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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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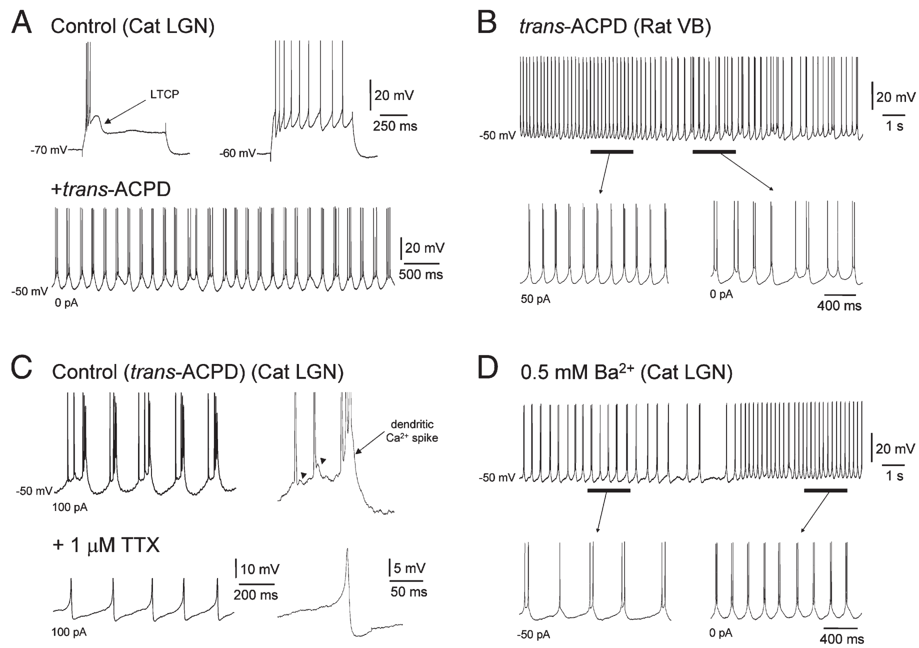

Fig. 1 – mGluR-activation induces HT bursting at α/θ frequencies in TC neurons. (A) Top: intracellular recordings form a cat LGN TC neuron *in vitro* showing basic burst (left) and tonic (right) modes of firing following the injection of a brief positive current step elicited from −70 mV and −60 mV, 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.