THE ROYAL SOCIETY

Published online 12 November 2002

Glutamate receptor functions in sensory relay in the thalamus

T. E. Salt

Institute of Ophthalmology, University College London, London EC1V 9EL, UK (t.salt@ucl.ac.uk)

It is known that glutamate is a major excitatory transmitter of sensory and cortical afferents to the thalamus. These actions are mediated via several distinct receptors with postsynaptic excitatory effects predominantly mediated by ionotropic receptors of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and *N*-methyl-D-aspartate varieties (NMDA). However, there are also other kinds of glutamate receptor present in the thalamus, notably the metabotropic and kainate types, and these may have more complex or subtle roles in sensory transmission. This paper describes recent electrophysiological experiments done *in vitro* and *in vivo* which aim to determine how the metabotropic and kainate receptor types can influence transmission through the sensory thalamic relay. A particular focus will be how such mechanisms might operate under physiological conditions.

Keywords: *N*-methyl-D-aspartate; kainate; metabotropic glutamate receptor; mGluR1; γ-aminobutyrate

1. INTRODUCTION

The role of the acidic amino acid, L-glutamate, as a major (if not *the* major) transmitter of excitatory projections throughout the brain is extensively documented and well established. It is also almost certainly the case that the excitatory pathways to and from the thalamus, whether sensory inputs, or cortical inputs and outputs also fall into this category. The identified receptors upon which glutamate is known to act have been cloned and extensively characterized, and they can be placed into two major categories, the ionotropic receptors and the metabotropic receptors (tables 1 and 2) (Nakanishi 1992; Wisden & Seeburg 1993; Hollmann & Heinemann 1994; Conn & Pin 1997). The ionotropic glutamate receptors can be placed into three major types, the NMDA receptors, AMPA receptors, and kainate receptors. NMDA and AMPA are selective agonists for the NMDA and AMPA receptors, respectively. Kainate is an agonist at kainate receptors but it also has significant activity at AMPA receptors, thus reducing its usefulness as a pharmacological tool. Each of these receptor types is a heteromeric receptor–cation channel complex composed of a selection of subunits, thus adding further complexity to the possible pharmacological and functional characteristics of the receptors found in the brain (table 1). Eight metabotropic glutamate receptor subtypes (mGlu1–mGlu8) have been characterized to date, and splice variants of some of these have also been identified. The eight receptors can be placed into three groups (I, II, III) on the basis of their sequence homology, their pharmacological characteristics and the types of intracellular transduction cascade to which they may couple in *in vitro* expression systems (table 2) (Nakanishi 1992; Conn & Pin 1997). As a generalization, the group I receptors (mGlu1, mGlu5) predominantly mediate postsynaptic actions, whereas the group II receptors (mGlu2, mGlu3) and group III receptors (mGlu4, mGlu6–8) predominate presynaptically, regulating transmitter release. It is, however, becoming evident that the situation is more complex than this, and that receptors of all three groups can have either pre-, post- or extrasynaptic actions (Conn & Pin 1997).

The complexity introduced by the variety of glutamate receptor types is compounded by their non-uniform distribution within the brain and within the neuropil, synapses and extra-synaptic areas (Nakanishi 1992; Nusser *et al.* 1994; Lujan *et al.* 1997). This offers a multitude of potential signalling and modulatory possibilities for synaptically and extrasynaptically released glutamate (Kullmann 2000). Within the thalamus the distribution of a considerable number of the various glutamate receptors has been described in some detail (Martin *et al.* 1992; Petralia *et al.* 1996; Godwin *et al.* 1996; Liu 1997; Jones *et al.* 1998; Liu *et al.* 1998; Mineff & Valtschanoff 1999; Neto *et al.* 2000; Mineff & Weinberg 2000; Tamaru *et al.* 2001; Bolea *et al.* 2001). This paper seeks to provide a brief overview of some of the well-known synaptic roles of glutamate receptors in the sensory thalamic relay nuclei, and then on the basis of more recent work to indicate other more speculative synaptic roles and how this might relate to sensory transmission through the thalamus under physiological conditions. This draws heavily on data obtained from studies in the VB and LGN, which are probably the thalamic nuclei where synaptic transmission has been most extensively studied.

2. SENSORY INPUTS TO THALAMIC RELAY NUCLEI

It has been known for some years that the sensory inputs to the VB and LGN are mediated by a combination

One contribution of 22 to a Discussion Meeting Issue 'The essential role of the thalamus in cortical functioning'.

Table 1. Ionotropic glutamate receptor subunits.
(Abbreviations used: ATPA, (RS)-2-amino-3(3-hydroxy-5-tbutylisoxazol-4-yl) propanionate; GYKI 52466, 1-(4-amino-phenyl)-4-methyl-7,8-methylene-dioxy-5*H*-2,3-benzodiazepine; SYM2206, (±)-4-(4-aminophenyl)-1,2-dihydro-1-methyl-2-propylcarbamoyl-6,7-methylenedioxyphthalazine.)

		agonists		antagonists	
receptor	subunits	receptor selective	subunit selective	receptor selective	subunit selective
NMDA	NR1 NR2A–D	NMDA		D-AP5	
AMPA	GluR1–GluR4	AMPA (kainate)		GYKI52466 SYM2206	
kainate	GluR5 GluR6, GluR7 KA1, KA2	kainate	ATPA		LY382884

Table 2. Metabotropic glutamate receptor subtypes.
(Abbreviations used: APDC, 2*R*,4*R*-4-aminopyrrolidine-2,4-decarboxylate; CCG-1, (2*S*,1′*S*,2′*S*)-2-(2-carboxycyclopropyl) glycine; CHPG, 2-chloro-5-hydroxyphenylglycine; 4CPG, (*S*)-4-carboxyphenylglycine; CPPG, α-cyclopropyl-4-phosphonophenylglycine; DHPG, 3,5-dihydroxyphenylglycine; L-AP4, L-2-amino-4-phosphonobutyric acid; L-SOP, L-serine-*O*-phosphate; LY341495, 2*S*-2-amino-2 (1*S*,2*S*-2-carboxcyclopropyl-1-yl)-3-(xanth-9-yl)propanoic acid; LY354740, (+)-2-aminobicyclo [3.1.0]hexane-2,6dicarboxylate; LY367385, (+)-2-methyl-4-carboxyphenylglycine; MAP4, (*S*)-2-amino-2-methyl-4-phosphonobutanoic acid; MPEP, 2-methyl-6-(phenylethynyl)-pyridine; PPG, 4-phosphonophenylglycine.)

			agonists		antagonists	
group	receptor	transduction	subtype selective	group selective	subtype selective	group selective
I	mGlu1 mGlu5	IP3 /Ca^{2+} cascade	CHPG	DHPG	LY367385 MPEP	4CPG
II	mGlu2 mGlu3	inhibitory cAMP cascade		LY354740, CCG-1, APDC		LY341495
III	mGlu4 mGlu6 mGlu7 mGlu8	inhibitory cAMP cascade	PPG	L-AP4, L-SOP		MAP4, CPPG

of NMDA receptors and non-NMDA ionotropic receptors (Salt 1986; Crunelli *et al.* 1987; Sillito *et al.* 1990; Salt & Eaton 1991; Salt & Eaton 1996), and it has become clear that this reflects a fast EPSP/C component mediated by AMPA receptors in conjunction with an NMDA-receptor-mediated synaptic component (Paulsen & Heggelund 1994; Turner *et al.* 1994; Turner & Salt 1998; Kielland & Heggelund 2001). These *in vivo* and *in vitro* electrophysiological findings are supported by ultrastructural evidence showing the localization of NMDA and AMPA receptor subunits postsynaptic to sensory terminals (Liu 1997; Mineff & Weinberg 2000). There seems to be little evidence for a contribution to sensory responses of additional glutamate receptors from *in vitro* physiological studies, even though experiments have been designed that have attempted to reveal roles for, for example, metabotropic glutamate receptors (Turner & Salt 1998). By contrast, the situation appears to differ in *in vivo* experiments, where there appear to be sensory responses that have a contribution from mGlu receptors, and it is probable that this reflects recruitment of additional circuitry, possibly corticothalamic inputs (see § 3) (Eaton *et al.* 1993; Salt & Turner 1998*b*; Rivadulla *et al.* 2002).

3. CORTICAL INPUTS TO THE THALMIC RELAY NUCLEI

The corticofugal inputs to the thalamic relay have been the focus of much study and speculation over many years (Jones 1985; Koch 1987; Sherman & Guillery 1996, 2000). Electrophysiological studies of these pathways have focused on the role of NMDA receptors (see Scharfman *et al.* 1990; Deschenes & Hu 1990; Eaton & Salt 1996) and, latterly, mGlu receptors (see McCormick & Von Krosigk 1992; Eaton & Salt 1996; Golshani *et al.* 1998; Turner & Salt 2000*b*; Hughes *et al.* 2002). A particular focus has been the function of mGlu1 receptors, as these have been localized postsynaptically in LGN predominantly beneath terminals of corticothalamic fibres (Martin *et al.* 1992; Vidnyanszky *et al.* 1996; Godwin *et al.* 1996).

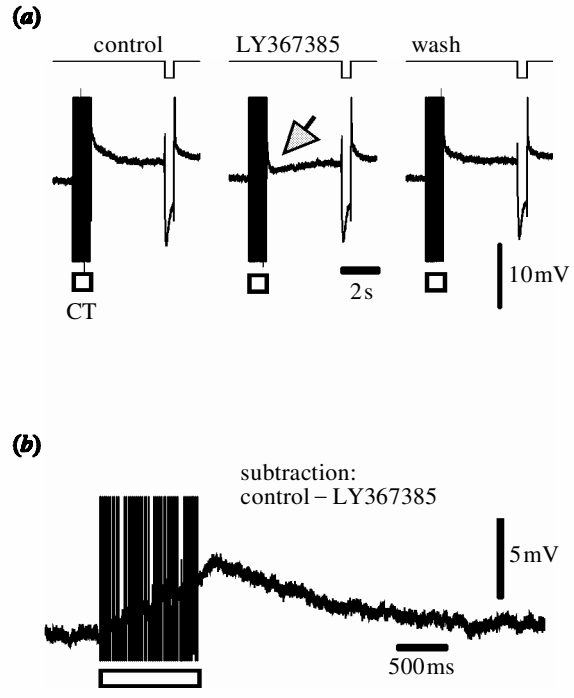

Figure 1. Mediation of corticothalamic responses by mGlu1 receptors. Intracellular recordings made with sharp electrodes from a thalamic relay neuron in a slice preparation of rat lateral geniculate nucleus (Turner & Salt 2000*b*). All recordings were made in the presence of antagonists to AMPA, kainate and NMDA receptors (GYKI52466, CNQX, AP5, MK801). (*a*) Responses to stimulation of the corticothalamic input with a train of stimuli (50 Hz, 1 s, as indicated by the marker bar, CT) under control conditions, during application of the mGlu1 receptor antagonist LY367385 (300 μM) and after washout of the antagonist. The response to a −0.1 nA current pulse is also shown in each trace. Note that the antagonist reduced the depolarizing response to stimulation of the corticothalamic input (arrow). (*b*) Subtraction of the record obtained in the presence of antagonist from control: this reveals the depolarizing component of the response which is attributable to activation of mGlu1 receptors.

Activation of mGlu receptors in thalamic relay neurons causes a slow depolarizing response associated with an increase in membrane resistance, as seen in many other parts of the brain, probably due a reduction in a potassium conductance (McCormick & Von Krosigk 1992; Turner & Salt 1998; Hughes *et al.* 2002), and this has been shown to be mediated specifically via mGlu1 receptors (figure 1) (Turner & Salt 2000*b*; Hughes *et al.* 2002).

Nevertheless, it is also evident that there is a substantial AMPA-receptor-mediated component to corticothalamic synapses in sensory relay nuclei (Turner & Salt 1998; Golshani *et al.* 2001), a finding supported by ultrastructural evidence which indicates that there are AMPA receptor subunits which are predominantly GluR2/3 and GluR4 located postsynaptically at corticothalamic synapses in VB (Mineff & Weinberg 2000; Golshani *et al.* 2001). More recently a low level of kainate receptor subunits (GluR5/6/7) has been found postsynaptically beneath corticothalamic synapses in VB, although initial *in vitro* electrophysiological evidence does not appear to indicate a synaptic role for these receptors (Bolea *et al.* 2001).

4. SENSORY RESPONSES OF THALMIC RELAY NEURONS *IN VIVO*: RECRUITMENT OF CORTICOTHALAMIC INPUTS

The isolated corticothalamic synaptic component that is mediated via mGlu1 receptors *in vitro* appears to be rather small, thus raising questions about its physiological relevance (Turner & Salt 2000*b*). Recently it has been suggested that synaptic activation of mGlu1 receptors may underlie the initiation of a slow oscillation of thalamic neurons that appears to be due to an interaction with several intrinsic membrane conductances of thalamic relay cells (Hughes *et al.* 2002). Such oscillations are a feature of sleep *in vivo*, and have been shown to be dependent upon an intact cortical input to the thalamus (Timofeev & Steriade 1996). Thus, the level of cortical activity could regulate the sleep-related activity of thalamic neurons via mGlu1 receptor activation (Hughes *et al.* 2002). However, it is also highly likely that there is a contribution from corticofugal systems to sensory responses *in vivo*, and this has been investigated over many years (Tsumoto *et al.* 1978; Murphy & Sillito 1987; Sillito *et al.* 1994) (and see Sherman & Guillery (2002) and Sillito & Jones (2002)). It has been speculated that the influence of the cortical input may operate via NMDA receptors or mGlu receptors (Koch 1987; Sherman & Guillery 2000), largely because transmission via these receptor types would allow the non-linear amplification of excitatory inputs mediated via, for example, AMPA receptors. This is a particularly attractive hypothesis in the case of mGlu1 receptors, as these are restricted to corticothalamic synapses and because NMDA-receptor mediated responses have been shown to be modulated by activation of group I (i.e. mGlu1/mGlu5) receptors in several brain areas (Fitzjohn *et al.* 1996; Doherty *et al.* 1997; Pisani *et al.* 1997; Martin *et al.* 1998; Holohean *et al.* 1999), as has modulation of AMPA-receptor-mediated responses (Cerne & Randic 1992; Bond & Lodge 1995; Jones & Headley 1995; Dev & Henley 1998; Calabresi *et al.* 1999). In the VB, activation of mGlu1 receptors potentiates responses mediated via either AMPA or NMDA receptors *in vivo* (figure 2) (Salt & Binns 2000), and it is probable that this is due to the direct effects of mGlu1 activation on neuronal membrane potential and resistance (McCormick & Von Krosigk 1992; Turner & Salt 1998) rather than a specific interaction at the receptor level, or that the potentiation seen is a combination of these factors (Salt & Binns 2000). Thus, although the isolated corticothalamic synaptic potential (which can be attributed to mGlu1 receptors *in vitro*) appears to be rather small (Turner & Salt 2000*b*), it would be able to exert a profound influence on ionotropic receptor-mediated responses, if the sensory stimulus was appropriate to recruit activity in the corticothalamic output. This may not be the case in all situations. However, using certain natural somatosensory or visual stimuli which may appropriately activate cortical areas *in vivo* it has been shown that thalamic responses to sensory stimuli are reduced in the presence of mGlu1 antagonists in both VB (figure 3) (Salt & Turner 1998*b*) and the LGN (figure 4) (Rivadulla *et al.* 2002), and this may reflect activation of the cortical input to the thalamic relay neurons. A feature of some of these stimuli is that they are of a sustained nature, and it may be the case that this is critical to

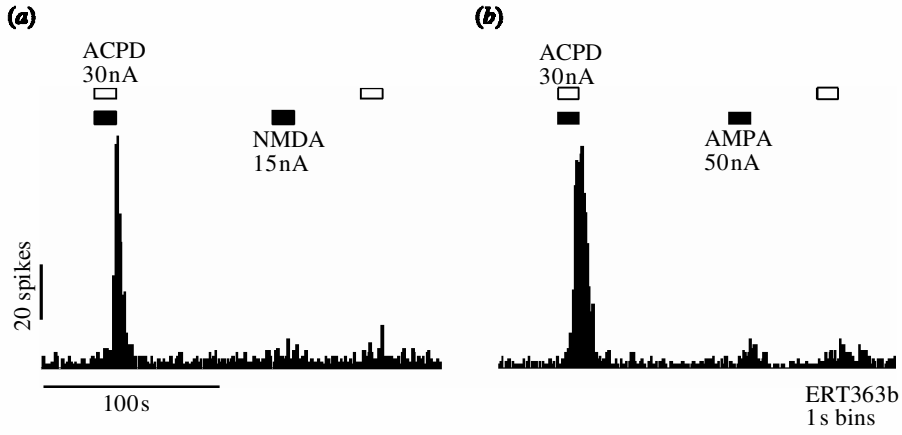

Figure 2. Potentiation of NMDA and AMPA receptor-mediated responses of a rat VB neuron by activation of metabotropic glutamate receptors. The histograms of action potential firing were counted into 1 s epochs, recorded from a single VB neuron *in vivo* under anaesthesia (Salt & Binns 2000). The iontophoretic applications of NMDA and AMPA are indicated by the solid and stippled marker bars above the records and the applications of the metabotropic agonist ACPD are shown by open markers. Note that the application of NMDA, AMPA or ACPD alone had only small effects on the firing rate of this neuron. However, the co-application of ACPD with either NMDA (*a*) or AMPA (*b*) resulted in the marked potentiation of responses.

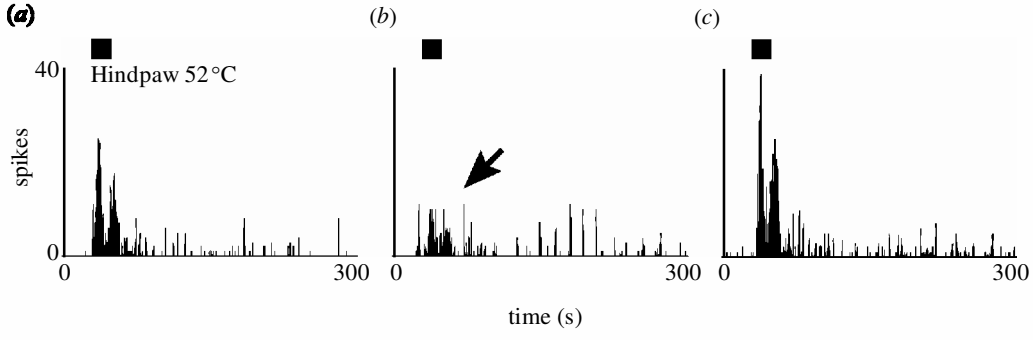

Figure 3. The involvement of mGlu1 receptors in nociceptive somatosensory responses of rat VB thalamus neurons. The histograms of action potential firing were counted in 1 s epochs, recorded from a single VB neuron *in vivo* under anaesthesia with a multi-barrel iontophoretic electrode (Salt & Turner 1998*b*). Stimulation of the hindpaw with a noxious thermal stimulus is indicated by the solid marker bar. (*a*) A record taken under control conditions, (*b*) during the iontophoretic ejection of the mGlu1 receptor antagonist LY367385, and (*c*) 5 min after the end of the antagonist ejection (recovery). Note the reduction of the nociceptive sensory response by the antagonist (arrow).

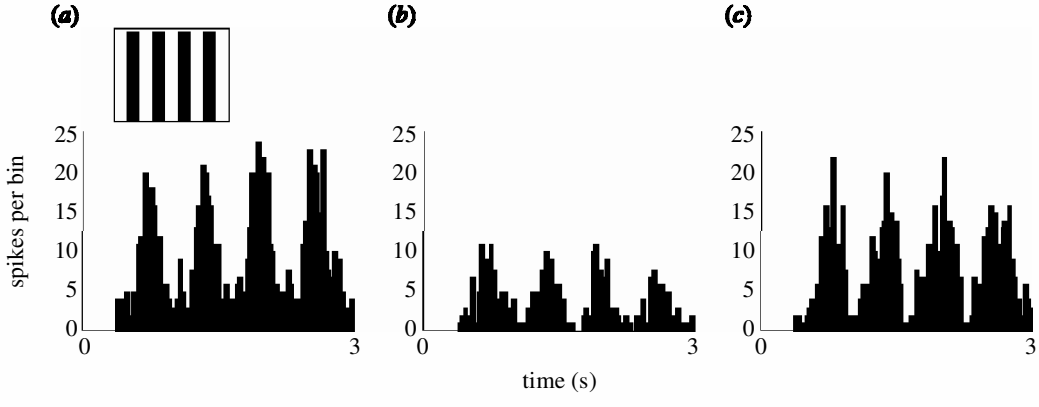

Figure 4. The blockade of mGlu1 receptors with LY367385 decreases the LGN responses to moving visual stimuli in the anaesthetized cat (Rivadulla *et al.* 2002). The histograms illustrate the response of an on-centre 'X' cell to a full-field sinusoidal drifting grating (inset above the histogram) of optimal characteristics (*a*) before and (*b*) in the presence of the antagonist LY367385 (ejected iontophoretically using 60 nA for 6 min), and (*c*) after a recovery period of 15 min. The histograms were constructed from 15 presentations of the stimulus. The representation of the stimulus has a merely graphic purpose and does not reflect its actual properties. Taken with permission from Rivadulla *et al.* (2002) © 2002 Society for Neuroscience.

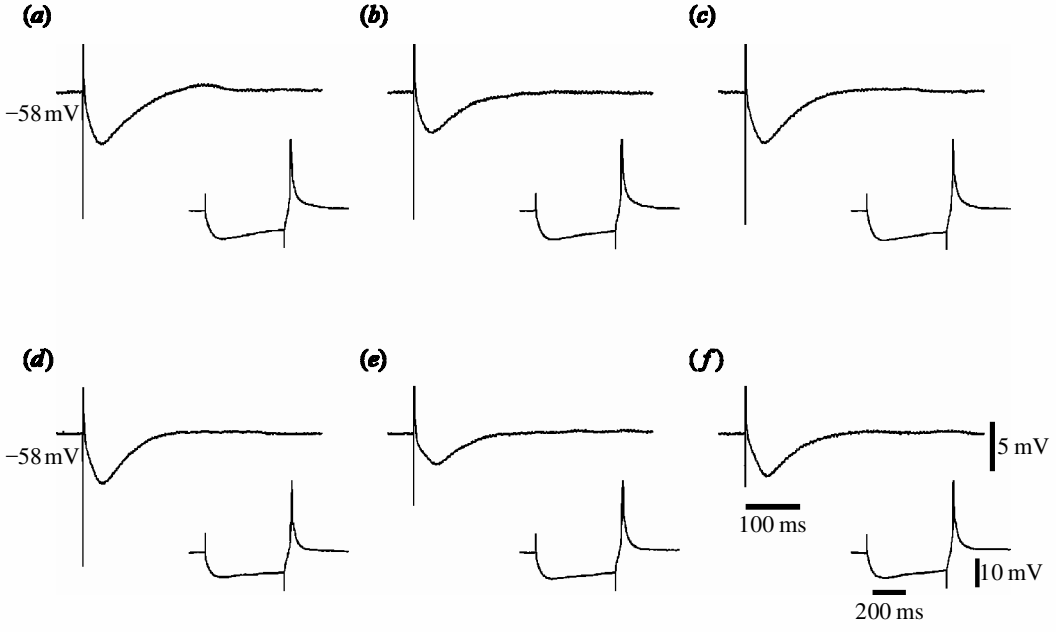

Figure 5. IPSPs recorded from a VB thalamus neuron in a slice preparation with a sharp intracellular electrode in response to stimulation of the TRN. All records were in the presence of the AMPA antagonist GYKI52466 (100 μM) and the NMDA antagonists MK801 (3 μM) and D-AP5 (100 μM). Each pair of traces is the response to stimulation of the TRN and the response to a −0.1 nA current pulse through the recording electrode (inset). (*a*–*c*) Responses (*a*) before (control), (*b*) during, and (*c*) after (wash) the bath application of 10 μM kainate. Note the reduction in IPSP amplitude with little effect on the response to current injection. (*d*–*f*) Similarly, the group II mGlu receptor agonist LY354740 ((*d*) before (control), (*e*) during, and (*f*) after (wash) application of 10 μM LY354740) reduced the amplitude of the IPSP, with little effect on the responses to the current injection.

revealing the portion of the cortical output onto thalamic relay neurons that is mediated via mGlu1 receptors.

5. MODULATION OF GABA-ERGIC INHIBITION IMPINGING UPON THALMIC RELAY NEURONS: A ROLE FOR 'SYNAPTIC SPILLOVER' IN SENSORY TRANSMISSION *IN VIVO*?

As discussed elsewhere in this issue (Jones 2002; Sherman & Guillery 2002), the GABAergic inhibitory output from the TRN onto relay cells is a major contributor to the overall response profile of the relay cells (Jones 1985; Sherman & Guillery 2000). It is clearly important to understand how this inhibition may be controlled. Furthermore, in the rodent VB this can be considered to be virtually the sole source of GABAergic inhibition onto relay cells (Ralston 1983; Harris & Hendrickson 1987) and therefore the rodent VB provides an excellent model for studying this inhibitory system in greater isolation. It has been known for some time that activation of group II or group III mGlu receptors within the rat VB results in a reduction of TRN-originating inhibition onto relay cells evoked by sensory stimulation *in vivo* (Salt & Eaton 1995; Salt & Turner 1998*a*). In keeping with this, we have found *in vitro* that the IPSP evoked in VB upon stimulation of the TRN under conditions of ionotropic glutamate receptor blockade is decreased by group II or group III mGlu receptor activation (figure 5) (Turner & Salt 2000*a*). Detailed information on the distribution of group III receptors in VB is not available. However, ultrastructural information from rat and mouse VB indicates that group II receptors are localized in glial processes, some of which appear to be surrounding GABAergic terminals (Liu *et al.* 1998; Mineff & Valtschanoff 1999), and more recently mGlu3 receptors have been found to be concentrated on GABAergic axons in VB arising from TRN (Tamaru *et al.* 2001). All of these receptor locations are removed from sites of synaptically released glutamate, and thus this raises the possibility that these receptors are activated by glutamate which spills out of the conventional synaptic area, possibly under conditions of intense synaptic activity. This concept of 'synaptic spillover' has been postulated on the basis of *in vitro* experiments from several non-thalamic brain areas (Semyanov & Kullmann 2000; Mitchell & Silver 2000; Kullmann 2000). Another class of glutamate receptor that has been similarly implicated in the modulation of inhibition in several brain areas is the kainate receptors (Rodriguez-Moreno *et al.* 1997; Clarke *et al.* 1997; Frerking & Nicoll 2000; Ali *et al.* 2001; Lerma *et al.* 2001). Consistent with these findings, we have found recently that TRN-evoked IPSPs recorded in rat VB relay cells *in vitro* are reduced by activation of the kainate receptors when AMPA and NMDA receptors are blocked (figure 5) (Binns *et al.* 2002). This again raises the possibility that the kainate receptors may be activated by glutamate via a synaptic spillover mechanism.

A pertinent question then, is whether such synaptic mechanisms are activated under more physiological conditions, *in vivo*, and if they are what contribution they might make to sensory processing in the thalamus. To investigate this, we have used a recently developed selective kainate receptor antagonist (LY382884) as a tool in a series of complementary *in vivo* and *in vitro* electrophysiological experiments in rat VB (Binns *et al.* 2002). We found firstly that there appears to be no direct involvement of kainate receptors in sensory (leminiscal) transmission

onto VB relay cells, a finding that is consistent with recent mouse VB data presented by others (Bolea *et al.* 2001). However, under *in vivo* physiological conditions, use of the antagonist LY382884 as a probe revealed that there is indeed activation of kainate receptors during sensory stimulation and that blockade of these receptors results in an enhancement of the GABAergic inhibition that is evoked during sensory stimulation (Binns *et al.* 2002). Taken together with our *in vitro* finding that kainate receptor activation reduces IPSPs in VB, this indicates that under physiological conditions of sensory stimulation there is the activation of kainate receptors, which normally has a disinhibitory effect via a reduction of the recurrent GABAergic inhibition arising from activation of TRN. Thus, application of an antagonist (LY382884) to these receptors under these conditions would lead to an increase in this inhibition, thereby causing a net reduction of sensory transmission. As there are no axo-axonic synapses onto the GABAergic axons in VB (Ohara & Lieberman 1993), the transmitter (presumably glutamate) activating the kainate receptors that modulate GABA transmission is likely to have arisen by spillover from a nearby synapse (probably lemniscal). This indicates that a synaptic spillover mechanism could indeed be operating under physiological conditions in VB, and that the role of this might be to govern the balance between excitatory and inhibitory transmission at the VB relay cell. This would provide a novel means for prolonged or intense sensory stimuli to override afferent inhibition, and may be of importance as a local attentional mechanism within VB.

Experimental work from the author's laboratory is supported by the Wellcome Trust and Novartis. The author is indebted to Dr J. P. Turner, Dr K. E. Binns and Dr E. Sermasi for helpful and stimulating discussions over many years and for contributing much of the experimental data that underlies this paper.

REFERENCES

Ali, A. B., Rossier, J., Staiger, J. F. & Audinat, E. 2001 Kainate receptors regulate unitary IPSCs elicited in pyramidal cells by fast-spiking interneurons in the neocortex. *J. Neurosci.* **21**, 2992–2999.

Binns, K. E., Turner, J. P. & Salt, T. E. 2002 The role of kainate (GluR5) receptors in sensory responses of rat ventrobasal thalamus (VB) neurones. *Br. J. Pharmacol.* **135**(Suppl.), 85P.

Bolea, S., Liu, X. B. & Jones, E. G. 2001 Kainate receptors at corticothalamic synapses do not contribute to synaptic responses. *Thalamus Related Systems* **1**, 187–196.

Bond, A. & Lodge, D. 1995 Pharmacology of metabotropic glutamate receptor-mediated enhancement of responses to excitatory and inhibitory amino acids on rat spinal neurones *in vivo*. *Neuropharmacology* **34**, 1015–1023.

Calabresi, P., Centonze, D., Gubellini, P., Marfia, G. A. & Bernardi, G. 1999 Glutamate-triggered events inducing corticostriatal long-term depression. *J. Neurosci.* **19**, 6102–6110.

Cerne, R. & Randic, M. 1992 Modulation of AMPA and NMDA responses in rat spinal dorsal horn neurons by trans-1-aminocyclopentane-1,3-dicarboxylic acid. *Neurosci. Lett.* **144**, 180–184.

Clarke, V. R. J. (and 14 others) 1997 A hippocampal GluR5 kainate receptor regulating inhibitory synaptic transmission. *Nature* **389**, 599–603.

Conn, P. J. & Pin, J. P. 1997 Pharmacology and functions of metabotropic glutamate receptors. *A. Rev. Pharmacol. Toxicol.* **37**, 207–237.

Crunelli, V., Kelly, J. S., Leresche, N. & Pirchio, M. 1987 On the excitatory postsynaptic potential evoked by stimulation of the optic tract in the rat lateral geniculate nucleus. *J. Physiol.* **384**, 603–618.

Deschenes, M. & Hu, B. 1990 Electrophysiology and pharmacology of the corticothalamic input to lateral thalamic nuclei: an intracellular study in the cat. *Eur. J. Neurosci.* **2**, 140–152.

Dev, K. K. & Henley, J. M. 1998 The regulation of AMPA receptor-binding sites. *Mol. Neurobiol.* **17**, 33–58.

Doherty, A. J., Palmer, M. J., Henley, J. M., Collingridge, G. L. & Jane, D. E. 1997 (R,S)-2-chloro-5-hydroxyphenylglycine (CHPG) activates mGlu5 but not mGlu1 receptors expressed in CHO cells and potentiates NMDA responses in the hippocampus. *Neuropharmacology* **36**, 265–267.

Eaton, S. A. & Salt, T. E. 1996 Role of NMDA and metabotropic glutamate receptors in cortico-thalamic excitatory post-synaptic potentials *in vivo*. *Neuroscience* **73**, 1–5.

Eaton, S. A., Birse, E. F., Wharton, B., Sunter, D. C., Udvarhelyi, P. M., Watkins, J. C. & Salt, T. E. 1993 Mediation of thalamic sensory responses in vivo by ACPD-activated excitatory amino acid receptors. *Eur. J. Neurosci.* **5**, 186–189.

Fitzjohn, S. M., Irving, A. J., Palmer, M. J., Harvey, J., Lodge, D. & Collingridge, G. L. 1996 Activation of group I mGluRs potentiates NMDA responses in rat hippocampal slices. *Neurosci. Lett.* **203**, 211–213.

Frerking, M. & Nicoll, R. A. 2000 Synaptic kainate receptors. *Curr. Opin. Neurobiol.* **10**, 342–351.

Godwin, D. W., Van Horn, S. C., Erisir, A., Sesma, M., Romano, C. & Sherman, S. M. 1996 Ultrastructural localization suggests that retinal and cortical inputs access different metabotropic glutamate receptors in the lateral geniculate nucleus. *J. Neurosci.* **16**, 8181–8192.

Golshani, P., Warren, R. A. & Jones, E. G. 1998 Progression of change in NMDA, non-NMDA, and metabotropic glutamate receptor function at the developing corticothalamic synapse. *J. Neurophysiol.* **80**, 143–154.

Golshani, P., Liu, X. B. & Jones, E. G. 2001 Differences in quantal amplitude reflect GluR4-subunit number at corticothalamic synapses on two populations of thalamic neurons. *Proc. Natl Acad. Sci. USA* **98**, 4172–4177.

Harris, R. M. & Hendrickson, A. E. 1987 Local circuit neurons in the rat ventrobasal thalamus—a GABA immunocytochemical study. *Neuroscience* **21**, 229–236.

Hollmann, M. & Heinemann, S. 1994 Cloned glutamate receptors. *A. Rev. Neurosci.* **17**, 31–108.

Holohean, A. M., Hackman, J. C. & Davidoff, R. A. 1999 Mechanisms involved in the metabotropic glutamate receptor-enhancement of NMDA-mediated motoneurone responses in frog spinal cord. *Br. J. Pharmacol.* **126**, 333–341.

Hughes, S. W., Cope, D. W., Blethyn, K. L. & Crunelli, V. 2002 Cellular mechanisms of the slow (< 1 Hz) oscillation in thalamocortical neurons *in vitro*. *Neuron* **33**, 947–958.

Jones, E. G. 1985 *The thalamus*. New York: Plenum.

Jones, E. G. 2002 Thalamic circuitry and thalamocortical synchrony. *Phil. Trans. R. Soc. Lond.* B **357**, 1659–1673. (DOI 10.1098/rstb.2002.1168.)

Jones, E. G., Tighilet, B., Tran, B. V. & Huntsman, M. M. 1998 Nucleus- and cell-specific expression of NMDA and non-NMDA receptor subunits in monkey thalamus. *J. Comp. Neurol.* **397**, 371–393.

Jones, M. W. & Headley, P. M. 1995 Interactions between metabotropic and ionotropic glutamate receptor agonists in the rat spinal cord *in vivo*. *Neuropharmacology* **34**, 1025–1031.

Kielland, A. & Heggelund, P. 2001 AMPA receptor properties at the synapse between retinal afferents and thalamocortical cells in the dorsal lateral geniculate nucleus of the rat. *Neurosci. Lett.* **316**, 59–62.

Koch, C. 1987 The action of the corticofugal pathway on sensory thalamic nuclei: a hypothesis. *Neuroscience* **23**, 399–406.

Kullmann, D. M. 2000 Spillover and synaptic cross talk mediated by glutamate and GABA in the mammalian brain. *Prog. Brain Res.* **125**, 339–351.

Lerma, J., Paternain, A. V., Rodriguez-Moreno, A. & Lopez-Garcia, J. C. 2001 Molecular physiology of kainate receptors. *Physiol. Rev.* **81**, 971–998.

Liu, X. B. 1997 Subcellular distribution of AMPA and NMDA receptor subunit immunoreactivity in ventral posterior and reticular nuclei of rat and cat thalamus. *J. Comp. Neurol.* **388**, 587–602.

Liu, X. B., Munoz, A. & Jones, E. G. 1998 Changes in subcellular localization of metabotropic glutamate receptor subtypes during postnatal development of mouse thalamus. *J. Comp. Neurol.* **395**, 450–465.

Lujan, R., Roberts, J. D. B., Shigemoto, R., Ohishi, H. & Somogyi, P. 1997 Differential plasma membrane distribution of metabotropic glutamate receptors mGluR1 alpha, mGluR2 and mGluR5, relative to neurotransmitter release sites. *J. Chem. Neuroanat.* **13**, 219–241.

McCormick, D. A. & Von Krosigk, M. 1992 Corticothalamic activation modulates thalamic firing through glutamate 'metabotropic' receptors. *Proc. Natl Acad Sci. USA* **89**, 2774–2778.

Martin, L. J., Blackstone, C. D., Huganir, R. L. & Price, D. L. 1992 Cellular localization of a metabotropic glutamate receptor in rat brain. *Neuron* **9**, 259–270.

Martin, W. J., Tsou, K. & Walker, J. M. 1998 Cannabinoid receptor-mediated inhibition of the rat tail-flick reflex after microinjection into the rostral ventromedial medulla. *Neurosci. Lett.* **242**, 33–36.

Mineff, E. & Valtschanoff, J. 1999 Metabotropic glutamate receptors 2 and 3 expressed by astrocytes in rat ventrobasal thalamus. *Neurosci. Lett.* **270**, 95–98.

Mineff, E. M. & Weinberg, R. J. 2000 Differential synaptic distribution of AMPA receptor subunits in the ventral posterior and reticular thalamic nuclei of the rat. *Neuroscience* **101**, 969–982.

Mitchell, S. J. & Silver, R. A. 2000 Glutamate spillover suppresses inhibition by activating presynaptic mGluRs. *Nature* **404**, 498–502.

Murphy, P. C. & Sillito, A. M. 1987 Corticofugal feedback influences the generation of length tuning in the visual pathway. *Nature* **329**, 727–729.

Nakanishi, S. 1992 Molecular diversity of glutamate receptors and implications for brain function. *Science* **258**, 597–603.

Neto, F. L., Schadrack, J., Berthele, A., Zieglgänsberger, W., Tölle, T. R. & Castro-Lopes, J. M. 2000 Differential distribution of metabotropic glutamate receptor subtype mRNAs in the thalamus of the rat. *Brain Res.* **854**, 93–105.

Nusser, Z., Mulvihill, E., Streit, P. & Somogyi, P. 1994 Subsynaptic segregation of metabotropic and ionotropic glutamate receptors as revealed by immunogold localization. *Neuroscience* **61**, 421–427.

Ohara, P. T. & Lieberman, A. R. 1993 Some aspects of the synaptic circuitry underlying inhibition in the ventrobasal thalamus. *J. Neurocytol.* **22**, 815–825.

Paulsen, O. & Heggelund, P. 1994 The quantal size at retinogeniculate synapses determined from spontaneous and evoked EPSCs in guinea-pig thalamic slices. *J. Physiol.* **480**, 505–511.

Petralia, R. S., Wang, Y. X., Niedzielski, A. S. & Wenthold, R. J. 1996 The metabotropic glutamate receptors, mGluR2 and mGluR3, show unique postsynaptic, presynaptic and glial localizations. *Neuroscience* **71**, 949–976.

Pisani, A., Calabresi, P., Centonze, D. & Bernardi, G. 1997 Enhancement of NMDA responses by group I metabotropic glutamate receptor activation in striatal neurones. *Br. J. Pharmacol.* **120**, 1007–1114.

Ralston III, H. J. 1983 The synaptic organization of the ventrobasal thalamus in the rat, cat and monkey. In *Somatosensory integration in the thalamus* (ed. G. Macchi, A. Rustioni & R. Spreafico), pp. 241–250. Amsterdam: Elsevier.

Rivadulla, C., Martinez, L. M., Varela, C. & Cudeiro, J. 2002 Completing the corticofugal loop: a visual role for the corticogeniculate type 1 metabotropic glutamate receptor. *J. Neurosci.* **22**, 2956–2962.

Rodriguez-Moreno, A., Herreras, O. & Lerma, J. 1997 Kainate receptors presynaptically downregulate GABAergic inhibition in the rat hippocampus. *Neuron* **19**, 893–901.

Salt, T. E. 1986 Mediation of thalamic sensory input by both NMDA and non-NMDA receptors. *Nature* **322**, 263–265.

Salt, T. E. & Binns, K. E. 2000 Contributions of mGlu1 and mGlu5 receptors to interactions with N-methyl-D-aspartate receptor-mediated responses and nociceptive sensory responses of rat thalamic neurones. *Neuroscience* **100**, 375–380.

Salt, T. E. & Eaton, S. A. 1991 Sensory excitatory postsynaptic potentials mediated by NMDA and non-NMDA receptors in the thalamus *in vivo*. *Eur. J. Neurosci.* **3**, 296–300.

Salt, T. E. & Eaton, S. A. 1995 Distinct presynaptic metabotropic receptors for L-AP4 and CCG1 on GABAergic terminals: pharmacological evidence using novel α-methyl derivative mGluR antagonists, MAP4 and MCCG, in the rat thalamus *in vivo*. *Neuroscience* **65**, 5–13.

Salt, T. E. & Eaton, S. A. 1996 Functions of ionotropic and metabotropic glutamate receptors in sensory transmission in the mammalian thalamus. *Prog. Neurobiol.* **48**, 55–72.

Salt, T. E. & Turner, J. P. 1998*a* Modulation of sensory inhibition in the ventrobasal thalamus via activation of Group II metabotropic glutamate receptors (mGluRs) by (2R,4R)-APDC. *Exp. Brain Res.* **121**, 181–185.

Salt, T. E. & Turner, J. P. 1998*b* Reduction of sensory and metabotropic glutamate receptor responses in the thalamus by the novel mGluR1selective antagonist (S) 2-methyl-4-carboxy-phenylglycine. *Neuroscience* **85**, 655–658.

Scharfman, H. E., Lu, S. M., Guido, W., Adams, P. R. & Sherman, S. M. 1990 N-Methyl-D-aspartate receptors contribute to excitatory postsynaptic potentials of cat lateral geniculate neurons recorded in thalamic slices. *Proc. Natl Acad. Sci. USA* **87**, 4548–4552.

Semyanov, A. & Kullmann, D. M. 2000 Modulation of GABAergic signaling among interneurons by metabotropic glutamate receptors. *Neuron* **25**, 663–672.

Sherman, S. M. & Guillery, R. W. 1996 Functional organization of thalamocortical relays. *J. Neurophysiol.* **76**, 1367–1395.

Sherman, S. M. & Guillery, R. W. 2000 *Exploring the thalamus*. New York: Academic.

Sherman, S. M. & Guillery, R. W. 2002 The role of thalamus in the flow of information to the cortex. *Phil. Trans. R. Soc. Lond.* B **357**, 1695–1708. (DOI 10.1098/rstb.2002.1161.)

Sillito, A. M. & Jones, H. E. 2002 Corticothalamic interactions in the transfer of visual information. *Phil. Trans. R. Soc. Lond.* B **357**. (In this issue.) (DOI 10.1098/rstb.2002.1170.)

Sillito, A. M., Murphy, P. C. & Salt, T. E. 1990 The contribution of the non-N-methyl-D-aspartate group of excitatory amino acid receptors to retinogeniculate transmission in the cat. *Neuroscience* **34**, 273–280.

Sillito, A. M., Jones, H. E., Gerstein, G. L. & West, D. C. 1994 Feature-linked synchronization of thalamic relay cell firing induced by feedback from the visual cortex. *Nature* **369**, 479–482.

Tamaru, Y., Nomura, S., Mizuno, N. & Shigemoto, R. 2001 Distribution of metabotropic glutamate receptor mGluR3 in the mouse CNS: differential location relative to pre- and postsynaptic sites. *Neuroscience* **106**, 481–503.

Timofeev, I. & Steriade, M. 1996 Low-frequency rhythms in the thalamus of intact-cortex and decorticated cats. *J. Neurophysiol.* **76**, 4152–4168.

Tsumoto, T., Creutzfeldt, O. & Legendy, C. R. 1978 Functional organization of the corticofugal system from visual cortex to lateral geniculate nucleus in the cat (with an appendix on geniculo-cortical mono-synaptic connections). *Exp. Brain Res.* **32**, 345–364.

Turner, J. P. & Salt, T. E. 1998 Characterization of sensory and corticothalamic excitatory inputs to rat thalamocortical neurones *in vitro*. *J. Physiol.* **510**, 829–843.

Turner, J. P. & Salt, T. E. 2000*a* Group II and III metabotropic glutamate receptors and the control of nrt input to rat thalamocortical neurones *in vitro*. *Soc. Neurosci. Abstr.* **26**, 1470.

Turner, J. P. & Salt, T. E. 2000*b* Synaptic activation of the Group I metabotropic glutamate receptor mGlu1 on the thalamocortical neurones of the rat dorsal lateral geniculate nucleus *in vitro*. *Neuroscience* **100**, 493–505.

Turner, J. P., Leresche, N., Guyon, A., Soltesz, I. & Crunelli, V. 1994 Sensory input and burst firing output of rat and cat thalamocortical cells: the role of NMDA and non-NMDA receptors. *J. Physiol.* **480**, 281–295.

Vidnyanszky, Z., Görcs, T. J., Negyessy, L., Kuhn, R., Knöpfel, T. & Hamori, J. 1996 Immunohistochemical visualization of the mGluR1a metabotropic glutamate receptor at synapses of corticothalamic terminals originating from area 17 of the rat. *Eur. J. Neurosci.* **8**, 1061–1071.

Wisden, W. & Seeburg, P. H. 1993 Mammalian ionotropic glutamate receptors. *Curr. Opin. Neurobiol.* **3**, 291–298.

GLOSSARY

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate
CNQX: 6-nitro,7-cyanoquinoxaline-2,3-dione
D-AP5: D-(2)-amino-5-phosphono-pentanoate
EPSP: excitatory postsynaptic potential
IPSP: inhibitory postsynaptic potential
LGN: lateral geniculate nucleus
NMDA: *N*-methyl-D-aspartate
TRN: thalamic reticular nucleus
VB: ventrobasal thalamus