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Review

MAGUK proteins: New targets for pharmacological intervention in the glutamatergic synapse

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Abstract

In the postsynaptic density of excitatory glutamatergic synapses, membrane associated guanylate kinase (MAGUK) proteins, such as Post-Synaptic Density 95 (PSD-95), organize ionotropic glutamate receptors and their associated signalling proteins regulating the strength of synaptic activity. Modifications of MAGUK proteins function in the glutamatergic synapse such as alterations of MAGUK proteins interaction with N-Methyl-D-Aspartate (NMDA) receptors regulatory subunits are common events in several neurodegenerative disorders. Thus, a better knowledge and understanding of MAGUK structure and function as well as of the molecular events regulating MAGUK-mediated interactions in the glutamatergic synapse could lead to the identification of new targets for pharmaceutical intervention for neurodegenerative diseases.

Keywords: Neurodegenerative disorders; Glutamate; Postsynaptic density; Scaffolding proteins

Contents

1. Structure and function of membrane associated guanylate kinase (MAGUK) proteins

Excitotoxicity is thought to be a major mechanism in many human disease states such as ischemia, trauma, epilepsy and chronic neurodegenerative disorders. Briefly, synaptic over-activity leads to the excessive release of glutamate that activates postsynaptic cell membrane receptors, which, upon activation, open their associated ion channel pore to produce ion influx. To date, although molecular basis of glutamate toxicity remain uncertain, there is general agreement that N-methyl-D-aspartate (NMDA) subtype of ionotropic glutamate receptors plays a key role in mediating at least some aspects of glutamate neurotoxicity (Sattler and Tymianski, 2001; Lynch and Guttmann, 2002). On this view, research has focused on the discovery of new

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compounds able to reduce either glutamate release or activation of postsynaptic NMDA receptors (Kemp and McKernan, 2002). Non selective NMDA receptor antagonists are effective in many experimental animal models of disease, and some of these compounds have entered clinical trials. Although NMDA receptor antagonists prevent excitotoxicity in cellular and animal models, these drugs have limited clinical usefulness (Kemp and McKernan, 2002). In particular, side effects such as psychosis, nausea, vomiting, memory impairment and neuronal cell death accompany complete NMDA receptor blockade, emphasizing the crucial role of the NMDA receptor in normal neuronal processes. On this view, the initial enthusiasm for this approach has waned, even if well-tolerated compounds, such as memantine, have been shown to be able to block excitotoxic cell death in a clinically tolerated manner (Lipton, 2005).

More recently, the concept that the exact signalling pathways downstream NMDA receptor activation could represent a key variable element as well as a new pharmacological target for different neurological disorders has been put forward. Variations in NMDA receptor complex composition in the postsynaptic compartment could represent an important process in neurodegenerative disorders, for both the mechanisms involved in cell death and the application of specific therapies. In this view, the discovery of the molecular mechanisms regulating the abundance of synaptic NMDA receptors is essential to understand how synaptic plasticity and excitotoxicity events are regulated.

Several studies in the last decade have clearly shown that NMDA receptors' synaptic localization and binding to scaffolding proteins, such as membrane-associated guanylate kinase (MAGUK) family, play a major role in the control of downstream signals resulting from receptor activation (Lau and Zukin, 2007; Elias and Nicoll, 2007). MAGUK proteins belong to a family of synaptic proteins homologous to the product of the Drosophila gene *Disc Large* and include: Post-Synaptic Density 95 (PSD-95), Synapse Associated Protein 97 (SAP97), chapsyn-110/PSD-93 and SAP102. This family of proteins is characterised by the presence of three association domains, called PDZ domains in virtue of the fact that similar domains are found in postsynaptic density (PSD) proteins, in Drosophila Discs Large and in ZO-1, by an epithelial tight junction protein, an src-homology-3 domain (SH3) and by an enzymatically inactive guanylate kinase-like (GK) domain (Kim and Sheng, 2004).

Each member of MAGUK protein family is distributed differently in the brain cell compartments. PSD-95 and PSD-93 are highly enriched in the PSD, especially due to their high palmitoylation degree (El-Husseini et al., 2000). SAP102 and SAP97 are found in dendrites and axons and are abundant in the cytoplasm as well as at synapses. Not only MAGUK proteins have a different subcellular localization, they are also expressed in different stages of life: SAP102 is highly expressed in early postnatal development, whereas PSD-95 and PSD-93 predominate at later stages (Kim and Sheng, 2004).

Although they show similar specificities of protein interaction *in vitro*, MAGUK family members interact with different (but overlapping) sets of proteins *in vivo*. The COOH-terminal cytoplasmic tails of NR2 subunits of NMDA receptor directly interact, at least *in vitro*, with PDZ domains of all members of the MAGUK family (Kim and Sheng, 2004). In particular, the last three amino acids of the carboxyl termini of NR2A and NR2B subunits have a C-terminal consensus motif threonine/serine-X-valine (T/SXV, where X is any amino acid) that has been demonstrated to be responsible for efficient binding to PDZ domains of MAGUK protein members such as PSD-95 (Niethammer et al., 1996). PSD-95, in turn, binds to the amino terminal of neuronal nitric oxide synthase (nNOS), a Ca^{2+}-activated form of nitric oxide synthase (NOS), through its PDZ domain. Therefore, PSD-95 may concentrate nNOS near the NMDA receptor at postsynaptic sites in neurons (Christopherson et al., 1999) thereby connecting NMDA receptors to specific signal transduction pathways (Kennedy, 2000). On the other hand, the interaction with SAP97 appears to be more relevant for processing alpha-amino-3-hydroxy-5-methyl-4- isoxazole propionic acid (AMPA) receptor subunits (Rumbaugh et al., 2003; Mauceri et al., 2004) and NR2A subunits of NMDA receptors (Mauceri et al., 2007), whereas SAP102 is crucial for driving NR2B complexes to spines (Sans et al., 2003).

Of relevance, modifications of MAGUK protein function in the glutamatergic synapse have been recently described in several neurological disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Ischemia, Schizophrenia and neuropathic pain. In particular, modifications of MAGUK proteins interactions with NMDA receptors regulatory subunits are a common event in several neurodegenerative disorders (Gardoni et al., 2006; Aarts et al., 2002). Thus, a better knowledge and understanding of MAGUK structure and function as well as of the molecular events regulating MAGUK-mediated interactions in the glutamatergic synapse could lead to the identification of new targets for pharmaceutical intervention in neurodegenerative disorders.

2. Role of MAGUK proteins in the pathogenesis of Alzheimer's Disease

In the last few years, a number of observations reported a close relationship between cognitive impairment and synaptic failure within cortex and hippocampus of Alzheimer's Disease patients (DeKosky and Scheff, 1990; Bertoni-Freddari et al., 1996). Furthermore, data obtained in Alzheimer's Disease brains and amyloid precursor protein (APP) transgenic mice revealed that synaptic dysfunction is an early event preceding physical deterioration of neuronal structures (Oddo et al., 2003; Palop et al., 2003). Although deficits in numerous neurotransmitters accrue as the disease progresses, the early symptoms appear to correlate with dysfunction of cholinergic and glutamatergic synapses (Selkoe, 2002). In particular, alterations of glutamatergic synapses have been shown to be one of the earliest events in the initiation of the cognitive decline in Alzheimer's Disease and have long been considered the best pathological correlate of cognitive decline in Alzheimer's Disease (Coleman and Yao, 2003). In addition, although a clear dysfunction of nerve terminal has been reported (Hsia et al., 1999), preferential loss of postsynaptic compared with presynaptic elements in Alzheimer's Disease has been suggested based on decreases in drebrin, a postsynaptic actin-binding protein (Harigaya et al., 1996; Shim and Lubec, 2002).

More recently, a specific role for MAGUK proteins in Alzheimer's Disease has been clearly put forward. As first, PSD-95 has been shown to be decreased in Alzheimer's Disease synaptosomes and this is confirmed by the observation that PSD-95 decreases greater than synaptophysin in APPsw (Tg2576) transgenic mice56 and in Alzheimer's Disease temporal cortex (Gylys et al., 2004). In addition, it is notable that using confocal double-label immunofluorescence, it has been clearly demonstrated that synthetic Aβ-derived diffusible ligands establish a very high colocalization degree with PSD-95. However, PSD-95 is not probably the most important MAGUK member involved in Alzheimer's Disease (Lacor et al., 2004). In fact, modifications of SAP97 function have been put forward as a key element in Alzheimer's Disease pathogenesis. First of all, few years ago, Nawa and co-workers reported a disturbance of SAP97/GluR1 interaction in Alzheimer's Disease brain (Wakabayashi et al., 1999), suggesting a defect in trafficking and functioning of SAP97 in the course of the disease. More relevant, very recent data of our group show that SAP97 is responsible for driving ADAM10 (alpha-secretase) to the postsynaptic membrane (Marcello et al., 2007). This event, primed by NMDA receptor activation, is mandatory for a physiological ADAM10 activity on APP. Intriguingly, ADAM10/SAP97 interaction positively modulates APP metabolism toward non-amyloidogenic processing. On the other hand, perturbing ADAM10/SAP97 interaction *in vivo* leads to a shifting of APP metabolism toward amyloidogenic products. Whether this mechanism entails a disturbance in the structural organization and the function of the glutamatergic synapse has still to be demonstrated, even if it is generally accepted that this synaptic circuitry is a target for toxic action of Aß oligomers. In fact, Aß oligomers inhibit (Walsh et al., 2002; Wang et al., 2002) and disrupt normal expression of a synaptic immediate early gene essential for long-term memory formation (Lacor et al., 2004). Thus, SAP97 can work as a bridge between key elements of the primary pathogenic events of Alzheimer's Disease, such as ADAM10, and key elements of the secondary pathogenic events, such as the glutamatergic synaptic dysfunction, adding new pieces to the puzzle in the understanding of the complex and coordinated events leading to Alzheimer's Disease pathogenesis.

3. Interaction between NMDA receptor subunits and MAGUK in L-DOPA Induced Dyskinesia

The main pathological feature of Parkinson's disease is the degeneration of dopamine-containing nigrostriatal neurons leading to the motor symptoms observed in this disorder. Accordingly, pharmacological dopamine replacement with L-3,4-dihydroxyphenylalanine (L-DOPA) represents the most effective treatment of Parkinson's disease. In addition to its dopaminergic projections, the striatum also receives a massive glutamatergic innervation arising from most cortical areas, conveying sensorimotor, limbic, and cognitive information (Calabresi et al., 1996). The NMDA receptor complex has been shown to be altered in both experimental parkinsonism and Parkinson's disease in humans (Calabresi et al., 2000; Dunah and Standaert, 2001). Moreover, NMDA receptor antagonists exert a beneficial effect in this disorder (Papa and Chase, 1996; Vila et al., 1999).

At the molecular level, it has become increasingly evident that the NMDA receptor complex is intimately involved in the regulation of corticostriatal long-term potentiation (Calabresi et al., 1996), which is altered in experimental parkinsonism (Menegoz et al., 1995; Ulas and Cotman, 1996; Ingham et al., 1998; Dunah et al., 2000). Recent observations show an altered assembly of PSD-95 and alphaCaMKII to NR2A–NR2B subunits of the NMDA receptor in the dopamine-denervated striatum compared with the contralateral side (Picconi et al., 2004). Indeed, increased alphaCaMKII binding to NR2A–NR2B paralleled by a reduced association of PSD-95 has been described providing support for a pathophysiological role of disturbed interactions between NMDA receptor associated proteins in experimental parkinsonism.

Abnormal function of NMDA receptor has been suggested to be correlated also with the development of L-DOPA-induced dyskinesia. In particular, subcellular redistribution of NR2B subunits of NMDA receptor from synaptic to extrasynaptic sites has been described as a key element in the complex modifications of the glutamatergic synapse in L-DOPA-induced dyskinesia (Gardoni et al., 2006). Interestingly, no alteration of NR2B synaptic localization has been found in L-DOPA treated non-dyskinetic animals. Of relevance, these events are paralleled, and most probably triggered, by profound modifications of NMDA receptor NR2B subunit association with members of the MAGUK protein family, in particular with SAP97 and SAP102 (Gardoni et al., 2006). Finally, the use of a synthetic peptide (TAT-NR2B C-tail), able to affect the normal synaptic localization of NR2B subunit by disrupting the interaction of this subunit with MAGUK proteins, is sufficient to induce a dyskinetic motor behaviour in L-DOPA treated non-dyskinetic animals (Gardoni et al., 2006).

On the other hand, another group recently reported that experimental Parkinsonism in rats appears to be associated with decreased synaptic membrane localization and increased vesicular localization of PSD-95 and SAP97 (Nash et al., 2005). In contrast, L-DOPA induced dyskinesia is associated with increased total levels of PSD-95 and SAP97, reflecting an increase at the synaptic membrane, whereas vesicular levels of both proteins are decreased. But in topography PSD-95 and SAP97 behaved differently. While PSD-95 mRNA levels were elevated homogenously across the striatum after repeated L-DOPA treatment within the 6-hydroxydopamine (6-OHDA) lesioned striatum, elevation of SAP97 mRNA was restricted to the dorsal caudate-putamen and nucleus accumbens (Nash et al., 2005). Even if there are apparent discrepancies between the two studies, probably related to the different lesioning paradigms and L-DOPA treatment used, they both confirm a central role for MAGUK proteins in modulating NMDA receptor function in experimental parkinsonism as well as in L-DOPA induced dyskinesia.

4. Modulation of PSD-95 interaction with NR2B subunit as possible stroke treatment

Neuronal injury caused by cerebral ischemia is believed to be mediated by excessive activation of glutamate receptors. Most of the studies focused on ischemia-induced changes in NMDA

receptor complex in the postsynaptic density structure because of its temporal and spatial proximity to the initial events, which occur after an ischemic challenge. Changes in the composition and morphology of forebrain postsynaptic density have been reported to occur after an ischemic challenge. In addition, molecular interactions involving PSD-95 are modified by an ischemic challenge, in the most vulnerable CA1 region of the hippocampus. Ischemia also resulted in a decrease in the size of protein complexes containing PSD-95, but had only a small effect on the size distribution of complexes containing the NMDA receptor, indicating that molecular interactions involving PSD-95 and the NMDA receptor are modified by an ischemic challenge (Takagi et al., 1999). Cerebral ischemia differentially affects also the association of different tyrosine kinase with the postsynaptic compartment: the level of PSD-associated PYK2 and trkB increased during the ischemic episode whether focal adhesion kinase (FAK) levels decreased. Src and Fyn levels appear increased with a short delay after reperfusion. In addition, transient cerebral ischemia increases tyrosine phosphorylation of NMDA receptor subunits NR2A and NR2B, but has no effect on the amounts of individual NMDA receptor subunits in the postsynaptic density. The ischemia-induced increase in the interaction of NR2A and NR2B with the SH2 domains of Src and Fyn suggests a possible mechanism for the recruitment of signalling proteins to the synapse and may contribute to altered signal transduction in the post-ischemic hippocampus.

Of great relevance, recent studies suggested to treat stroke transducing neurons with peptides able to disrupt the interaction of NMDA receptor NR2B subunits with the postsynaptic density protein PSD-95 (Aarts et al., 2002). This procedure dissociated NMDA receptors from downstream neurotoxic signalling without blocking synaptic activity or calcium influx and protected cultured neurons from excitotoxicity, reducing focal ischemic brain damage in rats, and improved their neurological function. This approach circumvents the negative consequences associated with blocking NMDA receptors and may constitute a practical stroke therapy.

5. Involvement of synaptic MAGUK proteins in chronic pain

Chronic pain is a complex disease that is often poorly managed by current drugs, particularly the neuropathic pain caused by injury to the peripheral or central nervous system. Even if antagonists of NMDA receptors have emerged as potential drugs for pain management, the initial enthusiasm for this approach has waned, because the therapeutic ratio for most NMDA antagonists is poor thus limiting their utility.

Recently, two members of the MAGUK protein family, PSD-95 and PSD-93, have been mainly involved in the modulation of neuropathic pain. Two recent studies performed using both knockdown and genetic mutant or knockout techniques have examined PSD-95 and PSD-93 role in neuropathic pain, and have shown the importance of NMDA-receptor–MAGUK interactions in chronic pain (Garry et al., 2003; Tao et al., 2003). Genetic deficiency of PSD-93 member of MAGUK family not only reduces NMDA receptor dependent synaptic function but also associated persistent pain by direct modification of NMDA receptor subunits surface expression (Tao et al., 2003). In particular, genetic deletion of PSD-93 resulted in the reduction of surface NR2A and NR2B expression with a concomitant reduction of NMDA receptor -mediated EPSCs in spinal dorsal horn neurons (Tao et al., 2003). Moreover, PSD-93 knock-out mice exhibited blunted NMDAR-mediated excitatory postsynaptic responses and dependent persistent pain. On the other hand, mutant mice expressing PSD-95 terminated after the first two PDZ domains completely lack the reflex sensitization to light mechanical stimuli that is expected following sensory sciatic nerve injury (neuropathic pain), whereas the sustained phase pain response to formalin remains normal. Nevertheless, knockdown studies with antisense oligonucleotides for PSD-95 and PSD-93 yield similar results. Knockdown of PSD-95 results in reduced sensitivity in a neuropathic pain model, whereas knockdown of PSD-93 reduced both inflammatory and neuropathic pain behaviours.

One important consideration is that these molecular interventions differ, making direct comparison difficult. Clarification of whether PSD-95 and PSD-93 play differential roles in particular chronic pain states requires systematic analysis of equivalent mutants, knockouts and antisense-knockdown animals in identical pain models.

Interestingly, MAGUK proteins have distinct expression and distribution patterns in the spinal cord of rats and mice. PSD-95 and SAP102 are distributed mainly in lamina I and outer lamina II of the superficial dorsal horn, whereas PSD-93 is expressed predominantly in laminae I and II and outer lamina III (see Tao and Raja, 2004). SAP97 is undetectable in the laminae of the spinal cord. Moreover, the expression of the postsynaptic NMDA receptor subunit NR2B is limited in laminae I and II, whereas the NR2A subunit exhibits a wider dorsal horn distribution. These results suggest that the MAGUK proteins might associate with NMDA receptor complexes of different NMDA receptor subunit composition in the spinal cord, and be implicated in the transmission and processing of central pain signalling.

6. Alterations of PSD-95 function in Huntington's Disease

NMDA receptor-mediated excitotoxicity has been suggested to be involved in the pathogenesis of Huntington disease, an autosomal dominantly inherited disorder caused by expansion of a polyglutamine repeat in the protein designated huntingtin (htt). It has been reported that normal huntingtin binds to PSD-95 scaffold protein, resulting in the inhibition of NMDA receptor activity. Overexpression of the normal huntingtin N terminus significantly attenuates neuronal toxicity induced by both NMDA receptors and the mutated huntingtin, and co-expression of wild-type PSD-95 inhibits the neuroprotective action of normal huntingtin. This suggests that PSD-95 is a mediator of neuronal toxicity induced by NMDA receptors and mutated huntingtin (Sun et al., 2001). In addition, in a transgenic model of Huntington disease, a decrease in membrane-associated neuronal nitric oxide synthase (nNOS), a decrease in PSD-95- family proteins, which link nNOS to the NMDA receptor complex was observed (Luthi-Carter et al., 2003; Jarabek et al., 2004).

7. Conclusions

Excitotoxicity is thought to be a major mechanism in many human disease states such as ischemia, trauma, epilepsy and chronic neurodegenerative disorders. On this view, research in the last decade has focused in the discovery of new compounds able to either reduce glutamate release or activation of postsynaptic NMDA receptors. Recently, however, a significant improvement in understanding the biochemical properties of the multitude of NMDA receptor subtypes has offered the possibility of developing more effective and clinically useful drugs. In particular, it is now clear that synaptic NMDA receptor number and subunit composition are not static, but are dynamically modified during development and synaptic plasticity events. In addition, the increasing knowledge of the structure and function of the postsynaptic NMDA complex has lead to the identification of key proteins elements, such as MAGUK proteins, that have a fundamental role in governing NMDA receptor localization at synapse and, consequently, NMDA receptor function. These results lead to consider MAGUK proteins as new specific molecular targets whose pharmacological or genetic manipulation might lead to innovative therapies for brain disorders. As befits their central role in the organization of glutamate-receptor complexes, MAGUK proteins have been shown by genetic, electrophysiological and morphological studies to be essential for controlling the structure, strength and plasticity of glutamatergic synapses. The next stage of investigations promises to reveal more insights into the *in vivo* significance of synaptic MAGUK proteins, beyond their protein interactions and cell-biological functions. Of relevance, modifications of MAGUK protein function in the glutamatergic synapse has been already described in several neurological disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Ischemia, Schizophrenia and neuropathic pain.

Thus, the increasing knowledge of MAGUK structure and function, MAGUK-mediated interactions could become a fascinating target for pharmaceutical intervention in the glutamatergic synapse, thereby increasing the possible approaches for the pharmacological treatment of brain diseases.

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