Metabotropic glutamate receptors: intracellular signaling pathways

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Metabotropic glutamate receptors are classified into three groups, primarily on the basis of sequence similarity and whether they positively couple to the phospholipase C cascade or negatively couple to adenylyl cyclases. The past decade of research, drawing on sophisticated molecular approaches, has revealed a multitude of additional intracellular components that assemble as protein scaffolds around neuronal metabotropic glutamate receptors, establishing functional links to postsynaptic density structures, to membrane-bound enzymes and ion channels, and to the nucleus. Characterization of these novel transduction mechanisms is providing new insights into the roles of metabotropic glutamate receptors in the regulation and modulation of diverse functions in the nervous system.

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Current Opinion in Pharmacology 2007, **7**:56–61

This review comes from a themed issue on
Neurosciences
Edited by Karima Chergui, Bertil Fredholm and Per Svenningsson

Available online 19th October 2006

1471-4892/$ – see front matter

DOI 10.1016/j.coph.2006.08.008

Introduction

The metabotropic glutamate receptors (mGluRs) were discovered when it was observed that exposing neurons to glutamate activated not only ionotropic receptors but also stimulated phospholipase C (PLC) [1,2]. Soon thereafter, a family of eight distinct mGluR subtypes was identified, and the palette of associated intracellular signaling mechanisms was greatly extended [3]. The mGluRs are classified according to structural and functional criteria into Group I (mGluR1 and mGluR5), Group II (mGluR2 and mGluR3), and Group III (mGluR4, mGluR6, mGluR7, and mGluR8) [4]. Here, we provide a brief update of new developments that expand and clarify our understanding of the transduction mechanisms mediating responses initiated by mGluRs. A major advance in this field, the retrograde signaling by endocannabinoids following the activation of postsynaptic mGluRs, will not be discussed explicitly here as this topic is the subject of several comprehensive recent reviews (e.g. see [5]).

Transduction within the mGluR

Upon binding of glutamate, a conformational change in homodimeric mGluRs promotes the coupling of G proteins to specific intracellular domains. Structural studies, beginning with the crystallization and characterization of the agonist-bound and 'unliganded' forms of the glutamate binding site of mGluR1, provided initial insights into the underlying process [6]. Agonist binding stabilizes the closed conformation of the extracellular domain and results in G protein activation that is dependent upon a disulfide bridge between conserved cysteine residues in the extracellular agonist binding loop and the third transmembrane domain [6,7]. This disulfide bridge mediates intrareceptor signaling by inducing an allosteric interaction between the glutamate binding domain and the heptahelical domain [7]. Thus, agonist binding changes the relative positions of the helical domains of these dimeric receptors to permit G protein activation.

A peculiar property reported for several metabotropic responses, including those mediated by mGluRs [8], is their voltage sensitivity. It has now been shown that this voltage dependence resides within the receptor itself. It appears that depolarization modifies the conformation of the second and third intracellular loops, thus affecting the association with G proteins [9]. These depolarization-dependent changes in G protein binding, in turn, alter the proportion of receptors in the high-affinity state for agonist [10].

G-protein-independent signaling

The canonical cascade coupling metabotropic receptors with their intracellular effectors begins with the activation of G proteins, hence the name G-protein-coupled receptors. Over the past decade, however, several studies have reported metabotropic responses that do not involve G proteins [11]. Evidence that mGluRs can also function in this manner came from experiments showing that activation of mGluR1 in hippocampal neurons simultaneously triggers both G-protein-dependent and -independent signaling to induce distinct currents [12,13]. The same conclusion was reached in a study using hippocampal pyramidal neurons from transgenic mice lacking the G proteins associated with postsynaptic mGluRs, in which inward currents mediated by mGluRs nevertheless persisted [14]. It is interesting that, for certain neuronal responses, specific mGluRs appear to

preferentially utilize G-protein-dependent pathways whereas, for other responses, the G-protein-independent mechanism predominates. For example, activation of mGluRs can lead to potentiation of responses mediated by N-methyl-D-aspartate (NMDA)-type glutamate receptors, which are critical for the induction of many forms of synaptic plasticity. In CA3 pyramidal neurons, which express both mGluR1 and mGluR5, NMDA receptor potentiation by mGluR5 was found to be G-protein-dependent, whereas potentiation by mGluR1 could proceed independently of G protein activation [15]. In the same cells, a mGluR1- and mGluR5-induced cationic current necessitates the cooperative activation of both G-protein-independent and G-protein-dependent pathways, with the former targeting calcium-sensitive cationic channels that conduct the current and the latter eliciting the release of the requisite calcium from intracellular stores (Figure 1) [16].

β-arrestins and mGluR signaling

Following their activation, metabotropic receptors undergo rapid desensitization through a process involving phosphorylation by G-protein-coupled receptor kinases, which then allows the binding of the adaptor proteins β-arrestin 1 and β-arrestin 2 that direct receptor endocytosis through targeting to clathrin-coated pits [17]. This mechanism also holds for the mGluRs, although a phosphorylation-independent form of desensitization mediated by G-protein-coupled receptor kinase-2 has been observed, as recently reviewed [18]. In addition to their role in receptor desensitization, β-arrestins act as scaffolding elements for the recruitment of signaling proteins that regulate diverse cellular functions [11,17,18]. A variety of direct and indirect evidence indicates that mGluRs associate with β-arrestins in the initiation of intracellular cascades effecting neuronal responses. Both the G-protein-independent actions of mGluR1 that lead to the induction of cationic current [12] and the potentiation of NMDA currents [15] in the hippocampus were shown to require activation of the non-receptor tyrosine kinase Src. In this case, it is likely that β-arrestin is acting as the adaptor to couple a Src-family kinase to the activated mGluR, as has been shown for Src activation by numerous other metabotropic receptors [11,17]. A more recent study has identified a role for β-arrestin 2 in the recruitment of Src to Group III mGluRs, leading to the activation of mitogen-activated protein kinase (MAPK) pathways [19].

Figure 1

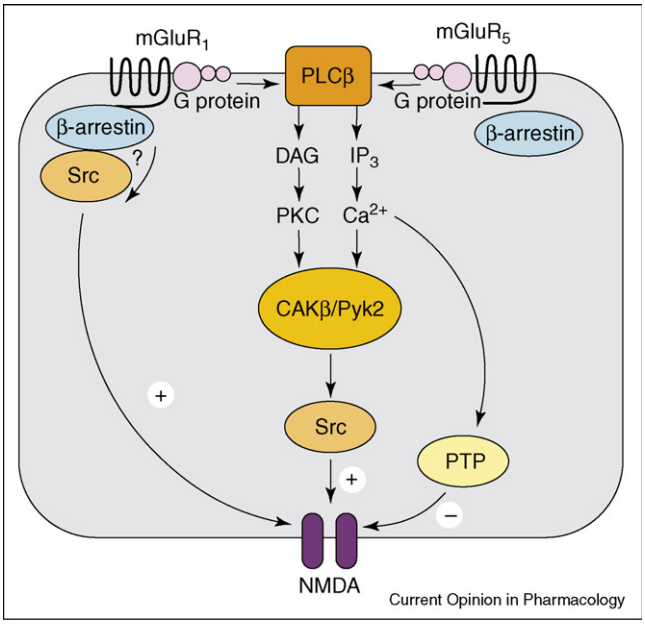


Diagram illustrating the mechanisms proposed to underlie the modulation of NMDA responses by Group I mGluRs. The G-protein-dependent activation of PLCβ triggers divergent signaling cascades leading both to potentiation of NMDA responses (centre of scheme) and to calcium-dependent activation of tyrosine phosphatases that depress NMDA responses. When G proteins are experimentally blocked, a parallel pathway utilized by mGluR1 is revealed (left-hand side of scheme) that activates Src, probably via the adaptor protein β-arrestin, leading to potentiation of NMDA responses. CAKβ/Pyk2, cell adhesion kinase β/proline-rich tyrosine kinase; DAG, diacylglycerol; PKC, protein kinase C; PTP, protein tyrosine phosphatase. Note that, for simplicity, mGluRs which function as dimers are depicted as monomers.

Ubiquitous actions of calcium

Almost every step in the signaling pathways associated with mGluRs requires, or is modulated by, calcium. Beginning with the receptors themselves, both the potency and efficacy of glutamate action at Group I mGluRs is enhanced with increasing concentrations of extracellular calcium [20]. Importantly, the efficacy of mGluR signaling is modulated by physiologically relevant changes in extracellular calcium, such that calcium depletion in the synaptic cleft, as occurs during burst firing, causes significant inhibition of postsynaptic mGluR function [21•]. Intracellularly, significant release of calcium is observed after synaptic activation of dendritic mGluRs, which can propagate as waves and even reach the cell nucleus under appropriate conditions [22].

Recent studies have shed light on the modulation by calcium of the transduction pathway between mGluRs and NMDA receptors. Work performed by John MacDonald and colleagues has delineated a transduction pathway that potentiates NMDA receptor currents through the sequential activation of metabotropic receptors, PLCβ, protein kinase C, CAKβ/Pyk2 (cell adhesion kinase β/proline-rich tyrosine kinase) and Src [23,24]. Interestingly, when initiated by mGluRs, this pathway requires inositol-1,4,5-trisphosphate (IP_3) receptor-dependent intracellular calcium release; calcium influx through NMDA receptors or voltage-dependent calcium channels does not lead to potentiation of NMDA responses [25]. However, if intracellular calcium rises excessively, an antagonistic G-protein-dependent pathway prevails that reduces NMDA responses [15,26].

Thus, neurons that express NMDA receptors contain both mGluR-dependent facilitatory and depressing pathways to ensure the precise regulation of this physiologically crucial receptor. Furthermore, either the facilitating or the depressing pathway can dominate depending upon the cell type [26], and is likely to be regulated by factors such as differences in calcium signaling pathways or in intrinsic calcium buffering capacity. Such bidirectional modulation under the control of intracellular calcium concentration was also found to determine whether mGluR5-dependent plasticity of NMDA responses results in long-term potentiation (LTP) or long-term depression (LTD) at the perforant path–granule cell synapse [27]. These findings provide an explanation for the discrepancies in the literature concerning facilitatory versus depressing NMDA receptor modulation by mGluRs, and highlight the significance of differences in preparations and experimental conditions that could influence ambient intracellular calcium concentrations. Differences in NMDA receptor modulation could also contribute to the distinct susceptibilities of various neuronal cell types to ischemic cell death. Indeed, in hippocampal CA1 pyramidal neurons, transient energy deprivation results in Src-dependent upregulation of NMDA receptor function associated with delayed neuronal death whereas, in neighboring CA3 pyramidal neurons, which are known to be more resistant to ischemia, the same protocol activates tyrosine phosphatases and does not lead to either NMDA receptor potentiation or cell death [28]. The calcium-sensitive equilibrium between tyrosine kinases and phosphatases might also be important in determining the phosphorylation state of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which in turn will determine whether synapses are in a potentiated [29] or depressed state [30].

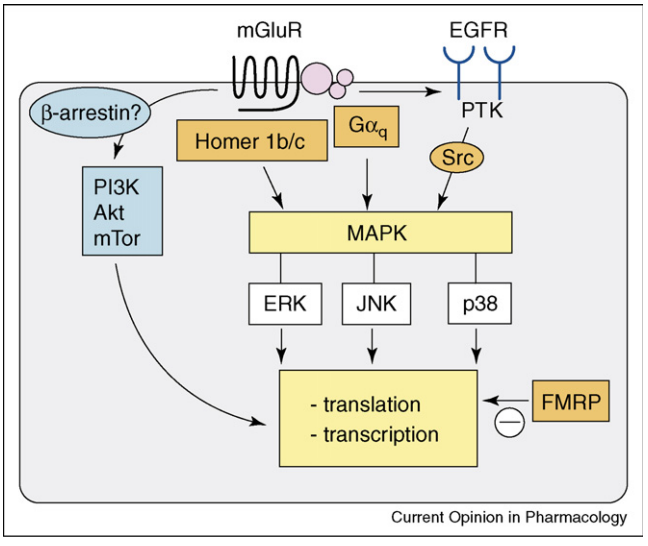
Modulation of transcription and translation by mGluRs

The consolidation of synaptic plasticity is dependent upon protein synthesis. The ability of mGluRs to initiate this process was shown by studies demonstrating a role for mGluR-dependent protein synthesis in the maintenance of epileptiform discharge [31] and in hippocampal synaptic plasticity [32,33]. Interestingly, the protein synthesis necessary for mGluR-dependent hippocampal LTD depends upon local translation of mRNA near the synapse, and not upon transcription [32]. Concurrently, it was reported that mGluR-dependent LTP was reduced after blockade of extracellular signal-regulated kinase (ERK)1/2–MAPK signaling [34]. More recent studies have refined our understanding of the signaling mechanisms linking Group I mGluRs to MAPK activation and the role that these pathways play in protein synthesis-dependent neuronal plasticity. MAPK cascades are triggered by stimuli at the extracellular membrane and culminate in the phosphorylation and activation of MAPKs comprising ERKs, c-Jun N-terminal kinases (JNKs) and p38s, which promote translation and activate transcription factors to increase protein synthesis. Stimulation of mGluR5 leads to weak activation of ERK1/2 through the PLCβ/IP_3/Ca^{2+} pathway and much stronger activation via the scaffolding protein Homer 1b/c [35]. Conversely, Homer 1a inhibits mGluR-dependent activation of MAPK, a mechanism important in downregulating chronic pain signaling [36•]. Robust activation of ERK and JNK MAPKs is also achieved by mGluR5-dependent transactivation of the epidermal growth factor receptor [37,38].

The mGluR-dependent synaptic plasticity associated with persistent epileptiform discharge [39], hippocampal LTD [40] and hippocampal LTP in oriens/alveus interneurons [29] has been shown to depend both upon ERK activation and upon a transduction pathway that employs a tyrosine kinase, rather than PKC, to phosphorylate and activate ERK1/2. In addition, Group I mGluRs activate a transduction pathway involving phosphoinositide 3-kinase (PI3K), Akt and mammalian target of rapamycin (mTor), which modulates mRNA translation in parallel with the ERK pathway to induce LTD [41]. Several studies have also shown the involvement of p38 MAPKs in mGluR-dependent LTD (Figure 2) [42–44,45••].

Translation and transcription factors targeted by MAPK cascades following mGluR activation have recently been

Figure 2



Activation of mGluRs can modulate both local postsynaptic translation of mRNA and nuclear transcription. The underlying signaling pathways typically target MAPKs, either originating at mGluRs via Homer or G protein activation, or following transactivation of the epidermal growth factor receptor (EGFR), thus inducing protein tyrosine kinase (PTK) activity of the intracellular domain and leading to Src activation. The fragile X mental retardation protein (FMRP) modulates mGluR signaling by virtue of its inhibitory effects on translation. The PI3K–Akt–mTor pathway represents a further signaling cascade that regulates translation in parallel to the MAPK pathways.

characterized. Activity of the cap-dependent translation protein eIF4E was shown to be under the control of both the ERK pathway [32,46•] and the PI3K–Akt–mTor pathway [46•], a finding which clarifies the mechanism underlying mGluR-dependent LTD. The mGluR-dependent phosphorylation of JNK increases transcription mediated by activator protein-1 [38], and activation of p38 regulates nuclear factor-κB (NF-κB) [45••]. In knockout mice lacking the NF-κB member c-Rel, late-phase LTD, as well as performance in a passive avoidance task, was diminished [45••]. An additional factor modulating mGluR-dependent protein synthesis is a negative regulator of translation called fragile X mental retardation protein (FMRP), the levels of which rise in dendrites following activation of group I mGluRs. Thus, in mice lacking FMRP, mGluR-dependent LTD is enhanced [47], as is the propensity for epileptiform activity owing to over-activation of protein translation [48•]. These findings suggest that antagonists of either Group I mGluRs or the downstream elements of the ERK signaling pathway may be useful in the treatment of fragile X syndrome [49].

mGluRs can also target transcription factors independent of MAPK or PI3K activation. Enhanced activation of mGluR4 in developing cerebellar granule cell cultures reduces Gli-1, a transcription factor in the Sonic Hedge Hog pathway [50]. This mGluR4-dependent effect was associated with reduced proliferation of cerebellar neural precursor cells and an increase in their differentiation into mature granule cells [50].

Conclusions and outlook

mGluRs play key roles in the modulation of diverse cellular responses. Recent structural advances have provided new insights into how changes in receptor conformation can initiate response transduction. In addition, molecular analysis is providing rich detail into the surprisingly divergent signaling pathways employed by these receptors, which modulate targets not only in the membrane but also in the cytoplasm and nucleus.

Although metabotropic receptors and the responses they mediate are becoming well characterized, the conditions under which mGluRs are synaptically activated remain to be established. Postsynaptic mGluRs are located at perisynaptic or extrasynaptic sites and, as such, will sense relatively low concentrations of glutamate diffusing out of the synaptic cleft. Yet, in most studies, high concentrations of agonist are applied to preparations that often exceed the EC_{50} values for mGluRs by one to two orders of magnitude [4]. A challenge for future studies will be to design experiments that mimic mGluR activation levels occurring during physiological network activity.

An important focus of current research is the linking of molecular data on mGluRs with specific sensory and behavioral functions. Apart from enhancing our understanding of diverse neuronal mechanisms, this approach is generating leads that promise new therapies for the treatment of a wide spectrum of psychiatric and neurological disorders [51].

Acknowledgements

Work in the laboratory of Urs Gerber is supported by the Swiss National Science Foundation and the NCCR on Neural Plasticity and Repair.

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