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Research Report

Novel modes of rhythmic burst firing at cognitively-relevant frequencies in thalamocortical neurons

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ABSTRACT

It is now widely accepted that certain types of cognitive functions are intimately related to synchronized neuronal oscillations at both low (α/θ) (4–7/8–13 Hz) and high (β/γ) (18–35/30–70 Hz) frequencies. The thalamus is a key participant in many of these oscillations, yet the cellular mechanisms by which this participation occurs are poorly understood. Here we describe how, under appropriate conditions, thalamocortical (TC) neurons from different nuclei can exhibit a wide array of largely unrecognised intrinsic oscillatory activities at a range of cognitively-relevant frequencies. For example, both metabotropic glutamate receptor (mGluR) and muscarinic Ach receptor (mAchR) activation can cause rhythmic bursting at α/θ frequencies. Interestingly, key differences exist between mGluR- and mAchR-induced bursting, with the former involving extensive dendritic Ca^{2+} electrogenesis and being mimicked by a non-specific block of K^+ channels with Ba^{2+}, whereas the latter appears to be more reliant on proximal Na^+ channels and a prominent spike after-depolarization (ADP). This likely relates to the differential somatodendritic distribution of mGluRs and mAChRs and may have important functional consequences. We also show here that in similarity to some neocortical neurons, inhibiting large-conductance Ca^{2+}-activated K^+ channels in TC neurons can lead to fast rhythmic bursting (FRB) at ~40 Hz. This activity also appears to rely on a Na^+ channel-dependent spike ADP and may occur *in vivo* during natural wakefulness. Taken together, these results show that TC neurons are considerably more flexible than generally thought and strongly endorse a role for the thalamus in promoting a range of cognitively-relevant brain rhythms.

1. Introduction

Since the discovery of the EEG by Hans Berger in the early part of the last century (Berger, 1929) oscillatory brain activity and its potential relationship with a range of behavioural variables has been a dominant theme in neuroscience research. In the 50–60 years following inception of the EEG, the main focus of research on brain oscillations was, unsurprisingly, the classical alpha (α) (8–13 Hz) rhythm. This rhythm, the first EEG oscillation to be documented, is concentrated at occipital sites, reflecting its origins in the visual system, and is most pronounced during periods of relaxed wakefulness (Berger,

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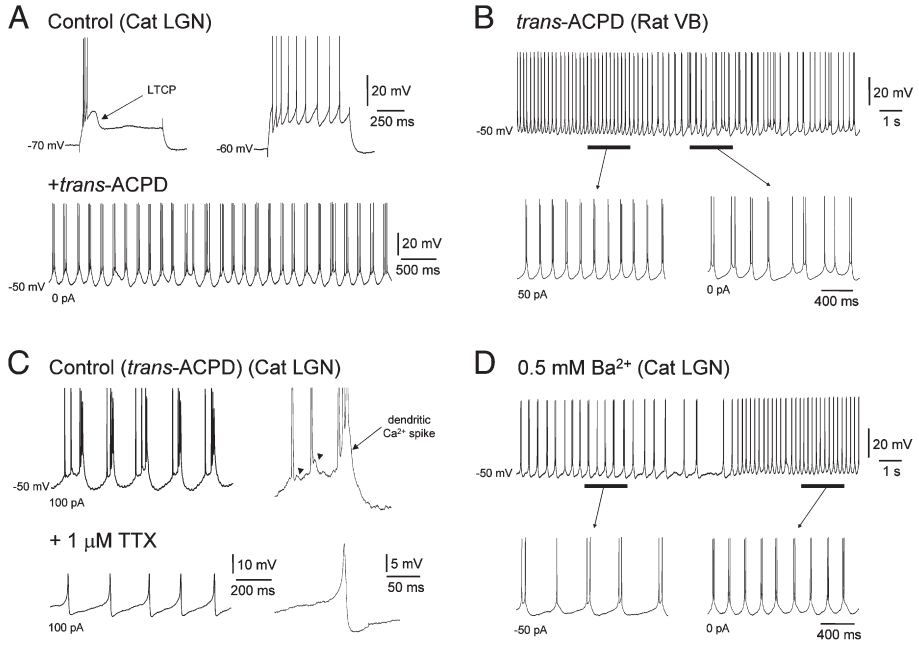

Fig. 1 – mGluR-activation induces HT bursting at α/θ frequencies in TC neurons. (A) Top: intracellular recordings form a cat LGN TC neuron *in vitro* showing basic burst (left) and tonic (right) modes of firing following the injection of a brief positive current step elicited from −70 mV and −60 mV, respectively. Bottom: application of the mGluR agonist, *trans*-ACPD (100 μM), brings about a third mode of firing termed HT bursting. (B) Whole-cell patch clamp recording from a rat VB TC neuron *in vitro* exhibiting HT bursting in the presence of 25 μM *trans*-ACPD. The underlined sections are expanded below and show HT bursting at two different levels of steady injected current as indicated. (C) Top: intracellular recording of mGluR-induced HT bursting in a cat LGN TC neuron *in vitro*. The trace to the right is an enlargement of a single HT burst which shows evidence of dendritic Ca^{2+} spike involvement as well as small spike ADPs (see arrowheads). Bottom: following a block of action potentials with 1 μM TTX, dendritic Ca^{2+} spikes become clearly evident. (D) Intracellular recording of a cat LGN TC neuron *in vitro* in the presence of 0.5 mM Ba^{2+} showing activity that is essentially indistinguishable from mGluR-induced HT bursting. Again, the underlined sections are expanded below and show Ba^{2+}–induced bursting at two distinct levels of steady injected current as indicated.

1929; Adrian and Matthews, 1934; Adrian and Yamagiwa 1935; Hughes and Crunelli 2005). Because the α rhythm is particularly evident when the eyes are closed, it has been widely considered to represent a simple idling of the visual cortex. However, its expression is not exclusively restricted to the eyes-closed condition (Mulholland, 1965) and an extremely large body of psychophysical literature spanning several decades has shown that α activity is inseparably linked to a host of perceptual and cognitive phenomena (Lindsley, 1952; Lansing, 1957; Anliker, 1963, 1966; VanRullen and Koch, 2003). For example, α rhythm frequency is robustly correlated with both reaction time (Surwillo, 1961) and perceived simultaneity (Kristofferson, 1967) and α activity is strongly linked with various aspects of long term memory (Klimesch, 1996, 1999).

Despite a recent tangible re-emergence of interest in the significance and mechanisms of α rhythms (Schürmann et al., 2000; Makeig et al., 2002; VanRullen and Koch, 2003; Hughes et al. 2004; Hughes and Crunelli 2005; Mazaheri and Jensen 2006; VanRullen et al. 2006; Palva and Palva 2007; Becker et al. 2008), research on brain oscillations in the last 10–20 years has mainly focused on fast oscillations in the β/γ (18–35/30–70 Hz) band (Gray et al., 1989; Gray and Singer 1989; Whittington et al. 1995; Başar-Eroglu et al. 1996; Roelfsema et al. 1997; Tallon-Baudry et al. 1996, 1997; Buhl et al. 1998; Fisahn et al. 1998; Csicsvari et al. 2003; Cunningham et al. 2003, 2004; Hajos et al. 2004; Mann et al. 2005; Traub et al. 2005; Bartos et al. 2007; Fries et al. 2007; Jensen et al. 2007). Initial interest in these oscillations was largely motivated by the finding that following an appropriate visual stimulus, local field potential (LFP) recordings in the cat primary visual cortex (i.e. V1) can exhibit robust oscillations at around 40 Hz (i.e. in the γ band) that are tightly phased-related to local neuronal firing (Gray and Singer, 1989). During these oscillations neurons with overlapping receptive fields and similar response characteristics were found to be synchronized with zero time-lag which suggested that γ activity may provide a means to temporarily connect groups of neurons which are functionally related (Gray et al., 1989). Zero time-lag synchronization during γ oscillations was also found to extend across different cortical territories and was noted to be especially strong between areas that perform related functions (Roelfsema et al., 1997). Ultimately, these and other findings led to the transient coupling of distributed neuronal assemblies by γ oscillations being widely touted as a solution to the binding problem (see for example Engel and Singer 2001), i.e. how the brain creates a stable and coherent percept from a distinct but related array of sensory signals, and ensured that the study of fast brain oscillations has been maintained as an area of strong interest in neuroscience.

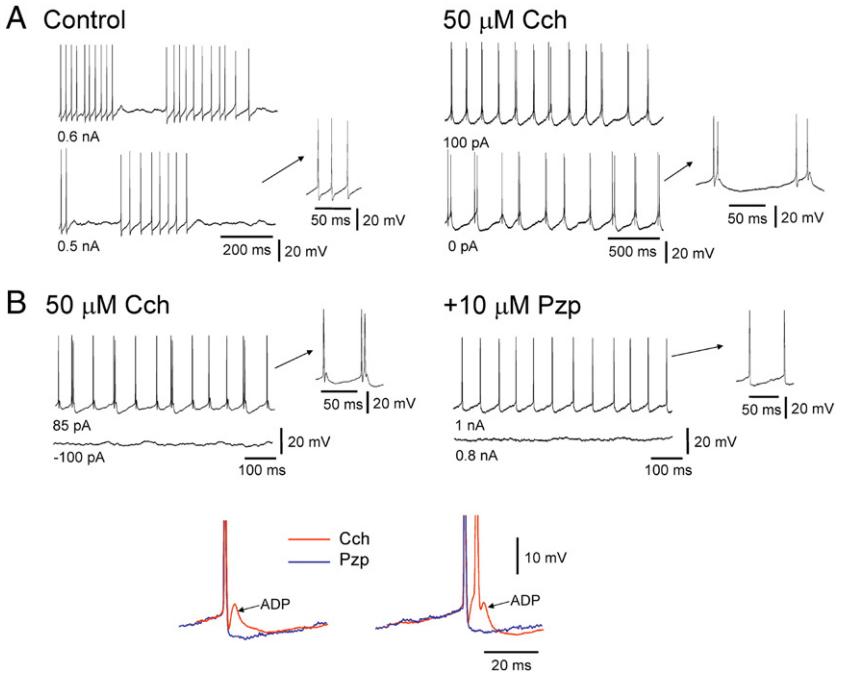

Fig. 2 – HT bursting can also be instated by mAchR activation but with distinct properties to those induced by mGLuR-activation. (A) Left traces: intracellular recordings from an LGN TC neuron in control conditions *in vitro* at different levels of steady injected current show conventional tonic firing. Right traces: following Cch application the output of the neuron at depolarized membrane potentials becomes characterised by rhythmic HT bursts. (B) left traces: HT bursting in another LGN TC neuron induced by Cch application *in vitro*. Right traces: addition of the mAchR antagonist pirenzipine (Pzp) converts HT bursting to conventional tonic firing. The enlarged traces below reveal that mAchR-induced HT bursting is dependent on a prominent spike ADP which, unlike that present following mGluR-activation (Fig. 1C, top right), can drive additional action potentials. Note, however, the clear lack of involvement of dendritic Ca^{2+} spikes. Modified and reproduced from Lőrincz et al. (2008) with permission.

1.1. *The role of the thalamus in cognitively-relevant brain oscillations*

Although the neocortex is clearly involved in shaping the ultimate EEG α rhythm signal (Hughes and Crunelli 2005), ever since the early days of EEG research, the thalamus has been suggested as an important site for its generation. However, the first real evidence for this was provided by experiments on dogs in the early 1970s (Lopes da Silva et al. 1973). These showed that naturally occurring α activity in the visual cortex is accompanied by coherent α oscillations in the primary visual thalamus (i.e. the lateral geniculate nucleus, LGN) (Lopes da Silva et al. 1973). Furthermore, because these LGN oscillations sometimes occurred independently of cortical α rhythms, it appeared that the thalamus was able to autonomously produce α activity. Similar results were later obtained in cats, both for an equivalent of the occipital α rhythm in the visual system (Chatila et al. 1992, 1993; Rougeul-Buser and Buser 1997) as well as for an analogue of the somatosensory μ rhythm (Bouyer, et al. 1982, 1983; Rougeul-Buser and Buser 1997). More recently, an abundance of human imaging data has emerged which also strongly supports a central role for the thalamus in the generation of EEG α activity (summarized in Hughes and Crunelli 2005; see also Feige et al., 2005; Goncalves et al., 2006).

Oscillations in the β/γ band are present in a wide variety of brain areas but are most commonly associated with the neocortex (Gray et al. 1989; Gray and Singer 1989; Gray and McCormick 1996; Buhl et al. 1998; Cunningham et al. 2004; Traub et al. 2005), hippocampus (Whittington et al. 1995; Fisahn et al. 1998; Csicsvari et al. 2003; Hajos et al. 2004; Mann et al. 2005) and olfactory bulb (Eeckman and Freeman 1990). As such, the thalamus has not traditionally been considered as a key player in the generation of fast oscillations. Indeed, the initial inability to observe fast oscillations in the LGN suggested that they were neither reflected in the thalamus nor that the thalamus was involved in their generation (Gray and Singer 1989). However, a subsequent study in anesthetized cats showed that over half of neurons in the LGN show robust oscillatory activity at around 50 Hz (Ghose and Freeman 1992). Later work also revealed the presence of fast oscillations in the LGN, not only under anaesthesia but also during natural wakefulness (Steriade et al. 1996). Crucially, this latter study also demonstrated that such oscillations are present in a variety of different thalamic nuclei, occur in tight synchrony with rhythmic activity in related cortical areas, and are highly correlated with oscillatory phenomena in individual TC neurons (Steriade et al. 1996; see also Steriade et al. 1991). This suggested that the thalamus may play a more active role in the generation of fast oscillations than had been previously thought.

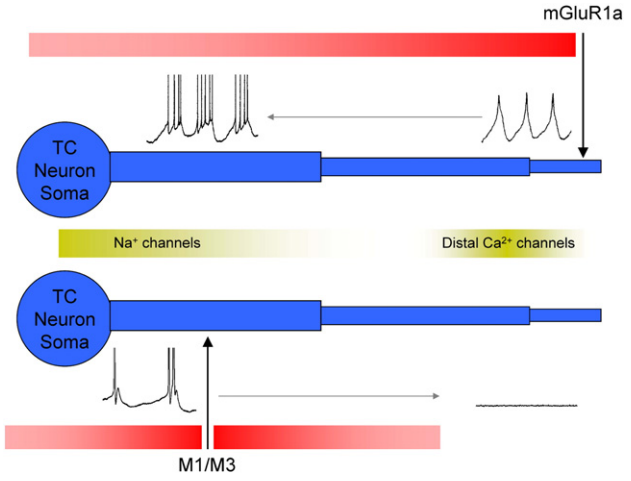

Fig. 3 – The differences between mGluR- and mAchR-induced HT bursting can be explained by a distinct somatodendritic receptor distribution. Proposed scheme to explain the difference between mGluR- and mAchR-induced HT bursting. Top: mGluR1a receptors are located at distal sites, presumably close to the Ca^{2+} channels that underlie dendritic spike generation. Thus, suppression of K^+ channels in this region facilitates the generation of Ca^{2+} spikes which then propagate to the soma where they interact with proximal Na^+ channels to produce bursts of action potentials. Note that because the domain of influence of mGluR1a activation extends to the soma (red shaded bar), activating these receptors is able to depolarize the neuron sufficiently close to action potential threshold to facilitate bursting. Bottom: mAchRs are located at more proximal sites and are therefore unable to trigger distal Ca^{2+} spikes. However, they are ideally situated to enhance dendritic Na^+ channel-dependent events, hence the appearance of a prominent spike ADP following activation of these receptors.

1.2. *Activation of metabotropic glutamate receptors (mGluRs) or muscarinic Ach receptors (mAchRs) induces rhythmic bursting at α/θ frequencies in TC neurons*

Given that the thalamus is involved in synchronized oscillations at both low and high cognitively-relevant frequencies, a key goal is to understand the intrinsic properties in thalamic neurons that are central to this involvement. Under normal conditions, TC neurons recorded intracellularly *in vitro* show two distinct modes of firing (Llinás and Jahnsen 1982). When these cells are relatively hyperpolarized (less than or equal to approximately −65 mV) a brief injection of positive current leads to a transient depolarization lasting around ~100–200 ms which is crowned by a high-frequency burst of action potentials (i.e. burst mode) (Fig. 1A, top left) (Llinás and Jahnsen 1982). This transient depolarization is typically referred to as a low-threshold Ca^{2+} potential (LTCP) or low-threshold spike (LTS) and is generated by a T-type Ca^{2+} current (Coulter et al. 1989; Crunelli et al. 1989; Hernandez-Cruz and Pape 1989; Suzuki and Rogawski 1989). In contrast, when TC neurons are relatively depolarized (greater than or equal to approximately −60 mV), a brief injection of positive current leads to tonic firing or single spike activity (i.e. tonic or relay mode, see below) (Fig. 1A, top right) (Llinás and Jahnsen 1982). The discovery of these two modes of firing has laid the foundation for several basic ideas regarding how the thalamus operates with broad agreement existing that LTCPs are mainly associated with low frequency oscillations during sleep and anaesthesia (McCarley et al. 1983; Domich et al. 1986; Nunez et al. 1992; Steriade et al. 1993; Crunelli et al. 2006; but see Sherman 2001) whereas tonic firing occurs more commonly during wakefulness and is important for the faithful relay of sensory information to the neocortex.

Recently, we found that activating metabotropic gluatamate receptors (mGluRs), either pharmacologically or via electrically stimulating corticothalamic fibres, led to around 25% of TC neurons in the cat LGN recorded *in vitro* exhibiting a third mode of firing which we termed high-threshold (HT) bursting (Fig. 1A, bottom) (Hughes et al., 2002, 2004). HT bursting occurs rhythmically at ~3–15 Hz, thus encompassing both the α (8–13 Hz) and θ (4–7 Hz) bands, and unlike LTCP-mediated bursting is present when neurons are relatively depolarized (greater than −55 mV) (Hughes et al., 2002, 2004; Hughes and Crunelli 2005). Importantly, single unit recordings of LGN TC neurons from freely moving cats showed that activity with indistinguishable properties to HT bursting occurs coherently with α oscillations in the intact brain (Hughes et al. 2004; Hughes and Crunelli 2005, 2007). We have since found that following an equivalent activation of mGluRs, HT bursting with broadly similar properties to those noted in the cat LGN can also be observed in other areas of the cat thalamus, including the ventrolateral (VL) nucleus, i.e. the motor thalamus, and the ventrobasal complex (VB), i.e. the somatosensory thalamus, where it may play a role in promoting synchronized μ oscillations (Bouyer et al. 1982; Hughes and Crunelli 2005). mGluR-induced HT bursting is also present in TC neurons from principal thalamic nuclei of both the rat and mouse (Fig. 1B).

Following application of the Na^+ channel blocker tetrodotoxin (TTX) to block action potentials, mGluR-induced HT bursting is replaced by a residual oscillation comprising rhythmic dendritic Ca^{2+} spikes (Fig. 1C) (Jahnsen and Llinás 1984; Williams and Stuart 2000; Hughes et al. 2004), indicating that these events are the primary driving force behind burst activity (Hughes et al. 2004). Indeed, dendritic Ca^{2+} spikes can be regularly observed in HT bursting cells even before TTX treatment (Fig. 1C) whilst a blockade of Ca^{2+} channels with Ni^{2+} converts HT bursting into regular tonic firing (Hughes et al. 2004; Crunelli et al. 2006). Because the mGluR subtype that is responsible for inducing HT bursting (i.e. mGluR1a; (Hughes et al. 2004) is located at distal sites on TC neurons (Godwin et al. 1996; Erisir et al. 1997b) and thought to be negatively coupled to leak K^+ channels (von Krosigk et al. 1999; Turner and Salt 2000; Hughes et al. 2002), it is reasonable to assume that mGluR-dependent HT bursting is reliant on a strong suppression of dendritic K^+ conductance which in turn facilitates the generation of local Ca^{2+} spikes. In support of this, activity in TC neurons that is essentially indistinguishable from mGluR-induced HT bursting can also be instated by non-selectively reducing K^+ conductance through the application 0.5 mM Ba^{2+} (Fig. 1D), whereas artificially reducing linear K^+ conductance solely at the soma, using the dynamic clamp technique (see Hughes et al. 1999, 2002 and Blethyn et al. 2006), is unable to recreate HT bursting (data not shown).

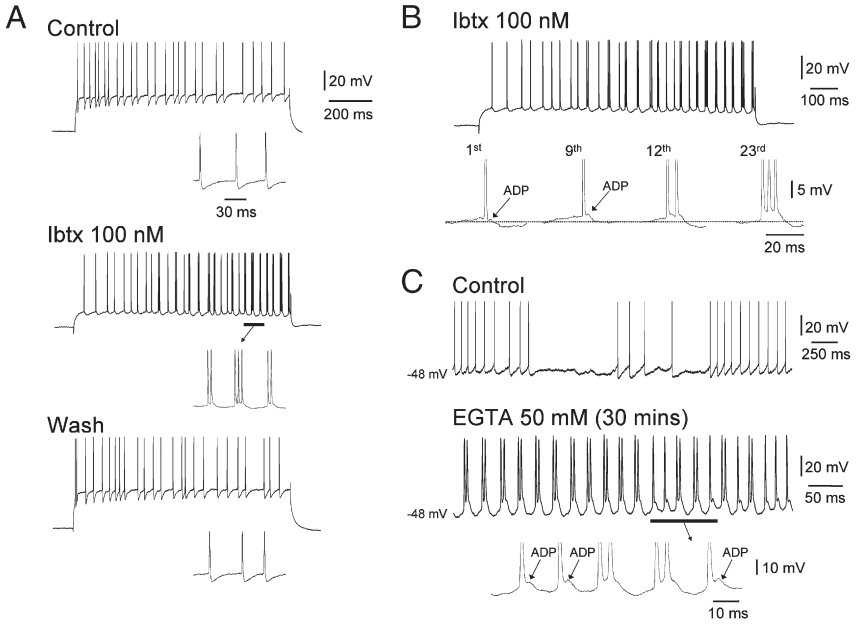

Fig. 4 – Inihition of BK channels leads to rhythmic bursting at ~40 Hz in TC neurons. (A) Response of a TC neuron in the rat LGN *in vitro* to a positive current pulse in control conditions (top), following 100 nM Ibtx application (middle) and after Ibtx washout (bottom). Ibtx reversibly induces rhythmic burst firing at 30–40 Hz. In each panel, the underlined sections are enlarged below as indicated. (B) A closer inspection of the response of the neuron shown in A following Ibtx application reveals that burst activity arises from the progressive build up of a spike ADP. (C) Top trace: activity of a TC neuron from the cat LGN in control conditions *in vitro* after depolarization with steady current reveals conventional tonic firing. Bottom trace: after recording for 30 min with 50 mM EGTA in the electrode, at the same level of injected current this neuron exhibits rhythmic burst firing at 40–50 Hz. Again, this bursting is associated with a prominent spike ADP as shown by the enlarged section below.

Because several other types of receptors on TC neurons are also negatively coupled to leak K^+ channels (McCormick, 1992), we recently asked whether their activation might also lead to HT bursting in TC neurons. In particular, we were interested to test whether or not pharmacologically activating muscarinic Ach receptors (mAchRs), which play a central role in arousal regulation through their effects in the thalamocortical system (McCormick, 1992), would have similar effects on TC neuron firing to activating mGluRs. Indeed, through an effect largely mediated by M1/M3 receptors, the ACh receptor agonist carbachol (Cch) applied *in vitro* brings about HT bursting at ~3–15 Hz in subsets of TC neurons from a variety of principal thalamic nuclei including the LGN, VB and VL (Fig. 2) as well as from the centrolateral (CL) nucleus, a member of the non-specific intralaminar nuclei (data not shown).

1.3. *mGluR- and mAchR-induced bursting exhibit subtle differences that may have important functional consequences*

Interestingly, whilst the properties of HT bursting induced by Cch are broadly similar to those of HT bursting induced by mGluR-activation, there is one notable distinction between the two types of activity. Specifically, whilst mGluR-induced HT bursting is overtly associated with dendritic Ca^{2+} spikes (Fig. 1C) (see above), this is rarely the case for mAChR-induced HT bursting (Fig. 2). Rather, HT bursting in this context seems to be generated by a prominent spike afterdepolarization (ADP) (Lőrincz et al. 2008) (Fig. 2B). This ADP appears to be generated by Na^+ channels (Hughes et al. 2004) and whilst also being present following mGluR1a activation (Fig. 1C, top right, arrowheads), it possesses a much greater amplitude and functional significance following mAchR activation (Fig. 2B, bottom).

A possible explanation for the distinction between mGluR- and mAchR-induced HT bursting relates to the differential distribution of these receptors on the somatodendritic axis of TC neurons (Fig. 3). mAchRs are located at relatively proximal sites (Erisir et al., 1997a, b) and their domain of influence may therefore not extend to the more distal regions where Ca^{2+} spike generation occurs (Jahnsen and Llinás, 1984). On the other hand, they are ideally situated to modulate proximal Na^+ channel-dependent events (Williams and Stuart, 2000) explaining the appearance of a large spike ADP following Cch application. In contrast to mAchRs, and as mentioned above, mGluRs are a located more distally in a position that is presumably close to the dendritic Ca^{2+} spike generating machinery. However, because the domain of influence of mGluRs extends to the soma (von Krosigk et al., 1999; Turner and Salt, 2000; Hughes et al., 2002), activation of these receptors can also affect proximal Na^+ channel-dependent events, albeit to a lesser extent than mAchR activation. One interesting aspect of the difference between mGluR- and mAchR-induced HT bursting is that the former will obviously be associated with a large amount of dendritic Ca^{2+} influx.

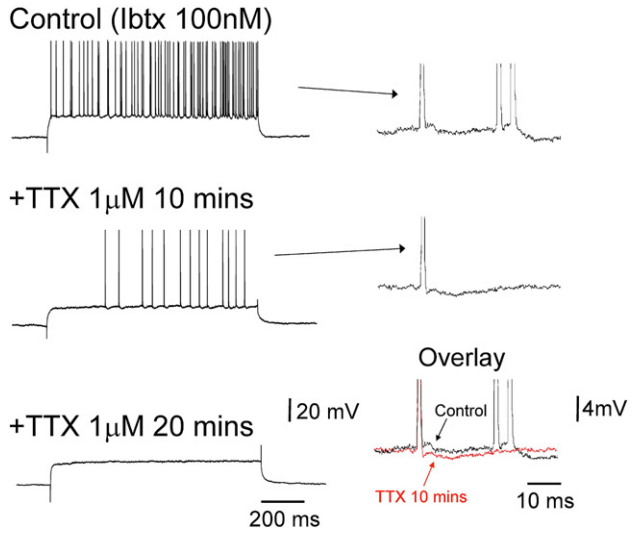

Fig. 5 – The spike ADP underlying rhythmic bursting at ~40 Hz in TC neurons is dependent on Na^+ channels. Top trace: response of a rat LGN TC neuron *in vitro* to a positive current step during application of 100 nM Ibtx showing rhythmic bursting at 20–60 Hz. Middle trace: after 10 min of TTX treatment the neuron reverts to a pattern of single spike activity. The enlarged sections to the right show that this is due to a preferential suppression of the spike ADP by TTX. Bottom trace: after 20 min TTX abolished all action potential output.

This hints at the possibility that whilst mAChR-induced HT bursting may perform a simple electrical pacemaker role (Lőrincz et al., 2008), mGluR-induced bursting may also be associated with profound biochemical changes within the neuron, potentially leading to alterations in synaptic strength and gene expression.

1.4. *Inhibiting large-conductance Ca^{2+}-activated K^+ channels brings about intrinsic bursting at ~40 Hz in TC neurons*

Prominent spike ADPs similar to those observed during mAChR-induced HT bursting are also a common feature of rhythmic bursting in several other types of neurons. For example, such events play a central role in repetitive bursting at 40–80 Hz in pyramidal cells of the electrosensory lateral line lobe of the weakly electric fish, an activity which, interestingly, is blocked by selectively applying TTX to the proximal apical dendritic region (Lemon and Turner, 2000). Similarly, spike ADPs are an important determinant of the so-called chattering or fast rhythmic bursting (FRB) activity which occurs at 20–80 Hz, is present in a subset of layer II/III neocortical pyramidal neurons (Gray and McCormick, 1996; Brumberg et al., 2000) and which, again, is highly sensitive to an inhibition of Na^+ channels (Brumberg et al., 2000). With regard to FRB, it appears that persistent rather than transient Na^+ channels are the key component in generating ADPs because potentiating these channels by applying either the Na^+ channel toxin, ATX II (Brumberg et al., 2000), or the NO donor, *S*-nitroso-*N*-acetylpenicillamine (SNAP) (Traub et al., 2003), can transform regular spiking (RS) layer II/III neurons into FRB cells, with this transformation being reversed by the putative persistent Na^+ channel blocker, phenytoin (Traub et al., 2003). More specifically, it appears that a delicate balance between afterhyperpolarization (AHP)-generating currents and persistent Na^+ channels is what determines the mode of firing in these cells because both experimental and modelling studies show that a transformation from RS to FRB behaviour can also be readily achieved by blocking large-conductance Ca^{2+}-activated (BK) K^+ channels with iberiotoxin (Ibtx) (Traub et al., 2003).

Given that TC neurons have the clear capacity to generate Na^+ channel-dependent spike ADPs and that a high immunoreactivity specifically for BK channels is present in the dorsal thalamus of the rodent brain (Sausbier et al., 2006), we recently tested whether application of Ibtx to TC neurons of the LGN maintained *in vitro* could induce FRB. In doing so, we found that Ibtx, applied at 100 nM, was able to consistently and reversibly induce FRB at 20–60 Hz in all TC neurons tested (Fig. 4A). Furthermore, as with layer II/III neocortical cells, this type of activity involved a clear spike ADP (Fig. 4B) and was preferentially blocked by TTX, being abolished well before a full block of action potentials was achieved (Fig. 5). Interestingly, we have found that manipulations which reduce the supply of intracellular Ca^{2+}, either by decreasing $[Ca^{2+}]_o$ to 0 mM or chelating intracellular Ca^{2+} with EGTA or BAPTA (Fig. 4C), are also able to induce FRB-like behaviour in TC neurons, in a similar way to that predicted by simulation studies to occur for cortical pyramidal neurons (Traub et al., 2003). This finding is consistent with experiments showing that disrupting Ca^{2+}-induced Ca^{2+}-release in TC neurons can also bring about a similar behaviour to FRB (Budde et al., 2000) and hints at a complex management of firing in these cells which may be potentially influenced by various regulatory systems which couple to the cyclic ADP ribose pathway (Budde et al., 2000), via increases in intracellular cyclic GMP (Graeff et al., 1998), or to protein kinase A (PKA) (Traub et al., 2003), via stimulation of cyclic AMP.

The finding that an inhibition of BK channels leads to rhythmic bursting at ~40 Hz in TC neurons *in vitro* is noteworthy because previous *in vivo* studies utilising single unit extracellular recordings have shown that, during both natural wakefulness and REM sleep, a subset of TC neurons in the cat CL nucleus exhibit rhythmic bursting at ~40 Hz with similar properties to those described here (Steriade and Glenn, 1982; Steriade et al., 1993). Indeed, intracellular recordings of these cells obtained during barbiturate anaesthesia revealed that this type of bursting is intrinsic and involves a clear spike ADP which bears a striking resemblance to that seen in our *in vitro* recordings (Steriade et al., 1993). The additional lack of prominent spike AHP and narrow action potential width in these CL TC neurons led the investigators to speculate that their unusual behaviour arose from a combination of reduced Ca^{2+}-activated K^+ current and increased Na^+ conductance, a suggestion which, again, is fully in line with our *in vitro* data. Mirroring these findings from the CL thalamus, we have recently noted that some TC neurons in the cat LGN also exhibit brief periods of rhythmic bursting at 40–60 Hz during natural wakefulness (Fig. 6). Thus, we suggest that rhythmic bursting in the γ band may occur in cells from a variety of both

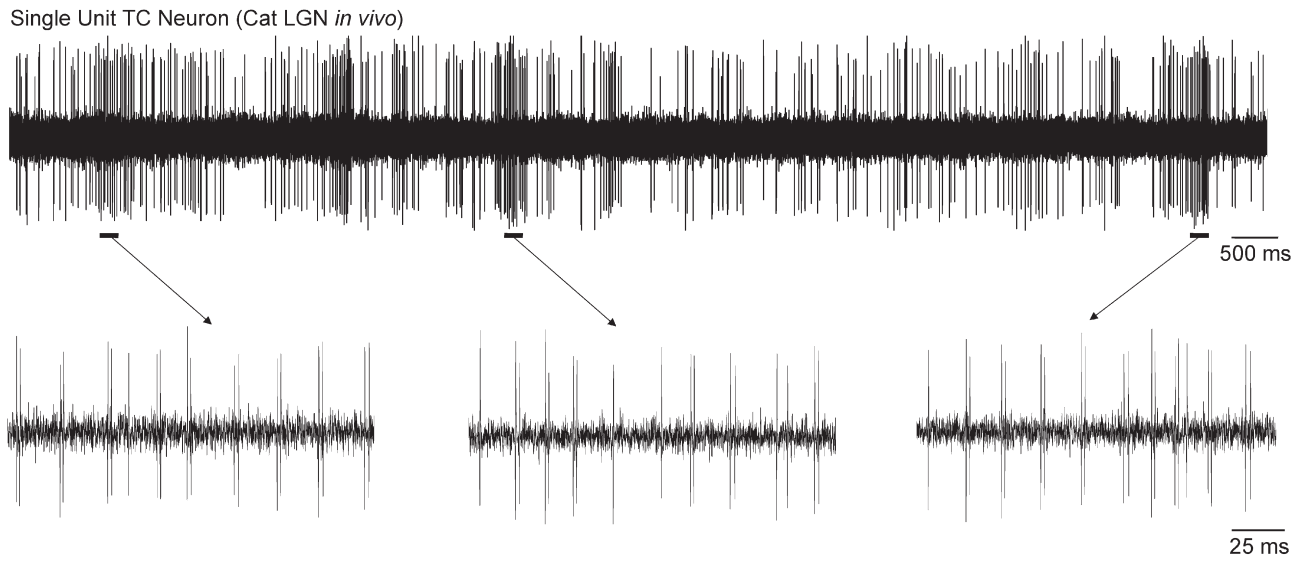

Fig. 6 – TC neurons recorded from the LGN of naturally waking cats can exhibit brief periods of rhythmic bursting at ~50 Hz. Single unit recording of a TC neuron from the cat LGN during natural wakefulness. The underlined sections are enlarged below and reveal episodes of rhythmic bursting at 40–60 Hz.

specific and non-specific thalamic nuclei where it could play a role in driving behaviourally-relevant, synchronized γ oscillations as is the case for FRB in the neocortex (Cunningham et al., 2004).

2. Summary

Synchronized oscillations at both low (α/θ) (4–7/8–13 Hz) and high (β/γ) (18–35/30–70 Hz) frequencies have close links with a variety of cognitive and perceptual phenomena. Whilst such oscillations are known to involve the thalamus, very little is known about the way in which thalamic neurons engage in and promote oscillatory activity. We have shown here how, under certain conditions, TC neurons in a variety of nuclei and species can display several types of intrinsic oscillatory activity which have previously gone largely unrecognised (Sherman, 2001; Llinás and Steriade, 2006). In particular, TC neurons are able to generate two distinct types of rhythmic HT bursting at α/θ frequencies following either mGluR or mAchR activation, respectively, and can show a ~40 Hz activity, similar to the FRB behaviour of some layer II/III neocortical pyramidal cells (Brumberg et al., 2000; Traub et al., 2003; Cunningham et al., 2004), following a suppression of BK channels. Whilst intrinsic oscillatory activity is also a common and important feature of other brain areas, we propose that these novel modes of operation of TC neurons may be a key component in shaping synchronized brain oscillations at both low and high cognitively-relevant frequencies. Finally, we suggest that a disruption of the mechanisms that underlie these unusual forms of intrinsic oscillatory activity may be an important aspect of several pathological scenarios that affect cognitive performance (Llinás et al., 1999), or are associated with excessive rhythmicity in thalamocortical networks (Crunelli and Leresche, 2002).

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