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Activation requirements for metabotropic glutamate receptors

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HIGHLIGHTS

- We examined Group I and II mGluR responses to variable stimulation parameters.
- The activation patterns of Group I and II mGluRs were very similar in nature.
- High-frequency/intensity stimulation is not necessary to activate these receptors.
- mGluRs can often be activated by only 2 stimulation pulses but never by one.

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ABSTRACT

It has been common experimentally to use high frequency, tetanic, stimulation to activate metabotropic glutamate receptors (mGluRs) in cortex and thalamus. To determine what type of stimulation is actually necessary to activate mGluRs we examined the effects of varying stimulation duration and intensity on activating mGluR responses. We used a thalamocortical and an intracortical slice preparation from mice and performed whole cell recordings from neurons in the ventral posterior medial nucleus or in layer 4 of primary somatosensory cortex (S1) while electrically stimulating in layer 6 of S1. Extracellular ionotropic glutamate receptor antagonists and $GABA_A$ receptor antagonists were used to isolate Group I or Group II mGluR responses. We observed that high frequency stimulation is not necessary for the activation of either Group I or Group II mGluRs. Either could be activated with as few as 2–3 pulses at stimulation frequencies around 15–20 Hz. Additionally, increasing the number of pulses, intensity of stimulation, or stimulation frequency increased amplitude and duration of the mGluR response.

1. Introduction

Metabotropic glutamate receptors (mGluRs) are G-protein-coupled receptors that can be found in many parts of the mammalian brain, including the thalamus and cortex [16]. Unlike the fast action of ionotropic glutamate receptors (iGluRs), mGluRs are slow to respond, and the effects of their activation can last for several hundreds of milliseconds, or even seconds [6,18,40].

Due to their distribution, Group I and Group II mGluRs are of particular interest with regards to cortical and thalamic function [10,15,17,26,27,29,34]. A major difference between these two receptor groups is that while activation of Group I mGluRs results in postsynaptic depolarization of the cell, activation of Group II mGluRs has hyperpolarizing postsynaptic effects [8,10,13,19,23].

In thalamus and cortex, mGluRs can be activated by inputs that exhibit a modulatory (or Class 2) synaptic profile such as the projection from layer 6 to layer 4 in several cortical areas [10,23,24], from cortical layer 6 to thalamus [30,33] and some intracortical pathways [7,9]. On the other hand, mGluRs do not become activated by glutamatergic inputs with driver (or Class 1) synaptic characteristics, such as the retinogeniculate pathway [33], the mammilothalamic pathway [32] and some thalamocortical [22,37,38] and corticothalamic [33] projections.

Experiments making use of *in vitro* slice preparations have typically used high-frequency (>50 Hz) and often high intensity (>150 pA) stimulation of an afferent pathway to activate mGluRs [2,4,20], especially in cases where stimulation of axons was involved [32]. This raises questions regarding how commonly mGluRs are activated under more physiological conditions. For instance, some studies have suggested that much less activity is required among glutamatergic afferents to activate Group I mGluR responses in thalamus [30] and cerebellum [14].

To help clarify this issue, we chose to characterize the stimulation parameters required to activate Group I and Group II mGluRs

Abbreviations: EPSP, excitatory post synaptic potential; iGluR, ionotropic glutamate receptor; mGluR, metabotropic glutamate receptor; MGNv, ventral portion of the medial geniculate nucleus; S1, primary somatosensory cortex; VPM, ventral posterior medial thalamic nucleus.

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in two modulatory pathways: the projection from layer 6 to layer 4 in the primary somatosensory cortex (S1) and the feedback projection from layer 6 of S1 to the ventral posterior medial nucleus (VPM) of the thalamus.

2. Methods

2.1. Slice preparation

All procedures were approved by the Institutional Animal Care and Use Committee of the University of Chicago. BALB/c mice (Harlan) of either sex (age 7–16 days postnatal) were anaesthetized with isoflurane and decapitated. For studying corticothalamic projections, thalamocortical slices (500 μm thick) were prepared by blocking the brain at a 55° angle from the midsagittal plane and then gluing the blocked side onto a vibratome platform (Leica, Germany) for slicing [1]. For studying intracortical projections, we prepared 400 μm-thick coronal slices. Following sectioning, the brain slices were placed in oxygenated artificial cerebrospinal fluid containing (in mM) 125 NaCl, 3 KCl, 1.25 NaH_2PO_4, 1 $MgCl_2$, 2 $CaCl_2$, 25 $NaHCO_3$ and 25 glucose.

2.2. Electrophysiology

Whole-cell recordings in current clamp mode were performed as described before [37]. Recording glass pipettes (input resistances 3-8 MΩ) were filled with intracellular solution containing (in mM) 117 K-gluconate, 13 KCl, 1 $MgCl_2$, 0.07 $CaCl_2$, 10 HEPES, 0.1 EGTA, 2 Na_2-ATP, and 0.4 Na-GTP; pH 7.3, 290 mOsm. For both corticothalamic and intracortical projections, electrical stimulation of layer 6 was delivered by a concentric bipolar electrode (FHC, Bowdoinham, ME). For studying the corticothalamic pathway, recordings were performed in VPM, and for studying intracortical projections, recordings were performed in layer 4 barrels of primary somatosensory cortex.

$GABA_A$ receptors were blocked with SR95531 (20 μM) to prevent inhibitory inputs from the thalamic reticular nucleus in corticothalamic pathway experiments or from cortical interneurons in the intracortical pathway experiments. CGP-46381 (50 nM) was used to block $GABA_B$ receptors. Short term plasticity was assessed as described before [37]. This was done in order to identify the type of input of the stimulated pathway given that only Class 2 inputs are known to activate mGluRs [35]. Isolation of mGluR responses was achieved by blocking ionotropic glutamate receptors with AMPA and NMDA receptor antagonists (DNQX, 50 μM, and AP5, 100 μM respectively). The effects of stimulation intensity, frequency, and number of pulses on mGluR response amplitude and duration were assessed under these conditions. Stimulation intensities ranged from 25 μA to 250 μA for all experiments. The number of pulses was varied from 1 to 60 pulses, and frequencies ranged from 10 Hz to 125 Hz. The duration of each pulse was always 0.1 ms. A response was defined as any depolarization or hyperpolarization exceeding 0.5 mV, lasting at least 450 ms, and occurring within 2 s of stimulation. mGluR response amplitude was measured as the peak amplitude of the response (from baseline), occurring at any time during the response. Group II mGluRs were isolated by blocking type 1 and 5 mGluRs (i.e. Group I mGluR) with LY367385 (40 μM) and MPEP (30 μM), respectively, while Group I mGluRs were isolated by blocking Group II mGluRs with MPPG (300 μM).

mGluR response duration was measured as the time from the initial change in membrane potential to the time the membrane potential returned to baseline. The time to peak mGluR response was measured as the time from the onset of response to when the peak response amplitude occurred. After all measurements were taken, responses were verified as being mediated by Group I or Group II mGluRs by using the relevant antagonists (see above).

3. Results

We performed a series of recordings in 41 excitatory[1] neurons that received direct input from layer 6 (18 in VPM, 23 in layer 4 of S1). In both VPM and layer 4 cells, low frequency stimulation (10 Hz) of layer 6 resulted in EPSPs exhibiting paired-pulse facilitation and an increasing amplitude with increasing stimulation intensity (Supp. Fig. 1), in agreement with previous reports [22,33]. Subsequently, iGluR antagonists were applied to the bath and allowed to wash in for 10 min. Complete block of iGluRs was confirmed by the absence of EPSPs following low frequency (10 Hz), high intensity (200–250 μA) stimulation of layer 6 (Supp. Fig. 1). The subsequent demonstration of mGluR activation (see below) demonstrated that these layer 6 afferents are Class 2 in nature [7,37–39].

3.1. mGluR responses

We were able to elicit mGluR responses in all 41 cells of this study. For cells in thalamus receiving layer 6 input, these responses were always mediated by Group I mGluRs [32,33]. On the other hand, neurons in layer 4 showed responses that were mediated by both Group I and/or Group II mGluRs [23,24], and these responses were isolated using the appropriate antagonists. We studied 14 neurons with Group I mGluR responses and 9 neurons with Group II mGluR responses in layer 4. As noted in Section 4, prior evidence indicates that these responses are due to activation of postsynaptic mGluRs.

Increasing the number of pulses, while keeping stimulation frequency and intensity constant, produced an increase in the peak response amplitude, time to peak response, and response duration. This was true for both Group I and Group II mGluR responses (Figs. 1A, B, and 2a–c). Response amplitude increased in a logarithmic fashion with the greatest increase in amplitude occurring over a range of 2–20 pulses (average increase ± SD over this range: of 2.51 ± 1.0 mV for Group I and 1.8 ± 0.18 mV for Group II) with less significant increases for 20-60 pulses (average increase over this range: 1.21 ± 0.28 mV for Group I and 0.39 ± 0.76 mV for Group II, Fig. 2a, Supp. Table 1). An analysis of the change in response amplitude over number of pulses for these two ranges showed significantly larger increases in response amplitude over the 2–20 pulse range for both Group I and Group II responses (Mann–Whitney, $p < 0.05$ for Group I; $p < 0.01$ for Group II). On the other hand, the time to peak showed a positively monotonic relationship with the number of pulses (Fig. 2b). We observed mGluR responses with as few as 2 pulses, as long as the inter-pulse interval was less than approximately 75 ms, which is consistent with previous findings [30]; however, mGluR responses were never seen following a single pulse, regardless of stimulation intensity (Fig. 1I, J and Supp. Fig. 2).

Next, we assessed the effect of stimulation frequency on the mGluR responses. Increasing the frequency of stimulation once again caused an increase in response amplitude for both Group I and Group II mGluR responses (Figs. 1C, D and 2d). For Group I mGluR responses, response amplitude showed a logarithmic increase as stimulation frequency was increased and response duration showed a similar pattern (Fig. 2 d and f). Group I mGluR response time to peak increased across stimulation frequencies of 10–40 Hz by an average of 0.64 ± 0.9 s over that range (time to peak was significantly larger at 40 Hz than 10 Hz, Mann–Whitney,

[1] In the rodent, VPM is devoid of interneurons, while all cells we recorded from in layer 4 were regular-spiking.

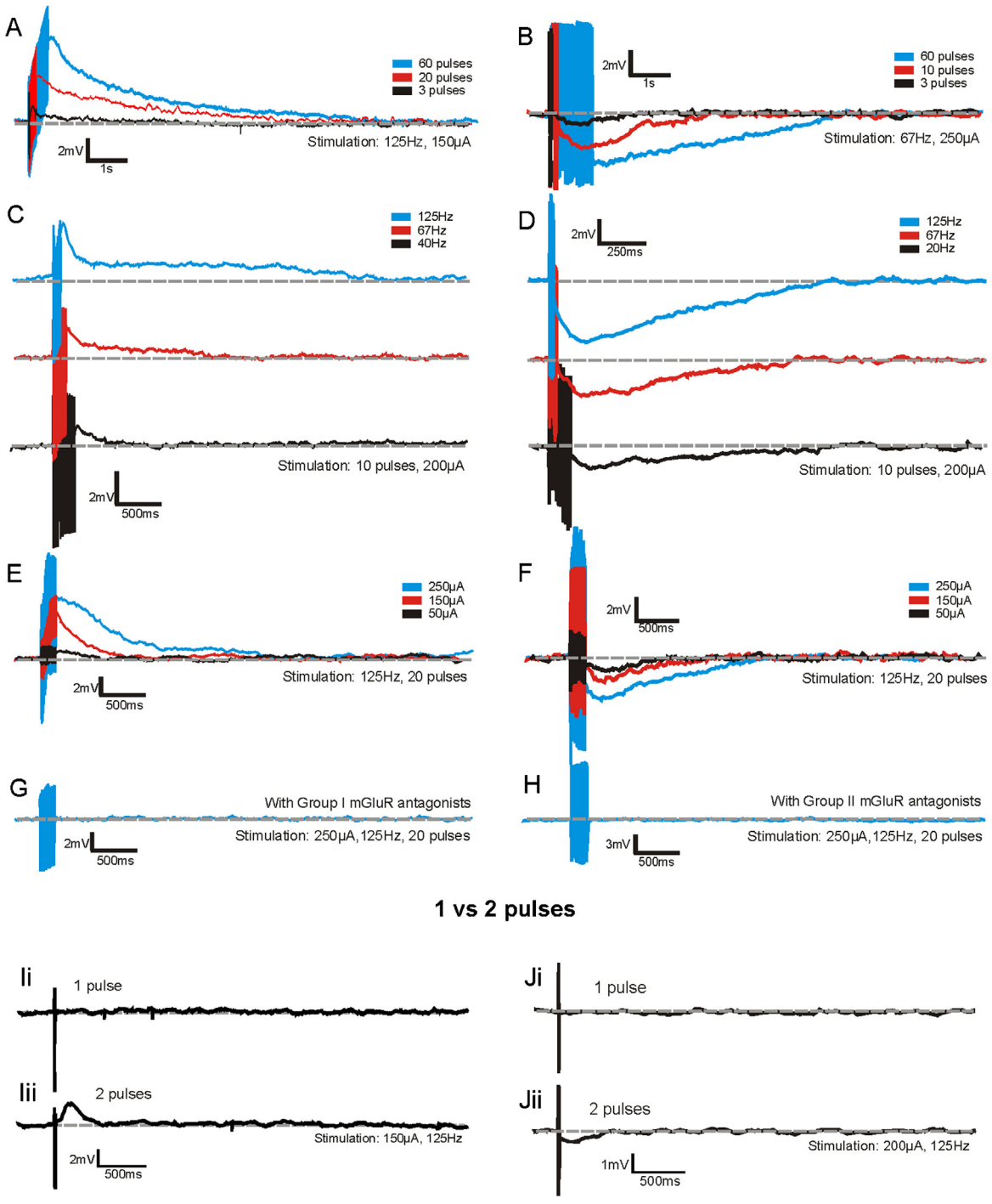

Fig. 1. Examples of Group I and II mGluR responses in VPM and/or layer 4 of S1. Effect of increasing pulse number on Group I mGluR responses of a VPM neuron (A) and Group II mGluR responses in a layer 4 neuron (B). Effect of increasing stimulation frequency on Group I mGluR responses of a VPM neuron (C) and Group II mGluR responses in a layer 4 neuron (D) (traces have been separated for clarity). Effect of increasing stimulation intensity on Group I mGluR responses of a neuron in layer 4 (E) and Group II mGluR responses in a layer 4 neuron (F). For the same neurons as in E and F, the Group I and II mGluR responses were eliminated by Group I mGluR antagonists (LY367385 and MPEP) and Group II mGluR antagonists (MPPG) respectively (G and E). Lower panel: Activation of mGluR responses requires a minimum of 2 stimulation pulses. (Ii) A single stimulation pulse in layer 6 of S1 does not produce any response in a VPM cell of a slice bathed in iGluR antagonists. (Iii) Two stimulation pulses in layer 6 of S1 of the same slice produce a clear Group I mGluR response in the above VPM cell. (Ji) A single stimulation pulse in layer 6 of S1 does not produce any response in a layer 4 cell of a slice bathed in iGluR antagonists. (Jii) Two stimulation pulses in layer 6 of S1 in the same slice produce a clear Group II mGluR response in the above layer 4 cell.

$p < 0.01$), but then decreased by an average of 0.46 ± 0.04 s between frequencies of 40 and 125 Hz (time to peak was significantly shorter at 125 Hz than at 40 Hz, Mann–Whitney, $p < 0.05$, see Fig. 2e and Supp. Table 1).

Group II mGluR responses showed a different pattern in response to increasing stimulation frequency; specifically, responses of larger amplitude and duration were achieved at lower stimulation frequencies than for Group I mGluR responses (Fig. 2d and f). For instance, at a stimulation of 20 Hz, average Group II mGluR response amplitudes were -1.98 ± 0.67 mV, lasting 3.15 ± 1.56 s, while Group I mGluR responses were 0.99 ± 0.63 mV, lasting 1.92 ± 1.71 s (Mann–Whitney, absolute response magnitude, $p < 0.05$; response duration, $p < 0.05$). Response amplitude for Group II mGluR began to plateau around 40 Hz and response

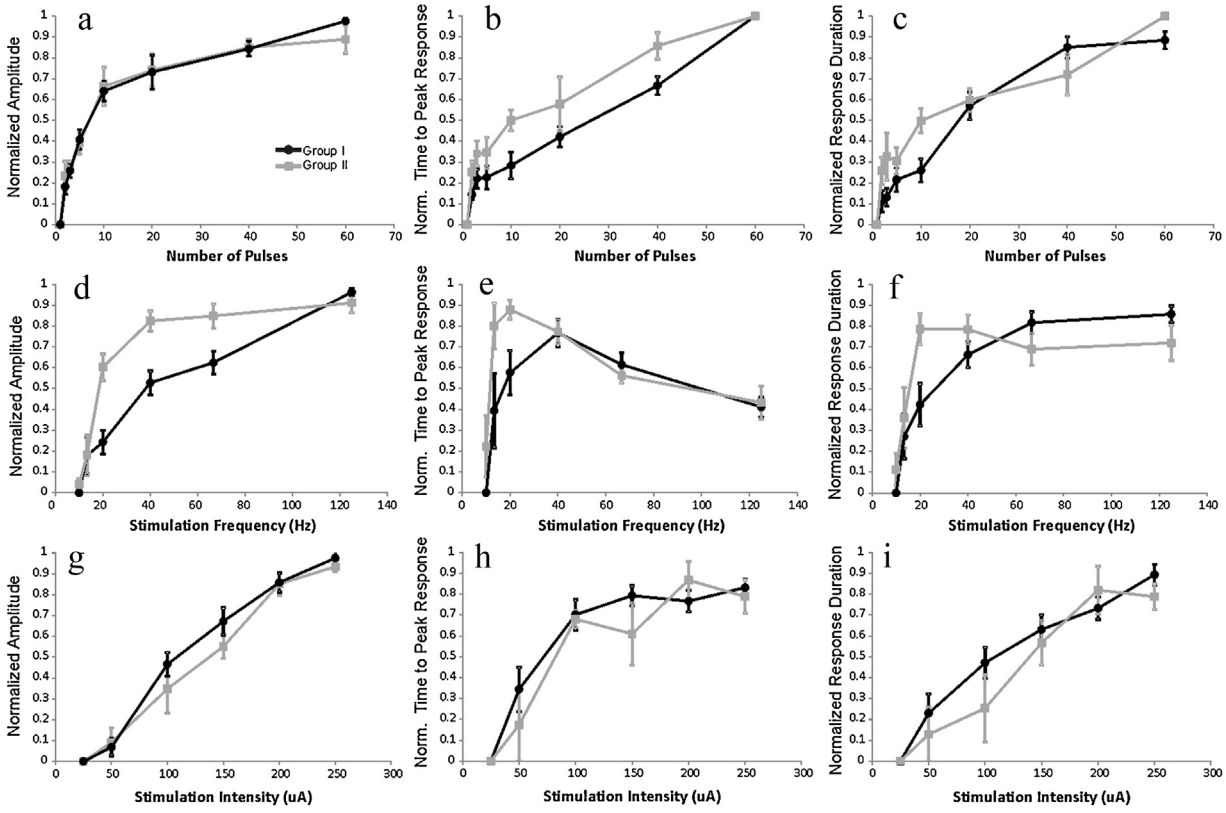

Fig. 2. Group I (black lines, $n = 32$) and Group II (gray lines, $n = 9$) mGluR responses for different stimulation parameters. The first column represents the relationship between normalized mGluR amplitude and the number of stimulation pulses, stimulation frequency and stimulation intensity. The second column represents the relationship between normalized time-to-peak mGluR response and the number of stimulation pulses, stimulation frequency and stimulation intensity. The third column represents the relationship between normalized mGluR response duration and the number of stimulation pulses, stimulation frequency and stimulation intensity. With regard to Group I mGluR responses, data collected from VPM and layer 4 of S1 have been pooled together. Error bars represent SEM. Data were normalized using the value of the greatest response amplitude, time-to-peak, or duration, produced by each cell for each particular stimulation parameter (i.e. number of pulses, frequency, or intensity).

duration peaked at 20 Hz. The time to peak of Group II mGluR responses showed a similar pattern to that of Group I mGluR responses, peaking at middle stimulation frequencies and then decreasing at higher frequencies (Fig. 2e). However, the Group II mGluR responses once again achieved the peak value at lower frequencies (20 Hz) than Group I mGluR responses (40 Hz). We observed Group I mGluR responses at stimulation frequencies around 15 Hz but never for 10 Hz stimulation. On the other hand, some layer 4 neurons ($n = 3$) exhibited Group II responses at frequencies as low as 10 Hz, further evidence that Group II mGluR responses were more prominent at lower stimulation frequencies.

Our third stimulation parameter was intensity, which is thought to relate to the number of afferent axons activated, because more of the highly convergent Class 2 inputs are activated at higher stimulation intensities [32,33,37–39]. Increasing stimulation intensity resulted in increases in response duration, amplitude, and time to peak for both Group I and II mGluR responses (Figs. 1E, F, and 2g–i). Both response amplitude and duration increased gradually as stimulation intensity increased (Fig. 2g and i). On the other hand, time to peak showed the greatest increases up to 100–150 μA of stimulation but failed to show any significant increases for larger stimulation intensities (Fig. 2h). The threshold for eliciting mGluR responses was between 50-75 μA for cells of both pathways tested. Cells in VPM had a threshold of 70.8 ± 9.7 μA whereas cells in layer 4 had a slightly lower threshold of 65.4 ± 12.7 μA; this was not statistically significant ($p = 0.42$).

Following the examination of the mGluR responses in each cell, the appropriate Group I or Group II mGluR antagonists were added to the bath in order to conclusively demonstrate the metabotropic origin of these responses (see Fig. 1G and H).

In general, most cells clearly responded with stimulation as low as 5–10 pulses at 20–40 Hz. For both Group I and II mGluR responses, the largest amplitude responses were seen at high stimulation intensities and/or large numbers of pulses (Supp. Fig. 2).

4. Discussion

We measured various components of mGluR responses in a corticothalamic and an intracortical pathway while varying the frequency and intensity of stimulation as well as the number of pulses used. We found that, as a general rule, increases in all three parameters resulted in increased mGluR response amplitude and duration, an effect observed for both Group I and Group II mGluR responses. Overall, the activation patterns of the two Groups of mGluRs across the different stimulation parameters were highly comparable, although Group II mGluRs required somewhat lower stimulation frequencies to reach maximum response amplitude and duration.

Even though Group II mGluRs are often associated with presynaptic locations [28,36], the effects that we observed here were presumed to be postsynaptic based on earlier experiments from our laboratory [23]. Similarly Group I mGluR responses in layer 4 of S1 and VPM have also been previously reported to be postsynaptic [24,33].

Our findings regarding Group I mGluR activation resemble those reported by McCormick and von Krosigk [30] in the thalamus and by Dzubay and Otis [14] in the cerebellum, in that mGluR responses can be induced with as little as 2 stimulation pulses, at relatively low stimulation frequencies of around 15–20 Hz and with stimulation intensities as low as 50-75 μA. We extended this finding to

intracortical pathways, and we demonstrated that Group II mGluRs can also be activated by such modest stimulation parameters. Thus, while a larger presynaptic response is associated with greater mGluR activation, such activation begins at relatively low rates of afferent input. A study of the olfactory bulb described mGluR responses following even a single stimulation pulse [11], but in our examples, a single pulse was never sufficient.

4.1. Comparing the effects of different frequency of stimulation on iGluRs and mGluRs

Depending on the synaptic properties of a specific input, increases in stimulation frequency can have very different effects on the postsynaptic iGluR response. More specifically, for inputs that generate paired-pulse depression (e.g. Class 1/driver response), increases in stimulation frequency result in increased synaptic depression, where the iGluR-mediated EPSPs become smaller with decreasing interstimulus intervals during the stimulus train. Conversely, for inputs that generate paired-pulse facilitation (e.g. Class 2/modulatory response), like the ones we have examined here, increases in stimulation frequency result in increased synaptic facilitation, where iGluR-mediated EPSPs continue to grow throughout the stimulus train [25], and this increase follows a logarithmic pattern [12]. It is worth noting that Class 2 inputs are the sole activators of mGluRs, which as we have shown here can generate responses that also grow in a logarithmic fashion following increases in stimulation frequency. The increase in iGluR response amplitudes for Class 2 inputs following increases in stimulus frequency is thought to be the result of elevated amounts of neurotransmitter release [12,42]. This same mechanism may be responsible for the effect we observed here for mGluRs. These differences in dynamics between Class 1 and 2 inputs may serve different purposes. For Class 1 inputs, thought to be the main input source for information processing (reviewed in [35]), the paired-pulse depression provides adaptation to ongoing levels of activity [5], thereby opposing response saturation at high input levels and extending the dynamic input/output range across the synapse. For Class 2 inputs, the increasing postsynaptic responses with greater input strength for both iGluR and mGluR components may simply lead to increasing modulatory functions.

4.2. mGluRs as modulators

Unlike iGluRs, the fast activation of which makes them suitable for the reliable and timely transmission of information across synapses, the role of mGluRs appears to be one of a modulator of neuronal excitability, including involvement in mechanisms of both short-term and long-term synaptic plasticity. Due to the slower kinetics and the long-lasting postsynaptic effects of their activation, mGluRs are not suitable for signal transmission; rather they are better suited for influencing the way in which signal transmission of other (e.g., Class 1) inputs takes place [35]. More specifically, activation of Group I mGluRs can maintain a cell at a depolarized state for relatively long periods of time, thus increasing its excitability and therefore enhancing the signal transmission of other incoming inputs [41]. Group I mGluRs have also been implicated in mechanisms of long-term potentiation and depression [3,21, see 31]. On the other hand, activation of postsynaptic Group II mGluRs can result in relatively prolonged periods of hyperpolarization and therefore decreased cell excitability, where signals arriving from other inputs cannot be relayed efficiently, resulting in an overall reduced flow of information. Another modulatory effect of Group II mGluRs is to reduce EPSP amplitude and influence short term plasticity mechanisms in cortex [10,26]. Finally, prolonged changes in membrane potential achieved by mGluR activation would play a role in the control of voltage-gated ionic conductances with long inactivation time constants (e.g., I_T), and this represents another modulatory function for both Groups of mGluRs.

5. Conclusions

We have demonstrated that high-frequency, prolonged stimulation, involving convergence of many inputs is not required to evoke mGluR responses in thalamus and cortex in vitro. Functionally, this implies that mGluRs can become activated even during periods of low frequency presynaptic firing, thus making their involvement in synaptic communication and postsynaptic modulatory processes more physiologically relevant than it has sometimes been supposed.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2013.02.004.

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