Control of neuronal excitability by Group I metabotropic glutamate receptors

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Abstract Metabotropic glutamate (mGlu) receptors couple through G proteins to regulate a large number of cell functions. Eight mGlu receptor isoforms have been cloned and classified into three Groups based on sequence, signal transduction mechanisms and pharmacology. This review will focus on Group I mGlu receptors, comprising the isoforms mGlu₁ and mGlu₅. Activation of these receptors initiates both G protein-dependent and -independent signal transduction pathways. The G-protein-dependent pathway involves mainly G α_q , which can activate PLC β , leading initially to the formation of IP₃ and diacylglycerol. IP₃ can release Ca²⁺ from cellular stores resulting in activation of Ca²⁺-dependent ion channels. Intracellular Ca²⁺, together with diacylglycerol, activates PKC, which has many protein targets, including ion channels. Thus, activation of the G-protein-dependent pathway affects cellular excitability through several different effectors. In parallel, G protein-independent pathways lead to activation of non-selective cationic currents and metabotropic synaptic currents and potentials. Here, we provide a survey of the membrane transport proteins responsible for these electrical effects of Group I metabotropic glutamate receptors.

Keywords Neuron · mGlu receptor · Action potential · HCN channels · KIR channels · TRPC channels · Na⁺/Ca²⁺ exchanger · SK channels

Introduction

This article reviews actions of Group I metabotropic glutamate receptors (mGlu) on neuronal excitability. This group of receptors, comprising mGlu₁ and mGlu₅, share sequence homology, coupling through protein G $\alpha_{q/11}$, pharmacology, and post-synaptic localization that distinguish them from the other six mGlu isoforms found in the mammalian genome (Cartmell and Schoepp 2000; Foord et al. 2005; Nakanishi 1992). Our focus is on short-term changes in membrane current that directly result from Group I mGlu receptor activation and the subsequent mobilization of second messenger systems. The goal is an understanding of how these currents affect neuronal excitability and of their physiological roles.

In addition to direct modulation of post-synaptic membrane currents and excitability described here, Group I mGlu receptors have many other important roles in the nervous system. Their activation can trigger release of endocannabinoids that feed back onto the nerve terminal, inhibiting the presynaptic Ca²⁺ transient and neurotransmitter release, a form of presynaptic short-term plasticity (Kreitzer and Regehr 2001; Kushmerick et al. 2004; Maejima et al. 2001; Morishita et al. 1998; Ohno-Shosaku et al. 2002; Varma et al. 2001; Yoshida et al. 2002). Group I mGlu receptors are also involved in the generation of long-term synaptic plasticity, often in partnership with pre-synaptic CB1 receptors (Chevalleyre and Castillo 2004; Edwards et al. 2006; Gladding et al. 2009; Kano and Wantanabe 2017; Olmo et al. 2016). Finally, Group I mGlu receptors also play a trophic role in development and maintenance of the nervous system and are

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involved in disease processes (Kano and Watanabe 2017; Ribeiro et al. 2017; Uesaka et al. 2015).

Structure of mGlu receptors

Metabotropic glutamate receptors are the prototypic members of Class 3 (now Class C) GPCR (Alexander et al. 2015; Foord et al. 2005), sharing little amino acid similarity with rhodopsin-like receptors or the secretin family. Alternative splicing produces several variants of mGlu₁ and mGlu₅ with long (mGlu_{1a}, mGlu_{5a-b}) or short (mGlu_{1b-d}, mGlu_{5d}) carboxyl terminals with differences in cellular localization, and G-protein signaling efficacy and desensitization (Grandes et al. 1994; Malherbe et al. 2002; Mary et al. 1998). Although no complete crystal structure exists for any mGlu receptor, standard biochemical analysis of the primary structure, together with high-resolution structures determined separately for key parts of the protein, allow a plausible overall structural model to be pieced together.

Like all known GPCR, the mGlu receptors contain seven transmembrane α -helices that form the 7TM domain (Nakanishi 1992). Besides its obvious structural role to anchor the receptor in the membrane, the 7TM domain contains binding sites for allosteric modulators (Dorée et al. 2014; Wu et al. 2014) and for the G-protein (Pin et al. 1994). The extracellular N terminal contains a large structure called the “Venus flytrap domain”, first described for GABA_B receptors (Galvez et al. 1999), which contains the orthosteric ligand binding site (Kunishima et al. 2000; Muto et al. 2007; Tsuchiya et al. 2002). The Venus flytrap domain is connected to the 7TM domain by a rigid cysteine-rich linker that communicates orthosteric ligand binding to receptor activation (Muto et al. 2007). After the seventh transmembrane segment, the 7TM domain gives way to a large intracellular C-terminal domain. As mentioned above, splice variants have either long or short C-terminal domains. These domains contain binding sites for many binding partners. Unfortunately, there are no crystal structures for either the long or short forms of the intracellular C-terminal, possibly because these domains are more flexible and unstructured in the absence of specific binding partners (Enz 2012). Nonetheless, magnetic resonance and molecular dynamics simulations provide models of its interactions with other proteins including Homer (Enz 2012).

Like the other Class C GPCR, mGlu receptors are functional dimers (Jingami et al. 2003; Kunishima et al. 2000). When extracted from plasma membranes, mGlu₁ and mGlu₅ purify as homodimers linked through cysteine–cysteine bridges in the N-terminal extracellular domain (Romano et al. 1996). In these experiments, covalently linked heterodimers were not observed. Later, FRET experiments demonstrated that some mGlu subunits (including mGlu₁ and mGlu₅), when coexpressed, come

close enough together that they may form a functional heterodimer (Dumazane et al. 2011). In addition, the isolated extracellular N-terminal domain from mGlu₁ appears to bind to the N-terminal of mGlu₅ (and vice versa) (Beqollari and Kammermeier 2010). These two findings open the possibility that co-expressed mGlu₁ and mGlu₅ may form functional heterodimers.

Pharmacology

The development and characterization of selective agonists and antagonists for mGlu receptors has greatly facilitated the study of their role in physiological and pathological responses (Hovelsø et al. 2012; Maksymetz et al. 2017; Nicoletti et al. 2011; Niswender and Conn 2010; Zou et al. 2017). Metabotropic glutamate receptors have binding sites for two classes of ligands. The orthosteric binding site for glutamate and competitive ligands is located on the large extracellular N-terminal Venus flytrap domain (O'Hara et al. 1993; Takahashi et al. 1993; Costantino et al. 1999). Conformational changes to this domain that occur when an orthosteric agonist binds communicate through the rigid cysteine-rich linker to the 7TM domain. This process results in receptor activation (Costantino et al. 1999; Rondard and Pin 2015; Takahashi et al. 1993). The other binding site, for positive and negative allosteric modulators, is located within the 7TM domain (Carroll et al. 2001; Gregory and Conn 2015; Litschig et al. 1999). Binding of a negative allosteric modulator to this site results in non-competitive inhibition of the receptor. Positive allosteric modulators do not activate the receptor, but can change the EC₅₀ for an orthosteric agonist or increase its maximum effect (Ellaithy et al. 2015; Kinney et al. 2005; Knoflach et al. 2001; Layton 2005; Sengmany et al. 2017). The history of mGlu receptor pharmacology and drug development, as well as comprehensive lists of disclosed compounds with orthosteric or allosteric activity, is well documented (Alexander et al. 2011; Ferraguti et al. 2008; Pin et al. 1999; Schoepp et al. 1999). Here, we will review the pharmacology of mGlu receptors only as it pertains to the electrophysiological results that follow.

Orthosteric agonists used to study Group I mGlu receptors include ACPD, quisqualate, and DHPG. ACPD is selective for mGlu over ionotropic (iGlu) receptors, but does not discriminate between mGlu isoforms (Aramori and Nakanishi 1992; Schoepp and Conn 1993). Quisqualate is selective for Group I among the mGlu receptors, but it also potently activates AMPA receptors (Horne and Simmonds 1989), a fact that limits its usefulness for studying the role of mGlu receptors in the nervous system. The lead Group I orthosteric agonist is (s)-3,5-dihydroxyphenylglycine (DHPG) (see review in Wiśniewski and Car 2002). DHPG activates mGlu₁ and mGlu₅ with EC₅₀ $\approx$ 10 μ M (Chen et al. 2016; Gao et al.

2015; Li et al. 2016; Sekizawa and Bonham 2006), with no significant effect on any other mGlu isoforms (Ito et al. 1992; Schoepp et al. 1994). Within Group I, isoform-selective agonists are very limited. CHPG is selective for mGlu₅ over mGlu₁, but it has a very low potency (Doherty et al. 1997), and has been reported to inhibit mGlu₁ receptors overexpressed in sympathetic neurons (Kammermeier 2012). Selective mGlu₁ agonists are still lacking.

Several competitive or non-competitive (i.e. orthosteric or allosteric) antagonists have been used to study Group I mGlu receptors. MCPG, AIDA, and LY367385 are competitive mGlu receptor antagonists. MCPG is non-selective (Hayashi et al. 1994), AIDA is selective for mGlu₁ over mGlu₅ (Moroni et al. 1997), and LY367385 is selective for mGlu₁ (Clark et al. 1997). Selective non-competitive inhibitors (negative allosteric modulators) include CPCCOEt for mGlu₁ (Litschig et al. 1999) and MPEP and MTEP for mGlu₅ (Brodtkin et al. 2002; Gasparini et al. 1999; Lea and Faden 2006).

In addition to the agonists and antagonists listed above, several other drugs that are commonly used to study specific signaling pathways and downstream effectors are useful tools to characterize mGlu receptor functions. The involvement of G proteins can be tested with GDP β S or GTP γ S. These non-hydrolysable GTP analogs non-selectively inactivate or hyperactivate, respectively, G-protein-mediated pathways (Heuss et al. 1999). Selective inhibition of G α_i or G α_q can be achieved with pertussis toxin (PTX) and UBO-QIC, respectively (Schrage et al. 2015), although these two drugs will also affect G $\beta\gamma$ functions (Gao and Jacobson 2016). The involvement of G α_s can be probed with cholera toxin, which leads to its constitutive activation. Downstream of the G-protein, several drugs are available to inhibit specific signaling pathways. For example, U73122 inhibits the phospholipase C and there are selective inhibitors for protein kinases PKA, PKC, and PKG, among others (Brager and Jonston 2007; Ji et al. 2012; Li et al. 2016; Nugent et al. 2009; Sekizawa et al. 2006; Shen and Johnson 2013; Shim et al. 2016). Finally, Ca²⁺-dependent signaling can be blocked by intracellular application of strong Ca²⁺ buffering, such as millimolar BAPTA (Kushmerick et al. 2004; Li et al. 2016; Sekizawa and Bonham et al. 2006). The use of these drugs has permitted the characterization of Group I signaling pathways (see below).

Signal transduction pathways

Activation of the Group I metabotropic glutamate receptors triggers an increase in the production of IP₃, a hallmark of coupling through the G $\alpha_{q/11}$ G-protein subunit (Berridge and Irving 1984; Sladeczek et al. 1985). Despite this apparent preference for protein G $\alpha_{q/11}$,

pertussis toxin, a highly selective inhibitor of G $\alpha_{i/o}$, inhibits responses of Group I mGlu receptors overexpressed in *Xenopus* oocytes (Houamed et al. 1991; Masu et al. 1991; Sugiyama et al. 1987) and natively expressed in neurons (Bertaso et al. 2010; Holohean et al. 1999; Kreibich et al. 2004; Linn 2000). Moreover, some effects mediated by Group I mGlu receptors persist even after disabling G-protein function with GDP β S (e.g., Guérineau et al. 1995). It is thus clear that activated Group I mGlu receptors can engage multiple parallel G-protein-dependent and -independent signaling pathways.

The canonical pathway begins with the binding of an orthosteric agonist to mGlu₁ or mGlu₅ receptors that activates the G $\alpha_{q/11}$ G-protein subunit. A major target of activated G $\alpha_{q/11}$ is PLC β , which catalyzes the hydrolysis of the membrane phospholipid PI(4,5)P₂, forming soluble IP₃ and membrane-bound DAG (Abdul-Ghani et al. 1996; Krueger et al. 2010). Activation of PLC and hydrolysis of PI(4,5)P₂ has two major consequences. The first involves mobilization of Ca²⁺, as released IP₃ can open ligand-gated Ca²⁺ channels (IP₃R) in the endoplasmic reticulum, releasing Ca²⁺ to the cytoplasm. Ca²⁺ released from the reticulum can interact with many different cellular Ca²⁺ sensors, potentially causing a large number of complex effects (Berridge and Irving 1984). The second consequence of PLC β activation is depletion of PI(4,5)P₂ from the plasma membrane which will affect channels that require PI(4,5)P₂. Native cells express several types of well-characterized ion channels that are gated by cytoplasmic Ca²⁺ (Faber 2009; Latorre et al. 2016), and ion channels that require PI(4,5)P₂ in the plasma membrane to open (Suh and Hille 2008). Thus, both the rise in free Ca²⁺ and the depletion of PI(4,5)P₂ from the plasma membrane can change the membrane conductance. In addition to these two mechanisms, a third pathway for changes in membrane conductance is through the actions of the G $\beta\gamma$ dimer released during G protein activation that can modulate ion channels (Logothetis et al. 1987). Finally, an increase in cytoplasmic Ca²⁺ may stimulate electrogenic Na⁺/Ca²⁺ exchanger currents (Blaustein and Lederer 1999), providing yet another mechanism for current generation through the canonical pathway.

Activated GPCR are targets for phosphorylation by G-protein-coupled receptor kinases and binding by β -arrestin (Wisler et al. 2014), which can lead to desensitization through receptor endocytosis. In addition to its well-known role in promoting clathrin-mediated desensitization, β -arrestin can also promote interactions with other signaling molecules, notably Src, which can lead to G protein-independent actions of Group I mGlu receptors (Heuss et al. 1999). Activation of Group I mGlu receptors can also lead to G-protein-independent pathways, leading to changes in membrane excitability, notably activation of

TRPC channels. This subject will be addressed below in the context of the cerebellar Purkinje cell.

Direct excitatory effects of mGlu receptors

Acute activation of Group I mGlu receptors have electrophysiological effects in a number of cell types. These actions, which can be excitatory or inhibitory, express themselves in several different ways, including depolarization or hyperpolarization of the resting potential, changes in the frequency of action potentials, and changes to the resting membrane resistance. To quantify these effects, measurements of membrane current under voltage clamp provide a direct measurement of underlying conductance changes. On the other hand, judging the impact of such conductance changes on cellular function usually requires the recording of membrane potentials under current clamp. When possible, we will compare results obtained using these two recording configurations.

A second set of important variables are species and age. The studies reviewed here were carried out in rat or mouse. For technical reasons, experiments on brain slices are often carried out in younger animals. During the post-natal period, expression patterns of mGlu receptors changes in several brain areas (von Gersdorff and Borst 2002; López-Bendito et al. 2002). Electrophysiological effects described below may relate either to a role of mGlu receptors in developmental changes of synaptic structure or play a physiological role in the adult animal (or both) depending on the age ranges in which they are expressed.

A third important question relates to the physiological or pathophysiological role of mGlu receptors in neuronal and synaptic function. Many of the effects of mGlu receptors described below were provoked with synthetic agonists. This raises two questions. The first is pharmacological: are the drugs full and unbiased agonists when compared to the natural endogenous ligand L-glutamate? The second relates to physiological function: under what conditions can these receptors be activated by endogenous glutamate, either at ambient levels or released synaptically? Observing effects of synaptically released glutamate on mGlu receptors is difficult because the maximal amplitude of mGlu currents are usually < 10% of iGlu currents at the same synapse (often < 1%). Thus, measurement of mGlu currents requires the use of high concentrations of iGlu receptor blockers, and interpretation of results often depends on the assumption that iGlu receptor responses are completely blocked. Another concern is that synaptic activation of mGlu receptor is sometimes only apparent when evoked in the presence of glutamate reuptake inhibitors such as TBOA or DHK (Gueler et al. 2007). One explanation is that, in brain slice experiments in which surface cells are

preferentially studied, bath perfusion prevents the build-up of ambient glutamate to the extent that may occur in an intact brain. Although plausible, this idea is difficult to test.

Electrogenic $\text{Na}^+/\text{Ca}^{2+}$ exchanger

The $\text{Na}^+/\text{Ca}^{2+}$ exchanger is a ubiquitous plasma membrane protein important for control of cytoplasmic Ca^{2+} (Blaustein and Lederer 1999). This protein mediates secondary active transport of Ca^{2+} using the Na^+ gradient for energy, with a stoichiometry of 3 Na^+ ions for each Ca^{2+} ion transported. Thus, transport of Ca^{2+} out of the cell by $\text{Na}^+/\text{Ca}^{2+}$ exchange generates inward current. The mammalian nervous system amply expresses three NCX isoforms (Nicoll et al. 1990, 1996; Li et al. 1994), and therefore $\text{Na}^+/\text{Ca}^{2+}$ exchange currents are expected whenever cytoplasmic Ca^{2+} is elevated, including in response to activation of Group I mGlu receptors.

Despite this simple logic, there are some reasons to question the relevance of $\text{Na}^+/\text{Ca}^{2+}$ exchange as an explanation for Group I mGlu receptor-dependent membrane current. In general, active transporters like the $\text{Na}^+/\text{Ca}^{2+}$ exchanger generate fluxes that are orders of magnitude lower than open ion channels. Therefore, the relative contribution of $\text{Na}^+/\text{Ca}^{2+}$ exchange to Group I mGlu receptor currents will depend on the level of exchanger expression and the Ca^{2+} concentrations achieved. A second concern is with regard to specificity. In cells that express more than one type of G_q -coupled receptor (not to mention the numerous other mechanisms that may generate Ca^{2+} transients), it is difficult to understand how $\text{Na}^+/\text{Ca}^{2+}$ exchange could generate a specific response. Finally, the limited number of pharmacological tools to study $\text{Na}^+/\text{Ca}^{2+}$ exchange has hindered conclusive testing. Substitution of Na^+ by Li^+ or choline inhibits $\text{Na}^+/\text{Ca}^{2+}$ exchange, but will also inhibit other Na^+ -dependent transporters. Selective block of $\text{Na}^+/\text{Ca}^{2+}$ exchange can be obtained with the 20-aa peptide XIP (Li et al. 1991), although its use in live cells is made difficult by the fact that it binds to an intracellular site on the exchanger with only moderate affinity ($k_d = 5 \mu\text{M}$; Hale et al. 1997). Another drug used to block the exchanger, KB-R7943, is much more potent for reverse mode transport (Iwamoto et al. 1996). To block normal mode transport requires concentrations that may generate non-selective effects (Santo-Domingo et al. 2007).

Despite these caveats and difficulties, convincing evidence for a role of $\text{Na}^+/\text{Ca}^{2+}$ exchange in mediating Group I mGlu receptor currents has been reported for neurons of the basal lateral amygdala. These cells have complex regulation by mGlu receptors. The non-selective agonist trans-ACPD causes a biphasic response consisting of an initial hyperpolarization followed by a later depolarization (Rainnie et al. 1994). The initial hyperpolarization is caused by activation of a Ca^{2+} -activated K^+ conductance and is mediated by Group II mGlu

receptors (Holmes et al. 1996; Rainnie et al. 1994). Selective Group I agonists (i.e. quisqualate or DHPG) provoke only the secondary depolarization (Holmes et al. 1996). The current activated by selective Group I mGlu receptor agonists in BLA neurons is not associated with a change in membrane resistance, shows little voltage dependence, and can be blocked by (1) intracellular BAPTA, (2) substitution of extracellular Na^+ by Li^+ or choline, and (3) intracellular XIP peptide (Keele et al. 1997). Together, these results implicate $\text{Na}^+/\text{Ca}^{2+}$ exchange as the mechanism for Group I mGlu receptor current in BLA neurons. Low mM concentrations of CHPG also evoked this current, suggesting that activation of mGlu₅ is responsible for these effects (Keele et al. 2000).

In olfactory bulb dopaminergic neurons, DHPG generates an inward current and membrane depolarization without a change in membrane conductance. These excitatory effects of DHPG are blocked by intracellular BAPTA, U73122 and, critically, KB-R7943, which, taken together, implicate electrogenic $\text{Na}^+/\text{Ca}^{2+}$ current as the effector (Jian et al. 2010). Interestingly, although these cells express both mGlu₁ and mGlu₅, activation of $\text{Na}^+/\text{Ca}^{2+}$ exchange current by DHPG was specifically associated with mGlu₁. Selective activation of mGlu₅, achieved by using either DHPG in the presence of the selective mGlu₁ antagonist CPGCOEt or the selective mGlu₅ agonist CHPG, resulted in inhibition rather than excitation of the neuron.

TRPC channels

Transient receptor potential (TRP) channels are a superfamily of cation channels. Gating of TRP channels is controlled by a broad range of physical and chemical stimuli that vary between and within TRP families. Common elements among TRP channels are their Ca^{2+} permeability and potentiation by receptors coupled to G_q (reviewed by Wu et al. 2010). Members of the TRPC family (C for “classic” or “canonical”) are expressed in the brain where they participate in synaptic functions mediated by mGlu receptors (reviewed by Hartmann and Konnerth 2015). As described below, Group I mGlu receptors activate TRPC channels in several brain regions including the hippocampus (CA3 and oriens/alveus interneurons), cerebellum (Purkinje cells and molecular layer interneurons) and striatal cholinergic interneurons.

In the hippocampus, synaptic glutamate and selective Group I mGlu receptor agonists activate a non-selective cation current. Surprisingly, activation of this current was not blocked by GDP β S or GTP γ S, indicating that G-proteins were not required to couple activation of the mGlu receptor to its effector (Guérineau et al. 1995). Rather, activation of this Group I mGlu receptor current depends on Src family protein tyrosine Kinases (Heuss et al. 1999). Using the selective agonist DHPG, Gee et al. (2003) showed that activation of Group

I mGlu receptors in CA3 can also activate cation currents in a G-protein and Ca^{2+} -dependent manner. Interestingly, in this case, activation of both mGlu₁ and mGlu₅ receptors was required for full activation of the current; when applied separately, both LY367385 (mGlu₁ antagonist) and MPEP (mGlu₅ antagonist) significantly reduced the Group I mGlu receptor current. DHPG has been reported to be a biased toward the canonical G-protein/PCL/IP₃ pathway compared to glutamate (Emery et al. 2012; Hathaway et al. 2015). This may explain some of the differences observed when receptors are stimulated with DHPG versus synaptic glutamate. Identification of the cation conductance in CA3 neurons as a TRPC channel was made based on the shape of the I–V curve as well as its sensitivity to (non-selective) TRPC antagonists (La^{3+} , MDL12,330A and 2APB).

The co-existence of G-protein-dependent and -independent pathways linked to cationic current was also observed in hippocampal oriens/alveus interneurons. In this case, G-protein-independent and Src/ERK-dependent activation of TRPC channels contributes a distinct fast component to responses generated by mGlu₁ but not by mGlu₅ (Topolnik et al. 2006).

In the cerebellum, glutamate released from parallel fiber synapses onto Purkinje cells causes a slow EPSC mediated by mGlu receptors and G proteins (Hirono et al. 1998, 2001; Tempia et al. 1998). This current can be mimicked by ACPD or DHPG (Hartmann et al. 2008), but unlike other Group I-mediated responses is resistant or partially resistant to strong intracellular Ca^{2+} buffering (BAPTA), inhibition of PLC (U-73122), and inhibition of PKC. Kim et al. (2003) presented convincing evidence that mGlu₁ can regulate TRPC1 both in heterologous expression systems and in Purkinje cells. However, later studies showed that the Group I mGlu receptor current is reduced by the selective TRPC3 antagonist Pry3 (Ady et al. 2014), is absent in TRPC3 KO mice and present in TRPC1 KO mice (Hartmann et al. 2008). Together, these data indicate that TRPC3 channels are responsible, at least partially, for the Group I mGlu receptor current at the cerebellar parallel fiber to the Purkinje cell synapse.

In addition to Purkinje cells, Group I mGlu receptors generate slow inward currents in other cerebellar cell types. DHPG increases the firing rate of cerebellar molecular layer GABAergic interneurons (basket cells and stellate cells), and synaptically released glutamate generates a slow inward current sensitive to mGlu₁ inhibitors (Karakossian and Otis 2004). The biophysical and pharmacological properties of this current implicate TRPC1 channels in this response. Just as for Purkinje cells, Group I mGlu receptor current in cerebellar molecular layer interneurons is resistant to inhibition of PLC (Kubota et al. 2014). It is also partially resistant to blocking of G protein signaling with GDP β S, and sensitive to Src and ERK protein kinase inhibitors (Kubota et al. 2014), similar to that observed in hippocampal CA3 (see above). Thus, like in CA3, Group I mGlu receptors in cerebellar molecular layer

interneurons activate both Gq-dependent and -independent pathways that converge to activate TRPC channels.

Similar results were observed in striatal cholinergic interneurons. In these cells, DHPG generates a TRPC current (based on its I–V relationship and sensitivity to FFA) (Berg et al. 2007). Thus, expression of mGlu receptors-mediated activation of TRPC cationic current occurs in a representative cell type of at least three neurochemical cell types: glutamatergic (hippocampal CA3, cerebellar Purkinje cells), GABAergic (hippocampal oriens/alveus interneurons, cerebellar molecular layer interneurons) and cholinergic (striatal interneurons).

The coupling mechanism whereby activation of Group I mGlu receptors activates TRPC channels is only partially understood (Hartmann and Konnerth 2015). TRPC1 channels can be activated by diacylglycerol (DAG), but at least in the cerebellum PLC does not appear to be necessary for TRPC3 activation (Glitsch 2009; Hirono et al. 1998). Another source for DAG is PLD, which can activate TRPC channels. Group I mGlu receptors can activate PLD through the Rho protein (Kanumilli et al. 2002), and, unlike PLC, inhibition of PLD blocks the slow EPSC in cerebellar Purkinje cells (Glitsch 2009). In cerebellar Purkinje cells from stromal interaction molecule 1 KO animals, Group I mGlu receptor-mediated calcium transients and TRPC3-mediated slow EPSCs are absent, indicating an essential role for this ER calcium sensor in Group I mGlu receptor signaling (Hartmann et al. 2014).

HCN channels

Hyperpolarization and cyclic nucleotide (HCN)-activated ion channels mediate I_h cation currents in excitable cells (Biel 2009). These channels activate in response to hyperpolarization, and this voltage dependence gives rise to a characteristic “sag” during long depolarizations (i.e. a slow partial return toward resting membrane potential). HCN currents can be identified based on their slow activation by hyperpolarizing voltage steps and selective blockade by ZD7288. Sensitivity to cAMP makes I_h currents susceptible to modulation by GPCRs, perhaps most famously exemplified by the effect of adrenaline acting through β -adrenergic receptors and cardiac HCN channels to accelerate the heart rate (Brown et al. 1979). HCN isoforms are expressed in the brain (Ludwig et al. 1998; Santoro et al. 1998) where they modulate excitability and action potential firing patterns (reviewed by Shah 2014). In addition to modulation by cAMP, HCN channels are inhibited by PKC-dependent pathways (Brager and Johnston 2007; Cathala and Paupardin-Tritsch 1997; Williams et al. 2015). The ability of Group I mGlu receptors to activate PKC and protein tyrosine kinase, provides opportunity for modulation of HCN channels by Group I mGlu receptors in cells that coexpress these proteins.

Two examples of acute modulation of HCN channels by mGlu₁ activation are found in retinal ganglion cells (Li et al. 2016) and cingulate cortex pyramidal neurons (Gao et al. 2016). Both cell types coexpress HCN channels and mGlu₁. Activation of Group I mGlu receptors with DHPG causes inhibition of I_h and an increase in excitability in these cells via a pathway that depends on PKC. Retinal ganglion cells appear to be under tonic inhibition by Group I mGlu receptors because application of antagonists increased firing in the absence of exogenous agonist (Li et al. 2016). A third example of modulation of HCN channels and I_h by Group I mGlu receptor modulation is found in cerebellar Purkinje cells. In these cells, increased levels of mGlu₁ caused an increase of I_h and hypoexcitability via a pathway dependent on PKA. Interestingly, this effect of mGlu₁ on Purkinje cells was due to its basal (i.e. agonist-independent) activity because it was blocked by an inverse agonist (Bay 36–7620) but not by the non-competitive antagonist CPCCOEt (Shim et al. 2016). The mechanism by which mGlu₁ activates PKA was not determined, but may be by direct activation of G_s Protein.

SK channels

Small-conductance Ca^{2+} -activated potassium channels are widely expressed in the nervous system (Faber 2009). They underlie part of the after-hyperpolarization in CA1 pyramidal neurons (Bond et al. 2004) and are modulated by Group I mGlu receptor agonists (Anwyl 1999). In dopaminergic neurons of the ventral tegmental area and substantia nigra, synaptic glutamate acts through mGlu₁ receptors to release stored Ca^{2+} that activates SK channels resulting in a slow glutamatergic IPSP (Fiorillo and Williams 1998). A similar result has been observed in primary culture of cerebellar Purkinje cells (Netzeband and Gruol 2008).

Kir channels

Inwardly-rectifying K channels (Kir) produce currents that activate at voltages near or more negative to the resting potential, and deactivate with depolarization. As such, they stabilize the resting potential and oppose subthreshold depolarizations. However, unlike a pure leak K^+ conductance, inward rectification by KIR results in progressive decline of repolarization force for larger depolarizations, and eventual release by deactivation. Inhibition of Kir channels may therefore lead to depolarization as well as a generalized increase of excitability. Kir channels lack the voltage-sensing domains of KV channels. Their apparent voltage dependence arises from involves voltage-dependent block by intracellular ions. They can also be blocked from the extracellular side by low concentrations of the ions Ba^{2+} and Cs^+ (Hibino et al. 2010).

Cloned Kir channels have been classified into seven families numbered Kir1.x–Kir7.x (Hibino et al. 2010). The Kir3.x family are also known as GIRK channels because they require the binding of $G_{i/o}$ beta-gamma subunits to activate. Activation of Kir3 channels by binding $G_{i/o}$ beta gamma subunits is perhaps the best-characterized mechanism of action of neurotransmitter action through a GPCR. In contrast to activation by $G_{i/o}$ beta gamma, G_q coupled receptors inhibit Kir channels (Sharon et al. 1997), apparently through multiple mechanisms. KIR channels require $PI(3,4)P_2$ for activation (Hille et al. 2014). Activation of PLC downstream of a G_q protein-coupled receptor can therefore inhibit these channels by depleting $PI(3,4)P_2$ from the plasma membrane (Kammermeier 2012; Kobrinsky et al. 2000) in addition to activating PKC (Keselman et al. 2007). Besides these G_q -protein-dependent mechanisms, Group I mGlu receptors can also inhibit Kir3 channels through a G-protein-independent mechanism that appears to require only an increase in intracellular Ca^{2+} (Kramer and Williams 2016).

Retinal ganglion cells coexpress KIR2 channels and mGlu₁ (Li et al. 2016). As mentioned in “HCN channels” above, Group I mGlu receptor agonists depolarize these cells and increase the firing rate. Voltage clamp experiments demonstrate that activation of Group I mGlu receptors inhibits two components of current activated by hyperpolarization, one sensitive to ZD7288 (i.e., HCN current) and the other sensitive to Ba^{2+} , (i.e., a putative KIR current). Retinal Muller cells also coexpress Group I mGlu receptors and KIR channels. In these cells, Kir4.1 current is inhibited by DHPG acting through mGlu₅ (Ji et al. 2012). In both retinal cell types, the response to DHPG appears to be Ca^{2+} -dependent because it can be blocked by intracellular BAPTA. In ganglion cells, pharmacological inhibition of PLC, PKC, and CaMKII inhibited the response, whereas in Muller cells, CaMKII was not required.

Conclusions

We have attempted to provide a survey of the membrane transport proteins (mostly channels) that are modulated by Group I mGlu receptors and account for their effects on membrane potential and excitability. Many questions remain. For example, despite much progress, the pathway that links mGlu₁ to activation of TRPC3 in cerebellar Purkinje cells is still unclear. Also unclear are the desensitization mechanisms that can generate opposite responses when short synaptic-like pulses of agonist versus long steady-state applications are employed to activate receptors. What is clear is the wide range of cell types in which activation of Group I mGlu receptors leads to rapid changes in membrane excitability. Surely, other examples remain to be discovered.

Compliance with ethical standards

Conflict of interest Ana Maria Bernal Correa declares that she has no conflicts of interest. Jennifer Diniz Soares Guimarães declares that she has no conflicts of interest. Everton dos Santos e Alhadadas declares that he has no conflicts of interest. Christopher Kushmerick declares that he has no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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