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Phosphorylation of group I metabotropic glutamate receptors in drug addiction and translational research

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Abstract

Protein phosphorylation is an important posttranslational modification of group I metabotropic glutamate receptors (mGluR1 and mGluR5 subtypes) which are widely distributed throughout the mammalian brain. Several common protein kinases are involved in this type of modification, including protein kinase A, protein kinase C, and extracellular signal-regulated kinase. Through constitutive and activity-dependent phosphorylation of mGluR1/5 at specific residues, protein kinases regulate trafficking, subcellular/subsynaptic distribution, and function of modified receptors. Increasing evidence demonstrates that mGluR1/5 phosphorylation in the mesolimbic reward circuitry is sensitive to chronic psychostimulant exposure and undergoes adaptive changes in its abundance and activity. These changes contribute to long-term excitatory synaptic plasticity related to the addictive property of drugs of abuse. The rapid progress in uncovering the neurochemical basis of addiction has fostered bench-to-bed translational research by targeting mGluR1/5 for developing effective pharmacotherapies for treating addiction in humans. This review summarizes recent data from the studies analyzing mGluR1/5 phosphorylation. Phosphorylation-dependent mechanisms in stimulant-induced mGluR1/5 and behavioral plasticity are also discussed in association with increasing interest in mGluR1/5 in translational medicine.

Keywords

mGluR; PKA; PKC; MAPK; ERK; striatum; nucleus accumbens; G protein-coupled receptors

Introduction

A key neurotransmitter in the mammalian brain is glutamate. This transmitter interacts with two types of glutamate receptors: ionotropic and metabotropic glutamate receptors (mGluRs). Activation of the former carries out fast synaptic transmission, whereas activation of the latter usually modulates the strength and efficacy of glutamatergic synapses. All mGluR subtypes, a total of eight of them so far cloned, are G protein-coupled receptors (GPCRs) and are grouped into three functional groups.[1] Among them, group I mGluRs (mGluR1 and mGluR5 subtypes) are the focus of current investigations for roles of mGluRs

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Conflict of interest

The authors declare that they have no conflict of interest.

in the regulation of synaptic transmission and plasticity and in the pathogenesis of various neurological and neuropsychiatric disorders, including drug addiction.[1,2] Group I mGluRs are coupled to phospholipase Cβ1 (PLCβ1) via $G_{\alpha q}$ proteins. Upon activation, mGluR1/5 increase PLCβ1-mediated phosphoinositide hydrolysis, yielding diacylglycerol and inositol-1,4,5-triphosphate to trigger Ca^{2+} and protein kinase C (PKC) signaling pathways, respectively.

mGluR1/5 are membrane-bound receptors and are mostly postsynaptic.[3,4] Like other GPCRs, mGluR1/5 possess four typical intracellular domains: three loops and a C terminus (CT). The CT tail is large in terms of the number of amino acids, especially for these long-form splice variants (mGluR1a, mGluR5a, and mGluR5b). These CT domains thus render mGluR1/5 accessibility to various submembranous and cytosolic binding partners.[5-7] Protein kinases are an important group of these mGluR1/5-associated proteins, which carry out the phosphorylation-dependent regulation of the receptor. Increasing evidence indicates that several common protein kinases, including protein kinase A (PKA), PKC and mitogen-activated protein kinases (MAPKs), directly interact with mGluR1/5 CT, phosphorylate specific serine or threonine sites in the CT region, and thereby regulate trafficking, distribution, and function of phosphorylated receptors.[8,9]

Kinase-mediated phosphorylation of mGluR1/5 could be an activity-dependent event. In response to changing synaptic input, mGluR1/5 undergo drastic adaptive changes in their subcellular distribution and function in a phosphorylation-dependent manner. These adaptive changes constitute essential elements in the long-term remodeling of excitatory synaptic transmission and contribute to enduring synaptic plasticity related to a persistent state of a given mental disorder.[8,9] Drug addiction is among such experience-and adaptation-dependent disorders. Chronic exposure to addictive drugs, such as the psychostimulant cocaine and amphetamine, is thought to cause neuroadaptations in the mesolimbic reward brain region where mGluR1/5 are enriched,[10] which leads to enduring drug seeking behavior in experimental animals. The recent progress endorses the role of mGluR1/5 in the course of drug-induced neuroadaptations, establishing mGluR1/5 as the potential central site for developing therapeutic agents for treating addiction. This review then summarizes new research results in this area and analyzes the potential role of mGluR1/5 phosphorylation in drug addiction and the possible significance of mGluR1/5 in translational research in addiction.

PKA-mediated mGluR1/5 phosphorylation

PKA is a major effector downstream to $G_{\alpha s}$- and $G_{\alpha i/o}$-coupled GPCRs. An early study indicates that PKA is among kinases regulating group I mGluRs. Using whole-cell patch-clamp recording in rat brain slices, Poisik et al.[11] found that dopaminergic depletion or pharmacological stimulation of dopamine D1 receptors (D1Rs) or D2 receptors (D2Rs) had a significant impact on the signaling property of both mGluR1 and mGluR5 in the globus pallidus. Direct manipulations of PKA activity also modified mGluR1/5 signaling. Thus, PKA links dopamine signals to mGluR1/5. However, evidence for direct phosphorylation and regulation of mGluR5 has not been obtained until a recent study. Uematsu et al.[12] have recently identified that a serine site (S870) in the mGluR5 CT domain was phosphorylated

by PKA *in vitro*. With a phospho- and site-specific antibody developed subsequently, the authors were able to detect S870 phosphorylation in the mouse striatum, where mGluR5 is highly expressed,[10] under basal conditions. S870 phosphorylation in striatal slices was enhanced by forskolin, an adenylyl cyclase activator leading to PKA activation, indicating that mGluR5 S870 phosphorylation is subjected to the regulation by changing cAMP levels, although a significant change in S870 phosphorylation was not observed in striatal slice preparations following a treatment with the D1R agonist SKF81297. Functionally, as measured by mGluR5-stimulated phosphorylation of extracellular signal-regulated kinases (ERK),[13-15] non-phosphorylatable serine-to-alanine mutation of S870 prevented the mGluR1/5 agonist DHPG to stimulate ERK phosphorylation. Thus, PKA phosphorylation of mGluR5 at S870 is required for the receptor to activate ERK.

Glutamatergic transmission is implicated in the addictive property of drugs of abuse. Within the glutamate system, a great deal of evidence supports the role of group I mGluRs.[16] In various animal models of addiction, the group I mGluR antagonists, particularly the mGluR5 antagonists, reduced self-administration of virtually all drugs of abuse.[16] Genetic depletion of mGluR5 also abolished the reinforcing effect of cocaine.[17] Like glutamate, dopaminergic transmission is another key component of the limbic reward system essential for addiction. As a core intracellular effector of dopamine signaling, PKA plays a central role in drug action. It is possible that the PKA-mGluR5 coupling acts as a key step in integrating the input from two systems (glutamate and dopamine), which is essential for constructing long-term adaptations in the reward system related to enduring synaptic and behavioral plasticity. At present, direct evidence for this assumption is lacking. However, given the importance of mGluR1/5 and PKA for drug action, both of them are speculated to interact with each other intimately in response to drugs and to thereby control drug effects.

PKC-mediated mGluR1/5 phosphorylation

PKC phosphorylation of mGluR1/5 has been extensively investigated. Early studies showed that the PKC inhibitor Ro318220 blocked the mGluR1/5 agonist-induced phosphorylation of mGluR1/5,[18] while the PKC activator mimicked the effect of the mGluR1/5 agonist.[19] This reveals the ability of PKC to phosphorylate mGluR1/5. In mapping accurate sites harboring PKC-mediated phosphorylation, threonine 840 (T840) in the proximal region of mGluR5a CT was identified as the phosphorylation site. Other PKC-sensitive serine/threonine site(s) are believed to exist because the PKC-mediated phosphorylation was still seen in an mGluR5 peptide lacking T840.[20]

PKC may control patterns of intracellular Ca^{2+} transients induced by stimulating mGluR1/5. Phosphorylation of mGluR5a T840 by PKC (likely the Ca^{2+}-independent PKCδ rather than Ca^{2+}-dependent PKCγ) is essential for producing Ca^{2+} oscillations in mGluR5a-expressing cells.[21,22] Another study indicates that serine 839 (S839) is probably the responsible residue, while the adjacent T840 only plays a permissive role in PKC phosphorylation of S839.[23] Another functional role of PKC is its participation in the negative feedback regulation of mGluR1/5. Group I mGluRs undergo homologous desensitization in response to repeated or prolonged agonist stimulation.[24] PKC inhibitors reduced the agonist-induced mGluR1/5 desensitization in cultured neurons[25,26] or *Xenopus* oocytes expressing mGluR5a.[27] In

contrast, PKC activators induced a desensitization-like reduction of mGluR1/5 signaling in hippocampal slices[28] or *Xenopus* oocytes.[27] Multiple sites in the first and second intracellular loops and CT of mGluR5a (T606, S613, T665, S881, and S890) are important for PKC to carry out this role as mutation of them blocked the PKC-dependent desensitization of the receptor.[27]

PKC is a key kinase processing drug effects.[29] The role of PKC is achieved, at least in part, by phosphorylating and regulating mGluR1/5. Prenatal cocaine exposure disrupted mGluR1 activity and glutamatergic transmission in association with behavioral changes.[30] This prenatal cocaine-induced effect might be mediated through a signaling mechanism involving PKC phosphorylation of mGluR1. Based on Bakshi et al.[31] (2014), prenatal cocaine caused a sustained PKC-mediated mGluR1 hyper-phosphorylation at serine residues. This in turn uncoupled mGluR1 from its anchoring protein, Homer1, and its signaling transducer, $G_{q/11}$, leading to reduced efficacy of mGluR1 signaling in the frontal cortex and hippocampus. Consistent with the prenatal cocaine model, reduction of mGluR1 transmission in the nucleus accumbens (NAc) occurred in a cocaine self-administration model, which contributes to cue-induced cocaine craving.[32] It will be intriguing to investigate whether the PKC-mediated phosphorylation of mGluR1 is also involved in the mGluR1 response to cocaine self-administration. Regarding mGluR5, both the mGluR5 antagonist MPEP and PKC inhibitor Ro318220 injected into the shell of the NAc attenuated cocaine seeking.[33] Cocaine seeking was also associated with an increase in phosphorylation of PKCγ in the shell. Thus, activation of the mGluR5-PKCγ pathway in the NAc shell promotes cocaine seeking. As to possible substrates of PKC, GluA2 which contains a PKC phosphorylation site (S880) was considered to be a target.[33] In addition, given the fact that PKC phosphorylates mGluR1/5, PKC might act to form a feedback loop to regulate mGluR5. Future studies will investigate whether and how this interesting PKC-bridged feedback pathway responds to drug exposure and modulates drug-induced synaptic and behavioral plasticity.

MAPK-mediated mGluR1/5 phosphorylation

Like other protein kinases aforementioned, MAPKs are involved in the phosphorylation and regulation of group I mGluRs based on recent studies. MAPKs are serine/threonine kinases and are densely expressed in adult brain postmitotic neurons. These kinases are activated via sequential events at four levels: Ras/Rac GTPases, MAPK kinase kinases (Raf or MEKKs), MAPK kinases (MEKs), and MAPKs.[34] Three subclasses of MAPKs are currently known. ERK is a prototypic subclass of MAPKs. Other two subclasses are c-Jun N-terminal kinases/stress-activated protein kinases (JNK/SAPK) and p38 MAPKs.[35] MAPKs share basic biochemical properties such as binding to a similar domain and phosphorylating a common proline-directed motif (S/TP).[36] However, different subclasses are heterogeneous in upstream activators, downstream substrates, binding and phosphorylation motifs, and thus physiological roles.

ERK1 and mGluR5 are associated with each other in HEK293T cells and in mouse forebrain lysates,[37] indicating a potential of mGluR5 to be a substrate of ERK. Both mGluR1 and mGluR5 share a conserved Homer-binding site (PPSPF) in which an SP motif is noteworthy.

ERK is known as a proline-directed kinase and phosphorylates a consensus motif of SP and TP. Thus, the SP motif in the Homer-binding site (S1154 for mGluR1a and S1126 for mGluR5) could a potential phosphorylation site subjected to ERK. This assumption is supported by a recent study. Using a phospho- and site-specific anti-mGluR5-S1126 antibody, Hu et al. found that activation of ERK induced mGluR5 phosphorylation in HEK293T cells.[37] Basal phosphorylation was also detected in cultured cortical neurons by the same antibody. This phosphorylation was reduced by the MEK inhibitor U0126 and was revealed in cerebellar mGluR1a of wild type but not mGluR1a knockout mice. Apparently, ERK acts as an endogenous kinase that possesses the ability to phosphorylate mGluR1/5 at the Homer binding site under normal conditions.

ERK phosphorylation of mGluR5 is also a regulatable event. In response to changing synaptic input, ERK-mediated mGluR5 phosphorylation undergoes detectable changes. Pharmacological stimulation of mGluR1/5 with DHPG (30 min) increased mGluR5-S1126 phosphorylation in mouse cultured cortical neurons.[37] This suggests an existence of an ERK- and phosphorylation-dependent homologous feedback pathway in the regulation of mGluR5 signaling in response to agonist stimulation. In addition, brain-derived neurotrophic factor (BDNF) activated ERK[38] which elevated mGluR5-S1126 phosphorylation in mouse cultured cortical neurons.[37] The BDNF effect was blocked by U0126.[39] A dopamine D1 receptor agonist SKF38393 also increased S1126 phosphorylation in cultured striatal neurons.[39] Thus, BDNF and D1Rs are thought to activity-dependently regulate group I mGluRs via an ERK-sensitive heterologous signaling pathway.

Recent evidence shows that ERK-mediated mGluR1/5 phosphorylation is implicated in processing the addictive property of drugs of abuse. Repeated administration of cocaine is known to cause a greater motor response to subsequent cocaine exposure, i.e., behavioral sensitization, an animal model of drug addiction. Recently, acute administration of cocaine was found to enhance phosphorylation of mGluR5 at S1126 in the mouse striatum.[39] This inducible mGluR5 S1126 phosphorylation is deemed to be an essential neurochemical element in processing behavioral sensitization to cocaine because cocaine-induced behavioral sensitization was markedly reduced in mice bearing the mutant mGluR5 which cannot be phosphorylated at S1126. In analyzing a possible mechanism that underlies the role of S1126 phosphorylation, it is noted that depotentiation of corticostriatal long-term potentiation (LTP) is a form of synaptic plasticity observed in corticostriatal synapses.[40] This form of synaptic plasticity was absent in rodents treated with repeated cocaine administration. Thus, failure of the depotentiation of corticostriatal LTP was proposed as a synaptic correlate of cocaine-induced behavioral sensitization.[40,41] Interestingly, the D1 receptor agonist SKF38393 inhibited the depotentiation of corticostriatal LTP in wild type mice, but not in mutant mice deficient S1126 phosphorylation.[39] Thus, mGluR5 phosphorylation at S1126 appears to, at least in part, mediate the inhibition of the depotentiation of corticostriatal LTP in response to repeated dopamine stimulation, which may constitute synaptic plasticity important for motor sensitization to cocaine.

Translational research

Along with the accumulation of convincing evidence supporting group I mGluRs as key central substrates of stimulants, mGluR1/5 emerge as promising sites for developing therapeutic agents.[42] Based on the accurate role of mGluR1/5 identified in preclinical studies, both agonists and antagonists could be tested as therapeutic agents in clinical translational studies. Of note, the agents that target and modulate group I mGluRs have apparent advantages as compared to those affecting ionotropic glutamate receptors. The agents affecting mGluR1/5 are thought to have a minimal impact on fast synaptic transmission and be less likely producing general depression of neural activity or cognitive side effects that are usually associated with the chronic therapy with the ionotropic glutamate receptor antagonists. Additionally, group I mGluR agents should have little peripheral adverse effects on the autonomic nervous system because mGluR1/5 are almost not present in target organs of this system.

A number of clinical trials have been conducted to test the therapeutic property of compounds acting on mGluR5 for medical disorders such as migraine, anxiety, depression, Fragile X syndrome, and L-dopa-induced dyskinesias in Parkinson's disease.[16,43] These compounds include the mGluR5 antagonist fenobam and mGluR5 negative allosteric modulators ADX10059 and ADX48621.[16,42] Available clinical data show that these agents are safe and well tolerated in humans, establishing interest and eagerness to evaluate their effectiveness in treating addiction in future clinical trials. On the other hand, mGluR5 positive allosteric modulates (PAMs) were found to increase NMDA receptor activity and enhance synaptic plasticity, improving cognitive function. In animal studies, mGluR5 PAMs showed the ability to correct cognitive deficits and other drug effects, indicating the clinical utility of mGluR5 PAMs in treating certain cognitive disorders in drug addiction.[16] While at present there are limited clinical investigations of group I mGluR agents specific for addiction, more clinical trials are expected in the future to validate the utility and effectiveness of mGluR1/5 agents for treating this disorder.

Conclusions

mGluR1/5 have been one of focuses in studying neurobiology of glutamate receptors. Like ionotropic glutamate receptors, mGluR1/5 are regulated by a phosphorylation mechanism. The known protein kinases that exhibit the ability to phosphorylate and regulate mGluR1/5 include PKA, PKC, and MAPK/ERK. These kinases act as mGluR1/5-associated proteins and interact with the receptors via a specific binding domain. The direct interaction of a kinase with the receptor enables the kinase to phosphorylate a specific residue or a cluster of residues usually in the long CT domain. Kinase-induced phosphorylation could be constitutive or modified by changing synaptic input. Both basal and activity-induced phosphorylation is important for regulating expression and function of modified receptors. In a psychiatric disorder model (addiction), mGluR1/5 phosphorylation in the mesolimbic system is sensitive to stimulants. Chronic stimulant exposure causes long-term changes in phosphorylation status of mGluR1/5 and in activity of kinases that phosphorylate mGluR1/5, which participates in the remodeling of excitatory synaptic transmission, leading to persistent drug seeking behavior. mGluR1/5 thus become a promising target in translational

research aimed to find effective therapies for addiction. While mGluR1/5 phosphorylation represents one of important topics in the field, its study is evidently at an infant stage. Future studies will need to identify additional kinases that can interact with and phosphorylate mGluR1/5 to modulate the receptor activity under normal or drug-stimulated conditions. More importantly, the responsivity and sensitivity of a given kinase in association with mGluR1/5 phosphorylation in a specific brain region needs to be investigated in response to drug exposure. If there is a change in mGluR1/5 phosphorylation after drug treatment, significance of this change is expected to be defined subsequently. Finally, crosstalk among different kinases in phosphorylating mGluR1/5 is believed to occur. In addition, other types of posttranslational modifications, such as palmitoylation, ubiquitination, sumoylation, etc., may occur to mGluR1/5.[9] These modifications may work in concert to regulate mGluR1/5. As such, future studies will analyze roles of crosstalk among different kinases and modifications in processing drug addiction and will conduct clinical translational research based on new knowledge from studying crosstalk.

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