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mGluRs Modulate Strength and Timing of Excitatory Transmission in Hippocampal Area CA3

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Abstract Excitatory transmission within hippocampal area CA3 stems from three major glutamatergic pathways: the perforant path formed by axons of layer II stellate cells in the entorhinal cortex, the mossy fiber axons originating from the dentate gyrus granule cells, and the recurrent axon collaterals of CA3 pyramidal cells. The synaptic communication of each of these pathways is modulated by metabotropic glutamate receptors that fine-tune the signal by affecting both the timing and strength of the connection. Within area CA3 of the hippocampus, group I mGluRs (mGluR1 and mGluR5) are expressed postsynaptically, whereas group II (mGluR2 and mGluR3) and III mGluRs (mGluR4, mGluR7, and mGluR8) are expressed presynaptically. Receptors from each group have been demonstrated to be required for different forms of pre- and postsynaptic long-term plasticity and also have been implicated in regulating short-term plasticity. A recent observation has demonstrated that a presynaptically expressed mGluR can affect the timing of action potentials elicited in the postsynaptic target. Interestingly, mGluRs can be distributed in a target-specific manner, such that synaptic input from one presynaptic neuron can be modulated by different receptors at each of its postsynaptic targets. Consequently, mGluRs provide a mechanism for synaptic specialization of glutamatergic transmission in the hippocampus. This review will highlight the variability in mGluR modulation of excitatory transmission within area CA3 with an emphasis on how these receptors contribute to the strength and timing of network activity within pyramidal cells and interneurons.

Keywords Metabotropic glutamate receptor · Long-term plasticity · Short-term plasticity · Hippocampus · Spike transmission

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Introduction

Glutamate is the major excitatory neurotransmitter in the nervous system. The synaptic release of glutamate, and its reception by ionotropic glutamate receptors, provides the primary source of information transfer in the central nervous system. As with any form of communication, the ability to provide nuance to a piece of information is useful and often necessary to convey appropriate messages. Thus, in addition to the presence of postsynaptic ionotropic glutamate receptors, pre- and postsynaptic metabotropic receptors are frequently present to fine-tune the synaptic communication between neurons. The importance of metabotropic glutamate receptors (mGluRs) is highlighted by their linkage to numerous disorders including epilepsy and schizophrenia [1–3]. The mechanisms by which these receptors modulate synaptic communication have been the subject of ongoing study for decades, yet we are just beginning to understand how frequently the regulation of synaptic transmission by mGluRs dictates the output of a circuit. In this review, we will focus primarily on hippocampal area CA3 to highlight some of the instances

where mGluRs are strong regulators of both synaptic strength and the timing of network activity.

mGluRs are categorized into three different groups based on gene product and sensitivity to specific agonists [4]. Group I mGluRs are composed of splice variants of mGluR1 and mGluR5 receptor subtypes. The activity of these receptors has been shown to be coupled to phosphatidylinositol hydrolysis via phospholipase C, which increases intracellular Ca^{2+} concentration, activates ryanodine-sensitive calcium stores [5–7], and modulates the activity of different voltage-gated channels [8–10]. Group II mGluRs are comprised of mGluR2 and mGluR3, while mGluR4, mGluR6, mGluR7, and mGluR8 make up group III mGluRs. Of these, all but mGluR6 can be found within hippocampal area CA3. Both group II and III mGluRs have been shown to be negatively coupled to adenylyl cyclase (AC), decreasing the production of cyclic AMP (cAMP), and frequently resulting in a decrease in transmitter release [11, 12].

The distribution of mGluRs has been investigated anatomically using in situ hybridization, immunohistochemistry, and electron microscopy. Additional studies have utilized electrophysiological and pharmacologic techniques to determine the functional distribution of mGluRs. From these studies, we have come to understand that, though mGluRs have a wide distribution, subtypes of mGluRs are selectively expressed in different groups of neurons. Furthermore, the presynaptic distribution of mGluRs can follow a target-cell-dependent distribution pattern.

Anatomical Distribution of mGluRs Within Area CA3

Group I mGluRs are expressed in the periphery of the postsynaptic densities of asymmetrical synapses [13] and are located throughout all the hippocampal fields. Although there is some overlap, mGluR1 and mGluR5 have distinct patterns of distribution. mGluR1 is highly expressed in some pyramidal cells of area CA3, the molecular and granular layers of the dentate gyrus, with high levels of expression in the somata of granule cells. Furthermore, area CA3 interneurons show a relatively uniform pattern of distribution of mGluR1 in all the CA3 lamina [14–16]. It is noteworthy that a splice variant of mGluR1, mGluR1α, is expressed predominantly by interneurons containing somatostatin and, in some cases, neuropeptide Y [14], although expression in other subtypes of interneurons has been reported [17]. Like other group I mGluRs, mGluR1α shows a preferential localization to the periphery of the postsynaptic densities of hippocampal cells, and an extrasynaptic localization to both dendrites and somatic membrane has been observed [14]. In contrast, mGluR5 is highly expressed in the dendritic processes of the molecular layer of the dentate gyrus, the hilus, and minimally expressed in str. lucidum of CA3 [15, 16]. Partly as a result of this widespread distribution, group I mGluRs have been shown to mediate neuronal excitability, network synchronization [18, 19], and different forms of synaptic plasticity involving both principal and inhibitory cells of the hippocampus (Fig. 1).

In contrast to group I mGluRs, group II and III mGluRs are distributed presynaptically. Anatomic data demonstrate that group II mGluRs are found in the perisynaptic region of presynaptic terminals [16]. Within CA3, group II mGluRs are found on terminals of the medial perforant path (MPP) [16, 20] and on mossy fiber (MF) boutons [16]. Anatomical and physiological data have demonstrated the consistent presence of group II mGluRs on MF terminals at all postsynaptic cell types thus far investigated, including pyramidal cells [21], CA3 interneurons [22–25], and hilar interneurons [26–28]. Activation of group II mGluRs frequently results in a decrease in transmitter release [11], sometimes as a result of the phosphorylation of release machinery [29, 30] or activation of K^+ channels in the terminal [31] as a downstream result of inhibition of AC activity.

Group III mGluRs are also expressed presynaptically, but their distribution pattern is distinct from group II mGluRs. Rather than expression in perisynaptic regions, group III mGluRs are localized within the active zone of presynaptic terminals [16] and have been found to have a target-specific expression pattern in CA3, as they are distributed non-uniformly on synaptic boutons of pathways [16, 32]. The immunolocalization of mGluR4 on presynaptic terminals forming asymmetric synapses in CA3 is diffuse and prominent only in the inner and middle one third of the dentate gyrus molecular layer [16, 32, 33]. In contrast, the distribution of mGluR8 is pronounced in the str. lacunosum moleculare of CA3 and has been attributed to the axon terminals of the lateral perforant path [16, 34] because lesions to the entorhinal cortex decrease (though do not eliminate) this staining [16]. Recent physiological evidence suggests that some of the remaining mGluR8 staining observed in the str. lacunosum moleculare may be on MF axons en route to the str. lucidum [23], as these axons are coextensive with the perforant path (PP) in the str. lacunosum moleculare of area CA3 [35]. Supporting this possibility is the finding that mRNA for mGluRs 4 and 8 are found within dentate gyrus granule cells [34, 36–38]. Additionally, within area CA3, mGluR7 has been shown to be selectively expressed on MF terminals contacting interneurons, but not pyramidal cells [16]. There is also evidence for mGluR7 immunoreactivity in the PP and recurrent collateral (RC) axons of CA3 pyramidal cells [16]. Activation of group III mGluRs frequently results in a decrease in transmitter release that tends to be, at least in part, due to inhibition of the presynaptic voltage-gated

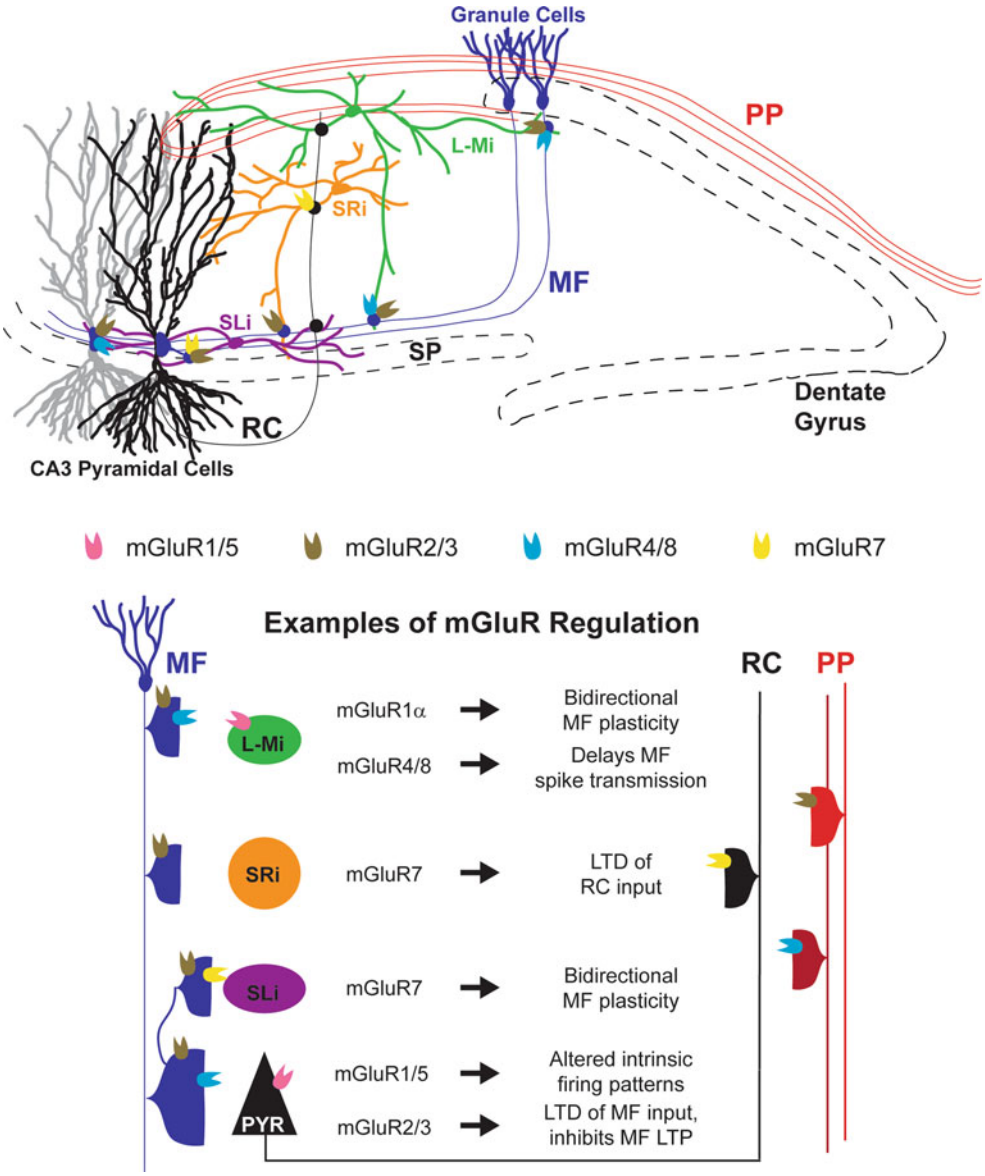

Fig. 1 Anatomical location and modulatory function of mGluRs in hippocampal area CA3. *Top panel* shows a schematic representation of the differential distribution of presynaptic mGluRs within the circuit of area CA3. *Bottom panel* shows a simplified cartoon of CA3 highlighting distribution of pre- and postsynaptic mGluRs with corresponding examples of the modulatory function of mGluRs. *L-Mi* str. lacunosum moleculare interneuron, *SRi* str. radiatum interneuron, *SLi* str. lucidum interneuron, *SP* str. pyramidale, *PYR* CA3 pyramidal cell, *MF* mossy fiber, *RC* recurrent collaterals, *PP* perforant path

calcium channel (VGCC) linked to the triggering of transmitter release from the nerve terminal [23, 31, 39, 40].

The distribution of mGluRs through the hippocampus (Fig. 1), and indeed the CNS at large, coupled with the variety of effecter mechanisms linked to the receptors, positions these receptors to strongly influence the dynamics of the network. These anatomical findings indicate that specific synapses may be independently regulated by mGluRs. For example, the MF input to str. lacunosum moleculare interneurons (L-Mi), which express mGluR1α, is modulated by mGluR2/3 and mGluR4/8 presynaptically [23, 41], whereas MF terminals contacting str. lucidum interneurons express mGluR7 and mGluR2/3 [42]. Consequently, though both interneurons receive glutamatergic MF input, the combination of modulating receptors is different, both pre- and postsynaptically, and the response to glutamate may be different. This is further highlighted when the affinities of the receptors for glutamate are considered, with mGluR7 requiring high concentrations of glutamate (~1 mM) and mGluR1α and mGluR4/8 requiring lower concentrations (9–13 and 3–38 μM, respectively) [4], thus making it likely that different patterns of glutamate release would be required for activation. The next sections will discuss the functional impact of the differential distribution among other examples of mGluR regulation of the CA3 network.

Regulation of Synaptic Strength by mGluRs

The strength of a connection is defined by the amplitude of the postsynaptic response to a transmitter release event.

However, synaptic strength is not static, as it can be transiently influenced by patterns of activity in the short term (short-term plasticity), as well as by patterns of activity that persistently change the strength of the connection (long-term plasticity). mGluRs can be activated by synaptically released glutamate and by spillover from neighboring synapses [43, 44], depending on their synaptic location and the affinity of the receptor for glutamate [45]. Because of this, different receptors will require varying levels of glutamatergic activity to become active. Consequently, if multiple mGluRs with different affinities or subcellular distributions are present at a synapse, they may be activated independently by different patterns of activity and subsequent changes in the concentration of extracellular glutamate, adding further functional complexity to the synaptic communication at that synapse.

Long-Term Synaptic Plasticity

mGluR-mediated long-term plasticity can be observed at many connections in the hippocampus [46–48]. Examples of this include an LTD at RC input to str. radiatum interneurons that requires mGluR7 activation [49], as well as the sensitivity of both RC and granule cell input to hilar border interneurons to the group I mGluR agonist DHPG [27]. The MF pathway of CA3 in particular, however, is regulated in multiple ways by mGluRs and provides an elegant example of the variety of functions mGluRs can serve in regulating the strength of an input to its various targets.

One of the "hallmarks" of MF input to CA3 pyramidal cells is the profound sensitivity to activation of group II mGluRs on the MF bouton [21, 50]. The expression of group II mGluRs has been shown to be important in regulating the strength of the connection as prolonged activation of these receptors during bouts of low frequency MF activity results in LTD [30, 51]. This LTD can be mimicked pharmacologically by the prolonged application of an mGluR2/3 agonist, which acutely decreases transmitter release [52, 53] and eventually results in a persistent decrease in the strength of the synapse ([30], but see [54]). Additionally, activation of mGluR2 has been shown to inhibit the expression of long-term potentiation [30, 55], thus strongly influencing the strength of the MF–CA3 pyramidal cell connection. The mechanism underlying mGluR2 regulation of MF input to CA3 pyramidal cells has been postulated to rely on the activation state of PKA [30]. mGluR2 is coupled to $G\alpha_{i2}$ [56], which, when activated, inhibits cAMP production and, subsequently, PKA activity [30]. Although the protein that is the target of PKA has not been definitively demonstrated in the hippocampal MF, it is thought to be a protein in the release machinery, possibly either a rabphillin or RIM1α [30], as both are substrates for PKA phosphorylation, and RIM1α is the target of mGluR2 activation in the cerebellar climbing fiber synapse [29]. Furthermore, genetically modified mice lacking either RIM1α or Rab3A have been shown to have impaired plasticity at the MF synapse [57, 58].

At MF input to str. lucidum interneurons, however, long-term plasticity is regulated by the presynaptic expression of mGluR7 rather than the group II mGluRs [42]. The target specific expression of mGluR7 on MF terminals contacting interneurons, but not pyramidal cells [16], allows for the connection between the MF and pyramidal cells or interneurons to be differentially regulated. The stereotyped high frequency activity that results in LTP at MF input to CA3 pyramidal cells instead induces an LTD at MF input to str. lucidum interneurons [24, 59]. The mechanism underlying this LTD involves inhibition of Ca^{2+} entry into the terminal through P/Q-type VGCCs [39]. Surprisingly, however, this inhibition is dependent on protein kinase C binding of PICK1 [42, 60], rather than PKA, which is downstream of AC activation, the classic pathway associated with group III mGluRs [4]. Furthermore, when mGluR7 is internalized as a result of extended periods of activation using the agonist L-AP4, an LTP is revealed, demonstrating bidirectional plasticity [42]. Interestingly, this LTP is dependent on the AC–cAMP–PKA pathway, and it is postulated that this is because mGluR7 is sequestering the requisite substrate for PKA activity, RIM1α [29, 61]. This synapse highlights the potential complexity that mGluR regulation can add to a connection, where the presence or absence of the receptor can modulate a synapse regardless of whether the receptor has been activated.

A third example of regulation of synaptic strength of MF input to its targets is found at the MF to L-Mi synapse. It was recently found that the group I mGluR, mGluR1 but not mGluR5, plays a fundamental role in the bidirectional plasticity of MF input to L-Mi [41]. In contrast to the LTD observed at MF to str. lucidum interneuron synapses, at the MF to L-Mi connection, high frequency stimulation of the MF elicits a robust posttetanic potentiation followed by a stable postsynaptically expressed LTP [41]. However, in slices with a pharmacological pretreatment to block mGluR1, the same protocol induced a presynaptic LTD [41].

mGluR1 activation frequently results in the liberation of Ca^{2+} from internal stores, which is commonly regulated by IP_3 and ryanodine receptors (RyR) [1]. In dentate gyrus and CA3 cells, the expression level of RyR is higher than IP_3 receptors [62], with strong immunoreactivity for RyR isotype 3 in the str. lacunosum moleculare [63]. In keeping with this, it was found that the inclusion of ryanodine (the RyR antagonist) in the recording pipette when recording from L-Mi not only blocked the induction of MF LTP, but

triggered a similar LTD to that obtained when the mGluR1 was blocked. Together, these data indicate that the interaction between IP_3R and RyR dynamically regulate increases in intracellular calcium [64] and thus determines the balance between MF LTP and LTD in L-Mi of area CA3 [41].

These examples highlight the different ways that mGluRs can persistently alter the strength of a synapse through both pre- and postsynaptically mediated mechanisms. Through varying combinations of these modulating receptors, it is possible to have different responses to the same pattern of activity (e.g., high frequency activity in the MF results in a presynaptic LTP at CA3 pyramidal cells, a presynaptic LTD mediated by mGluR7 activation in str. lucidum interneurons, and a postsynaptic LTP in L-Mi that requires mGluR1α activation; for further review, see [47]). In considering the role of mGluRs in regulating synaptic activity in vivo, it is important to remember that many of these induction protocols are outside of the normal physiological activity of the brain and provide us with information on mechanisms that are available to the neuron, but not necessarily utilized in vivo. More recent studies have begun to emphasize spike-timing-dependent mechanisms of long term plasticity that may better mimic in vivo mechanisms [65]. With that caveat, however, the information gained from the above (and similar) studies provide insight into the range of actions mGluRs can effect, and provide a better understanding of the flow of information through the hippocampus.

Short-Term Synaptic Plasticity

To address the potential role of mGluRs in modulating synaptic activity on a relatively short time scale, in this section, we will discuss evidence that mGluRs are involved in adjusting the strength of a connection on a second to subsecond time scale. The examples presented above demonstrate the involvement of mGluRs in long-term changes in synaptic strength. Much of synaptic activity, however, occurs in the short term.

Frequency facilitation is a presynaptic form of short-term plasticity where the amplitude of the postsynaptic response increases as the frequency of presynaptic activity increases from very low (~0.05 Hz) to moderate frequencies (1–5 Hz) [50, 66, 67]. Importantly, these frequencies are relevant to the function of CA3 as the frequency of granule cell firing in vivo is quite low [68, 69]. Within area CA3, both the RC and MF inputs to CA3 pyramidal cells and str. lucidum interneurons undergo frequency facilitation, though the facilitation observed at the MF is notably more robust [66, 67]. Interestingly, these moderate frequencies are sufficient to activate presynaptic mGluRs, as frequency facilitation is even more robust in the presence of the broad-spectrum mGluR antagonist, MCPG [67, 70]. Furthermore, at the MF to pyramidal cell synapse, a similar effect is seen when selectively preventing activation of group II mGluRs [70]. Thus, even at moderate frequencies (1 Hz), sufficient glutamate is present in the synaptic milieu to activate mGluRs in the pre-terminal region, affecting release of glutamate and changing the dynamics of the synapse.

Although the baseline firing of granule cells is quite low, bursts of activity in the gamma frequency band (40–60 Hz) have also been observed in CA3 of the hippocampus [71, 72]. Short-term plasticity recorded in vitro in response to high frequency bursts of activity in the form of paired pulse, and short train facilitation or depression is also known to be sensitive to the expression of presynaptic receptors, including mGluRs [11]. Activation of mGluRs during high frequency activity highlights the complex balance of factors that dictate transmitter release characteristics in a terminal (for review, see [73]). The perforant path (PP) is modulated by the expression of mGluRs on presynaptic terminals with the LPP expressing group III mGluRs and the MPP expressing group II. Activation of either of these receptors decreases transmitter release from the respective pathway and thus decreases the amplitude of the postsynaptic response [20, 74]. Interestingly, however, this decrease in the amplitude of single responses has the additional impact of altering the short-term plasticity of PP connections with its targets. Under control conditions, the MPP undergoes short-term depression at high frequencies of stimulation [75]. Activation of the group II mGluRs on the MPP causes the synapse to switch from depressing to facilitating [75]. Similarly, activation of group III mGluRs increases the amount of facilitation seen at LPP inputs to the dentate gyrus [76]. Thus, the impact of the activation of these mGluRs on PP terminals is not simply to decrease the strength of the synapse but to also change the integration of sequential release events by the postsynaptic target. This change in the strength of the connections can then lead to shifts in the timing of the postsynaptic cell's activity, as will be discussed in the next section.

mGluR-Mediated Regulation of Action Potential Firing

As the output neuron of CA3, CA3 pyramidal cell firing is a reflection of the total network activity in area CA3. This output can be influenced not only by adjusting the strength of its inputs but also by altering the balance and timing of inhibitory vs. excitatory inputs. Interestingly, within CA3, mGluRs are involved in regulating the firing of these pyramidal cells by altering both their intrinsic properties as well as the timing of their inputs.

Modulation of Intrinsic Properties Results in Changes of Synaptic Timing

The firing pattern of CA3 pyramidal cells is sensitive to activation of mGluRs. In granule cells of the dentate gyrus, activation of mGluR1 inhibits the calcium-activated potassium current responsible for the postspike afterhyperpolarization (I_{AHP}) [5]. Similar effects occur in pyramidal cells of CA3, as stimulation of mGluR1 modifies the firing pattern of pyramidal cells, transforming the regular one-spike firing pattern to bursts of action potentials [77, 78]. In both cases, mGluR1 blocks the I_{AHP} via G proteins [5, 9, 78]. It is noteworthy that in addition to the inhibition of I_{AHP}, mGluR1 has been reported to trigger an additional transduction mechanism: an MF-evoked postsynaptic response mediated by activation of a protein tyrosine kinase from the Src family. Interestingly, though this response requires activation of mGluR1, it is independent of G proteins [79], adding an additional potential mechanism through which mGluRs can act.

Inhibitory Input to CA3 Pyramidal Cells Is Modulated by mGluRs

In addition to changing the intrinsic properties of CA3 pyramidal cell firing by changing the activity of channels responsible for creating the after hyperpolarization of the action potential, mGluRs are linked to the timing of inhibitory inputs to CA3 pyramidal cells. Miles and Poncer [80] observed that chemical activation of mGluRs increases the frequency of inhibitory postsynaptic potentials recorded in CA3 pyramidal cells. Moreover, mGluR activation induced rhythmic activity of the inhibitory postsynaptic responses followed by a depolarization and decrease in the I_{AHP}. One potential source of the altered inhibitory input to CA3 pyramidal cells was reported by Mori and Gerber [81], who showed that synergistic activation of mGluR1/5 induces a slow EPSC in the CA3 interneurons located in the str. oriens and str. radiatum. Interestingly, this synergistic effect is mediated by the release of glutamate from the RC of CA3 associational fibers and not from the MF that directly contact the interneurons.

Perhaps the most important aspect of short-term plasticity is the determination of whether a particular pattern of input results in an action potential in the postsynaptic cell. Historically, the MF to pyramidal cell input has been termed a “detonator” synapse, where the initial, or at least paired, input was so strong as to nearly always result in transmission of an action potential from the MF to pyramidal cell [50]. In contrast, an in vivo report has demonstrated that MF input to interneurons does not reliably result in spike transmission. Instead, the probability of spike initiation increases throughout a train of high frequency input [68], a finding that has been supported with recent in vitro findings at both str. lucidum interneurons and L-Mi in CA3, where the probability of the interneuron firing in response to a single MF input was very low [23, 82].

Interestingly, however, MF input to these two groups of interneurons is under the control of different presynaptic mGluRs, with input to str. lucidum interneurons being modulated by mGluR7 [16, 42], an mGluR with low affinity for glutamate [4], and input to L-Mi being modulated by the high affinity mGluRs 4/8 [23]. At the MF to L-Mi synapse, we have recently demonstrated that the presence of mGluRs 4/8 regulates the timing of spike transmission between the MF and L-Mi. Because the affinity of mGluRs 4/8 is so high, short trains of high frequency activity (20–40 Hz) release enough glutamate to activate the mGluRs on MF terminals synapsing onto L-Mi. When activation of mGluRs 4/8 was prevented by application of the competitive antagonist MSOP, the probability of spike transmission was higher, and the latency to first action potential was shorter at MF input to L-Mi [23]. Consequently, activation of presynaptic mGluRs on MF terminals contacting L-Mi decreases transmitter release enough that the integration of MF input by the L-Mi is hindered, thus delaying feedforward inhibition to the CA3 pyramidal cell. Therefore, the presence of mGluRs on MF terminals can profoundly affect the timing of the output of the network.

Together, these examples demonstrate the various ways that mGluRs regulate the output of the CA3 network, through both regulating the intrinsic firing properties of CA3 pyramidal cells, as well as influencing the timing of inhibition converging on the pyramidal cells.

Summary

The examples provided above illustrate some of the many ways that mGluRs regulate the CA3 network (Fig. 1). It is worth noting that each of the three major excitatory inputs to CA3 (PP, MF, and RC) is modulated by mGluRs in a different way. Furthermore, mGluR activation has different outcomes based upon the location of the receptor, the source of glutamate, and the frequency of the input. Consequently, synapses can be independently modulated based on the complement of receptors present and the activity of the network. The effect of activation can range from changing the intrinsic properties of the cell, to decreasing transmitter release, to changing the polarity of long-term plasticity.

It should also be emphasized that these are receptors capable of responding to homosynaptic glutamate release as well as ambient glutamate levels depending on the receptor’s affinity. As several of the experiments cited

above reveal, low (~1 Hz) and moderate (5–20 Hz) frequencies of activity result in sufficient increases in extracellular glutamate to activate presynaptic mGluRs [23, 44, 70], emphasizing the ability of mGluRs to respond to even small changes in extracellular glutamate concentrations, similar to what has been reported for high affinity NMDA receptors [83, 84]. From these studies, it stands to reason that longer and/or high frequency periods of activity could be required to result in sufficient synaptic spillover to recruit extrasynaptic mGluRs, whereas mGluRs within the synaptic cleft may require less activity to become active.

Presynaptically, the differential localization of mGluRs, with group II mGluRs residing in the periterminal region and group III mGluRs localized within the active zone [16], allows for further diversification of their functions based upon microdomains of intracellular signaling machinery in spite of reports that both inhibit AC activity [4]. Although both receptor groups target AC, there is evidence that the two receptors have different sources for AC, as the effect of activation of both receptors is additive, where activation of group III mGluRs does not occlude the activation of group II mGluRs [23]. Additionally, the downstream targets of the two receptor groups can vary significantly even within the same pathway, with group III mGluRs frequently targeting VGCCs linked to release [23, 39] and group II mGluRs targeting release machinery or potassium channels [29–31]. The mossy fiber provides an especially elegant example of the complexity and variety of modulations mGluRs can effect. Although group II mGluRs have been found on all terminals investigated thus far, the effect of activation varies. At MF input to CA3 pyramidal cells, prolonged activation of group II mGluRs can lead to a long-term depression [30], while brief activation results in a profound (~90%) decrease in glutamate release and the subsequent postsynaptic response [21]. In contrast, activation of group II mGluRs decreases glutamate release at MF to interneuron synapses, and the acute effect is not as robust, decreasing the amplitude of the postsynaptic response by only ~60% [26, 41, 82]. Additionally, prolonged activation does not result in long-term depression at interneuron synapses.

In addition to group II mGluRs, MF terminals also express group III mGluRs in a target-specific manner, with mGluR7 determining the directionality of plasticity of MF input to str. lucidum interneurons [42]. Conversely, MF input to pyramidal cells and L-Mi is regulated by a high affinity group III mGluR that profoundly impacts the probability of spike transmission at the MF to L-Mi synapse [23]. Furthermore, L-Mi express the group I mGluR, mGluR1α, which determine the directionality of postsynaptically expressed long-term plasticity at the MF to L-Mi synapse [41].

Although CA3 is a relatively small region of the brain, it is important for learning and memory and serves as a useful model system for understanding the rules of synaptic connectivity and plasticity. As these examples highlight, network connectivity depends not just on synaptic transmission with ionotropic receptors and the balancing of excitation and inhibition but also on fine-tuning that synaptic communication. Because mGluRs have glutamate as a ligand and have specialized intracellular signaling pathways, synaptic localizations, and affinities, they are able to respond to and modulate the main excitatory signal propagating through a network in synapse-specific ways. Thus, mGluRs make the synaptic communication at each connection unique in spite of the ubiquitous release of glutamate as the neurotransmitter.

Within CA3, and even within just the MF system of the CA3 region, mGluRs have varying roles in synaptic communication, with some requiring high frequencies of activity to become active, and others requiring low frequency, but long duration bouts of activity. Because of these properties, predicting the effect of the global activation of one receptor type or another is very difficult. This problem is brought into sharp relief when considering efforts to target mGluRs as a treatment strategy for diseases like epilepsy or schizophrenia. Thus, efforts to understand modulation of network activity by mGluRs should continue, using strategies to understand the impact on the network at large, in addition to individual synapses.

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