Neuroscience

Regulation of Group I Metabotropic Glutamate Receptors by MAPK/ERK in Neurons

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Group I metabotropic glutamate receptors (mGluR1 and mGluR5 subtypes) are regulated by protein kinases. A recent focus is mitogen-activated protein kinases (MAPK). A prototypic subclass of MAPKs, extracellular signal-regulated kinases (ERK), is densely expressed in adult brain postmitotic neurons. This kinase resides in not only the cytoplasm around the nucleus, also the neuronal peripheral structures such as synapses. Recombinant ERK2 binds to C terminal tails of mGluR1a *in vitro* and native ERK1/2 forms complexes with mGluR1/5 in neurons *in vivo*. Association of ERK with mGluR1/5 enables the kinase to phosphorylate mGluR1/5 at a cluster of serine sites in the distal C terminus, including a serine residue within the Homer binding site. The ERK-mediated phosphorylation of mGluR1/5 promotes surface expression of mGluR1a in cerebellar neurons. ERK also regulates mGluR1/5 signaling and functions. Among different functional outputs surveyed, ERK exerts an output-specific role in either potentiating or inhibiting their activities. In sum, synaptic group I mGluRs are sufficient substrates of MAPK/ERK. Phosphorylation of mGluR1/5 by ERK has a significant impact on subcellular expression and function of phospho-modified receptors.

mGluR | striatum | cerebellum | hippocampus | synapse | phosphorylation | G protein-coupled receptors

Introduction

Glutamate is a key neurotransmitter in the mammalian brain. This transmitter interacts with both ionotropic and metabotropic glutamate receptors (mGluR) to achieve its action. mGluRs are a family of G protein-coupled receptors (GPCR). Base on post-receptor signaling pathways, eight mGluR subtypes are grouped into three functional groups (I, II, and III) (1). Group I mGluRs (mGluR1 and mGluR5 subtypes) have been most extensively investigated. These mGluR subtypes are coupled to phospholipase Cβ1 (PLCβ1) through $G_{\alpha q}$ proteins. Activation of mGluR1/5 increases PLCβ1-mediated phosphoinositide hydrolysis, yielding diacylglycerol and inositol-1,4,5-triphosphate (IP_3) to trigger Ca^{2+} and protein kinase C (PKC) signaling pathways, respectively. Noticeably, mGluR1/5 are mostly postsynaptic (2,3). Due to their wide spread distribution in brain regions, mGluR1/5 are actively involved in the regulation of cellular and synaptic activities (1,4) and are linked to various neuropsychiatric, neurodegenerative, and cognitive disorders (4,5).

As membrane-bound GPCRs, mGluR1/5 (mainly long-form splice variants such as mGluR1a, mGluR5a, and mGluR5b) possess a C terminus (CT) protruding into the cytoplasm. The CT tail is large in terms of the number of amino acids and renders mGluR1/5 accessibility to various binding partners (6-8). In fact, various mGluR1/5-associated proteins through interacting with mGluR1/5 CT regulate expression and function of the receptors (7,8). Among different sets of mGluR1/5-associated proteins, protein kinases represent an important group. Accumulated evidence indicates that protein kinases directly interact with intracellular domains of mGluR1/5. Via phosphorylating specific amino acid(s), a given protein kinase vigorously modulates mGluR1/5 in its distribution and function (9,10).

Mitogen-activated protein kinases (MAPK) are serine/threonine kinases which are densely expressed in adult brain postmitotic neurons. These kinases are activated via a sequential event involving Ras/Rac GTPases, MAPK kinase kinases (Raf or MEKK), and MAPK kinases (MEK) (11). There are three subclasses of MAPKs: extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinases/stress-activated protein kinases (JNK/SAPK), and p38 MAPKs (12). While these subclasses have similar biochemical properties in terms of binding to a specific domain and phosphorylating a common proline-directed motif (S/TP) (13), they are different in upstream activators, downstream substrates, binding and phosphorylation motifs, and thus physiological roles. The prototypic MAPK subclass is ERK which has been extensively studied in its pivotal roles in the modulation of synaptic transmission and plasticity (14,15). Especially, ERK has been recently found to be an important kinase phosphorylating and regulating mGluR1/5. This review then summarizes this recent progress.

ERK binds to mGluR1/5

ERK1 is associated with mGluR5 in HEK293T cells (16). Similarly, in mouse forebrain lysates, ERK1 and ERK2 were coimmunoprecipitated with mGluR5 (16). Another recent study investigated ERK interactions with mGluR1 (17). Both inactive and active forms of ERK2 directly bound to mGluR1a CT in *in vitro* binding assays with recombinant proteins. The binding site in mGluR1a CT resides in a membrane-proximal region of CT. Native ERK-mGluR1a interactions were studied in the adult rat cerebellum wherein mGluR1 but not mGluR5 is expressed abundantly (18,19). Since mGluR1a is functional at synaptic sites, a defined pool of synaptosomal proteins was extracted and used in coimmunoprecipitation to explore ERK-mGluR1a interactions in the synaptic location. ERK2 and to a lesser extent ERK1 was found to form complexes with mGluR1a in cerebellar neurons under normal conditions (17). In the complexes, the phosphorylated ERK (pERK, i.e., active form of ERK) was found to be predominantly the pERK2 isoform. Thus, ERK (primarily ERK2) is an mGluR1a-associated protein in cerebellar neurons and their interactions could occur at synaptic sites. Of note, ERK is traditionally viewed as a cytoplasmic protein. Once activated, ERK translocates to the nucleus from the cytoplasm to phosphorylate defined transcription factors in order to transcriptionally regulate synaptic transmission and plasticity (14,15,20). In addition, ERK and pERK are present in neuronal peripheral dendritic spines and synaptic zones (21-24). All MAPK cascade components colocalize with ERK2 within the post-

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synaptic density (PSD) (25,26). Thus, in addition to the nucleus, the synapse is a site where ERK resides and functions to regulate local substrates.

ERK phosphorylates mGluR1/5

ERK is a proline-directed kinase, meaning that it phosphorylates a consensus motif of serine-proline (SP) or threonine-proline (TP). mGluR1 and 5 both contain a conserved Homer-binding domain (-PPSPF-) in which SP (S1154 for mGluR1a and S1126 for mGluR5) is a potential phosphorylation site subjected to ERK. In fact, using a phospho- and site-specific anti-mGluR5-S1126 antibody, Hu et al. found that expression of constitutively active MEK, which activates ERK, induced mGluR5 phosphorylation in HEK293T cells (16). In cultured cortical neurons, basal immunoreactivity was detected by the anti-mGluR5-S1126 antibody, which was reduced by the MEK inhibitor U0126. Similarly, in adult rat brain tissue, a phospho-specific antibody demonstrated to recognize both mGluR1a and mGluR5 at the Homer binding site (ALTPPpSPFRD) detected phosphorylation signals (27). Phosphorylation was revealed by this antibody in cerebellar mGluR1a of wild type but not mGluR1a knockout mice. Thus, ERK seems to endogenously and dynamically phosphorylate mGluR1/5 at the Homer binding site under normal conditions.

A more detailed phosphorylation mapping study was reported recently. In this study (17), ERK2 strongly phosphorylated the distal part of the GST-fusion mGluR1a CT fragment *in vitro*, while ERK2 did not phosphorylate GST alone and three intracellular loops of mGluR1a (IL1, IL2, and IL3). The ERK2-induced mGluR1a CT phosphorylation was dephosphorylated by a phosphatase. In a site-directed mutation study, a cluster of serine residues in distal CT region were found to be the preferred phosphorylation sites. Noticeably, some phosphorylation sites align well with the consensus ERK phosphorylation motif (PXpSP). When using a motif-specific anti-PXpSP antibody, phosphorylation was found in recombinant mGluR1a CT and in native mGluR1a immunopurified from the synaptosomal pool of the rat cerebellum. The PXpSP immunoreactivity from cerebellar synaptic mGluR1a was reduced by U0126, indicating that ERK normally phosphorylates mGluR1a. The phosphorylation sites are notably different from the location where ERK2 binds to mGluR1a CT. Consistent with this, ERK binds and phosphorylates separated sites in most if not all ERK substrates (13). Interactions between ERK2 and mGluR1a are considered essential for the following phosphorylation step. Inhibition of ERK by U0126 reduced both ERK2-mGluR1a interactions and ERK-mediated phosphorylation of mGluR1a in rat cerebellar neurons.

Phosphorylation of mGluR5-S1126 could be an activity-dependent event. In mouse cultured cortical neurons, applying an mGluR1/5 agonist DHPG for 30 min increased mGluR5-S1126 phosphorylation (16). Since DHPG activated ERK (28), it is thought that the mGluR1/5 agonist activates ERK to trigger a phosphorylation-dependent homologous feedback pathway. Brain-derived neurotrophic factor (BDNF) is also known to activate ERK (29). Adding BDNF elevated mGluR5-S1126 phosphorylation in mouse cultured cortical neurons (16). BDNF produced the same effect in mouse cultured striatal neurons, which was blocked by U0126 (30). The dopamine receptor indirect agonist cocaine and a dopamine D1 receptor agonist SKF38393 increased S1126 phosphorylation in the adult mouse striatum and in cultured striatal neurons, respectively (30). Thus, BDNF and likely D1 signals trigger an ERK-sensitive heterologous signaling pathway to activity-dependently modulate group I mGluRs.

Regulation of surface expression of mGluR1/5 by ERK

Several mGluR1/5-associated proteins, such as Tamalin, calcineurin inhibitor protein and Norbin, modify expression of mGluR1/5 on the cell surface membrane (31-33). S1126-phosphorylated mGluR5 was enriched in the cell surface of mouse cultured striatal neurons (30). ERK has been found to play a supporting role in constitutive expression of mGluR1a in surface membranes under normal conditions. This was evidenced by the finding that inhibition of ERK by U0126 reduced the level of surface-expressed mGluR1a in rat cerebellar neurons as detected by a surface receptor crosslinking assays *in vivo* (17). It is unclear whether and how ERK-mediated phosphorylation of mGluR1a contributes to this event. Given the fact that the loss of surface-expressed mGluR1a was not accompanied by a concurrent increase in the intracellular pool of the receptor, the subtraction of surface mGluR1a may result from a decrease in synthesis and/or an increase in degradation of the surface receptor.

Phosphorylation of mGluR5 at the Homer binding site increased recombinant Homer binding to mGluR5 peptides containing the Homer binding site *in vitro* (27) and mediates the Preso1-induced Homer binding to mGluR5 in HEK293T cells (16). However, no change in mGluR5 surface expression was observed in *Homer1*$^{-/-}$*Homer2*$^{-/-}$*Homer3*$^{-/-}$ genotype (34).

Regulation of mGluR1/5 signaling by ERK

In mouse cultured dorsal spinal cord neurons, sustained treatment with glutamate combined with an NMDA receptor blocker APV and an AMPA receptor blocker NBQX to selectively stimulate mGluR induced a second and delayed Ca^{2+} rise in addition to an initial Ca^{2+} rise (16). This delayed Ca^{2+} response occurred in a higher percentage of neurons after adding U0126 at 2 min after onset of glutamate stimulation, indicating an ERK- and activity-dependent inhibition of mGluRs at least in this functional output pathway (the delayed Ca^{2+} rise) in these neurons. It is likely that ERK phosphorylation of Ca^{2+}-coupled mGluR1 or mGluR5 or both contributes to this negative feedback regulation, although direct evidence is lacking. However, ERK phosphorylation of mGluR1/5 may not inhibit all mGluR1/5-medaited outputs. Thus, the role of ERK in regulating mGluR1/5 signaling could be output specific. Indeed, Homer modulates group I mGluR signaling in an output-specific manner. While Homer binding inhibited the delayed Ca^{2+} responses of group I mGluRs in mouse cultured dorsal spinal horn neurons (16), Homer crosslinking increased mGluR1 coupling to intracellular IP_3 receptors in adult rat cerebellar neurons (35).

In cerebellar neurons, U0126 reduced the DHPG-stimulated IP_3 formation (17). A Tat-fusion peptide that selectively disrupted ERK2 interactions with mGluR1a also produced the similar effect (17). Thus, ERK2 activity is important for the efficacy of mGluR1 signaling in stimulating IP_3 formation.

Regulation of other mGluR1/5 functions by ERK

ERK phosphorylation of mGluR1/5 may have impact on other mGluR1/5-mediated functions. Whole-cell voltage-clamp recordings identified a slow inward current (SIC) which was an mGluR5-dependent NMDA current in response to DHPG in mouse cultured striatal neurons (30). The recording of this mGluR5-SIC was then used to test mGluR5 function. It was observed that BDNF and a D1 receptor agonist SKF38393 potentiated the mGluR5-SIC, indicating that the two agents may trigger a heterologous mechanism to potentiate mGluR5 signaling. The effect of BDNF was dependent upon ERK because U0126 blocked the BDNF-induced potentiation of the mGluR5-SIC. Moreover, an immediate-early gene form of Homer,

Homer1a, which is usually induced activity-dependently in response to changing synaptic input, plays an important role. It is likely that Homer1a interrupts the binding between constitutively expressed long forms of Homer (Homer1b/c, Homer2, and Homer3) and mGluR5 and thereby facilitates Pin1 to bind to and catalyze isomerization of ERK-phosphorylated mGluR5, resulting in an enhancement of the mGluR5-SIC (30).

S1126 phosphorylation of mGluR1/5 is essential for cocaine sensitization. Repeated administration of cocaine causes a greater motor response to subsequent cocaine exposure, i.e., behavioral sensitization, an animal model of drug addiction. Acute administration of cocaine induced phosphorylation of mGluR5 at S1126 in the striatum of adult mice *in vivo* (30). Behavioral sensitization in response to repeated cocaine was markedly reduced in mice that express mutant mGluR5 which cannot be phosphorylated at S1126. Additionally, depotentiation of corticostriatal long-term potentiation (LTP) occurred in corticostriatal synapses (36). This depotentiation was absent in slices prepared from rodents treated with repeated cocaine administration. Thus, failure of the depotentiation was proposed to be a synaptic correlate of cocaine-induced behavioral sensitization (37,38). Indeed, the D1 receptor agonist SKF38393 inhibited the depotentiation in wild type slices, while SKF38393 did not in slices derived from mutant mice deficient S1126 phosphorylation (30). Thus, mGluR5 phosphorylation at S1126 is required for dopamine inhibition of the depotentiation of corticostriatal LTP, which may serve as a metaplastic basis for motor sensitization.

Conclusions

Like ionotropic glutamate receptors, group I mGluRs are subject to the regulation by a phosphorylation-dependent mechanism. A recent focus is the MAPK/ERK which resides in not only the nucleus but also peripheral structures such as dendritic synapses. The synaptic sub-pool of ERK has been found to regulate a set of local substrates, including scaffolding proteins (PSD-95 and PSD-93) (39,40), cadherin-associated proteins (δ-catenin and plakophilin) (41), and Kv4.2 potassium channels (42,43). Group I mGluRs are another group of substrates of MAPK/ERK at the receptor level. ERK has been found to directly bind to mGluR1 and ERK-mGluR1 interactions are deemed to occur at synaptic sites. Synapse-enriched ERK2 phosphorylates mGluR1/5 at a Homer binding site as well as several other serine sites in the distal region of mGluR1/5 CT. Such phosphorylation is constitutively active and can be upregulated activity-dependently by changing synaptic input. Through phosphorylation, ERK modulates trafficking and expression of mGluR1/5 and controls mGluR1/5 signaling. This ERK-mGluR1/5 coupling in defined sets of synapses undergoes plastic changes in response to chronic disease models and plays an essential role in enduring synaptic and behavioral plasticity. While the studies on ERK and mGluR1/5 have made progresses, future studies are needed to define the specificity of ERK isoforms in phosphorylating specific sites and regulating a distinctive functional output of mGluR1 and mGluR5. Moreover, the role of the ERK-mGluR pathway in a specific brain circuit in a given neuropsychiatric or neurological disorder needs further investigation in the future. In addition to ERK, other subfamilies of MAPKs (JNK and p38) have potential to phosphorylate and regulate mGluR1/5. It will be intriguing to expand the study to these subfamilies to illustrate their roles in comparison with ERK.

If JNK and/or p38 are also involved in the regulation of mGluR1/5, crosstalk among ERK, JNK and p38 may exist. In addition, MAPKs may work in concert with other common protein kinases, such as protein kinase A, PKC and Ca^{2+}/calmodulin-dependent protein kinase II, to modulate mGluR1/5. In fact, these kinases have been demonstrated to regulate mGluR1/5 (10). Besides phosphorylation, other types of posttranslational modifications may participate in the regulation of mGluR1/5. Ubiquitination occurs in mGluR1a/5 (44). Palmitoylation and sumoylation take place in ionotropic glutamate receptors (10). Future studies need to explore other types of posttranslational modifications of mGluR1/5 and to dissect temporospatial and functional crosstalk among different types of modifications of the receptors.

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