GABA receptors and T-type Ca2+ channels crosstalk in thalamic networks

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Highlights:

- T-mediated burst firing recruits synaptic and extrasynaptic $GABA_A$ receptors
- Phasic and tonic $GABA_A$ currents control T-channel activation
- T-channel activity triggers long-term plasticity of $GABA_A$ synapses

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.

Keywords: Cav3; long-term potentiation; long-term depression; synapse; nucleus reticularis thalami; thalamocortical

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 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 LTSs in TC neurons (David et al., 2013).

Synaptic and extrasynaptic $GABA_A$ receptors

Interestingly, it was recently shown that such efficient GABA inputs do not only involve synaptic but also extrasynaptic $GABA_A$ receptors. Indeed, TC neurons express two types of $GABA_A$ receptors that differ by their localization, subunit composition and functional properties, predominantly $\alpha 1 \beta 2 \gamma 2$ for synaptic and $\alpha 4 \beta 2 \delta$ for extrasynaptic receptors (Jia et al., 2005; Kralic et al., 2006; Peden et al., 2008; Pirker et al., 2000). Classically, the synaptic $GABA_A$ receptors, that are characterized by a fast kinetic, a low sensitivity to GABA and a rapid desensitization, are responsible for the phasic IPSPs while the extrasynaptic receptors, that show a high sensitivity to GABA and a much slower desensitization, account for the tonic current activated by the ambient GABA (Semyanov et al., 2004). However, recent *in vitro* studies demonstrated that the extrasynaptic $GABA_A$ receptors also contribute to NRT burst-mediated phasic IPSPs (Herd et al., 2013; Rovo et al., 2014). Firstly, in $\alpha 1^{-/-}$ mice TC neurons that are devoid of synaptic $GABA_A$ receptors, stimulation of NRT neurons that potentially triggered NRT burst firing still evoked inhibitory postsynaptic currents (IPSCs) (Fig. 2B). Although delayed and reduced in amplitude, these residual IPSCs demonstrated that TC neuron extrasynaptic $GABA_A$ receptors were recruited by synaptic activity during NRT burst firing. Indeed, upon deletion of the extrasynaptically located $\alpha 4$ subunit the amplitude of the multiple peak IPSCs was not modified but the tail of the burst-mediated IPSCs was much reduced in pairs of monosynaptically connected NRT and TC neurons. Finally, even during NRT tonic firing, the decay rate of the evoked IPSCs in TC neurons was significantly faster in $\alpha 4^{-/-}$ or $\delta^{-/-}$ mice suggesting that extrasynaptic $GABA_A$ receptors

participate to single IPSC in wild type animals (Herd et al., 2013). Overall, these data demonstrate that recruitment of extrasynaptic $GABA_A$ receptors critically prolonged phasic inhibition, which should increase T-channel deinactivation and in turn facilitate rebound LTS generation.

Indeed, a later study confirmed these findings and enlarged them by showing the role of $GABA_A$ receptors in the generation of rebound LTSs during spontaneous oscillatory thalamic activities. In somatosensory TC neurons of the ventrobasal thalamic nucleus, Rovo et al. (Rovo et al., 2014) reported in addition to the spontaneous "classical" fast $GABA_A$ IPSCs the occasional presence of slower events. Following the focal removal of $\gamma 2$ subunits using local virus injections that suppressed synaptically localized $GABA_A$ receptors, the fast IPSCs were abolished when NRT neurons fired tonically but large and slow phasic $GABA_A$ IPSCs were still present when NRT neurons fired bursts, indicating a burst-specific recruitment of non-synaptic $GABA_A$ receptors (Fig. 2C1). Indeed bursting activities of TC neurons resulting from GABA evoked rebound LTSs were little affected by $\gamma 2$ subunit deletion (Fig. 2C2). Moreover during ketamine-xylazine induced slow oscillations, suppression of synaptic $GABA_A$ receptors had no effect on the burst properties in TC neurons of the posterior thalamic nucleus and only decreased the number of bursts and the intra-burst frequencies of action potentials without affecting the intra-burst action potential number in ventrobasal somatosensory TC neurons. Importantly, detailed analysis of sleep spindle waves in urethane anesthetized animals showed a similar rate of occurrence, number of cycles and lengths of spindle waves after removal of the fast synaptic inhibition (Fig. 2D). Finally, EEG analysis showed that bilateral focal thalamic deletion of the $\gamma 2$ subunits had no effect on the spindle oscillatory activities present during natural non-REM sleep, in contrast to the disruption of the slow oscillations observed when all types of thalamic $GABA_A$ receptors were blocked by local application of the $GABA_A$ antagonist gabazine (Rovo et al., 2014). Therefore, when NRT neurons are firing in bursts not only conventional synaptic $GABA_A$ receptors but also extrasynaptic $GABA_A$ receptors are recruited by GABA spillover. This extrasynaptic receptor recruitment appears especially important during thalamocortical oscillations since it provides by itself large enough phasic hyperpolarization to allow the recruitment of T-channels and the generation of rebound LTSs in TC neurons to sustain physiological activities.

Tonic $GABA_A$ current and T-channels

The various results reviewed above clearly demonstrate that activation of peri/extrasynaptic receptors, containing $\alpha 4 \beta 2 \delta$ subunits, by GABA spillover contributes to phasic GABAergic inhibition. However because of their high sensitivity, these receptors can also be activated by

the ambient GABA creating a tonic inhibitory current (Fig. 3A) and a number of studies described the properties of this tonic current in TC neurons (Belelli et al., 2005; Bright et al., 2007; Chandra et al., 2006; Cope et al., 2005; Jia et al., 2005). In this context, additional functional links can be established between activation of extrasynaptic $GABA_A$ receptors and T-channels recruitment. Thus, extracellular recordings of TC neurons in ventrobasal thalamic slices showed that the block of this tonic current by gabazine or its enhancement by the $GABA_A$ agonist THIP stops or promotes LTS burst firing (Cope et al., 2005) and modulate rebound LTS latency (Bright et al., 2007) (Fig. 3B). These results clearly suggest that tonic activation of the $GABA_A$ receptors brings TC neurons into a membrane potential range where a significant proportion of T- channels is available (Dreyfus et al., 2010; Perez-Reyes, 2003). These channels could then be activated by any incoming input resulting once again in the generation of an LTS. Along this line, it is interesting to mention that THIP, a potent hypnotic selective for extrasynaptic $GABA_A$ receptors, in both humans and rats promotes slow-wave sleep activities characterized by the rhythmic occurrence of LTSs in TC neurons (Faulhaber et al., 1997).

T-channel and GABA crosstalk during attentive behaviours

The impact of the T-channel and $GABA_A$ receptor crosstalk on TC neuron excitability, however, is not limited to LTS generation during sleep (Lambert et al., 2014) but is also crucial in TC neuron functions during the awake state. First, $GABA_A$ IPSPs – LTS sequences can be observed during sensory processing in awake animals. Thus, during natural viewing, when the receptive field is covered by a stimulus of the non-preferred sign, the inhibition associated to the “push-pull” sequence allows T-channels to deinactivate and upon reversion of the stimulus contrast, the retinal input can trigger an LTS burst (Wang et al., 2007). In this case, the GABAergic inhibition likely arises from local interneurons in the dorsal lateral geniculate nucleus although a role of the feedback inhibition through NRT cannot be ruled out. The synaptic or extrasynaptic nature of the $GABA_A$ receptors involved was not investigated but emphasis was made on the functional role of such $GABA_A$ IPSPs – LTS sequence in sensory processing. Indeed convincing evidence indicate that bursts play a role in vision (Alitto and Usrey, 2005; Niell and Stryker, 2010; Sherman, 2001) and that compared to tonic trains of spikes, they evoke postsynaptic action potentials with maximal efficacy, likely enhancing sensory information propagation (Swadlow and Gusev, 2001; Usrey et al., 1998). In addition, while for years T-channel functions beyond burst generation were difficult to unravel due to the lack of specific pharmacology (see (Lambert et al., 2014) for review) the recent synthesis of the first potent and selective T-type channel antagonists, mainly based on a piperidine chemical structure (Dreyfus et al., 2010; Shipe et al., 2008) has led to the discovery of new critical roles for T-currents during wakefulness. Indeed, using TTA-P2, it

has recently been demonstrated that in the range of resting membrane potentials observed in TC neurons of awake animals (Urbain et al., 2015), T-channels can be recruited by incoming excitatory inputs, amplifying the excitatory post-synaptic potentials (EPSPs), and therefore controlling tonic firing (Deleuze et al., 2012). Since the fraction of deinactivated T-channels increases upon hyperpolarisation, this T-mediated amplification is intrinsically voltage-dependent (Fig. 3C1) and helps to stabilize the firing probability against membrane hyperpolarization (Fig. 3C2). As a consequence, one can propose a novel functional link between extra-synaptic GABA receptors and T-channels since at least part of the decrease in tonic firing that should result from a GABA tonic current-induced hyperpolarization will be counteracted by a stronger recruitment of T-channels amplifying the incoming EPSPs.

2. T-channels and $GABA_B$ receptors

Activation of the metabotropic $GABA_B$ receptors also elicit a hyperpolarization that can deinactivate T-channels and lead to the generation of a rebound LTS (Crunelli and Leresche, 1991). The thalamus is one of the brain areas showing the highest $GABA_B$ receptor level (Bowery et al., 1987; Princivalle et al., 2000; Princivalle et al., 2001). These receptors are composed of two subunit isoforms, $GABA_{B1a}$ and $GABA_{B1b}$, that combine with a $GABA_{B2}$ subunit to form heteromeric $GABA_{B(1a,2)}$ and $GABA_{B(1b,2)}$ receptors (Bettler et al., 2004; Kaupmann et al., 1998). A subcellular localization study showed a similar localization of the different $GABA_B$ receptors, mostly on the dendrites of TC neurons. These receptors are predominantly extrasynaptic with a higher density around GABAergic than glutamatergic synapses on TC neuron dendrites (Kulik et al., 2002). In addition, $GABA_B$ receptors are also present presynaptically on GABAergic and glutamatergic (both sensory and corticothalamic) afferents where they control the release of GABA and glutamate, respectively (Emri et al., 1996; Le Feuvre et al., 1997; Luo et al., 2011; Ulrich and Huguenard, 1996). Already in the '80s it was shown that, in TC neurons of the dorsal lateral geniculate nucleus, $GABA_B$ IPSPs evoked by inhibitory interneurons activation following sensory afferent stimulation can elicit a rebound LTS (Crunelli et al., 1988; Crunelli and Leresche, 1991). Since these initial findings linking $GABA_B$ receptor and LTS generation, a number of studies focusing on the excitability of the thalamic network investigated how the occurrence of $GABA_B$ IPSPs contributes to oscillatory activities in the thalamocortical system. As described above, sleep spindle waves depend on the presence of bursts of action potentials in NRT neurons that activate $GABA_A$ receptor-mediated IPSPs in TC neurons with occasional rebound LTSs, setting the network oscillation at a frequency of 7–14 Hz (Deschenes et al., 1984). Interestingly, if the NRT bursts are markedly increased by, for example, strong cortical inputs, these fast IPSPs are converted into large amplitude, long duration (around 300ms) IPSPs followed by a potent rebound LTS. These slower IPSPs are due to the activation of both $GABA_A$ and $GABA_B$

receptors (Blumenfeld and McCormick, 2000). This data were interpreted by assuming that in condition of strong NRT burst firing the large amount of released neurotransmitter allowed a spillover of GABA to the extrasynaptically localized $GABA_B$ receptors. Hence, in conditions of strong NRT burst firing, the slow $GABA_A$ - $GABA_B$ IPSP followed by the rebound LTS resulted in a slowing down of the thalamic oscillations from the 7-14Hz spindle frequency to about 3-4 Hz (Bal et al., 2000; Blumenfeld and McCormick, 2000). This result illustrates how the dynamic interaction between $GABA_A$ - $GABA_B$ IPSPs and T-channel activation fundamentally sets the global intrathalamic network activity and explains how abnormalities in the GABAergic NRT to TC neuron synapse could result in pathological excitability.

3. Pathological consequences of disruption in the GABA / T current equilibrium

This issue has been particularly investigated in the context of absence seizures. These seizures are non-convulsive epileptic attacks present in many generalized genetic epilepsies that are characterized by a sudden and relatively brief impairment of consciousness, invariably accompanied by generalized and synchronous 2.5 - 4Hz spike-and-waves discharges in human EEG (Crunelli and Leresche, 2002). On the basis of the *in vitro* experiments performed in ferret thalamic slices, McCormick and his colleagues proposed that the recruitment of $GABA_B$ IPSPs due to a pathologically strong corticothalamic input, and their associated potent rebound LTSs, underlies absence seizure generation (Blumenfeld and McCormick, 2000) (see also (Bal et al., 2000)). While *in vivo* recordings in cat and rat models of absence epilepsy have so far failed to report the presence of $GABA_B$ IPSPs followed by rebound LTS in TC neurons during seizures, they nevertheless show rhythmic sequences of composite $GABA_A$ IPSPs which occur in synchrony with each spike and wave complex (Pinault et al., 1998; Steriade and Contreras, 1995). This suggests that the rhythmic occurrence of GABA IPSPs that frame the thalamic output is a fundamental component of the mechanism that lead to the generation of this pathological rhythm. In addition, tonic $GABA_A$ inhibition is increased in almost all rodent models of absence epilepsy (Cope et al., 2009) and, in the best established pharmacological model of absence epilepsy, the GHB model, the pathological rhythmic activity relies on the activation of $GABA_B$ receptors (Venzi et al., 2015). Whatever the receptor type involved, the high level of GABA inhibition present in TC neurons during spike-and-waves discharges is sustained by robust LTSs in NRT neurons at each spike and wave complex, as observed in fentanyl-anesthetized rat model of absence epilepsy (Slaght et al., 2002). In agreement with the importance of LTSs in NRT neurons, an increased T-current was observed in these neurons in absence epilepsy-prone compared to non-epileptic rats (Tsakiridou et al., 1995). In summary, although the precise cellular mechanisms are still debated, numerous evidences point to the importance of both GABA inhibitory tonus and T-current activation in the pathogenesis of absence epilepsy.

Interestingly, the pathogenicity of an impaired balance between thalamic T-channels and GABA receptors is now considered in a larger context than absence epilepsy. Indeed, an increasing number of clinical studies have reported the presence of slower theta thalamocortical oscillations in awake patients who present a wide variety of neurological and psychiatric conditions, including neurogenic pain, tinnitus and Parkinson's disease (Jeanmonod et al., 1996; Llinas et al., 1999; Steriade et al., 1993). While the mechanisms of such dysrhythmia are still to be explored, a common principle has been proposed implying an increase inhibitory tonus that removes thalamic T-channel inactivation (Llinas and Steriade, 2006).

4. T-channel activity controls GABA synapses

While the functional links between GABA IPSPs and LTS generation in the thalamic network have been studied for many years (Deschenes et al., 1984; Steriade et al., 1993), the reverse relationship has only recently started to be investigated (Pigeat et al., 2015; Sieber et al., 2013). Calcium imaging studies in NRT neurons showed that LTSs are associated with a widespread dendritic calcium influx via T-channels (Chausson et al., 2013; Crandall et al., 2010) and combining somatodendritic recordings, calcium imaging and computational modelling Connelly et al. (Connelly et al., 2015) further demonstrated that LTSs are global events that occur synchronously throughout the dendritic tree. In view of the existence of dendrodendritic synapses between NRT neurons, at least in certain species (Deschenes et al., 1985; Pinault et al., 1997; Yen et al., 1985), one may speculate that distal dendrite T-currents could contribute to dendritic GABA release and activation of these intra-NRT GABAergic synapses. In addition, a recent study demonstrated the existence of T-channel and syntaxin1A complexes in rat brains and showed a clear colocalization of these proteins in NRT neurons (Weiss et al., 2012), suggesting the potential involvement of T-channels in the synaptic mechanism of GABA release.

The importance of T-currents in the control of thalamic GABA synaptic function is also demonstrated by the presence of T-channel-dependent long-term synaptic plasticity, either potentiation (LTP) or depression (LTD). Indeed, in the associative posterior thalamic medial nucleus, an LTP of the GABAergic synapses is triggered by postsynaptic repetitive LTS-associated bursting activities in TC neurons (Sieber et al., 2013) (Fig 4A). LTSs provided a depolarizing drive throughout the dendritic arbor (Connelly et al., 2015) that activated high-voltage L-type calcium currents. The subsequent rise in intracellular calcium induced the production of nitric oxide, retrogradely activating presynaptic guanylyl cyclase and increasing GABA release probability (Sieber et al., 2013). In contrast, at the inhibitory synapses between NRT and primary sensory TC neurons, Pigeat et al. described an LTD (Pigeat et al., 2015) (Fig. 4B) that is triggered by pairing the stimulation of the reticulothalamic input to

rhythmic activation of post-synaptic T-currents, mimicking the pattern of LTSs occurrence during sleep delta waves. Importantly, this LTD mechanism required a specific funnelling of calcium though the T-channels and could not be triggered by Ca^{2+} entry through other members of the voltage-dependent Ca^{2+} channel family. The large influx of calcium through T-channels leads to the activation of the calcium-sensitive phosphatase calcineurin that dephosphorylates the $GABA_A$ receptors inducing their long-term desensitization. Therefore, the strict requirement of T-channel activation to trigger LTD of the GABAergic synapses suggests the existence of preferential links between these channels and other partners of the synaptic plasticity, such as $GABA_A$ receptors and/or calcineurin. Such interactions including direct protein–protein interactions have already been described between T-channels and other ionic channels (Anderson et al., 2013; Anderson et al., 2010; Engbers et al., 2012), but data demonstrating colocalization of $GABA_A$ receptors or calcineurin with T-channels are still lacking. In contrast to the LTP described in the posterior thalamic medial nucleus (Sieber et al., 2013), the LTD in primary sensory nuclei did not affect all GABAergic synapses but only a subset of NRT synapses (Pigeat et al., 2015). Indeed, transient application of $GABA_A$ receptors antagonist during the induction protocol demonstrated that the LTD was only triggered at activated $GABA_A$ synapses. Finally, it should be noted that this LTD is both homosynaptic and heterosynaptic as it is also closely gated by glutamate released from the corticothalamic afferents that activates metabotropic receptors on the post-synaptic TC neurons. Therefore, the crucial relationship between the intrathalamic GABA drive and the T-channel activity, as a main actor of both sensory information transfer and oscillatory susceptibility of the thalamocortical network, is finely tuned by the cortical feedback itself (Pigeat et al., 2015). In conclusion, although different in term of signs and mechanisms, these two studies clearly highlight that GABAergic synaptic responses are dynamically modulated by T- channel activation. Overall, from the analysis of the results summarized so far, a clear picture emerges of a bidirectional relationship between GABA receptors and T-channels that shapes the excitability of the thalamocortical system.

5. Perspective

This review mainly focuses on the inhibitory synapses between NRT afferents and TC neurons located in primary sensory nuclei. However, thalamic neurons localized in the other thalamic nuclei (higher order sensory nuclei, motor nuclei, midline and intralaminar nuclei) received, in addition to NRT afferents, inhibitory inputs originating from extra-thalamic sources, mainly basal ganglia, zona incerta, anterior pretectum and pontine reticular formation that can also evoked rebound LTS in TC neurons (Halassa and Acsady, 2016; Wanaverbecq et al., 2008). In contrast to the NRT GABAergic synapses, single axon terminals from the extra-thalamic GABAergic sources contact the postsynaptic TC neuron via

several active zones wrapped in a glial cover that probably restrict GABA spillover. Moreover, while NRT to TC neuron synapses show a marked paired-pulse depression (Bessaih et al., 2006), these GABAergic synapses of extrathalamic origin display little short-term plasticity (Giber et al., 2015; Wanaverbecq et al., 2008) supporting a more faithful transmission. Whether the complex bidirectional relationships described here between activation of GABA receptors and T-currents also contribute to the regulation of the excitability of these non-NRT inhibitory synapses remains to be investigated.

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References :

Alitto, H. J., Usrey, W. M., 2005. Dynamic properties of thalamic neurons for vision. Progress in brain research 149, 83-90.

Anderson, D., Engbers, J. D., Heath, N. C., Bartoletti, T. M., Mehaffey, W. H., Zamponi, G. W., Turner, R. W., 2013. The Cav3-Kv4 complex acts as a calcium sensor to maintain inhibitory charge transfer during extracellular calcium fluctuations. The Journal of neuroscience : the official journal of the Society for Neuroscience 33, 7811-7824.

Anderson, D., Mehaffey, W. H., Iftinca, M., Rehak, R., Engbers, J. D., Hameed, S., Zamponi, G. W., Turner, R. W., 2010. Regulation of neuronal activity by Cav3-Kv4 channel signaling complexes. Nature neuroscience 13, 333-337.

Bal, T., Debay, D., Destexhe, A., 2000. Cortical feedback controls the frequency and synchrony of oscillations in the visual thalamus. J Neurosci 20, 7478-7488.

Bal, T., McCormick, D. A., 1993. Mechanisms of oscillatory activity in guinea-pig nucleus reticularis thalami in vitro: a mammalian pacemaker. J Physiol (Lond) 468, 669-691.

Bal, T., von Krosigk, M., McCormick, D. A., 1995. Role of the ferret perigeniculate nucleus in the generation of synchronized oscillations in vitro. J Physiol (Lond) 483, 665-685.

Behuret, S., Deleuze, C., Bal, T., 2015. Corticothalamic Synaptic Noise as a Mechanism for Selective Attention in Thalamic Neurons. Frontiers in neural circuits 9, 80.

Belelli, D., Peden, D. R., Rosahl, T. W., Wafford, K. A., Lambert, J. J., 2005. Extrasynaptic GABAA receptors of thalamocortical neurons: a molecular target for hypnotics. The Journal of neuroscience : the official journal of the Society for Neuroscience 25, 11513-11520.

Bessaih, T., Bourgeais, L., Badiu, C. I., Carter, D. A., Toth, T. I., Ruano, D., Lambolez, B., Crunelli, V., Leresche, N., 2006. Nucleus-specific abnormalities of GABAergic synaptic transmission in a genetic model of absence seizures. Journal of neurophysiology 96, 3074-3081.

Bettler, B., Kaupmann, K., Mosbacher, J., Gassmann, M., 2004. Molecular structure and physiological functions of GABA(B) receptors. Physiol Rev 84, 835-867.

Blumenfeld, H., McCormick, D. A., 2000. Corticothalamic inputs control the pattern of activity generated in thalamocortical networks. J Neurosci 20, 5153-5162.

Bowery, N. G., Hudson, A. L., Price, G. W., 1987. GABAA and GABAB receptor site distribution in the rat central nervous system. Neuroscience 20, 365-383.

Bright, D. P., Aller, M. I., Brickley, S. G., 2007. Synaptic release generates a tonic GABA(A) receptor-mediated conductance that modulates burst precision in thalamic relay neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience 27, 2560-2569.

Cavdar, S., Bay, H. H., Yildiz, S. D., Akakin, D., Sirvanci, S., Onat, F., 2014. Comparison of numbers of interneurons in three thalamic nuclei of normal and epileptic rats. Neuroscience bulletin 30, 451-460.
Chandra, D., Jia, F., Liang, J., Peng, Z., Suryanarayanan, A., Werner, D. F., Spigelman, I., Houser, C. R., Olsen, R. W., Harrison, N. L., Homanics, G. E., 2006. GABAA receptor alpha 4 subunits mediate extrasynaptic inhibition in thalamus and dentate gyrus and the action of gaboxadol. Proceedings of the National Academy of Sciences of the United States of America 103, 15230-15235.
Chausson, P., Leresche, N., Lambert, R. C., 2013. Dynamics of Intrinsic Dendritic Calcium Signaling during Tonic Firing of Thalamic Reticular Neurons. PloS one 8, e72275.
Connelly, W. M., Crunelli, V., Errington, A. C., 2015. The Global Spike: Conserved Dendritic Properties Enable Unique Ca2+ Spike Generation in Low-Threshold Spiking Neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience 35, 15505-15522.
Cope, D. W., Di Giovanni, G., Fyson, S. J., Orban, G., Errington, A. C., Lorincz, M. L., Gould, T. M., Carter, D. A., Crunelli, V., 2009. Enhanced tonic GABAA inhibition in typical absence epilepsy. Nature medicine 15, 1392-1398.
Cope, D. W., Hughes, S. W., Crunelli, V., 2005. GABAA receptor-mediated tonic inhibition in thalamic neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience 25, 11553-11563.
Crandall, S. R., Govindaiah, G., Cox, C. L., 2010. Low-threshold Ca2+ current amplifies distal dendritic signaling in thalamic reticular neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience 30, 15419-15429.
Crunelli, V., Haby, M., Jassik-Gerschenfeld, D., Leresche, N., Pirchio, M., 1988. Cl- - and K+-dependent inhibitory postsynaptic potentials evoked by interneurones of the rat lateral geniculate nucleus. J Physiol (Lond) 399, 153-176.
Crunelli, V., Leresche, N., 1991. A role for GABAB receptors in excitation and inhibition of thalamocortical cells. Trends Neurosci 14, 16-21.
Crunelli, V., Leresche, N., 2002. Childhood absence epilepsy: genes, channels, neurons and networks. Nat Rev Neurosci 3, 371-382.
David, F., Schmiedt, J. T., Taylor, H. L., Orban, G., Di Giovanni, G., Uebele, V. N., Renger, J. J., Lambert, R. C., Leresche, N., Crunelli, V., 2013. Essential thalamic contribution to slow waves of natural sleep. The Journal of neuroscience : the official journal of the Society for Neuroscience 33, 19599-19610.
DeFelipe, J., Lopez-Cruz, P. L., Benavides-Piccione, R., Bielza, C., Larranaga, P., Anderson, S., Burkhalter, A., Cauli, B., Fairen, A., Feldmeyer, D., Fishell, G., Fitzpatrick, D., Freund, T. F., Gonzalez-Burgos, G., Hestrin, S., Hill, S., Hof, P. R., Huang, J., Jones, E. G., Kawaguchi, Y., Kisvarday, Z., Kubota, Y., Lewis, D. A., Marin, O., Markram, H., McBain, C. J., Meyer, H. S., Monyer, H., Nelson, S. B., Rockland, K., Rossier, J., Rubenstein, J. L., Rudy, B., Scanziani, M., Shepherd, G. M., Sherwood, C. C., Staiger, J. F., Tamas, G., Thomson, A., Wang, Y., Yuste, R., Ascoli, G. A., 2013. New insights into the classification and nomenclature of cortical GABAergic interneurons. Nature reviews. Neuroscience 14, 202-216.
Deleuze, C., David, F., Behuret, S., Sadoc, G., Shin, H. S., Uebele, V. N., Renger, J. J., Lambert, R. C., Leresche, N., Bal, T., 2012. T-type calcium channels consolidate tonic action potential output of thalamic neurons to neocortex. The Journal of neuroscience : the official journal of the Society for Neuroscience 32, 12228-12236.
Deschenes, M., Madariaga-Domich, A., Steriade, M., 1985. Dendrodendritic synapses in the cat reticularis thalami nucleus: a structural basis for thalamic spindle synchronization. Brain research 334, 165-168.
Deschenes, M., Paradis, M., Roy, J. P., Steriade, M., 1984. Electrophysiology of neurons of lateral thalamic nuclei in cat: resting properties and burst discharges. J Neurophysiol 51, 1196-1219.
Dreyfus, F. M., Tscherter, A., Errington, A. C., Renger, J. J., Shin, H. S., Uebele, V. N., Crunelli, V., Lambert, R. C., Leresche, N., 2010. Selective T-type calcium channel block in

thalamic neurons reveals channel redundancy and physiological impact of I(T)window. The Journal of neuroscience : the official journal of the Society for Neuroscience 30, 99-109.
Emri, Z., Turner, J. P., Crunelli, V., 1996. Tonic activation of presynaptic GABA(B) receptors on thalamic sensory afferents. Neuroscience 72, 689-698.
Engbers, J. D., Anderson, D., Asmara, H., Rehak, R., Mehaffey, W. H., Hameed, S., McKay, B. E., Kruskic, M., Zamponi, G. W., Turner, R. W., 2012. Intermediate conductance calcium-activated potassium channels modulate summation of parallel fiber input in cerebellar Purkinje cells. Proceedings of the National Academy of Sciences of the United States of America 109, 2601-2606.
Errington, A. C., Gibson, K. M., Crunelli, V., Cope, D. W., 2011. Aberrant GABA(A) receptor-mediated inhibition in cortico-thalamic networks of succinic semialdehyde dehydrogenase deficient mice. PloS one 6, e19021.
Faulhaber, J., Steiger, A., Lancel, M., 1997. The GABAA agonist THIP produces slow wave sleep and reduces spindling activity in NREM sleep in humans. Psychopharmacology 130, 285-291.
Giber, K., Diana, M. A., Plattner, V. M., Dugue, G. P., Bokor, H., Rousseau, C. V., Magloczky, Z., Havas, L., Hangya, B., Wildner, H., Zeilhofer, H. U., Dieudonne, S., Acsady, L., 2015. A subcortical inhibitory signal for behavioral arrest in the thalamus. Nature neuroscience 18, 562-568.
Halassa, M. M., Acsady, L., 2016. Thalamic Inhibition: Diverse Sources, Diverse Scales. Trends in neurosciences 39, 680-693.
Herd, M. B., Brown, A. R., Lambert, J. J., Belelli, D., 2013. Extrasynaptic GABA(A) receptors couple presynaptic activity to postsynaptic inhibition in the somatosensory thalamus. The Journal of neuroscience : the official journal of the Society for Neuroscience 33, 14850-14868.
Jahnsen, H., Llinas, R., 1984. Electrophysiological properties of guinea-pig thalamic neurones: an in vitro study. J Physiol 349, 205-226.
Jeanmonod, D., Magnin, M., Morel, A., 1996. Low-threshold calcium spike bursts in the human thalamus. Common physiopathology for sensory, motor and limbic positive symptoms. Brain : a journal of neurology 119, 363-375.
Jia, F., Pignataro, L., Schofield, C. M., Yue, M., Harrison, N. L., Goldstein, P. A., 2005. An extrasynaptic GABAA receptor mediates tonic inhibition in thalamic VB neurons. Journal of neurophysiology 94, 4491-4501.
Jones, E. G., 2007. The thalamus. Cambridge University Press, Cambridge.
Kaupmann, K., Malitschek, B., Schuler, V., Heid, J., Froestl, W., Beck, P., Mosbacher, J., Bischoff, S., Kulik, A., Shigemoto, R., Karschin, A., Bettler, B., 1998. GABA(B)-receptor subtypes assemble into functional heteromeric complexes. Nature 396, 683-687.
Kralic, J. E., Sidler, C., Parpan, F., Homanics, G. E., Morrow, A. L., Fritschy, J. M., 2006. Compensatory alteration of inhibitory synaptic circuits in cerebellum and thalamus of gamma-aminobutyric acid type A receptor alpha1 subunit knockout mice. The Journal of comparative neurology 495, 408-421.
Kulik, A., Nakadate, K., Nyiri, G., Notomi, T., Malitschek, B., Bettler, B., Shigemoto, R., 2002. Distinct localization of GABA(B) receptors relative to synaptic sites in the rat cerebellum and ventrobasal thalamus. Eur J Neurosci 15, 291-307.
Lambert, R. C., Bessaih, T., Crunelli, V., Leresche, N., 2014. The many faces of T-type calcium channels. Pflugers Archiv : European journal of physiology 466, 415-423.
Le Feuvre, Y., Fricker, D., Leresche, N., 1997. GABAA receptor-mediated IPSCs in rat thalamic sensory nuclei: patterns of discharge and tonic modulation by GABAB autoreceptors. J Physiol (Lond) 502, 91-104.
Llinas, R. R., Ribary, U., Jeanmonod, D., Kronberg, E., Mitra, P. P., 1999. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci U S A 96, 15222-15227.
Llinas, R. R., Steriade, M., 2006. Bursting of thalamic neurons and states of vigilance. J Neurophysiol 95, 3297-3308.

Luo, B., Wang, H. T., Su, Y. Y., Wu, S. H., Chen, L., 2011. Activation of presynaptic GABAB receptors modulates GABAergic and glutamatergic inputs to the medial geniculate body. Hearing research 280, 157-165.
Niell, C. M., Stryker, M. P., 2010. Modulation of visual responses by behavioral state in mouse visual cortex. Neuron 65, 472-479.
Peden, D. R., Petitjean, C. M., Herd, M. B., Durakoglugil, M. S., Rosahl, T. W., Wafford, K., Homanics, G. E., Belelli, D., Fritschy, J. M., Lambert, J. J., 2008. Developmental maturation of synaptic and extrasynaptic GABAA receptors in mouse thalamic ventrobasal neurones. The Journal of physiology 586, 965-987.
Perez-Reyes, E., 2003. Molecular physiology of low-voltage-activated t-type calcium channels. Physiological reviews 83, 117-161.
Pigeat, R., Chausson, P., Dreyfus, F. M., Leresche, N., Lambert, R. C., 2015. Sleep slow wave-related homo and heterosynaptic LTD of intrathalamic GABAAergic synapses: involvement of T-type Ca2+ channels and metabotropic glutamate receptors. The Journal of neuroscience : the official journal of the Society for Neuroscience 35, 64-73.
Pinault, D., Leresche, N., Charpier, S., Deniau, J. M., Marescaux, C., Vergnes, M., Crunelli, V., 1998. Intracellular recordings in thalamic neurones during spontaneous spike and wave discharges in rats with absence epilepsy. J Physiol (Lond) 509, 449-456.
Pinault, D., Smith, Y., Deschenes, M., 1997. Dendrodendritic and axoaxonic synapses in the thalamic reticular nucleus of the adult rat. J Neurosci 17, 3215-3233.
Pirker, S., Schwarzer, C., Wieselthaler, A., Sieghart, W., Sperk, G., 2000. GABA(A) receptors: immunocytochemical distribution of 13 subunits in the adult rat brain. Neuroscience 101, 815-850.
Princivalle, A., Regondi, M. C., Frassoni, C., Bowery, N. G., Spreafico, R., 2000. Distribution of GABA(B) receptor protein in somatosensory cortex and thalamus of adult rats and during postnatal development. Brain research bulletin 52, 397-405.
Princivalle, A. P., Pangalos, M. N., Bowery, N. G., Spreafico, R., 2001. Distribution of GABA(B(1a)), GABA(B(1b)) and GABA(B2) receptor protein in cerebral cortex and thalamus of adult rats. Neuroreport 12, 591-595.
Rovo, Z., Matyas, F., Bartho, P., Slezia, A., Lecci, S., Pellegrini, C., Astori, S., David, C., Hangya, B., Luthi, A., Acsady, L., 2014. Phasic, Nonsynaptic GABA-A Receptor-Mediated Inhibition Entrains Thalamocortical Oscillations. The Journal of neuroscience : the official journal of the Society for Neuroscience 34, 7137-7147.
Semyanov, A., Walker, M. C., Kullmann, D. M., Silver, R. A., 2004. Tonically active GABA A receptors: modulating gain and maintaining the tone. Trends in neurosciences 27, 262-269.
Sherman, S. M., 2001. Tonic and burst firing: dual modes of thalamocortical relay. Trends in neurosciences 24, 122-126.
Shipe, W. D., Barrow, J. C., Yang, Z. Q., Lindsley, C. W., Yang, F. V., Schlegel, K. A., Shu, Y., Rittle, K. E., Bock, M. G., Hartman, G. D., Tang, C., Ballard, J. E., Kuo, Y., Adarayan, E. D., Prueksaritanont, T., Zrada, M. M., Uebele, V. N., Nuss, C. E., Connolly, T. M., Doran, S. M., Fox, S. V., Kraus, R. L., Marino, M. J., Graufelds, V. K., Vargas, H. M., Bunting, P. B., Hasbun-Manning, M., Evans, R. M., Koblan, K. S., Renger, J. J., 2008. Design, synthesis, and evaluation of a novel 4-aminomethyl-4-fluoropiperidine as a T-type Ca2+ channel antagonist. J Med Chem 51, 3692-3695.
Sieber, A. R., Min, R., Nevian, T., 2013. Non-Hebbian long-term potentiation of inhibitory synapses in the thalamus. The Journal of neuroscience : the official journal of the Society for Neuroscience 33, 15675-15685.
Slaght, S. J., Leresche, N., Deniau, J. M., Crunelli, V., Charpier, S., 2002. Activity of thalamic reticular neurons during spontaneous genetically determined spike and wave discharges. J Neurosci 22, 2323-2334.
Steriade, M., Contreras, D., 1995. Relations between cortical and thalamic cellular events during transition from sleep patterns to paroxysmal activity. J Neurosci 15, 623-642.
Steriade, M., Deschênes, M., 1998. Cellular thalamic mechanisms. Elsevier, Amsterdam.
Steriade, M., Domich, L., Oakson, G., Deschenes, M., 1987. The deafferented reticular thalamic nucleus generates spindle rhythmicity. J Neurophysiol 57, 260-273.

Steriade, M., McCormick, D. A., Sejnowski, T. J., 1993. Thalamocortical oscillations in the sleeping and aroused brain. Science 262, 679-685.
Swadlow, H. A., Gusev, A. G., 2001. The impact of 'bursting' thalamic impulses at a neocortical synapse. Nat Neurosci 4, 402-408.
Tsakiridou, E., Bertollini, L., de Curtis, M., Avanzini, G., Pape, H. C., 1995. Selective increase in T-type calcium conductance of reticular thalamic neurons in a rat model of absence epilepsy. J Neurosci 15, 3110-3117.
Ulrich, D., Huguenard, J. R., 1996. GABAB receptor-mediated responses in GABAergic projection neurones of rat nucleus reticularis thalami in vitro. J Physiol (Lond) 493, 845-854.
Urbain, N., Salin, P. A., Libourel, P. A., Comte, J. C., Gentet, L. J., Petersen, C. C., 2015. Whisking-Related Changes in Neuronal Firing and Membrane Potential Dynamics in the Somatosensory Thalamus of Awake Mice. Cell reports 13, 647-656.
Usrey, W. M., Reppas, J. B., Reid, R. C., 1998. Paired-spike interactions and synaptic efficacy of retinal inputs to the thalamus. Nature 395, 384-387.
Venzi, M., Di Giovanni, G., Crunelli, V., 2015. A critical evaluation of the gamma-hydroxybutyrate (GHB) model of absence seizures. CNS neuroscience & therapeutics 21, 123-140.
von Krosigk, M., Bal, T., McCormick, D. A., 1993. Cellular mechanisms of a synchronized oscillation in the thalamus. Science 261, 361-364.
Wanaverbecq, N., Bodor, A. L., Bokor, H., Slezia, A., Luthi, A., Acsady, L., 2008. Contrasting the functional properties of GABAergic axon terminals with single and multiple synapses in the thalamus. The Journal of neuroscience : the official journal of the Society for Neuroscience 28, 11848-11861.
Wang, X., Wei, Y., Vaingankar, V., Wang, Q., Koepsell, K., Sommer, F. T., Hirsch, J. A., 2007. Feedforward excitation and inhibition evoke dual modes of firing in the cat's visual thalamus during naturalistic viewing. Neuron 55, 465-478.
Weiss, N., Hameed, S., Fernandez-Fernandez, J. M., Fablet, K., Karmazinova, M., Poillot, C., Proft, J., Chen, L., Bidaud, I., Monteil, A., Huc-Brandt, S., Lacinova, L., Lory, P., Zamponi, G. W., De Waard, M., 2012. A Ca(v)3.2/syntaxin-1A signaling complex controls T-type channel activity and low-threshold exocytosis. The Journal of biological chemistry 287, 2810-2818.
Yen, C. T., Conley, M., Hendry, S. H., Jones, E. G., 1985. The morphology of physiologically identified GABAergic neurons in the somatic sensory part of the thalamic reticular nucleus in the cat. The Journal of neuroscience : the official journal of the Society for Neuroscience 5, 2254-2268.

Figure 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).

Figure 2: Recruitment of extrasynaptic GABA receptors during NRT neuron burst firing

A. Intracellular recordings of NRT neuron (top trace) and TC neuron (bottom trace) activities during spindle oscillations. The rhythmic occurrence of LTSs, and associated high-frequency firing, in NRT neurons induce GABA IPSPs at spindle frequency in TC neurons that occasionally generate rebound LTSs.

B. Superimposed traces of GABA currents evoked by NRT neuron stimulation in TC neurons of wild-type (WT) mice and mice devoid of either the synaptic α_1 ($\alpha_1^{-/-}$) or the extrasynaptic α_4 ($\alpha_4^{-/-}$) or δ ($\delta^{-/-}$) $GABA_A$ receptor subunits. Note that the decay of the evoked multiple IPSC waveforms was accelerated in mice lacking the extrasynaptic subunits (α_4 and δ) but that significant, although reduced, GABA currents were still observed when the synaptic α_1 subunits were deleted (holding potential: -50 mV ; GABA Erev: -85 mV).

C. In TC neurons where the expression of the γ_2 subunit that anchors synaptic GABA receptors was locally suppressed (AAV-Cre), NRT neuron burst firing still generated a large GABA current (**1.**, holding potential: -30 mV). Such current could evoke a rebound LTS in TC neurons clamped at -70 mV (**2.**)

D. Cortical local field potential (LFP) recording (top) and thalamic multiunit activities (MUA) in adjacent channels (middle) during spindle oscillations observed under urethane anesthesia (black: raw traces; red: same traces pass-band filtered at 7–15

Hz). Wavelet analysis (bottom) of one raw multiunit channel shows the presence of thalamic oscillations at spindle frequency in these mice devoid of synaptic γ_2 subunits. Modified with permission from: A: (Steriade and Deschênes, 1998); B: (Herd et al., 2013); C & D: (Rovo et al., 2014).

Figure 3: Tonic $GABA_A$ current and thalamic T-current activation

A. Recording from a ventrobasal TC neuron under control conditions. Focal application of the $GABA_A$ receptor antagonist gabazine (GBZ 50 µM; white bar) blocks inward IPSCs and reveals an outward shift in baseline current indicative of the presence of a tonic $GABA_A$ current.

B. In a dorsal lateral geniculate TC neuron, application of low concentration (50 nM) of GBZ that preferentially block tonic $GABA_A$ current, caused a 3mV depolarization blocking the LTS repetitive burst firing. (**1.**). Extracellular single-unit recording of another neuron under control conditions showing repetitive LTS burst firing (top trace and inset) that is blocked by bath application of 50 nM GBZ (bottom trace) (**2.**).

C. Contribution of the T-current to the EPSPs in TC neurons. **1.**, EPSPs evoked in a ventrobasal TC neuron using the dynamic clamp technique to mimic sensory AMPA inputs. The neuron was maintained at three different membrane potentials in control condition (TTX) and in the presence of the T-channel blocker TTA-P2 (TTX+TTA-P2). T-current largely contributed to the responses evoked at -70 and -65 mV, and slightly prolonged the EPSP recorded at more depolarized membrane potential. **2.**, T-current stabilizes the firing probability of TC neurons across a large range of membrane potentials. Voltage traces recorded in a TC neuron maintained at average membrane potentials of -60, -65, and -70 mV while being submitted to AMPA conductances (gAMPA) of fixed amplitude. In control condition the firing of the neuron remained almost invariant across the entire voltage range (CTR) while it was strongly decreased upon hyperpolarization when T-currents were antagonized (TTA-P2). Dotted lines indicate -60mV.

Modified with permission from: A: (Errington et al., 2011); B: (Cope et al., 2005); C1: (Deleuze et al., 2012); C2: (Behuret et al., 2015).

Figure 4. T-currents control long-term synaptic plasticity of GABAergic intrathalamic synapses.

A. LTP of the inhibitory synapses in posterior medial nucleus. Graphs showing the normalized IPSP amplitudes recorded in TC neurons over time. Repetitive postsynaptic bursts alone resulted in an LTP of the IPSPs (**1.**). LTP induction required the recruitment of the nimodipine sensitive L-type calcium channels (**2.**). In the absence of the induction protocol, bath application of the NO donor, SNAP, is sufficient to induce LTP (**3.**).

Red bars indicate time period for averaging IPSP amplitude and representative averaged IPSPs during baseline (black) and after LTP induction (red) are presented in the inset.

B. LTD of the NRT inhibitory synapses in TC neuron. Normalized IPSP amplitudes plotted over time. Addition of TTA-P2 precluded the induction of the LTD (**1.**). Insets: Representative averaged IPSPs during baseline (black) and after LTD induction (grey). LTD induction is blocked by application of the metabotropic glutamate receptor antagonist, LY367395 (**2.**). $GABA_A$ receptor activation is required for LTD induction. IPSCs were evoked in TC neurons in response to the stimulation of two independent inhibitory pathways. One NRT pathway (black) was not stimulated during the induction protocol. Note that the depression of the IPSCs was only observed for the pathway that underwent the induction protocol including the synaptic stimulation (**3**). In all graphs gray area represents the induction period.

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Figure 5. Schematic illustration of the interactions between thalamic GABA receptors and T-currents.

Top enlargement: Release of GABA induced by tonic (grey shaded region) or T-channel mediated burst firing (grey + red shaded region) of NRT neurons at the NRT to TC synapse. During tonic action potential firing, GABA release preferentially targets the synaptic ($\alpha1\beta2\gamma$) $GABA_A$ receptors although some extrasynaptic ($\alpha4\beta2\delta$) receptors can also be recruited. Bursting of NRT neurons increases GABA release producing a spillover of GABA in peri/extrasynaptic domains recruiting both extrasynaptic $GABA_A$ and $GABA_B$ receptors. Activation of the three types of receptors generates a hyperpolarization that can elicit an LTS as rebound activity. Repetitive LTS activation produces a large influx of calcium through T- channels (i) and membrane depolarization that can activate other voltage-dependent channels (ii). i) The increase in calcium concentration leads to the activation of the calcium-sensitive phosphatase calcineurin. Calcineurin will then dephosphorylate the activated $GABA_A$ receptors inducing their long-term desensitization and an LTD of the synapse. ii)

Activation of the L-type calcium channels by the LTS associated depolarization produces a postsynaptic dendritic calcium increase that triggers the synthesis of nitric oxide (NO), retrogradely activating presynaptic guanylyl cyclase and resulting in the presynaptic expression of an LTP. Finally, at both NRT to TC neuron and intra-NRT synapses (bottom enlargement) activation of T-channels localized at the presynaptic terminals may directly control the release of GABA through its direct link to the SNARE protein, syntaxin1A (synt.). The contribution of tonic GABAergic inhibition is not illustrated.

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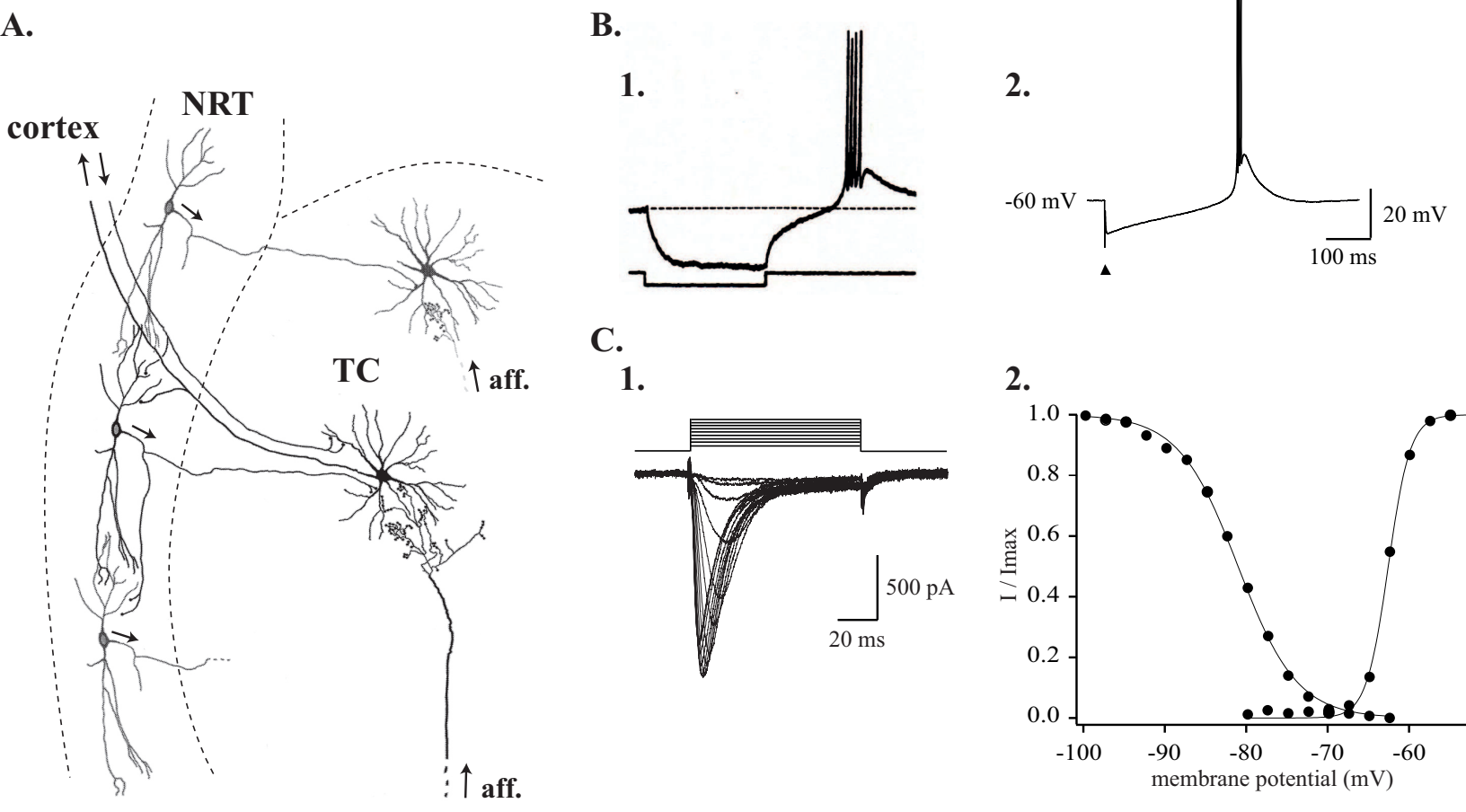

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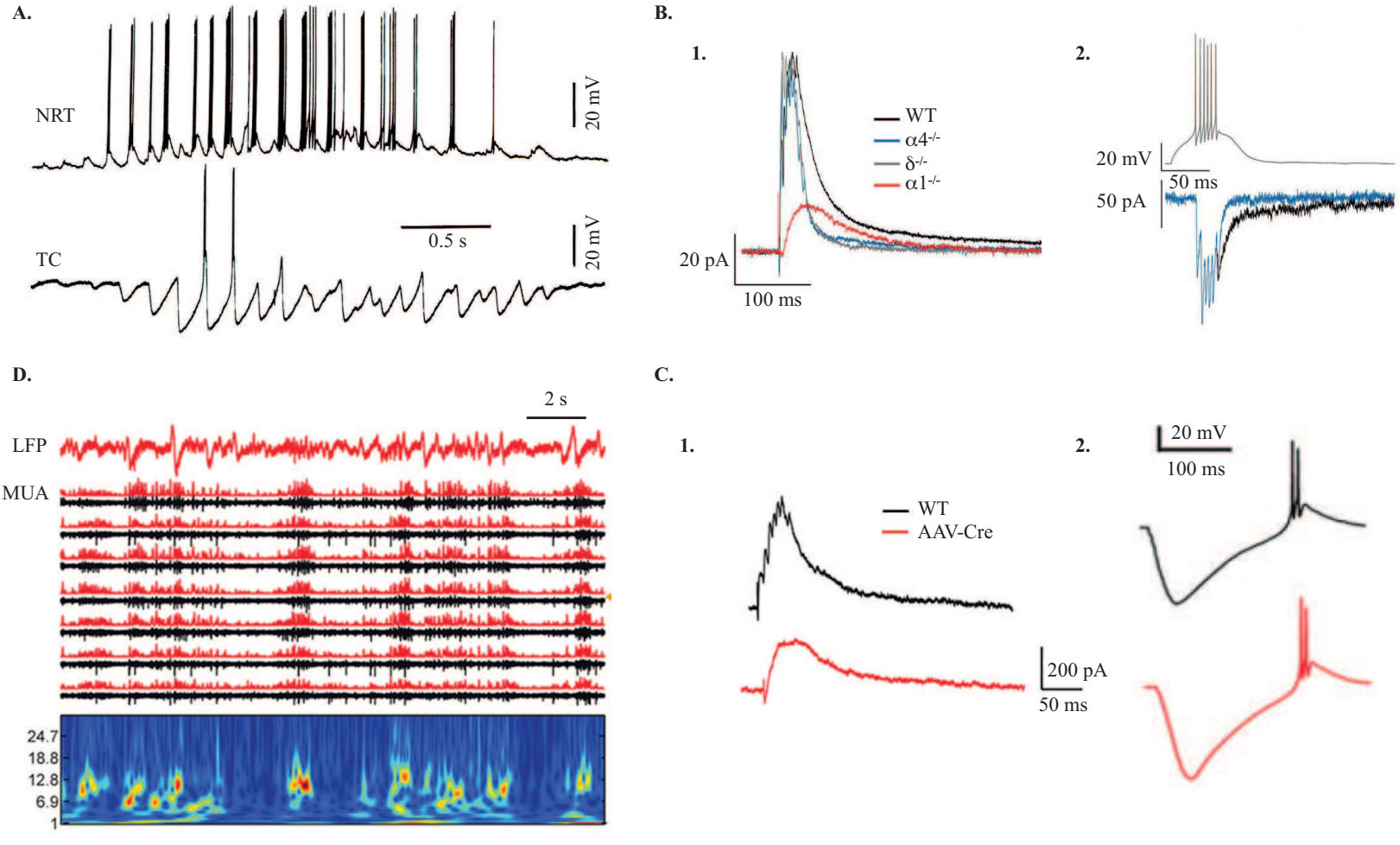

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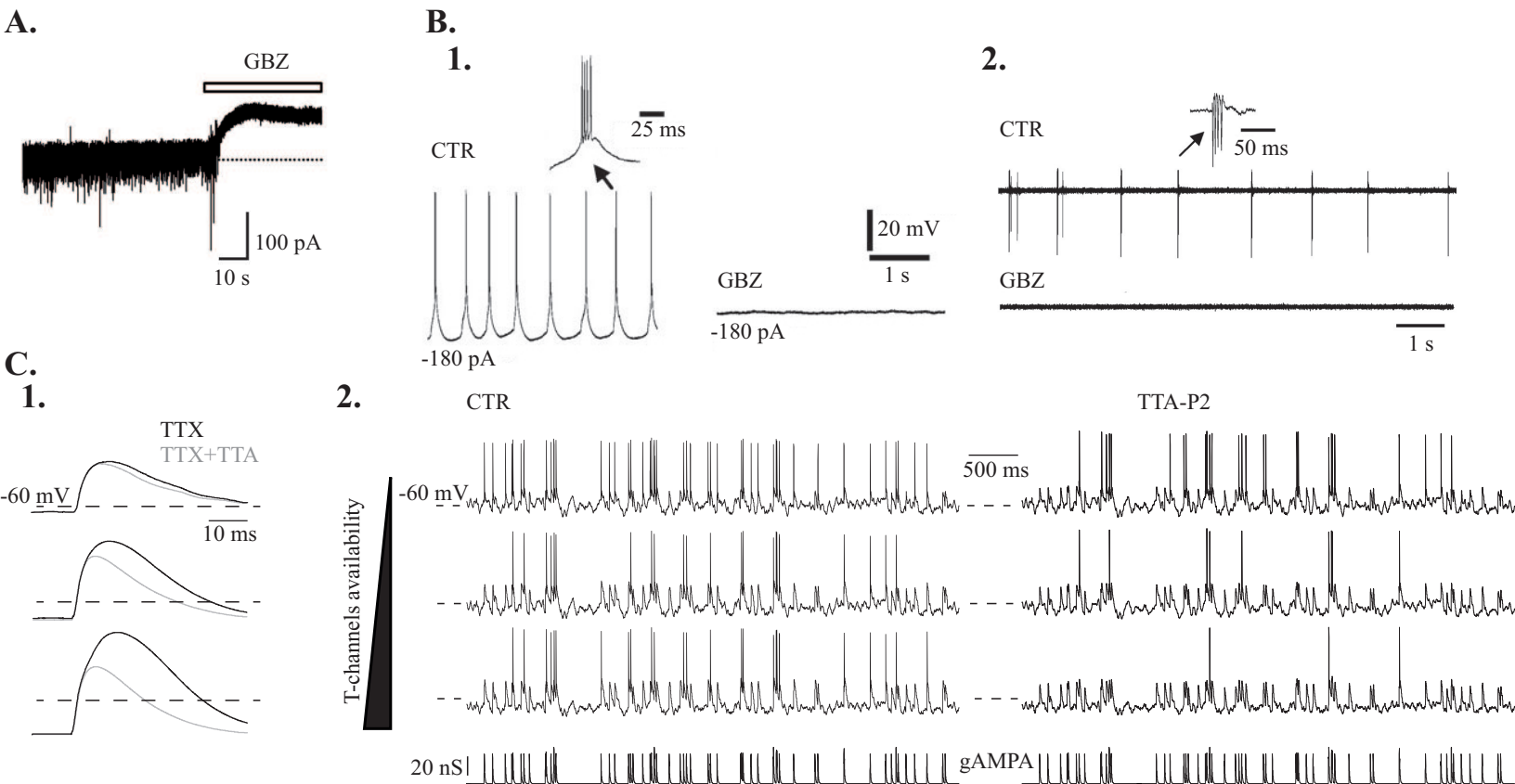

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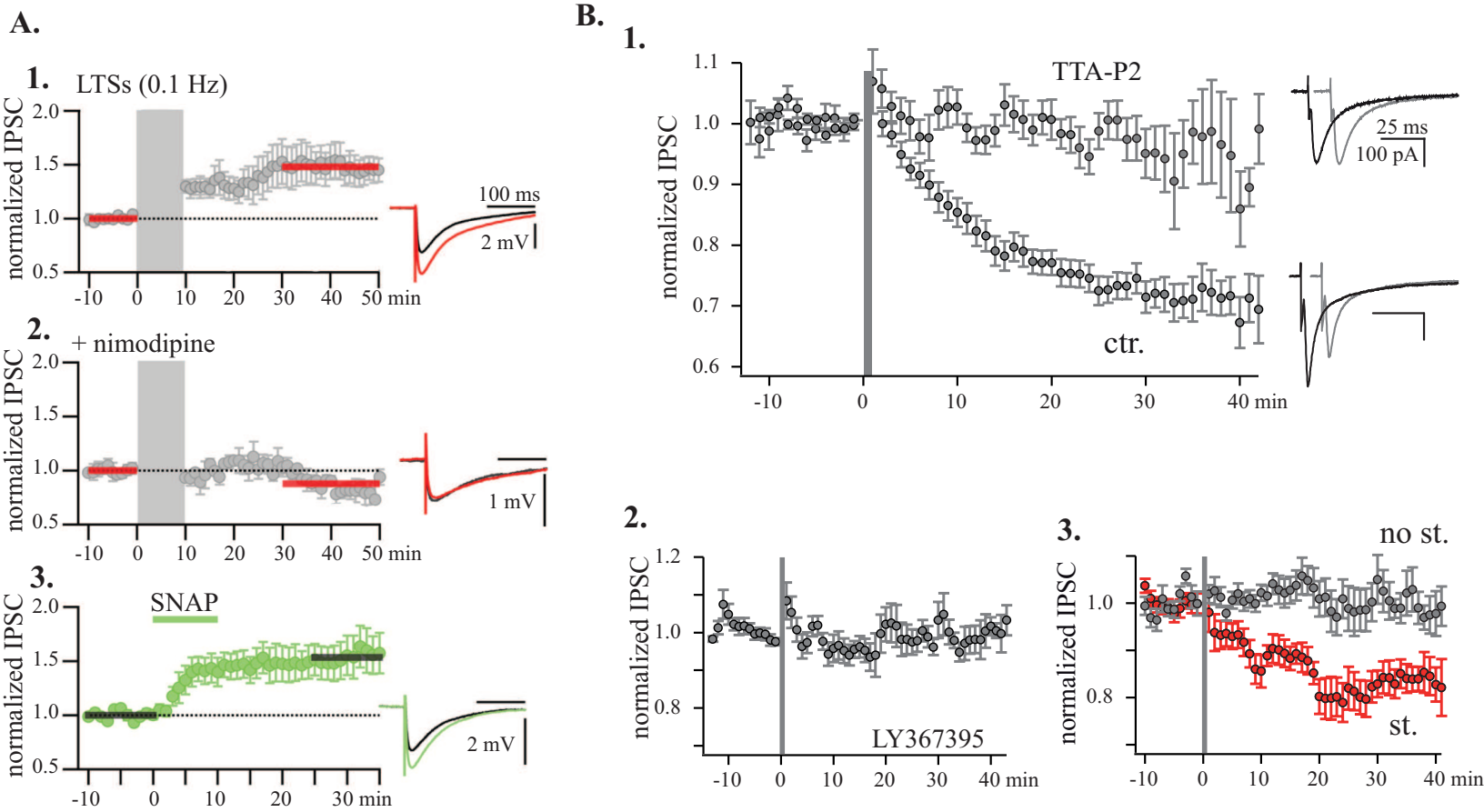

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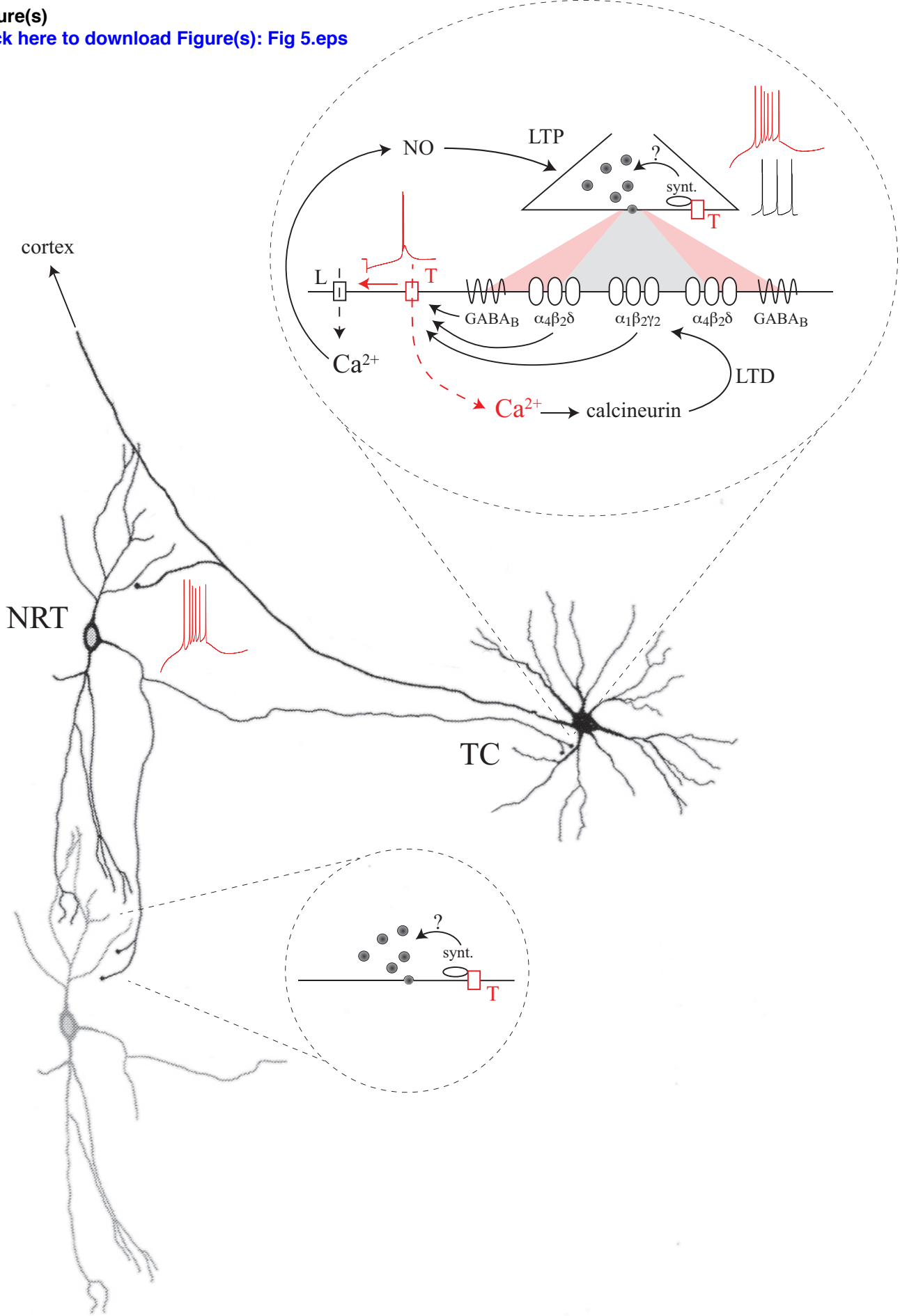

Fig. 5