Neuropharmacology xxx (2017) 1–9

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

GABA receptors and T-type Ca^{2+} channels crosstalk in thalamic networks

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ARTICLE INFO

Article history:
Received 10 April 2017
Received in revised form
1 June 2017
Accepted 6 June 2017
Available online xxx

Keywords:
Cav3
Long-term potentiation
Long-term depression
Synapse
Nucleus reticularis thalami
Thalamocortical

ABSTRACT

Although the thalamus presents a rather limited repertoire of GABAergic cell types compare to other CNS area, this structure is a privileged system to study how GABA impacts neuronal network excitability. Indeed both glutamatergic thalamocortical (TC) and GABAergic nucleus reticularis thalami (NRT) neurons present a high expression of T-type voltage-dependent Ca^{2+} channels whose activation that shapes the output of the thalamus critically depends upon a preceding hyperpolarisation. Because of this strict dependence, a tight functional link between GABA mediated hyperpolarization and T-currents characterizes the thalamic network excitability. In this review we summarize a number of studies showing that the relationships between the various thalamic $GABA_{A/B}$ receptors and T-channels are complex and bidirectional. We discuss how this dynamic interaction sets the global intrathalamic network activity and its long-term plasticity and highlight how the functional relationship between GABA release and T-channel-dependent excitability is finely tuned by the T-channel activation itself. Finally, we illustrate how an impaired balance between T-channels and GABA receptors can lead to pathologically abnormal cellular and network behaviours.

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Compared to other CNS regions, such as the cortex, hippocampus or cerebellum, the thalamic GABAergic network may appear at first glance very modest. While for example the morphological, molecular and physiological features of cortical interneurons are so diverse that researchers had to join force to propose a classification of these complex neuronal populations (DeFelipe et al., 2013), the intrathalamic GABAergic neurons come down to two types, the neurons located in the nucleus reticularis thalami and the local interneurons that are present in different thalamic nuclei. However, except in the dorsal lateral geniculate nucleus very few interneurons (less than 5% of the total neuronal population) are present in thalamic nuclei of rodents (Cavdar et al., 2014; Jones, 2007). Therefore, most of the available data on GABAergic inhibition in rodent primary thalamic nuclei deals with inhibitory

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http://dx.doi.org/10.1016/j.neuropharm.2017.06.006
0028-3908/

Please cite this article in press as: Leresche, N., Lambert, R.C., GABA receptors and T-type Ca^{2+} channels crosstalk in thalamic networks, Neuropharmacology (2017), http://dx.doi.org/10.1016/j.neuropharm.2017.06.006

mechanisms originating from the NRT (Fig. 1A). Despite this paucity of GABAergic cell types, the thalamic network is one of the most interesting systems where GABA impact on neuronal excitability can be studied. Indeed, both glutamatergic thalamocortical (TC) and GABAergic nucleus reticularis thalami (NRT) neurons present a high expression of T-type voltage-dependent Ca^{2+} channels whose activation, which generates the so-called rebound low-threshold spike (LTS) and is the bases of the thalamic bursting mode of firing, critically depends upon a preceding hyperpolarisation (Fig. 1B) (Deschenes et al., 1984; Jahnsen and Llinas, 1984). T-type voltage-dependent Ca^{2+} currents activate around -60 mV, are fully inactivated after a few tens of milliseconds and their steady-state inactivation is nearly complete at membrane potentials more depolarized than -60 mV (Perez-Reyes, 2003). Therefore, hyperpolarization allowing some channels to recover from inactivation is required to evoke a substantial T-current (Fig. 1C) creating a strict dependence of the LTS upon a preceding hyperpolarization such as those mediated by the $GABA_A$ and $GABA_B$ receptors.

In this review we will highlight how the functional impact of GABA receptors activation in thalamic neurons far exceeds the traditional "shunting" effect and shapes the whole thalamic network excitability. We will show how GABA released during either tonic or burst firing of GABAergic thalamic neurons targets diverse $GABA_A$ and $GABA_B$ receptors. We will discuss how the complex functional relationship between GABA release and T-channel-dependent excitability is finely tuned by the T-channel activation itself and how an impaired balance between T-channels and GABA receptors can lead to pathological activities.

1. T-channels and $GABA_A$ receptors

The archetypal and best-studied physiological activity pattern that exemplifies the crosstalk between GABA inhibitory post-synaptic potentials (IPSPs) and the T-current is the 7–14 Hz spindle oscillation wave that occurs during non-REM sleep (Deschenes et al., 1984; Steriade et al., 1993). During these waves, NRT neuron activity is characterized by the occurrence of high frequency bursts of action potentials generated by LTSs at spindle frequency. These bursts of action potentials elicit fast rising multicomponent $GABA_A$ IPSPs in TC neurons that, if strong enough, generate an LTS as rebound activity (Deschenes et al., 1984) (Fig. 2A). At the population level, the thalamocortical output is therefore characterized by the occurrence of high-frequency bursts at each oscillation cycle. The output firing associated to the LTSs provides excitatory synaptic drive back to NRT neurons as well as to cortical neurons. It is still unclear whether the repetitive LTS occurrence in NRT neurons at spindle frequency intrinsically originates in the NRT nucleus, as suggested by some *in vivo* studies (Steriade et al., 1987) or requires the interplay between NRT and TC neurons as shown *in vitro* (Bal and McCormick, 1993; Bal et al., 1995; von Krosigk et al., 1993). Notwithstanding this issue, the capability of spindle waves to drive cortical networks and generate the non-REM EEG spindle rhythm critically depends on the ability of the summating $GABA_A$ IPSPs to remove T-channel inactivation and thus allow the generation of

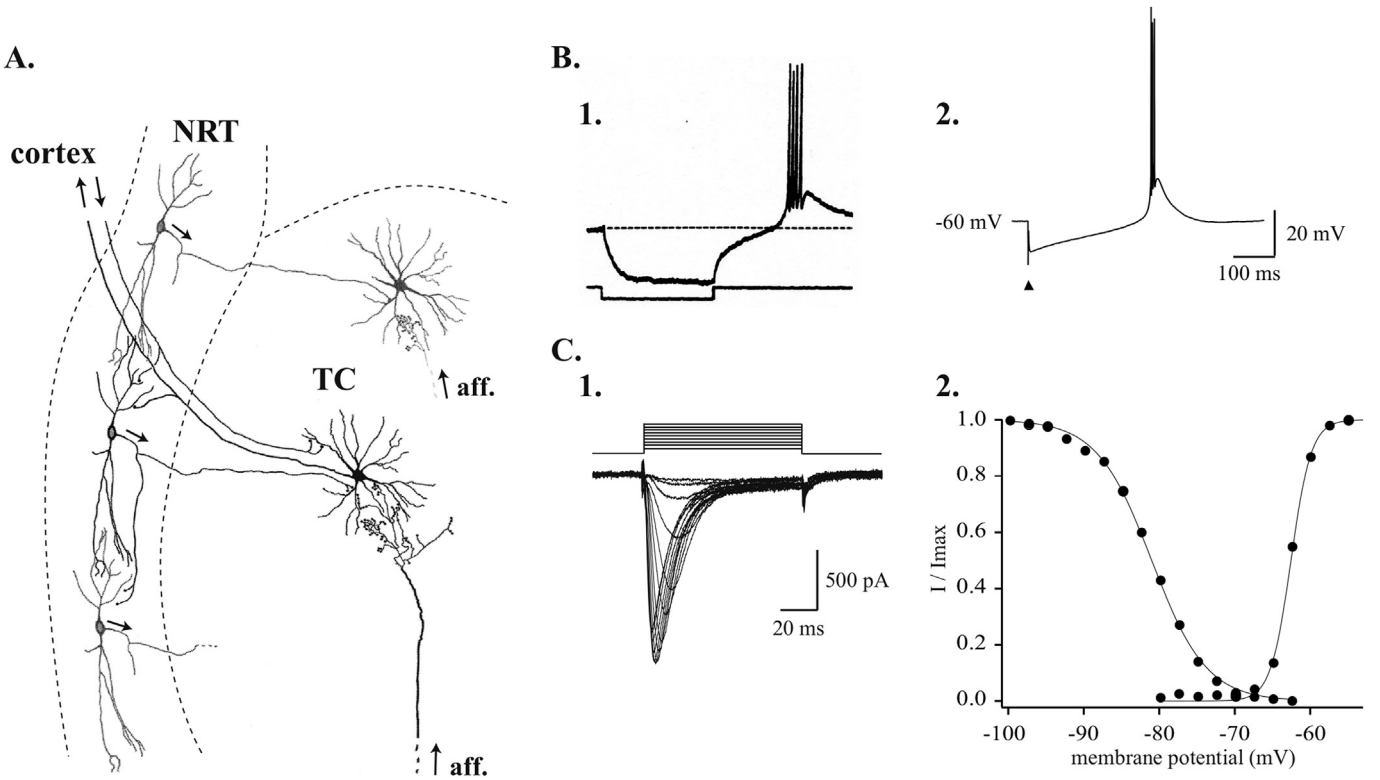

Fig. 1. GABA mediated hyperpolarization recruits thalamic T-currents
A. Schematic drawing of the thalamic network. The GABAergic neurons from the NRT innervate the glutamatergic TC neurons that project back to the NRT neurons and relay the information arising from extra-thalamic afferents (aff.) to the cortex.
B. Hyperpolarization of TC neurons resulting from either step current injection (**1.**, low trace) or NRT afferent activation (**2.**, plain triangle) deinactivates T-channels that open upon membrane repolarization generating a rebound LTS and associated high-frequency burst firing.
C. Superimposed traces of typical T-currents evoked in TC neurons by successive step depolarization at increasing membrane potentials (**1.**, holding potential: −100 mV, first step: −70 mV, step: 2.5 mV). Typical voltage-dependency relationships of the steady-state inactivation and activation for T currents recorded in TC neurons (**2.**).
B1: modified with permission from (Jahnsen and Llinas, 1984).

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