**T-type calcium channels in synaptic plasticity**

Nathalie Leresche and Régis C. Lambert

Sorbonne Universités, Université Pierre et Marie Curie (UPMC) UM119, CNRS UMR8246, INSERM U1130, Neuroscience Paris Seine (NPS), Paris, France

**ABSTRACT**

The role of T-type calcium currents is rarely considered in the extensive literature covering the mechanisms of long-term synaptic plasticity. This situation reflects the lack of suitable T-type channel antagonists that till recently has hampered investigations of the functional roles of these channels. However, with the development of new pharmacological and genetic tools, a clear involvement of T-type channels in synaptic plasticity is starting to emerge. Here, we review a number of studies showing that T-type channels participate to numerous homo- and heterosynaptic plasticity mechanisms that involve different molecular partners and both pre- and post-synaptic modifications. The existence of T-channel dependent and independent plasticity at the same synapse strongly suggests a subcellular localization of these channels and their partners that allows specific interactions. Moreover, we illustrate the functional importance of T-channel dependent synaptic plasticity in neocortex and thalamus.

The interest in the low-voltage activated T-type calcium currents goes back to the beginning of the 80s. At that time, the group of R. Llinas identified a Ca\(^{2+}\)-mediated rebound depolarization, the so-called low-threshold spike (LTS), that follows a transient hyperpolarization of inferior olive and thalamic neurons.\(^1-4\) Functionally, the Ca\(^{2+}\) current responsible for this depolarization was rapidly recognized as one of the key conductances underlying the characteristic rhythmic high-frequency burst firing activity of thalamic neurons during various NREM sleep stages.\(^5,6\) In parallel, studies mainly performed in primary sensory neurons\(^7-10\) demonstrated that this low-threshold Ca\(^{2+}\) current, named T-type current, is activated around $-60$ mV and fully inactivated after a few tens of milliseconds. Since steady-state inactivation of these channels is nearly complete at membrane potentials more depolarized than $-60$ mV, a hyperpolarization that allows some channels to recover from inactivation is required before a substantial T-type current can be evoked. Three genes (Cav3.1, 3.2, and 3.3) displaying multiple alternative splicings were later identified,\(^11-13\) with the 3 isoforms presenting specific expression in various regions of the nervous system.\(^14\) All T-type channels share the same basic biophysical properties with some key differences in the time courses of activation, inactivation, deactivation and recovery from inactivation and in the precise activation and inactivation voltage-dependence. From a functional point of view, these differences in the biophysical properties of the 3 isoforms and their splice variants should not be overlooked since they significantly impact the generation of LTSS.\(^15\)

While the contribution of T-type currents in neuron excitability was building up, evidence also started to accumulate concerning a putative role of these currents in long-term synaptic plasticity. However, pinpointing the contribution of T-type currents remained for a long time a challenging task since no tools were available to specifically suppress these currents. To circumvent this difficulty, some authors took advantage of the peculiar biophysical properties of these channels. For example, using the same protocol, the induction of a long-term potentiation (LTP) or a long-term depression (LTD) at a given synapse could be prevented by changing the potential of the postsynaptic neurons from an hyperpolarized value at which a large fraction of the T-type channel population was...
partly overlaps with those of the Cav3 channels,20 the sensitive K
most evidence was obtained in CNS areas showing a
an initial rise in postsynaptic Ca2 concentration occur-
_most forms of LTP and LTD described so far report
owing through various sources.30,31 Activation of T-type currents may contribute to such increase in 2 ways. On one hand, due to their low-threshold of activation, they can initiate a first depolarization that further recruit additional Ca2+ sources either through the activation of other voltage activated Ca2+ currents or/ and by removing the voltage-dependent magnesium block of NMDA receptor. On the other hand, the Ca2+ ions funneled through T-type channels may con-
stitute per se the required Ca2+ rise that triggers the molecular cascades leading to LTP or LTD.
The contribution of low-threshold Ca2+ channels to the dendritic depolarization associated to action potential back-propagation has been highlighted in a number of studies.32-34 For example in cortical layer V pyramidal neurons, while single action potentials are significantly attenuated when invading the distal regions of basal dendrites, action potential bursts efficiently depolarize these distal dendrites as a result of the activation of dendritic T- (or R) type calcium channels and the generation of calcium spikes. In these dendritic regions which receive the majority of synaptic inputs,35 the T-(R) bursts lead to a supra-linear increase in intracellular calcium compared to the generation of single action potentials or trains of spikes at lower frequencies.36,37 Interestingly, at the synapses between layer V pyramidal cells, pairing unitary excitatory postsynaptic potentials (EPSPs) with high-frequency action potential bursts, but not single action potentials, induced a robust LTP. Both Ni2+ at low concentration and NMDA receptor antagonists precluded this spike-timing dependent plasticity indicating that the large and long-lasting dendritic depo-
larization evoked by the T-(R) mediated action potential bursts allows the development of synaptic NMDA currents which contribute to LTP induction.36,37 The importance of T- (R) burst evoked dendir-
tic spikes for the antidromic propagation of action potentials and the induction of synaptic plasticity was also demonstrated at the synapses between layer 2/3 neurons and layer V pyramidal neurons. Addition of low Ni2+ concentration or intracellular application of QX-314 that blocked action potentials precluded the induction of the LTD evoked when pairing action potential bursts in layer V pyramidal neurons with extracellular synaptic stimulations of layer 2/3 neu-
rons.38 Similarly in CA1 hippocampal neurons, Magee and Johnston39 demonstrated that the coincidence of synaptic stimulation and action potential generation resulted in a large and widespread increase in den-
dritic Ca2+ and induced a significant spike-timing dependent potentiation of the EPSPs that was inhibited by both low Ni2+ concentration and nimodipine, suggesting the involvement of T-(R) and high thresh-
old L-type Ca2+ channels.
The role played by the T-type current mediated depolarization in the mechanisms of long-term plasticity is not restricted to excitatory synapses, but it was also demonstrated at inhibitory synapses such as the connection between Purkinje neurons and neurons of the deep cerebellar nucleus. Indeed, following the first reports describing the generation of low-threshold
| Brain area          | Synapse              | Nature of synapse | Type of plasticity | Evidence of T currents | Other partners                  | Ref. |
|---------------------|----------------------|-------------------|--------------------|------------------------|--------------------------------|------|
| Thalamus            | TC -> NRT            | Glut              | LTP                | Cav3.3 KO              | NMDAR (GluN2B)                  | 72   |
|                     | NRT -> TC VB         | GABA              | LTD postsynaptic   | Voltage dependence     | mGluR, GABA, R, CamK            | 45   |
|                     | NRT -> TC PO         | GABA              | LTP presynaptic    | Voltage dependence     | L type Ca²⁺ current, NO, Guanylate cyclase | 46   |
| Cortex              | White matter -> layer II/III (cat) | Glut              | LTP ?              | Ni²⁺                  | NMDAR R, Backpropagating APs, mGluR | 16   |
|                     | Layer IV -> layer II/III (rat) | Glut              | LTP ?              | Ni²⁺                  | Voltage dependence              | 82   |
|                     | Pairs of layer V pyramidal neurons | Glut              | LTP presynaptic   | Voltage dependence     | Ni²⁺, Mibefradil, Kurtoxin, Efonidipine | 36   |
|                     | layer IV -> layer II/III | Glut              | LTD presynaptic    | Voltage dependence     | IP3R-dependent stores, L type Ca²⁺ current, Presynaptic NMDAR, CB1R | 74   |
|                     | layer II/III -> layer V pyramidal neurons | Glut              | LTD ?              | Ni²⁺                  | Group II mGluR, Backpropagating APs | 38   |
|                     | layer II/III -> layer II/III pyramidal neurons | Glut              | LTD presynaptic    | Ni²⁺                  | Group I mGluR, PLC-activation, L type Ca²⁺ current, CB1R | 44   |
|                     | Schaffer collaterals -> CA1 | Glut              | LTP ?              | Ni²⁺                  | NMDAR, P type Ca²⁺ current, NMDAR, L type Ca²⁺ current | 55, 19, 39 |
|                     | Schaffer collaterals -> CA1 | Glut              | LTP ?              | Ni²⁺                  | NMDAR                           |      |
|                     | -> CA1               | Glut              | LTP ?              | Ni²⁺                  | NMDAR                           |      |
|                     | Schaffer collaterals -> CA1 | Glut              | LTD presynaptic    | Voltage dependence     | Ni²⁺, Mibefradil, Kurtoxin, Efonidipine, NMDAR | 17   |
|                     | Medial perforant pathway -> dentate granule cells | Glut              | LTP ?              | Voltage dependence     | Ni²⁺, Mibefradil, Kurtoxin, Efonidipine | 18   |
|                     | Stratum radiatum -> CA1 | Glut              | LTP ?              | Cav3.2 KO, mibefradil  |                                | 92   |
| Cerebellum          | Parallel fibers -> Purkinje cells | Glut              | LTP postsynaptic   | CaV3.1 KO             |                                | 77   |
|                     | Mossy fibers -> cerebellar nuclear neurons | Glut              | LTP ?              | Voltage dependence     | NMDAR (NR2D)                  | 93   |
|                     | Purkinje cells -> cerebellar nuclear neurons | Glut              | LTD ?              | Voltage dependence     | Action potentials              | 41   |
| Basal ganglia       | Globus pallidus -> subthalamic nucleus | GABA              | LTD ?              | mibefradil             | L type Ca²⁺ current            | 94   |
| Spinal cord         | C fibers -> Lamina I neurons | Glut              | LTP ?              | Ni²⁺                  | Neurokinin1R, Action potentials, NMDAR | 73   |
Ca\(^{2+}\) spikes at the end of transient hyperpolarization, it was soon established that inhibitory postsynaptic potentials (IPSPs) are ideally suited to activate rebound LTSs.\(^{40}\) Accordingly, in deep cerebellar neurons Aizenman et al.\(^{41}\) showed that trains of IPSPs reliably evoked an LTS crowned by a burst of action potentials that resulted in large Ca\(^{2+}\) transients and the induction of LTP. Conversely, conditions that limited this rebound firing, and the associated Ca\(^{2+}\) transient, resulted in LTD.\(^{41}\)

The contribution of the T-type current induced depolarization to the induction of long-term synaptic plasticity is fairly well established. However, to what extent does the rise in postsynaptic Ca\(^{2+}\) necessary to trigger synaptic plasticity specifically occur through T-type channels? Indeed, not only LTSs mediate large Ca\(^{2+}\) entry but also since T-type channels deactivate slowly, the calcium influx associated to the potential recruitment of T-type currents during brief depolarizing events, such as back-propagating action potentials or fast synaptic events, is especially large\(^{42,43}\) and mediate significant dendritic Ca\(^{2+}\) rises. However, to the best of our knowledge, the requirement of a specific funneling of Ca\(^{2+}\) through T-type channels as a prerequisite to induce synaptic plasticity was seldom investigated\(^{44}\) and only demonstrated at the inhibitory synapse between neurons of the nucleus reticularis thalami (NRT) and thalamocortical neurons of the ventrobasal somatosensory nucleus (Fig. 1A, synapse 1).\(^{45}\) At this synapse, pairing the stimulation of the reticulothalamic input to activation of the post-synaptic T-type current induced an LTD (Fig. 1B) that depends on a rise in intracellular Ca\(^{2+}\) concentration in the dendritic arbor (Fig. 1B). In the presence of a specific T-type channels blocker (TTA-P2), recruitment of high-voltage activated (HVA) Ca\(^{2+}\) currents, which evoked dendritic Ca\(^{2+}\) rise matching in amplitude the increase observed upon T-type channel activation, did not induce any synaptic plasticity (Fig. 2B & D). Furthermore, protocols that allowed significant Ca\(^{2+}\) entry from both T and HVA Ca\(^{2+}\) channels re-introduced an LTD that was resistant to HVA channel antagonist application (Fig. 2F). In contrast, in other studies reporting T-type dependent long-term plasticity, such as in the same CNS area at the synapse between NRT neurons and thalamocortical neurons of the associative posterior medial nucleus (PO; Fig. 1A synapse 2), application of the L-type HVA Ca\(^{2+}\) channel antagonist, nimodipine, precluded the induction of plasticity (Fig. 1Cb,\(^{46}\) suggesting that at these synapses Ca\(^{2+}\) entry through T-type channels was not sufficient to trigger plasticity. The link between the initial T-mediated depolarization and the recruitment of HVA Ca\(^{2+}\) channels can nevertheless be complex. Although at this synapse, the LTP required a LTS mediated postsynaptic depolarization that further activated L-type Ca\(^{2+}\) channels, the magnitude of the LTP was smaller if the LTS was evoked from a membrane potential of \(-76\) mV compared to \(-62\) mV. This is surprising since hyperpolarization of the posterior medial neuron increases the fraction of available T-type channels and hence should enhances the amplitude of the evoked T-type currents: it may be that activation of a fraction of the T-type channel population already induces a maximal amplitude LTS in thalamic neurons.\(^{29,47}\) As a consequence, the hyperpolarization from \(-62\) to \(-76\) mV should have had little effect on the amplitude of the LTS and only increased the T-mediated Ca\(^{2+}\) entry. Therefore, one may hypothesize that either the stronger Ca\(^{2+}\) entry specifically funneled through T-type channels impedes the LTP development or the more hyperpolarized value of the membrane potential at the onset of the LTS makes it difficult to recruit the dendritic L-type Ca\(^{2+}\) channels.

In conclusion, it is now well established that due to their biophysical properties and dendritic localization, T-type channels are major actors of both excitatory and inhibitory synaptic plasticity in many brain areas although at a number of synapses whether the crucial event is a specific Ca\(^{2+}\) entry through the T-type channels or the resulting depolarization remains to be clarified.

**Subcellular localization of T-type channels and synaptic plasticity**

The contribution of T-type channels to synaptic plasticity raises the question of the subcellular localization of these channels, in particular their proximity with the postsynaptic receptors within the dendritic arbor. Although few data are already available concerning their precise localization in the various neuronal compartments,\(^{48,49}\) calcium imaging technique, immunocytochemistry and electrophysiological recordings revealed that T-(R) calcium channels are not evenly distributed along dendrites.\(^{50-53}\) For example, in CA1 pyramidal neurons where Ni\(^{2+}\) dependent synaptic
Figure 1. (For figure legend, see page 126.)
plasticity mechanisms have been described at the Schaffer collateral synapses.\textsuperscript{19,39} Ni\textsuperscript{2+} sensitive channels are more abundant in the distal area of the apical dendrites.\textsuperscript{54} Accordingly, by recording field potentials at different locations, “proximal,” “middle” and “distal” along the apical dendrite of CA1 pyramidal neurons, Isomura et al.\textsuperscript{55} showed that while no significant difference among the magnitudes of the induced LTP was observed at these 3 dendritic locations in control condition, Ni\textsuperscript{2+} strongly inhibited the LTP induction in distal dendrites, slightly in middle dendrites, and did not significantly influenced LTP at proximal dendrites. Thus, for a given synaptic type, the specific T-(R) channel distribution may underlie different induction mechanisms of LTP along a dendrite. While the LTP of proximal synapses does not require T-type channel activation, recruitment of distal T-type channels is necessary to boost the amplitude of backpropagating action potentials allowing the activation of the NMDA receptors and the induction of LTP.

The relationship between the spatial extent of calcium influx through T-type channels and its ability to evoke synaptic plasticity has not been studied yet although recent electron microscopic studies reported a close proximity of Cav3.3 channels to synaptic contacts in cortical interneurons and NRT neurons\textsuperscript{49} and of Cav3.2 channels in NRT neurons,\textsuperscript{56} entorhinal cortical neurons\textsuperscript{57} and neurons located in lamina II/III of the dorsal horn of the spinal cord (Fig. 3Bab).\textsuperscript{58} Where are these channels located in respect to the other actors of the signaling mechanisms and how far should the Ca\textsuperscript{2+} entering through T-type channels spread to trigger synaptic plasticity? At the synapse between GABAergic NRT neurons and somatosensory thalamocortical neurons (Fig. 1A synapse 1), the only synapse where the specific requirement of calcium influx through T-type channels was demonstrated (see above), both T-type channels and GABA-A receptors are present on the whole dendritic shafts of thalamocortical neurons.\textsuperscript{59,60} Although T-type activation evokes a widespread Ca\textsuperscript{2+} increase in the dendritic arbor, LTD was only present at the GABA-A synapses that undergo the stimulation protocol (Fig. 1Bc).\textsuperscript{45} In addition, this LTD was blocked by transient application of a GABA-A receptor antagonist during the induction protocol, demonstrating that not only GABA release but also GABA-A receptor activation was required to trigger the postsynaptic LTD. Since these experiments were performed while voltage-
Figure 2. Long-term depression of the rat NRT-VB GABAergic synapse requires a specific funneling of Ca\(^{2+}\) through T-type channels. A. Dendritic Ca\(^{2+}\) responses evoked by somatic depolarizations in a thalamocortical neuron. Top, Stacked 2-photon microscopy image of a thalamocortical neuron dendritic branch filled with Alexa Fluor 594 and the Ca\(^{2+}\)-sensitive dye Fluo-5F (4 regions of interest are highlighted). The traces below present variations in the fluorescent dye ratio (ΔG/R) triggered at these locations by successive step depolarizations at 1.6 Hz demonstrating that the T-type channel antagonist, TTA-P2 (3 μM), almost abolished the Ca\(^{2+}\) influx evoked in response to depolarizing pulses from −80 to −30 mV while a large Ca\(^{2+}\) entry is still observed for step depolarizations to +10 mV that strongly recruit HVA Ca\(^{2+}\) channels. B. Average Ca\(^{2+}\) influx (estimated by integrating over time the fluorescent ratio, ΔG/R, s) at different distances from the soma were evoked by specifically recruiting HVA Ca\(^{2+}\) channels in the presence of TTA-P2 using somatic step depolarizations from −80 to −20 (triangles) or +10 mV (squares). Normalizing the values to the ones previously obtained by activating T-type channels in the absence of TTA-P2, showed that the Ca\(^{2+}\) responses evoked at +10 mV through HVA channels were double (***p < 0.001) while HVA-mediated Ca\(^{2+}\) entry at −20 mV were equivalent. C. Mean normalized amplitude of inhibitory currents evoked in thalamocortical neurons by nucleus reticularis thalami (NRT) fiber stimulation. Depolarizing the postsynaptic thalamocortical neurons from −80 mV to +10 mV in the continuous presence of TTA-P2 while applying short series of periodic (1.6 Hz) high-frequency stimulations (200 Hz, gray bar) to the NRT afferents, specifically and strongly recruited HVA Ca\(^{2+}\) channels but failed to induce LTD (n = 10). D. Similar results were obtained when the amplitude of the step depolarization was decreased to −20 mV to reduce HVA-channel activation, therefore matching the Ca\(^{2+}\) entry evoked by T-type channel activation (see B; n = 11). E. In the absence of TTA-P2, recruiting both HVA- and T-type channels during the induction protocol triggered LTD only when a significant Ca\(^{2+}\) influx through the T-type channels was evoked by a depolarization to −30 mV preceding the +10 mV step (n = 12). F. In this condition, LTD induction was not affected by the presence of the HVA-channel antagonists (1 μM ω-conotoxin GVIA, 20 μM nifedipine, 500 nM SNX-482; HVA ant; n = 7). Modified with permission from45.
clamping the postsynaptic neuron, they suggest that the intracellular mechanisms involved in this LTD require chloride influx or more likely state-dependent modification(s) of the GABA-A receptors. Finally, the LTD was also blocked by calcineurin, an antagonist of the calcium-sensitive phosphatase. Therefore, one may hypothetically that a spatially restricted interaction occurs between the T-mediated Ca$^{2+}$ influx and calcineurin that results in a state-dependent dephosphorylation of the activated GABA-A receptors. However, such mechanism remains hypothetical since data on a potential co-localization of GABA-A receptors, calcineurin and T-type channels are lacking. For now, such local functional interactions for T-type channels including direct protein-protein interactions have only been demonstrated for various K$^{+}$ channels$^{51-64}$ and pre-synaptic proteins. $^{65}$

So far all reported examples of T-type channel dependent synaptic plasticity, resulting in either pre or postsynaptic modification, involve T-type channels located on the postsynaptic neuron. However some electron microscope studies reported the presence of Cav3.2 channels on presynaptic-terminals (Fig. 3Ab,$^{58}$) and Cav3.1 channels are expressed at the terminals of inhibitory parvalbumin-positive interneuron in the CA1 hippocampal region. $^{66}$ In addition, Cav3.2 channels colocalize with proteins involved in synaptic release as syntaxin 1A in NRT neurons$^{67}$ while T-type channels are associated with syntaxin-1A and SNAP-25 in chromatin cells.$^{68}$
Functionally, Cav3.2 channels localized in layer III presynaptic-terminals of the entorhinal cortex were shown to contribute to the spontaneous release of glutamate (Fig. 3B,57) while in the hippocampal CA1 region calcium influx through Cav3.1 channels present in the terminals of parvalbumin positive axons triggers the asynchronous quantal GABA release evoked following nicotinic receptor activation.66 Whether these presynaptically located T-type channels also participate to long-term synaptic changes remains an open question.

**T-type channels: Partner of diverse long-term synaptic plasticity mechanisms**

As it can be inferred from the various studies presented so far, T-type channels are not associated to a specific type of synapses, excitatory or inhibitory, nor to a peculiar form of plasticity, LTP or LTD. Many reviews have been written on the molecular mechanisms of long-term synaptic changes (see69). Here, we selected a few examples to emphasize that T-type channels act in synergy with a number of the well-known signaling pathways and are implicated in both homo- and heterosynaptic plasticity.

Following the discovery of LTP at excitatory synapses,70 the requirement of NMDA receptor activation was clearly identified as one of its essential initial step.71 As already stated, T-type channels may contribute to this type of plasticity through the backpropagation of action potentials that relieves the magnesium block of synaptic NMDA receptors, resulting in calcium entry through these receptors and a Ca²⁺ rise in dendritic spines.36 Recently, the use of transgenic mice has allowed to definitely demonstrate the synergistic contribution of NMDA receptors and T-type channels to LTD in the thalamus. At the glutamatergic synapse between thalamocortical neurons and NRT neurons (Fig. 1A synapse 3), pairing synaptic inputs with LTS in the NRT neuron resulted in calcium increase, and requires a retrograde endocannabinoid signaling together with the activation of apparently presynaptic NMDA receptors.74 Similarly, T-type channels contribute to the presynaptic LTD observed at the synapse between layer II/III pyramidal cortical neurons that also required mGlu1 receptor activation, PLC activation and endocannabinoid retrograde messenger.44

The mechanisms presented so far to illustrate NMDA and mGlu receptor-dependent plasticity were homosynaptic. However, T-type channel dependent plasticity can also be both hetero and homosynaptic. Indeed, as already described (see above and Fig. 1Bc), the LTD at the GABAergic synapses between NRT neurons and somatosensory thalamocortical neurons (Fig. 1A synapse 1) is clearly homosynaptic since it requires activation of the depressed GABAergic synapses. However the full mechanism also requires

NMDA-dependent mechanism was suggested in the spinal cord. At the synapses between afferent C-fibers and lamina I projecting neurons, high-frequency stimulation induced an LTP that required the activation of neurokin 1 receptors. The transduction pathways produce a rise in calcium, likely by calcium release from intracellular stores, and a substance P-facilitated calcium influx through NMDA receptors.73 Although the high-frequency stimulation during the LTD induction protocol did not evoke an LTS but only action potential discharges, this LTD was also blocked by Ni²⁺ application. Detailed studies of the action potential waveforms revealed a significant action potential broadening that was attributed to T-(R) type channel activation and significantly participated to the firing induced Ca²⁺ rise. This study therefore suggests a cooperation of intracellular Ca²⁺ store, synaptically evoked NMDA current and action potential-triggered T-(R) type current to the increase in intracellular Ca²⁺ required to induce LTP at synapses from nociceptive fibers.73

T-type channels not only contribute to NMDA receptor- but also to metabotropic glutamatergic (mGlu) receptor-dependent LTD and LTD. For example, at the excitatory cortical layer IV to layer II synapse, T-type channels contribute to the LTD that involves the activation of group I mGlu receptors, the downstream activation of IP3 receptor-gated Ca²⁺ stores, together with calcium entry through L-type calcium channels. This plasticity is of presynaptic expression, since it is downstream to the postsynaptic calcium increase, and requires a retrograde endocannabinoid signaling together with the activation of apparently presynaptic NMDA receptors.74 Similarly, T-type channels contribute to the presynaptic LTD observed at the synapse between layer II/III pyramidal cortical neurons that also required mGlu1 receptor activation, PLC activation and endocannabinoid retrograde messenger.44

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heterosynaptic activation of mGlu receptors by the corticothalamic afferents (Fig. 1Bb). This activation, coupled to large influxes of calcium through T-type channels, triggers the calcium-sensitive phosphatase calcineurin that will then dephosphorylate GABA-A receptors inducing their long-term desensitization (Fig. 1B).

Finally, it should be noted that T-type channels may differentially contribute to the multiple forms of synaptic plasticity expressed a given synapse. As already mentioned, activation of the GABAergic synapse between Purkinje cells and deep cerebellar neurons evoked T-mediated rebound depolarizations that can produce either LTD or LTP. Aizenman and collaborators showed that the polarity of these synaptic changes is linked to the number of action potentials evoked by T-mediated rebound depolarizations. Whereas LTP were induced in conditions where pronounced rebound depolarization elicited significant spiking (>5 action potentials), LTD required rebound depolarizations that had little or no spiking. Although activation of high-voltage Ca\(^{2+}\) channels by action potentials can explain why a strong rebound firing is required to trigger LTP, the exact biochemical mechanisms coupling the rebound depolarization to either LTP or LTD of IPSPs are still unknown. These data highlight the fact that either form of plasticity can be evoked depending on the pattern of LTS activation. While at these synapses T-type channel activation is required to trigger both type of plasticity, it has also been shown at other synapses that these channels may contribute to one but not the other.

At the glutamatergic Schaffer collateral–CA1 cell synapse, either an NMDA or an mGlu receptor-dependent LTD can be induced depending on the recording conditions. While both forms are pathway specific, and require membrane depolarization and a rise in postsynaptic calcium, the activation of T-type channels was needed for the expression of mGlu but not NMDA receptor-LTD. Importantly, the mGlu receptor LTD is favored in conditions of reduced excitability, i.e., when the amplitude of the synaptic input is small and in the presence of GABAergic inhibition that would help deinactivating T-type channels. Both glutamate receptor subtypes are present in postsynaptic spines but the metabotropic and the ionotropic receptors are localized perisynaptically and at the post-synaptic density, respectively. A remarkable compartmentalization of the signaling transduction pathways could therefore be hypothesized with a localization of the T-type channels in the immediate vicinity of mGlu receptors limiting the activation of the specific pathway to the appropriate trigger.

Another example of the fine-tuning of T-type channel recruitment according to the type of synaptic plasticity was reported in Purkinje cells that show a high expression of Cav3.1 channels. Using both Cav3.1 KO mice and specific T-type channel antagonist (TTA-P2) application, Ly et al. showed that T-type channels are required for LTP induction at the glutamatergic parallel fiber–Purkinje cell synapse. However, the functional inactivation of Cav3.1 channels did not affect the LTD expressed at the same synapse when the induction protocol paired the stimulation of the parallel fibers with a subsequent stimulation of the climbing fibers (Fig. 4). In this case, high postsynaptic Ca\(^{2+}\) levels are required that presumably result from the activation of P/Q calcium channels after the strong depolarization ensuing climbing fiber activity and from release from intracellular Ca\(^{2+}\) stores.

Therefore, as briefly presented here and illustrated in the articles listed in Table 1, T-type channels participate to numerous synaptic plasticity mechanisms, both homo and heterosynaptic, involving different partners and both pre- and post-synaptic modifications (the main pathways underlying T-channel dependent plasticity at both excitatory and inhibitory synapses are schematically presented in Fig. 5). Although few data are available, the existence of T-dependent and T-independent plasticity at the same synapse strongly suggests a subcellular localization of these channels and their partners that allows specific interactions.

### Physiological consequences of T-dependent plasticity

How these various T-dependent synaptic plasticities contribute to brain functions is an emerging issue that can now be tackled with the help of the new pharmacological and genetic tools. Two sets of studies performed in the visual cortex and the thalamus illustrate their functional importance in developmental and sleep related plasticity, respectively.
Figure 4. T-type Ca\(^{2+}\) channel activation is necessary for long-term potentiation but not depression induction at the parallel fibers to Purkinje cell synapses. A. Time course of normalized excitatory post-synaptic current (EPSC) charges. The LTP induction protocol (performed at time 0) comprised 5 high-frequency (200Hz) stimulations of the parallel fibers (PFs) repeated each second for 5 min without stimulating the climbing fiber (CF) (see schematic representation on the right). LTP was induced in control condition (black dots, n = 8) but was blocked by the specific T-type channel antagonist, TTA-P2 (blue dots, n = 7), and absent in slices from Cav3.1\(^{-/-}\) mice (red dots, n = 7). Representative traces from 10 successive sweeps before and 30 min after the induction protocol are presented at the top in each case. B. Same data as in A for the LTD induction protocol. Doublets of PF stimuli (2 pulses, 200 Hz) followed by a 100 ms burst of CF activation (4 pulses, 400 Hz) every second during 5 min were used to successfully trigger LTD in each cases (n = 7 for the 3 sets of conditions). Modified with permission from\(^7\).
**Plasticity of visual responses**

During development, long-term synaptic plasticity contributes to the refinement of the responses of neuronal networks to sensory experiences. An attractive model to study this phenomenon is ocular dominance, i.e. the relative effectiveness of the left and right eyes in driving visual cortical neurons that drastically shifts toward the non-deprived eye after monocular deprivation. In the rat visual cortex, this susceptibility of ocular dominance preference to monocular deprivation is small around the time of eye opening, peaks at around 4 weeks, and disappears in adults. Interestingly, *in vitro* experiments showed that an LTP could be elicited at the excitatory layer IV and layers II/III synapses during this critical time period. Dark rearing delays similarly both the age-dependent decline of LTP and the period of ocular dominance.

![Diagram of synapses](image)

**Figure 5.** (For figure legend, see page 133.)
plasticity illustrating the time correlation between these phenomena. The synaptic plasticity requires the activation of T-type channels since it is precluded if the post-synaptic neuron is maintained at a depolarized potential or in the presence of T-type channel blockers. Direct measurement of the T-type current, presumably of the Cav3.2 type, showed a developmental profile in these neurons. The amplitude of the currents was very small before eye opening, peaked during the critical period and returned to a small value by adulthood while dark rearing prevented this developmental decline until adulthood. Similarly in the kitten visual cortex, in vitro experiments showed that the LTP evoked in layers II/IV neurons by white matter stimulation, which is maximal at the time of the critical period, requires the activation of LTSs in the post-synaptic neuron. The contribution of T-type channels to the visual response plasticity was also investigated in vivo. In rats subjected to monocular deprivation for a time period long enough to allow the full development of both depression of deprived eye responses and potentiation of non-deprived eye responses, infusion of mibebradil into the visual cortex abolished the potentiation of the visual evoked potentials. In contrast, the depression of the deprived eye responses that are likely mediated by NMDA receptor-dependent LTD was unchanged. Similarly, infusion of the specific T-type channel blocker TTA-I1 in the cat visual cortex reduced cortical plasticity triggered by monocular deprivation while preserving normal visual response properties. Altogether the results from these in vitro and in vivo experiments strongly suggest that T-type channels are essential to the development of experience-dependent enhancement of visual responses. How this synaptic plasticity could be related to changes in the number or properties of cortical Cav3 channels remain to be resolved.

**Sleep-associated synaptic plasticity**

Among the various theories on the cognitive roles of sleep, it is suggested that at least part of the sleep memory consolidation processes, involving reshaping of synaptic connectivity, occurs during the slow waves of non-REM sleep. At the network/cellular level these EEG rhythms are associated to oscillatory activities within the intrathalamic network (Fig. 1A) that are characterized by the rhythmic occurrence of high-frequency bursts of action potentials mediated by LTSs in both thalamocortical and NRT neurons. Using induction protocols that mimic the activities occurring in these neurons during slow sleep oscillations, 3 in vitro studies recently tackled the issue of long-term synaptic changes within the intrathalamic network. As already described above, different synapses were investigated, the excitatory thalamocortical to NRT neuron synapse (Fig. 1A synapse 3) and 2 inhibitory synapses between NRT neurons and either associative (PO) (Fig. 1A synapse 2) or sensory (VB) thalamocortical neurons (Fig. 1A synapse 1). Interestingly activation of T-type channels is required for the expression of long-term changes at the 3 synaptic types, albeit the sign of the changes, the signaling pathways and the plasticity loci were different.

**Figure 5.** (see previous page) T-type calcium channel-dependent LTP/LTD mechanisms at excitatory and inhibitory synapses. A. Excitatory synapses. Activation of postsynaptic T-type calcium channels induces a post-synaptic Ca\(^{2+}\) increase either directly (1) and/or as a consequence of the membrane potential (Vm) depolarization that can in turn either trigger the opening of the HVA Ca\(^{2+}\) channel (2) and/or relieve the Mg\(^{2+}\) block of NMDA receptors (2′). In addition to T channels activation, various types of metabotropic receptors can be recruited (3) further enhancing intracellular Ca\(^{2+}\) concentration by mobilizing the Ca\(^{2+}\) stores. The increase in Ca\(^{2+}\) concentration activates multiple intracellular pathways (4) mediating post-synaptic long-term plasticity or producing the retrograde messengers, nitric oxide (NO) or cannabinoid (CB) (5) that modify the presynaptic release probability. Finally, presynaptic T-type channels (6) directly interact with proteins involved in the exocytotic machinery like syntaxin 1A (syt) (syt). Further studies will clarify whether these presynaptic T-type channels are also involved in synaptic LTP/LTD. Note that a postsynaptic Ca\(^{2+}\) increase specifically supported by the Ca\(^{2+}\) influx through T-type channels has not yet been demonstrated as a required step for LTP/LTD induction at excitatory synapses. B. Inhibitory synapses. T-type channel activation depolarizes the postsynaptic membrane potential (Vm), opening L-type HVA Ca\(^{2+}\) channels (1). The resulting increase in intracellular Ca\(^{2+}\) concentration triggers NO production that diffuses retrogradely to the presynaptic element (2) and induces pre-synaptic LTP through guanylate cyclase activation. A different mechanism, independent of HVA channel activation, requires Ca\(^{2+}\) ions specifically entering in the post-synaptic dendrite through the T-type channels to activate the phosphatase calcineurin and trigger LTD (3). In this case, only activated GABA receptors are down-regulated suggesting a state-dependent interaction with either calcineurin or the T-type channels (4). In addition, LTD also requires the concomitant activation of metabotropic glutamate receptors (5) that may potentiate the T-mediated Ca\(^{2+}\) influx, recruit intracellular Ca\(^{2+}\) stores and/or modulate intracellular pathways. Note that T-type channels are also potentially present on inhibitory pre-synaptic terminals (6) where they directly interact with proteins involved in the exocytotic machinery like the syntaxin 1A (syt). In both A and B, dashed lines are used when no definite experimental evidence are available to support the proposed mechanism.
How these synaptic mechanisms contribute to sleep-associated cognitive functions remains to be established through in vivo investigations. It can however be hypothesized that the 2 long-term changes present at the inhibitory synapses may occur at different periods of the sleep rhythms and target specific thalamic networks. For example, the LTP of inhibitory synapses in associative thalamus is a homeostatic plasticity since it only required postsynaptic repetitive bursting activity (Fig. 1Cc) and therefore should develop in every thalamocortical neurons and affect every GABAergic synapse. Conversely, the LTD between NRT and sensory thalamocortical neurons required not only T-type current activation but also GABA-A and mGlu receptor activation (Fig. 1B). Therefore, this is a more restricted process that specifically affects sleep activated GABAergic synapses in a subset of thalamocortical neurons submitted to strong activation of their corticothalamic inputs, and hence may be involved in the precise functional reshaping of the sensory information pathway during sleep. Moreover from the requirement of the induction protocol frequencies, it can be inferred that the LTP at the NRT to associative thalamocortical neuron synapses should develop at early stages of NREM sleep when LTSs mainly occur at very low frequency during the thalamocortical neuron transitions from DOWN to UP states (Fig. 1Cc). Conversely, LTD at the NRT to sensory thalamocortical neuron synapses should be triggered during a deeper sleep state when the DOWN to UP state transitions are intermixed with delta-activity characterized by the occurrence of LTSs at a relatively higher frequency.87

**Conclusion – perspectives**

Although the first evidences pointing to a synaptic role of T-type channels were obtained more than 20 y ago, they have so far contributed little to the vast literature on synaptic plasticity (Table 1). Two main reasons may underlie this limited interest. First, for a long time, the current dogma has affirmed that T-type currents could play little role in physiological functions such as behaviorally related memory formation, which take place during the wake state when neurons are supposed to be depolarized and therefore T-type channel inactivated. However, it is now clear that in some brain areas, the density of T-type channels expressed in neurons is high enough to allow a significant number of deinactivated T-type channels at the membrane potentials reported in awake animals.88 For example, in the thalamus, the fraction of T-type channels that is available at depolarized potential participates to EPSP amplification and has a drastic effect on spike probability during wake states.89 Second, the lack of suitable T-type channel antagonists has hampered for many years the discovery of subtle functions for neuronal T-type currents and made impossible to definitely prove their implication in synaptic plasticity. However, the development of specific and potent antagonists29 now sets this issue, opening the way to a growing number of studies demonstrating new roles for T-type currents (see review in.90).

From the studies reported here, it can already be concluded that T-type currents are not restricted to a specific form of long-term synaptic plasticity and play a role in both excitatory and inhibitory synapses with the help of various intracellular partners (Fig. 5). Although, only postsynaptically localized T-type channels have been considered so far, some recent results point to a localization of the channels in presynaptic-terminals. Therefore, one may assume that data will rapidly be obtained demonstrating a role of presynaptic T-type channels in either long-term or short-term synaptic plasticity.

Finally, the specific requirement of Ca$^{2+}$ entering through T-type channels to trigger long-term plasticity at some synapses45 and the observation that at a given synapse where multiple forms of plasticity occur, only one depends on T-type channel activation77 open new exciting perspectives. Indeed, both results strongly suggest that the different molecular actors of the long-term plasticity are spatially localized and/or directly interact with T-type channels. Molecular approaches based on new genetically engineered tools should help to decipher these complex protein-protein interactions and bring about totally new insights into the physiology of these channels.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

**Acknowledgments**

The authors would like to thank Dr. V. Crunelli for critical reading of the manuscript.

**ORCID**

Nathalie Leresche [http://orcid.org/0000-0001-6705-9769]
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