addition, synaptic NMDA receptor activity can induce both STG phosphorylation [by activation of calcium/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC)] and STG dephosphorylation (by activation of protein phosphatase PP1 and PP2B) [38]. Phosphorylation of the STG PDZ ligand can disrupt STG interaction with NMDA receptor binding protein PSD-95 and thereby regulate synaptic AMPA receptor function [39,40]. Therefore, STG and its phosphorylation regulate the activities of AMPA/NMDA receptors at synapses of the central nervous system (CNS) and may be involved in the mechanisms of chronic pain.

STG Phosphorylation/Dephosphorylation and NMDA -Induced AMPA Receptor Trafficking

Studies from Dr. David Bredt's laboratory [38] have shown that synaptic STG is heavily phosphorylated at a set of conserved serine residues in its cytoplasmic carboxy-terminal tail. The extent of these phosphorylations is dynamically regulated by synaptic activity such that activation of CaMKII and PKC induces phosphorylation, whereas activation of protein phosphatase PP1 and PP2B leads to dephosphorylation of these sites. Phosphorylation facilitates synaptic trafficking of STG in a fashion dependent on the binding of the carboxy-terminal tail of STG to PDZ domains from PSD-95. This STG phosphorylation promotes synaptic trafficking of AMPA receptors. Bredt's group also found that treating cultured cortical and hippocampal neurons with NMDA vastly accelerated the dephosphorylation of STG in both time- and dose-dependent manners and that within 2 h of removing NMDA, the phosphorylation of STG recovered [38]. This NMDA-mediated STG dephosphorylation is entirely dependent on extracellular calcium and PP1 and is partly blocked by inhibiting PP2B; the recovery of STG phosphorylation after NMDA removal is via activation of CaMKII and PKC. In addition, Western blot analysis with phospho-STG-specific antibody indicates that the critical threonine within the STG PDZ binding site is phosphorylated by PKA [39,40]. This phosphorylation disrupts STG interaction and clustering with PSD-95 in transfected COS-7 cells [39]. A STG construct with a Thr-to-Glu mutation that mimics phosphorylation fails to cluster at synaptic spines and down-regulates synaptic AMPA receptor function in cultured hippocampal neurons [39]. Phosphorylation of the PDZ-binding site in STG by PKA may induce AMPA receptor internalization [39,40].

Synaptic NMDA receptor activity can induce both STG phosphorylation and dephosphorylation. Synaptic trafficking of AMPA receptors by STG phosphorylation requires the STG PDZ binding site to interact with PSD-95. In contrast to the roles for intracellular second messengers downstream of NMDA receptors, previous studies have shown that NMDA stimulation may induce AMPA receptor internalization [41] and subsequent degradation [41]. NMDA stimulation directly induces AMPA receptor dissociation from STG [27], which may explain receptor degradation [41]. These effects do not appear to require traditional ion channel activation or second messengers but rather result from agonist-mediated allosteric changes in AMPA receptor conformation. Consistent with this, structural studies indicate that agonist, but not antagonist, binding causes a large conformational change in AMPA receptors [42]. These emerging modes for agonist-mediated internalization of glutamate receptors provide mechanisms for highly localized plasticity of the synaptic membrane.

STG-Mediated Functional Linkage of AMPA/NMDA Receptors in the CNS

STG is CNS-specific and, like other neuronal calcium channel subunits, is enriched in synaptic plasma membranes. Immature

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or reduced synaptic transmission at parallel fiber–Purkinje cell synapses, Golgi cell–granule cell synapses, and mossy fiber–granule cell synapses has also been reported in STG mutant mice [43,44], suggesting a crucial role of the STG protein for normal synaptic transmission.

AMPA receptors, consisting of various combinations of the glutamate receptor subunits 1–4 (GluA1–4) [45], mediate the majority of fast excitatory synaptic transmission in the CNS. They recycle rapidly at the plasma membrane and contribute to the overall synaptic plasticity of the neuronal circuitry [41,46-52]. STG protein is essential for the trafficking of AMPA receptors from the Golgi complex to the plasma membrane and is required for the ultimate targeting of the receptors to the postsynaptic membrane [29]. STG's critical binding and trafficking domains that are involved in the migration of the AMPA receptors to the plasma membrane include the first extracellular loop and the intracellular carboxy terminus [27]. The final amino acids, trp-trp-pro-val (TTPV), which comprise a PDZ ligand at the carboxy tail of STG, are essential for the subsequent binding of postsynaptic proteins, such as PSD-95, to target the entire complex to its active site at the postsynaptic membrane [29,32,53]. Additionally, *in vitro* studies have revealed that STG binding enhances glutamate-induced currents at the synapse [33]. STG and other closely related members of the γ subunit family, including γ-3, γ-4 and γ-8, share a high degree of amino acid conservation, including the TTPV motif. These four proteins are referred to as transmembrane AMPA-receptor regulatory proteins (TARPs), and all can promote expression of functional AMPA receptors at the postsynaptic membrane [28]. TARP members associate independently with AMPA receptors and co-cluster with the receptors at the postsynaptic sites. Sharp et al. [54] have provided evidence that STG complexes with GluA1 *in vivo*. This has been confirmed and expanded upon by Tomita et al. [28] to include GluA2 and GluA4.

STG has two distinct roles in controlling AMPA receptor function. First, STG regulates delivery of AMPA receptors to the membrane surface, a function that does not require the PDZ-binding domain. Second, STG mediates synaptic targeting of AMPA receptors and this function does require the PDZ-binding carboxy terminus [29], which can interact with PSD-95. The PDZ-binding ligand is critical for STG and AMPA receptor synaptic clustering and function [55], as evidenced by the fact that synaptic AMPA receptors can be rescued in STG mutant granule cells by transfection with constructs coding for STG but not by transfection with STG lacking the carboxy-terminal PDZ-binding ligand [39]. In addition, PSD-95, a molecular scaffolding protein, has been shown to attach NMDA receptors to internal signaling molecules at neuronal synapses [56,57] and has been demonstrated to be involved in the central mechanism of chronic pain [58-60]. STG is a critical link because it interacts with AMPA receptors via one domain and with the NMDA receptor binding protein PSD-95 at another site [28,29,32] (Figure 1). Therefore, it is reasonable to postulate that there is a STG-mediated functional link between AMPA receptors and NMDA receptors at synapses. Much interest and research have gone into the concept that NMDA receptors and AMPA receptors couple at excitatory synapses since the "silent synapse" theory of synaptic plasticity was proposed in 1995 [61,62]. This theory requires a regulated coupling between NMDA receptors and AMPA receptors on dendritic spines. The use of dominant-negative mutants of GluA2 has shown that the synaptic targeting of NMDA receptors is dependent on the presence of synaptic AMPA receptors and that synaptic AMPA receptors and

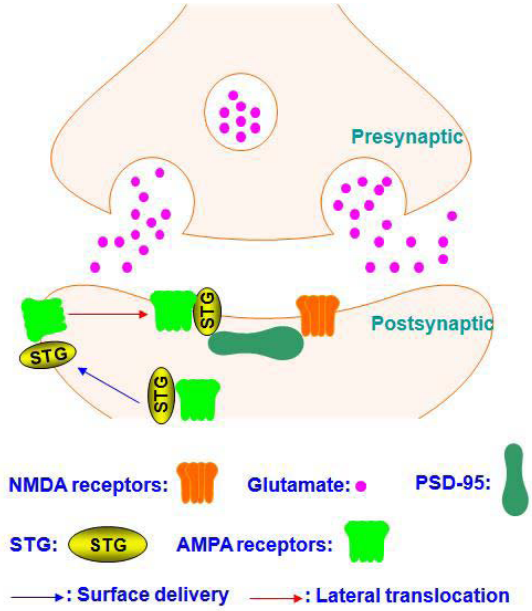

Figure 1: STG-mediated functional linkage between AMPA receptors and NMDA receptors at synapses. STG interacts with AMPA receptors in an intracellular compartment and promotes surface delivery of the interaction partners. By interacting with NMDA receptor-binding protein PSD-95, STG mediates lateral translocation of the STG-AMPA receptor complex to postsynaptic sites.

NMDA receptors are linked by STG and PSD-95 [63]. This system of AMPA receptor-dependent synaptic NMDA receptor localization exists in spinal neurons and hippocampal interneurons [63].

Conclusion

Our previous study has demonstrated that STG is expressed in the spinal dorsal horn and that STG interacts and co-localizes with AMPA receptors and NMDA receptor binding protein PSD-95 in the spinal dorsal horn [64]. A new role for STG in central sensitization of inflammatory pain has been found by interacting with AMPA receptors in the spinal cord [64]. A recent study [65] has indicated that susceptibility to chronic pain following nerve injury is genetically affected by *Cacng2*. Human *Cacng2* polymorphisms are associated with chronic pain in a cohort of cancer patients who underwent breast surgery [65]. These results suggest that spinal STG-mediated regulation of AMPA/NMDA receptors might serve as one of the spinal mechanisms for chronic pain processing. To define this possibility, we may investigate changes in STG and its phosphorylation in the spinal cord, surface expression and synaptic targeting of AMPA receptors in the spinal neurons, as well as AMPA receptor-mediated excitatory sensory synaptic transmission in the spinal dorsal horn neurons after chronic pain. We may also investigate the effect of expression of STG phosphorylation-mimic mutants on NMDA-induced AMPA receptor internalization and membrane trafficking in the spinal neurons as well as the effect of spinal over expression of dominant positive or negative mutants of STG phosphorylation targets on chronic pain behaviors. These studies could define the functional activities of spinal STG in chronic pain states and will determine the role of spinal STG-mediated cross-talk of AMPA/NMDA receptors in chronic pain. Therefore, STG could be a new target for development of a novel therapy for chronic pain. For

instance, STG antisense-mediated specific knockdown strategy, as we used in our previous study [64], might be employed to develop a new pain killer for clinical pain management.

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