Group I mGluR-induced Epileptogenesis: Distinct and Overlapping Roles of mGluR1 and mGluR5 and Implications for Antiepileptic Drug Design

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The group I metabotropic glutamate receptor subtypes, mGluR1 and mGluR5, have both distinct and overlapping actions in epileptogenesis. Data are reviewed revealing how activation of these receptor subtypes participates in the induction and maintenance of the long-lasting epileptiform discharges elicited in the hippocampal circuit. Differences in the cellular actions and regional distributions of mGluR1 and mGluR5 provide hints regarding the potential usefulness and limitations of subtype-specific antagonists as antiepileptic agents.

Introduction

Glutamate receptors are divided into two classes: ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). The iGluRs consist of *N*-methyl-D-aspartate (NMDA) receptors and non-NMDA receptors. The mGluRs are divided into three groups (for review, see 1–4). Group I includes mGluR1 and mGluR5, receptors that are coupled via $G_{q/11}$ protein and phospholipase Cβ (PLCβ) to inositol phospholipid metabolism. Group II includes mGluR2 and mGluR3, and group III includes mGluR4, mGluR6, mGluR7, and mGluR8. Group II and III mGluRs are negatively coupled to adenylate cyclase. Furthermore, splice variants of some mGluRs (mGluR1a, b, c, and d; mGluR4a and b; mGluR5a and b) differ in their carboxy-terminal sequences and in their coupling with intracellular pathways. With the use of selective agonists and antagonists of group I mGluRs, the roles of these receptors in various physiological and pathological conditions is unfolding (5,6). Substantial evidence now shows that activation of group I mGluRs is proconvulsant (7–9), and activation of group II and III mGluRs is anticonvulsant (10–12).

This review focuses on the epileptogenic properties of group I mGluRs. In particular, the differential roles of the subtypes mGluR1 and mGluR5 in cortical neuron excitability and epileptogenesis are discussed. Data regarding this issue are only just emerging. Available information is summarized, and four questions are addressed: (a) What are the distinct and overlapping roles of mGluR1 and mGluR5 in epileptogenesis? (b) Can the distinct roles of mGluR1 and mGluR5 in epileptogenesis be explained at the cellular level? (c) How can mGluR1 and mGluR5, coupled to a similar signaling cascade, elicit different effector responses? and (d) What is the distribution of mGluR1 and mGluR5 in the brain? Finally, the potential usefulness and limitations of antagonists against mGluR5 and mGluR1 in antiepileptic therapy are assessed.

What Are the Distinct and Overlapping Roles of mGluR1 and mGluR5 in Epileptogenesis?

Epileptogenesis, as with other synaptic plasticity processes in the brain, is distinguished by two temporal stages: an induction phase and a maintenance phase. During induction, cellular and biochemical mechanisms are activated to produce long-term modifications on the efficacy or density of effectors, which include ion channels and synaptic receptors. The induction phase is followed by the maintenance phase, in which the modifications of the effectors result in enhanced or depressed synaptic transmission [long-term potentiation (LTP) and long-term depression (LTD), respectively] or ictal discharges (in the case of epileptogenesis). Increasingly data indicate that the induction mechanisms underlying plasticity involve de novo protein synthesis. For example, induction of multiple forms of LTP and of group I mGluR-induced LTD is dependent on protein synthesis (13–15). Evidence suggests that the induction of group I mGluR-induced epileptogenesis also is protein synthesis dependent (16,17).

Activation of mGluR5 but not mGluR1 Induces Epileptogenesis

Epileptogenesis can be studied in vitro by inducing a persistent change in cortical excitability, resulting in long-lasting epileptiform activity. Selective group I mGluR agonists have been

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shown to do just that. In rodent hippocampal slices maintained in vitro, transient application of the selective group I mGluR agonist (*S*)-3,5-dihydroxyphenylglycine (DHPG) induces ictal-like discharges that persist for hours after removal of the agonist (18). This mGluR-mediated induction process can be blocked by inhibitors of protein translation (16) as well as tyrosine kinase inhibitors (17)—features in common with many long-lasting plasticity processes (13–15).

Synchronized epileptiform activity cannot be expressed in the presence of iGluR (NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]) blockers. Nevertheless, if group I mGluR activation takes place transiently during iGluR blockade, the permanent modification of the network excitability still occurs ("silent induction") and is revealed on removal of the iGluR blockers, at which time ictal-length discharges appear (19). Thus the induction of this form of epileptogenesis can be elicited by the activation of mGluRs alone, without a need for concomitant ongoing synchronized firing.

Through the use of subtype-selective antagonists, it has been possible to evaluate the separate roles of mGluR1 and mGluR5 in the induction of epileptogenesis (20). The results suggest that epileptogenesis in this model can be induced by the direct activation of mGluR5 alone but not by that of mGluR1 alone.

Synaptic Activation of Both mGluR1 and mGluR5 Maintains Group I mGluR-induced Epileptogenesis

Although the induction process underlying group I mGluR-induced epileptogenesis can be driven by mGluR5 activation alone, the maintenance of the seizure discharges involves mGluR1 and mGluR5. The persistent ictal-length discharges, which are induced by the transient activation of group I mGluRs and maintained in the absence of agonist, are blocked by the addition of group I mGluR antagonists (18,19). The results suggest that after induction, the ictal-length discharges are sustained by enhanced synaptic group I mGluR-mediated responses. Additional data reveal that, whereas both mGluR1 and mGluR5 are synaptically activated to maintain the ictal-length discharges, mGluR1 appears to play a more dominant role than mGluR5 (20).

Activation of Synaptic mGluR1 and mGluR5 Sustains Other Forms of Epileptiform Discharges

In addition to their contribution in the maintenance of agonist-induced, ictal-like discharges, postsynaptic mGluR1 and mGluR5 also are excited during ictal-length synchronized discharges elicited by 4-aminopyridine (4-AP) and bicuculline (21). Individually, the mGluR1 antagonist LY 367385 or the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) significantly reduces the length of these epileptiform discharges. The effects of the antagonists are additive, suggesting that mGluR1 and mGluR5 are synaptically activated during the expression of these 4-AP–induced epileptiform discharges, exerting both separate and synergistic actions to lengthen the discharges (21).

Additional data show that the synaptic sensitivity of mGluR1 and mGluR5 is relatively high in the cortex, as these receptors are activated by glutamate released during nonepileptic baseline neuronal activity (22). If activation of mGluR5 by exogenous agonists induces epileptogenesis, why is it that the synaptic activation of these receptors does not cause a similar effect? One possible explanation is that the signaling processes coupled to synaptic mGluR1 and mGluR5 are regulated. For example, stimulation of these synaptic receptors cannot activate the signaling cascade downstream from PLCβ activation (21). Thus transduction processes downstream from PLCβ, including the protein synthesis necessary for epileptogenesis, are not turned on after synaptic mGluR1 or mGluR5 activation. In contrast, agonist application excites extrasynaptic mGluR1 and mGluR5, in addition to the synaptically localized receptors. Conceivably, extrasynaptic mGluR1 and mGluR5 are not regulated in the same way as are the synaptic receptors, and epileptogenesis may be induced only via the unimpeded signaling processes coupled to extrasynaptic mGluR5 and mGluR1 receptors.

Can the Distinct Roles of mGluR1 and mGluR5 in Epileptogenesis Be Explained at the Cellular Level?

One prominent effect of group I mGluR stimulation is the appearance of a voltage-dependent cationic current (23,24). The current, which is detected only in the presence of group I mGluR agonist, is termed $I_{\mathrm{mGluR(V)}}$. $I_{\mathrm{mGluR(V)}}$ is turned off when the cell is hyperpolarized. It has an activation threshold of about –75 mV; its amplitude increases with depolarization, with a reversal potential of about –15 mV; and it is noninactivating. $I_{\mathrm{mGluR(V)}}$ produces significant changes in the firing properties of the cell, in that it causes prolonged periods of rhythmic firing followed by silent periods. Each period of firing can last from 2 to 15 seconds and is followed by silent periods of similar duration. The patterning of cell firing by $I_{\mathrm{mGluR(V)}}$ is considered to be the elementary event underlying the group I mGluR–induced, ictal-like synchronized discharges observed in the hippocampal neuronal population (24,25).

Available data suggest that $I_{\mathrm{mGluR(V)}}$, the cellular response necessary for the group I mGluR–induced epileptogenesis, is elicited by stimulation of mGluR1 and not mGluR5 (26). This inference is based on two observations: First, $I_{\mathrm{mGluR(V)}}$ is elicited only in CA3 pyramidal cells and not in CA1 pyramidal cells (26). Immunocytochemical studies show that CA1 pyramidal cells express primarily mGluR5 and are deficient in the

expression of mGluR1 (27,28). CA3 pyramidal cells, in contrast, express both mGluR1 and mGluR5. Second, $I_{mGluR(V)}$ is not activated in CA3 pyramidal cells of mGluR1 knockout mutant mice (26). Group I mGluR agonists also cannot elicit ictal-like discharges in the hippocampus of mGluR1 knockout mice (26). An mGluR1-activated inward current with properties similar to those of $I_{mGluR(V)}$ also was described by Heuss et al. (29).

As mentioned earlier, mGluR5 plays a more prominent role in the induction of epileptogenic discharges than does mGluR1 (20). It is possible that the mGluR5-mediated induction process enhances the mGluR1-mediated $I_{mGluR(V)}$ response in a manner such that the current is activated by synaptic glutamate release and is capable of sustaining ictal-like discharges during the maintenance phase. Enhancement of the mGluR1 response may consist of an upregulation of mGluR1 mRNA and protein expression, such as those observed accompanying the progression of electrically kindled seizures (30,31).

How Can mGluR1 and mGluR5, Coupled to a Similar Signaling Cascade, Elicit Different Effector Responses?

mGluR1 and mGluR5 are both coupled to $G_{q\text{-}11}$ protein. Activation of mGluR1 or mGluR5 causes the dissociation of the trimeric G protein into the Gα and G$\beta\gamma$ subunits. The Gα subunit then elicits inositol 1,4,5-trisphosphate (IP_3)/Ca^{2+} and diacylglycerol/protein kinase C (PKC) signaling processes. Despite the similarity in the signaling cascade, mGluR1 and mGluR5 can take on different roles in epileptogenesis, as previously discussed. Although the specific biochemical mechanisms enabling mGluR1 and mGluR5 to elicit distinct responses are unclear, available data suggest at least two possibilities: (a) different regulation by phosphorylation and (b) different organization of the signaling microdomains.

Different Regulation by Phosphorylation

Because of differences in amino acid sequence at particular sites, mGluR1 and mGluR5 may be regulated differently by phosphorylation. For example, in cultured cells expressing either mGluR1 or mGluR5, mGluR1 stimulation evokes single-peak Ca^{2+} responses, whereas stimulation of mGluR5 elicits oscillatory Ca^{2+} responses in the same cells (32). The difference in the Ca^{2+} response kinetics results from single amino acid substitution at corresponding positions in these receptors—aspartate is located at position 854 of mGluR1, and threonine, at position 840 of mGluR5 (32). PKC-induced phosphorylation of the threonine of mGluR5 is responsible for the oscillatory Ca^{2+} responses (32–34).

Different Organization of the Signaling Microdomains

The action of $G_{q/11}$-coupled receptors that shut off the M current (mediated by KCNQ-type K^+ channels) serves as an example on how divergent effects can be triggered by receptors, such as mGluR1 and mGluR5, coupled to the same PLCβ-mediated signaling cascade. Interestingly, closure of the KCNQ/M channels can cause epilepsy (35). KCNQ/M channels are closed by acetylcholine binding to M_1 muscarinic receptors or by bradykinin binding to B_2 receptors (36,37). When activated, both receptors stimulate the PLCβ pathway and appear to close the KCNQ/M channels through different mechanisms. This action is due to gating of the KCNQ/M channels by at least two molecules. First, the open state is maintained by binding of membrane phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)*P*2] (38). Second, KCNQ/M channels are closed when intracellular Ca^{2+} increases above 100 n*M* (39), presumably through an action on calmodulin, which is associated with the KCNQ/M channel subunits (40,41). The bradykinin-receptor stimulation activates the Ca^{2+} mechanism for channel closure (42), whereas muscarinic receptors effect channel closure through the decrease in membrane PtdIns(4,5)*P*2 as a result of PLCβ-mediated hydrolysis (38,42,43). The reason for this difference is that activation of bradykinin receptors elicits sufficient increase in Ca^{2+} level for the response, whereas any increase in Ca^{2+} elicited by activation of muscarinic receptor is too small (44).

Why would bradykinin receptors and muscarinic M_1 receptors, activating the same signaling pathway, elicit different levels of increased intracellular Ca^{2+}? Bradykinin receptors are organized in microdomains in which the receptor, the $G_{q\text{-}11}$ protein, PLCβ, and IP_3 receptors are closely associated, so that IP_3 signaling elicits vigorous Ca^{2+} responses (45). In contrast, M_1 receptors are not clustered as tightly with IP_3 receptors, and the spatial separation causes a reduced Ca^{2+} response (45).

These findings illustrate how two types of receptors, both engaging the PLCβ signaling pathway, can generate receptor-specific signals through a spatial segregation of the subcomponents of the PLCβ signaling protein complex. Whether the described mechanisms for bradykinin and muscarinic receptors also are engaged to enable mGluR1 and mGluR5 to elicit distinct cellular responses is unknown, but possible.

What is the Distribution of mGluR1 and mGluR5 in the Brain? Implications for the Potential Use of Group I mGluR Antagonists as Antiepileptic Agents

Immunocytochemistry and in situ hybridization studies for marking protein and mRNA, respectively, of mGluR1 and mGluR5 show that the receptors are well distributed over wide regions of the neocortex, hippocampus, and other mid- and hindbrain regions (46–48). Detailed studies within regions

of the brain revealed a differential pattern of mGluR1 and mGluR5 expression. Three examples of note are (a) Purkinje cells of the cerebellum express only mGluR1 and not mGluR5 (49,50); (b) CA1 pyramidal cells of the hippocampus express primarily mGluR5 and not mGluR1 (in contrast, CA3 pyramidal cells express both mGluR1 and mGluR5) (27,51); and (c) some interneurons in the hippocampus also may show exclusive mGluR5 expression (52).

Because of the dominant presence of mGluR1 in the cerebellum, disturbance of the receptor function affects motor function. Aiba et al. (53) generated a mouse strain deficient in mGluR1 by targeted disruption. They found that the mGluR1(-/-) mutant mice (which lack mGluR1) were viable but showed characteristic cerebellar symptoms, such as ataxic gait and intention tremor. Conquet et al. (54) independently generated mGluR1-deficient mice by targeted disruption. Their mGluR1(-/-) mice had severe motor dyscoordination and spatial-learning deficits. Finally, Sillevis Smitt et al. (55) demonstrated that autoantibodies against mGluR1a were responsible for severe paraneoplastic cerebellar ataxia in two patients in remission from Hodgkin disease. These data demonstrate the dominant role of mGluR1 in cerebellar function and motor control, limiting the usefulness of mGluR1 antagonists as potential antiepileptic drugs (AEDs).

Because mGluR5 is not expressed in cerebellar Purkinje cells, absence of mGluR5 function in knockout mutants (56) does not disturb motor function. In view of the physiological finding that mGluR5 is necessary for the induction of epileptogenesis (20), mGluR5 may represent a target for AED development. However, it should be noted that mGluR5 also subserves cognitive functions. Lu et al. (56) found that the mGluR5 (-/-) mutant mice were impaired in the acquisition and use of spatial information. The authors proposed that mGluR5 plays a key regulatory role in NMDA receptor–dependent LTP and that LTP in the CA1 region may underlie spatial learning and memory. Thus the usefulness of mGluR5 antagonists as AEDs depends on further analysis of the sensitivity of mGluR5 in these various functions. A case can be made for using the antagonist against epileptogenesis in conditions in which the mGluR5 function is exaggerated, such as in the fragile X mental retardation syndrome (57).

Finally, relevant to the issue of designing AEDs that can decrease mGluR function, emerging data show that the constitutive activity of mGluR1 and mGluR5 is controlled by Homer proteins, which bind directly to the receptor carboxy-terminal intracellular domain (58,59). Disruption of this interaction by mutagenesis or antisense strategies as well as expression of endogenous Homer1a can induce constitutive activity in mGluR1a or mGluR5 (60). These data suggest that mGluR1 and mGluR5 can be directly activated by both intracellular proteins and agonists. Thus it is possible that exaggerated group I mGluR action cannot be suppressed by receptor antagonists alone. Rational design of AEDs against metabotropic glutamate receptors also must take into account the peculiar gating mechanisms of these receptors.

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