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Function of mGlu1 receptors in the modulation of nociceptive processing in the thalamus☆

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ABSTRACT

As postsynaptic metabotropic subtype 1 (mGlu1) receptors are present in the thalamus, we have investigated the effect of potentiating and antagonising mGlu1 receptors on responses of thalamic neurones to noxious sensory stimulation. Extracellular recordings were made *in vivo* with multi-barrel iontophoretic electrodes from single neurones in the thalamus of urethane-anaesthetised rats. Responses to iontophoretic applications of the Group I mGlu agonist 3,5-dihydroxy-phenylglycine (DHPG) were selectively potentiated by co-application of the mGlu1 positive allosteric modulator Ro67-4853, whereas they were selectively reduced upon co-application of the mGlu1 receptor orthosteric antagonist LY367385. This indicates that thalamic DHPG responses are mediated primarily via mGlu1 receptors, consistent with the high postsynaptic levels of this receptor in the thalamus. Furthermore, potentiation of DHPG responses by Ro67-4853 were greater when the initial DHPG response was of a low magnitude. Ro67-4853 also potentiated responses of thalamic neurones to noxious thermal stimulation, whilst having little effect on the baseline activity of nociceptive neurones. By contrast, nociceptive responses were reduced by LY367385. In a further series of experiments we found that inactivation of somatosensory cortex by cooling resulted in a reduction of thalamic nociceptive responses. These results underline the importance of mGlu1 receptors in the processing of sensory information in the thalamus, particularly with respect to nociceptive responses. Furthermore, the involvement of mGlu1 receptors may reflect the activity of descending cortico-thalamic afferents.

1. Introduction

The neurotransmitter pharmacology of nociceptive processing is of great importance in our understanding of pain mechanisms and therapy. Understanding of the neurotransmitters and receptors involved in nociception is extensive at the level of the peripheral nervous system and the spinal cord (Lesage, 2004; Millan, 1999). However, at higher levels of the neuraxis, our knowledge is less comprehensive. The ventrobasal thalamus (VB) is a pivotal processing point for the integration of somatosensory information ascending from the spinal cord with a prominent descending cortico-thalamic input from Layer 6 of the corresponding somatosensory cortex (Sherman, 2012). Both of these pathways use glutamate as their excitatory transmitter. Previous work from this laboratory and others has shown that responses of thalamic neurones to noxious peripheral stimuli are largely mediated by glutamate receptors, in particular the ionotropic NMDA receptor (Bordi and Quartaroli, 2000; Eaton and Salt, 1990; Kolhekar et al., 1997) and the metabotropic glutamate (mGlu) receptors, mGlu1 and mGlu5 (Eaton et al., 1993; Salt and Binns, 2000; Salt and Turner, 1998).

There are eight mGlu receptor subtypes (mGlu1-mGlu8) that can be placed into three groups (Group I, II, III) based on sequence homology, intracellular transduction cascade, and agonist/antagonist pharmacology (Niswender and Conn, 2010). Group I receptors (mGlu1, mGlu5) are often (but not exclusively) localised postsynaptically where they may couple to inositol phosphate metabolism and enhance post-synaptic excitability via changes in K^+ conductances and/or modulation of ionotropic glutamate receptors (Niswender and Conn, 2010). In addition to selective agonists and antagonists, a novel class of pharmacological agents acting at mGlu receptors has more recently become available, the positive allosteric modulators (PAMs) (Nicoletti et al., 2011). PAMs act at sites on

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the receptor distinct from the orthosteric ligand (glutamate) binding site and enhance the activity of receptors in response to orthosteric agonists (Nicoletti et al., 2011). This has advantages in that PAMs can be highly selective for single mGlu receptor subtypes and can function to potentiate the physiological activation of receptors by endogenous glutamate. Both of these properties are useful for the investigation of physiological processes. We have shown that one such PAM, Ro67-4853 (Knoflach et al., 2001), can be used in *in vivo* experiments to potentiate responses mediated via mGlu1 receptors in an activity-dependent manner (Salt et al., 2012). Thus, Ro67-4853 is an appropriate tool to investigate possible mGlu1 involvement in thalamic nociceptive processing.

The present study aimed to investigate the involvement and function of mGlu1 receptors in nociceptive processing in the thalamus. We have achieved this by potentiating mGlu1 receptor mediated responses with the selective PAM Ro67-4853 and by reducing mGlu1 receptor activation using the selective antagonist LY367385 (Clark et al., 1997) whilst recording nociceptive responses of thalamic neurones. Furthermore, given the association of mGlu1 receptors with cortico-thalamic pathways (Godwin et al., 1996; Martin et al., 1992; Vidnyanszky et al., 1996), we investigated the effect of somatosensory cortex inactivation on nociceptive responses of thalamic neurones. We show that it is possible to substantially change nociceptive responses of thalamic neurones by increasing or decreasing the degree of mGlu1 receptor activation and that nociceptive responses of thalamic neurones are dependent upon a functional cortico-thalamic projection. This is important in understanding sensory processing and the design of novel analgesic therapies, and underlines the critical role of mGlu1 receptors in sensory processing in the thalamus.

2. Methods

Experiments were carried out in male adult Wistar rats (270–400 g) anaesthetised with urethane (1.2 g/kg, I.P.), as detailed previously (Salt, 1987; Salt and Binns, 2000; Salt et al., 2012). Animals were purchased from Harlan (UK) and were housed on a 12 h light/dark cycle with unlimited access to food and water. All procedures were subject to local ethical committee review, were approved by the Home Office (UK) and were in accordance with the Animals (Scientific Procedures) Act 1986. Electroencephalogram and electrocardiogram were monitored throughout and anaesthesia was maintained by additional I.P. administration of urethane as required. An approximately 5 mm-square unilateral craniotomy centred over the thalamus (3 mm lateral to the midline, 5 mm rostral to the inter-aural line (Paxinos and Watson, 1988)) was made and the dura resected to expose the surface of the cortex. In addition to overlying the thalamus, this area of cortex contains the hindlimb and trunk/tail representation of the S1 somatosensory cortex (Chapin and Lin, 1984). In some experiments the craniotomy was surrounded by a small open chamber cemented to the skull that could be filled with either mineral oil or physiological saline; in the remaining experiments the surface of the brain was protected by agar (2% in physiological saline).

Recording electrodes were stereotaxically lowered into the thalamus using a stepping microdrive. Extracellular recordings were made from single neurones in the VB and immediately dorsal thalamus using either tungsten-in-glass electrodes or, for pharmacological experiments, the central barrel of seven-barrel glass iontophoretic electrodes. Single neurone action potential spikes were gated using a hardware spike-discriminator whose output pulses were timed and recorded by a CED1401 interface and computer system with Spike2 software. The amplitude and shape of the gated action potentials were monitored throughout the recording session. Neurones were identified on the basis of their stereotaxic location (AP +5.0 mm from *lambda*, Lateral 2.9 mm from midline, Depth 4.6–5.2 mm from surface) and their responses to somatosensory (nociceptive and non-nociceptive) stimuli, as described previously (Guilbaud et al., 1980; Peschanski et al., 1980, 1983; Salt and Binns, 2000). Nociceptive responses were evoked by immersion of part of either the contralateral hindpaw or the tail in water of 52C for 20 s. Responses to such stimuli were typically increases in action potential firing during the course of the stimulus and outlasting the stimulus by up to 2 min, as described previously (Peschanski et al., 1980). Similar response profiles were observed irrespective of the recording electrode type or the type of craniotomy preparation. Noxious stimuli were repeated at regular 5-min intervals in experiments where modulation of nociceptive responses was investigated (see below).

For pharmacological experiments, substances under investigation were applied in the recording location from the six outer barrels of the electrode using the iontophoretic technique (Stone, 1985) with a Neurophore BH2 system. Each of the outer barrels contained a selection from one of the following substances: NMDA (N-methyl-D-aspartate, 50 mM, pH 8.0 in 150 mM NaCl); AMPA (S-*alpha*-Amino-3-hydroxy-5-methyl-4-isoxazolepropionate, 50 mM, pH 8.0 in 150 mM NaCl); LY367385 (100 mM in water, pH 8.0); DHPG (S-3,5-dihydroxy-phenylglycine, 50 mM in 150 mM NaCl, pH 3.5); Ro67-4853 (2 mM in 10% DMSO in 150 mM NaCl, pH 7.5), vehicle control (10% DMSO in 150 mM NaCl, pH 7.5), Pontamine Sky Blue dye (2% in 1 M NaCl), 1 M NaCl. All pharmacological agents were obtained from Tocris Bioscience (UK), apart from Ro67-4853, which was a gift from Roche Pharmaceuticals (Switzerland). DHPG was ejected as a cation, all other substances were ejected as anions. Agents were prevented from diffusing from the iontophoresis barrel by applying a retaining current (5–15 nA) of opposite polarity to the ejection current. Automatic current balancing was routinely performed through the 1 M NaCl-containing barrel. In experiments where the effects of either the PAM or antagonist on agonist responses were evaluated, regular repeated cycles of agonist ejections were set up and initiated by the computer system which also produced online peristimulus-histograms (PSTHs) of single-neurone activity. Agonist ejection parameters were adjusted so as to produce sub-maximal responses. The effects of the PAM or antagonist on agonist effects were assessed by continuous concurrent iontophoretic application of these agents during several cycles of agonist ejection. Thus, although it is not possible to give absolute tissue concentrations of agents, we are confident that the doses used are within the range of producing physiologically relevant and pharmacologically selective effects. In experiments where the effects of either the PAM or antagonist on nociceptive responses were investigated, these agents were ejected with similar iontophoretic parameters to those found to be effective on responses to agonists.

In experiments designed to investigate the influence of cortical activity on thalamic responses, we inactivated the S1 somatosensory cortex by cooling (Clemo and Stein, 1986; Diamond et al., 1992). After responses to noxious stimuli of a neurone were established, the warm physiological saline in the well overlying the cortex was gently aspirated and replaced with chilled (4C) saline every 2–3 min for up to 10 min and the effect on the nociceptive responses noted. Finally, the saline was replaced with warm saline and nociceptive responses were further recorded. In separate experiments, a miniature thermocouple was inserted into the cortex to a depth of 1 mm and it was found that the cooling procedure reduced the temperature at this point to 15C. When the thermocouple was moved down into the body of the thalamus, no change in temperature could be detected when the cortical cooling procedure was performed.

Responses to agonists or noxious stimuli were quantified as the number of action potentials evoked by agonist ejection or stimulus, from which PSTHs were plotted. The effects of the PAM, the antagonist, or cortical inactivation on these responses were assessed by calculating the agonist or stimulus response during these experimental manipulations as a percentage of the response under control conditions. In the case of nociceptive responses, distinct 'initial' and 'maintained' response components were computed: the initial component was the number of action potential spikes evoked during the nociceptive stimulus whereas the maintained response was the number of action potential spikes occurring during the minute immediately after the stimulus. Data from individual neurones were used to compute mean values of effects (±s.e.m.). Statistical comparisons of these values under control conditions and during experimental manipulations were made using the Wilcoxon Signed Rank test. Results were deemed to be significant when $P < 0.05$.

3. Results

Recordings were made from 25 neurones that were characterised as nociceptive thalamic neurones on the basis of their stereotaxic location and responses to noxious stimuli directed at the contralateral limbs and tail as described previously (Guilbaud et al., 1980; Peschanski et al., 1980). Typically these neurones were located above or lateral to the vibrissal representation in the VB complex, had low spontaneous firing rates (0.05–2.4 spikes per second) and responded to noxious stimuli with a graded increase in firing rate that outlasted the stimulus, as described previously (Eaton and Salt, 1990; Guilbaud et al., 1980; Peschanski et al., 1980; Salt and Binns, 2000).

Iontophoretic application of the Group I agonist DHPG (20–80 nA, 10–20 s) caused increases in action potential firing rate of the thalamic neurones, as previously described (Salt and Binns, 2000; Salt et al., 2012). Previous work from this laboratory has indicated that this excitatory response to DHPG is mediated predominantly via mGlu1 receptors (Salt and Binns, 2000). In order to evaluate the ability of Ro67-4853 to potentiate mGlu1 receptor mediated responses of nociceptive thalamic neurones, we co-applied this PAM (50–150 nA) during regular ejections of DHPG. We found that this potentiated the DHPG responses to 282 ± 87%

($n = 6$, $P < 0.05$) of their pre-Ro67-4853 control values on nociceptive neurones (Fig. 1). On vibrissae-responsive (non-nociceptive) neurones a similar effect (267 ± 33% of control, $n = 19$, $P < 0.01$) was seen. This effect was typically reversible within 10 min of the termination of the Ro67-4853 application. It appeared that the greatest degree of potentiation could be achieved when the control response to DHPG was relatively low in terms of increased firing of action potentials. This was borne out by the apparent inverse correlation between the potentiating effect of Ro67-4853 and the magnitude of the control response to DHPG ($P < 0.001$) (Fig. 1C).

These findings indicate that Ro67-4853 can potentiate the mGlu1-receptor-mediated responses to DHPG of thalamic nociceptive neurones, in agreement with our previous findings on vibrissa-responsive thalamic neurones (Salt et al., 2012). When Ro67-4853 was applied during noxious stimulation on 6 thalamic neurones, the nociceptive responses were potentiated to an overall 247 ± 99% of control values ($P < 0.05$), with a more pronounced effect on the latter (maintained) components of the nociceptive responses than on the initial component in 5 of the 6 neurones (Figs. 2 and 3A). The effect of Ro67-4853 reversed upon termination of the ejection. On 4 of these 6 neurones the responses to repeated noxious stimuli were further recorded during co-application of the mGlu1 receptor antagonist LY367385 (20–40 nA) (Fig 2). This antagonist reduced the nociceptive responses in these neurones and in a further 5 neurones where Ro67-4853 had not been tested LY367385 had a similar effect. Overall, on the 9 neurones where nociceptive responses were studied with LY367385, the antagonist reduced responses to 17 ± 9% of control levels with little difference in effect between initial and maintained components of the response profiles (Fig. 3B). In order to verify the selectivity of LY367385 on this population of neurones, we recorded from 8 neurones that were excited by regular ejections of DHPG, NMDA and AMPA. On all of these neurones, co-application of LY367385 reduced DHPG responses (to 6 ± 5% of control) while having little effect on responses to either NMDA or AMPA (Fig. 4).

In view of the possibility that the cortico-thalamic projection contributes to the mGlu1 receptor-mediated component of thalamic nociceptive responses, we carried out a set of experiments where we inactivated somatosensory cortical activity by cooling the cortex whilst recording thalamic nociceptive responses. In these experiments, there was a substantial reduction in the magnitude of nociceptive responses of thalamic neurones to 14 ± 8% of control ($n = 5$) (Fig. 5). Responses returned to near-control levels in all cases once the cortical cooling procedure had been terminated.

4. Discussion

We have previously reported that local application of the mGlu1 receptor PAM, Ro67-4853, can enhance DHPG-evoked excitations of somatosensory vibrissae-responsive VB neurones (Salt et al., 2012). The primary finding of the present study is that this PAM has similar effects on nociceptive thalamic neurones and is able to substantially enhance nociceptive responses of these neurones. Furthermore, in an extension to our previous studies, we have shown that nociceptive thalamic responses are sensitive to antagonism by a selective mGlu1 receptor antagonist (LY367385), and finally that the nociceptive responses are dependent on an intact cortical input.

Inactivation of the sensory cortex has been used as a means of investigating cortical influences on subcortical areas in a variety of species and sensory systems (Binns and Salt, 1996; Clemo and Stein,

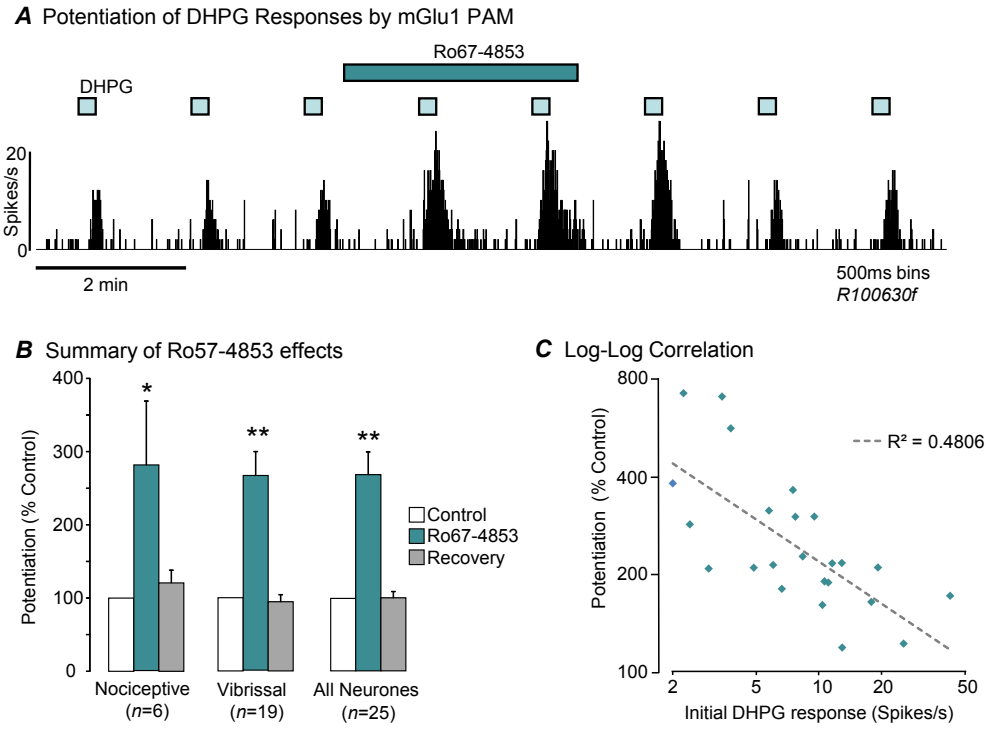

Fig. 1. Potentiation of DHPG responses by Ro67-4853. *A* – Action potential firing rate histogram (500 ms time bins) from a single VB neurone in response to regular applications of DHPG (indicated by marker bars). Co-application of Ro67-4853 (indicated by marker bar) potentiated the responses of the neurone to DHPG in a reversible manner. *B* – Overall effect of Ro67-4853 on DHPG responses. Bars represent mean % change from control (100%) of responses to DHPG during application of the PAM, and recovery of agonist responses after termination of PAM application. Ro67-4853 produced a similar significant potentiation of DHPG responses on both nociceptive and non-nociceptive (vibrissa-responsive) VB neurones. *C* – Scatter plot (logarithmic axes) of potentiation (% control) by Ro67-4853 versus magnitude of the initial (pre-PAM) response to DHPG. Note that the PAM produced greater potentiations when the initial response to DHPG was relatively small in terms of firing rate.* $P < 0.05$; ** $P < 0.01$.

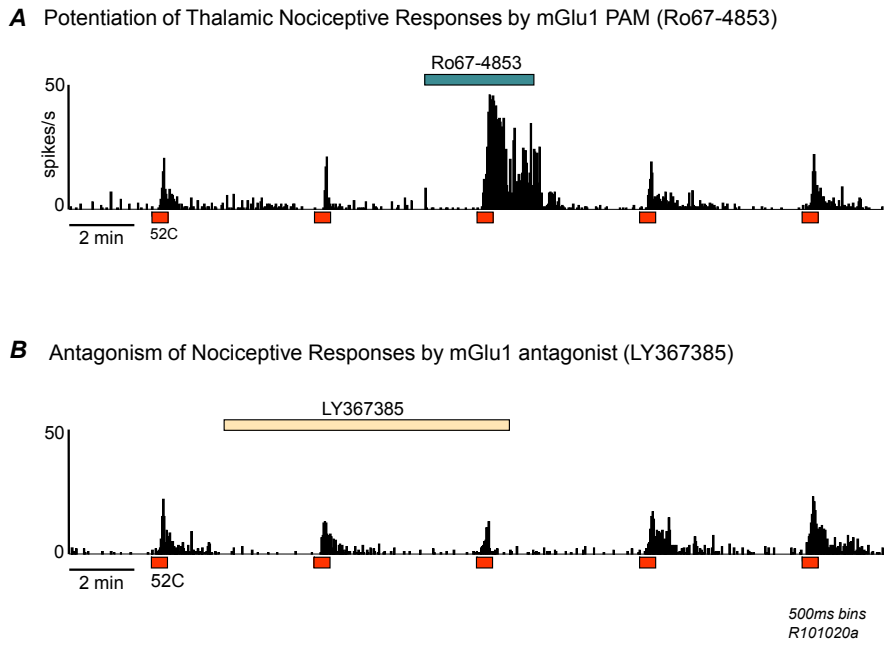

Fig. 2. Action potential firing rate histograms (500 ms time bins) of a single VB neurone, showing the effects of Ro67-4853 and LY367385 on the responses to regular noxious stimuli (marker bars, 52C). *A* – Application of Ro67-4853 (indicated by bar above record) potentiated the nociceptive responses in a reversible manner. *B* – Continuation of the recording illustrated in *A*, showing the reduction of the nociceptive responses by application of the antagonist LY367385 (marker bar above record).

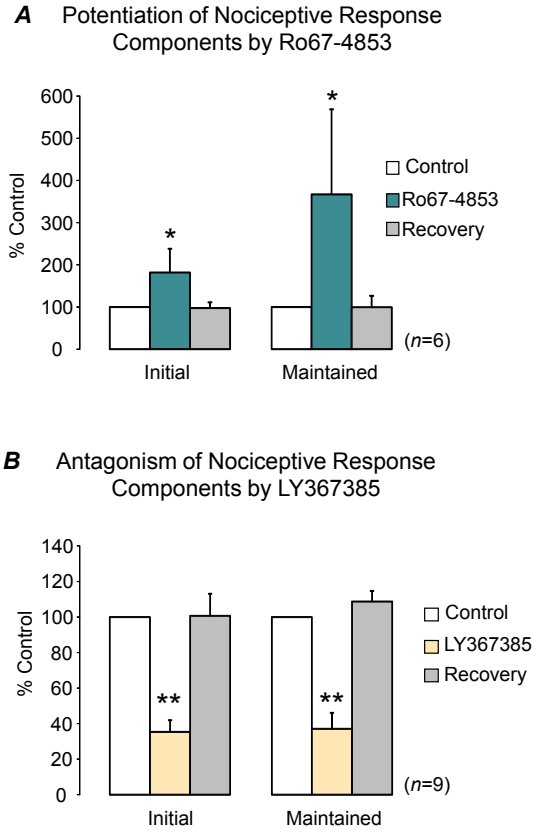

Fig. 3. Summary of the effects of Ro67-4853 and LY367385 on the initial and maintained nociceptive responses of VB neurones (see text for details). *A* – Potentiation of nociceptive response components by Ro67-4853. Note that the PAM had a greater effect on the maintained component. *B* – LY367385 antagonised both initial and maintained response components to a similar extent. * $P < 0.05$.

1986; Marrocco et al., 1982; Sillito et al., 1993, 1994; Wickelgren and Sterling, 1969) including the rat somatosensory cortex (Diamond et al., 1992; Yuan et al., 1985): cooling of somatosensory cortex appears to be a useful means of producing a reversible inactivation to study corticofugal influences on somatosensory thalamic processing in the rat (Diamond et al., 1992). Interestingly, Diamond et al. (1992) found that such a procedure had little effect on vibrissa responses of ventrobasal thalamus neurones although responses of Posterior Group (POm) thalamic neurones were reduced. In the present study, using similar procedures, we found that nociceptive responses were profoundly reduced by cortical inactivation, and this might at first reflect a greater involvement of cortico-thalamic circuitry in nociceptive responses compared to vibrissal responses but might also reflect patterns of vibrissal input (Salt et al., 2012).

Ro67-4853 has been documented as a PAM that is selective at mGlu1 receptors across a range of species with an EC_{50} of approximately 0.1 μM (Knoflach et al., 2001). This selectivity is borne out by our present finding that Ro67-4853 can enhance responses to DHPG in a similar manner to the potentiation seen on hippocampal neurones *in vitro* (Knoflach et al., 2001), and is consistent with the high levels of expression of mGlu1 receptors compared to mGlu5 receptors in the thalamus (Martin et al., 1992; Neto et al., 2000; Shigemoto et al., 1992). Our findings that nociceptive responses are potentiated by an mGlu1 PAM and reduced by an mGlu1 antagonist provide compelling evidence to suggest that mGlu1 receptors are activated during this physiological stimulation. The most likely physiological source of the mGlu1 receptor-mediated component of thalamic responses is the Layer 6 cortico-thalamic input to thalamic neurones in view of the anatomical location of these receptors on distal dendrites close to terminals likely of cortical origin (Godwin et al., 1996; Martin et al., 1992; Vidnyanszky et al., 1996). This is further supported by *in vitro* electrophysiological experiments where stimulation of the cortical input to thalamic neurones that can be reduced with mGlu1 antagonists (Reichova and Sherman, 2004; Turner and Salt, 2000).

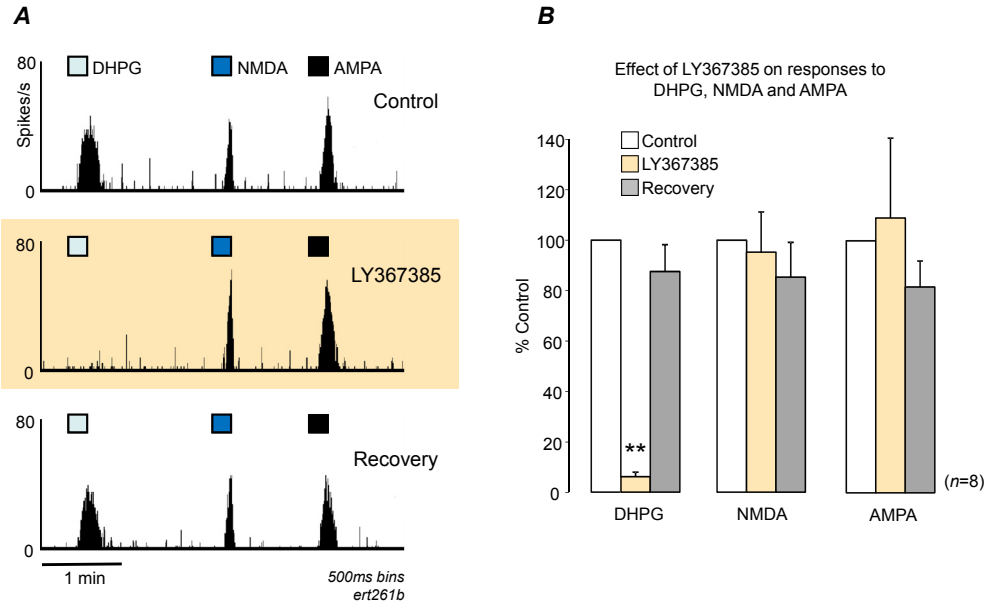

Fig. 4. Selective antagonism of DHPG by LY367385. *A* – Action potential firing rate histograms (500 ms time bins) of a single VB neurone, showing excitatory responses to applications of DHPG, NMDA and AMPA (as indicated by bars above the records). Upper record is a control sequence, the central record is taken during the co-application of LY367385, the lower record shows recovery from the effects of the antagonist. Note that LY367385 blocked responses to DHPG with little effect on responses to either NMDA or AMPA. *B* – Summary histograms showing the effects of LY367385 on the three agonists for data from 8 neurones. ** $P < 0.01$.

Consistent with this, we have found in the present study that inactivation of the somatosensory cortex reduces the nociceptive responses of thalamic neurones. Taken together, this suggests that responses of thalamic neurones to noxious stimuli are a consequence of recruitment of cortical circuitry in addition to sensory input. It is of interest that a similar suggestion has been made for thalamic responses in the somatosensory vibrissal system and the visual system *in vivo* and that the degree of recruitment may depend on the stimulus parameters that are used (Rivadulla et al., 2002; Salt et al., 2012).

It is evident that manipulation of mGlu1 activation either in an upward (with PAM) or downward (with antagonist) direction has a

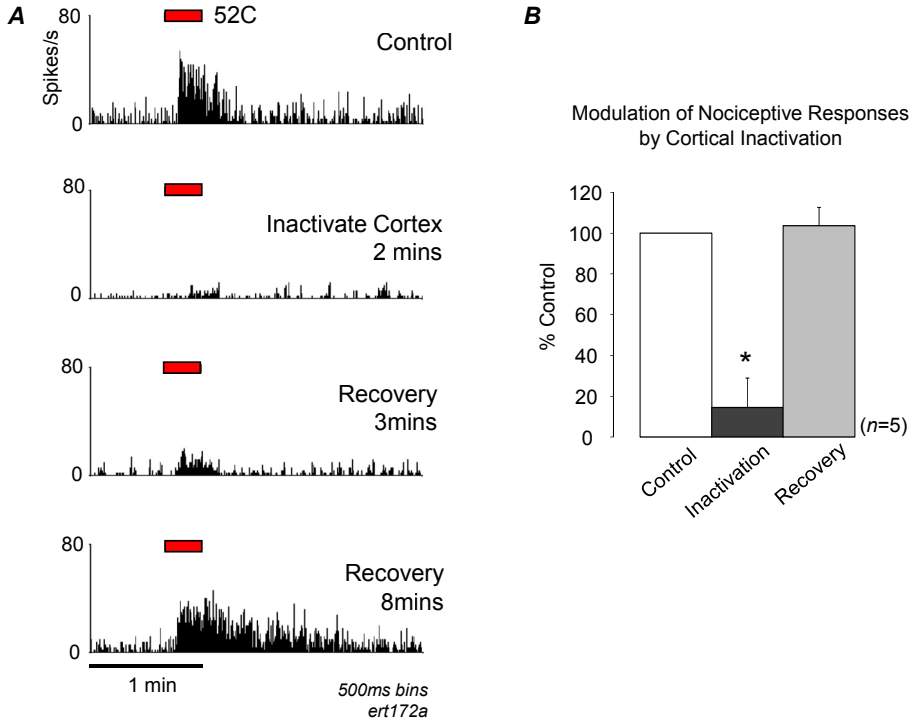

Fig. 5. Effects of cortical inactivation on nociceptive responses. *A* – Action potential firing rate histograms (500 ms time bins) of a single VB neurone, showing the responses to regular noxious stimuli (marker bars, 52C). The upper record is a control response, the second record is taken during cortical inactivation, the lower two records show recovery from the inactivation over several minutes. *B* – Summary histograms showing the effects of cortical inactivation for data from 5 neurones. * $P < 0.05$.

profound effect on the nociceptive responses of thalamic neurones *in vivo*. The substantial influence that cortical inactivation has on these responses further underlines this. This may at first sight seem somewhat surprising, as the apparent direct contribution of mGlu1 receptors to synaptic responses in thalamic slice experiments appears to be relatively small (Turner and Salt, 2000). This may in part be due to the relatively distal dendritic location of mGlu1 receptors (Godwin et al., 1996; Martin et al., 1992; Vidnyanszky et al., 1996), but it is also known that mGlu1 receptor activation can have very non-linear effects on thalamic neuronal membrane properties (McCormick and Von Krosigk, 1992; Turner and Salt, 2000; Williams et al., 1997), and this would enhance responses mediated via ionotropic receptors (*e.g.* NMDA or AMPA receptors). In addition direct positive modulation of NMDA receptors by mGlu receptors has been demonstrated, and we have previously shown that low, subthreshold, levels of mGlu1 activation can enhance thalamic neurone responses NMDA and AMPA receptor activation (Salt and Binns, 2000). Finally, it has been shown that activation of the mGlu1-phospholipase C beta 4 (PLC *beta* 4) molecular pathway can enhance the tonic firing mode of thalamic nociceptive neurones (Cheong et al., 2008). Thus mGlu1 receptors appear to be critically placed to play a dynamic role in controlling the responses to nociceptive stimuli of thalamic neurones. However, it is important to note that there is evidence to suggest some involvement of mGlu5 receptors in thalamic nociceptive responses, although this is unlikely to arise from cortical input (Salt and Binns, 2000). Interestingly, both Ro67-4853 and LY367385 appeared to have a much greater influence on thalamic nociceptive responses than the effects they produced on vibrissal responses reported by ourselves previously (Salt et al., 2012); this is parallelled by the large effect of cortical inactivation on nociceptive responses that we have described compared to the lack of effect of cortical inactivation on vibrissal responses of ventrobasal thalamus neurones (Diamond et al., 1992).

In conclusion, our findings demonstrate the pivotal contribution that mGlu1 receptors make to nociceptive processing at the thalamic level. This is important in terms of understanding nociceptive mechanisms and in the design of novel therapeutics. However, given that mGlu1 receptors have been implicated in synaptic plasticity (Nicoletti et al., 2011; Niswender and Conn, 2010), our findings suggest that plastic mechanisms may be activated under these conditions *in vivo*, and may underlie changes that may occur in chronic pain conditions. Moreover they underline the role that the cortical feedback may have in chronic pain and highlight the potential for development of pharmacological intervention targeting these mechanisms in the clinical treatment of chronic pain.

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The authors have no conflicts of interest.

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