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Pflugers Arch - Eur J Physiol (2009) 457:1161–1172
DOI 10.1007/s00424-008-0582-6

NEUROSCIENCE

Ca^{2+} signaling by T-type Ca^{2+} channels in neurons

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Received: 14 August 2008 / Accepted: 15 August 2008 / Published online: 11 September 2008
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Abstract Among the major families of voltage-gated Ca^{2+} channels, the low-voltage-activated channels formed by the Ca_v3 subunits, referred to as T-type Ca^{2+} channels, have recently gained increased interest in terms of the intracellular Ca^{2+} signals generated upon their activation. Here, we provide an overview of recent reports documenting that T-type Ca^{2+} channels act as an important Ca^{2+} source in a wide range of neuronal cell types. The work is focused on T-type Ca^{2+} channels in neurons, but refers to non-neuronal cells in cases where exemplary functions for Ca^{2+} entering through T-type Ca^{2+} channels have been described. Notably, Ca^{2+} influx through T-type Ca^{2+} channels is the predominant Ca^{2+} source in several neuronal cell types and carries out specific signaling roles. We also emphasize that Ca^{2+} signaling through T-type Ca^{2+} channels occurs often in select subcellular compartments, is mediated through strategically co-localized targets, and is exploited for unique physiological functions.

Keywords Ca_v3 channel · Low-threshold burst · Oscillation · Thalamus · SK channel · SERCA

Introduction

Voltage-gated Ca^{2+} channels (VGCCs) transduce electrical excitability into intracellular Ca^{2+} concentration increases and play an important role in a wide range of neuronal physiology. VGCCs are composed of three major subfamilies, which are encoded by the Ca_v1, Ca_v2, and Ca_v3 genes that give rise to ten different α_1 channel subunits. A great deal is known about Ca^{2+} influx through the high-voltage-activated (HVA) Ca^{2+} channels encoded by the Ca_v1 and Ca_v2 channel genes and their contributions to neuronal signaling (for review, see, e.g., [19]). In contrast, the Ca_v3 subfamily, generating the low-voltage-activated Ca^{2+} currents, also referred to as T-type Ca^{2+} currents [89], is poorly characterized in terms of the free Ca^{2+} concentration ($[Ca^{2+}]_i$) increases resulting from channel activation and the signaling functions exerted by Ca^{2+} ions entered through these channels. This deficit in our understanding is remarkable since T-type Ca^{2+} currents have long been known to uniquely influence neuronal excitability [47, 59, 105]; they are widely expressed throughout the central nervous system (CNS), sometimes at very high densities [106]; and they are recruited during quite specific physiological circumstances [47, 88].

T-type Ca^{2+} currents mediate the low-threshold burst discharges that occur during physiological and pathological forms of neuronal rhythmogenesis [47], such as the sleep-related slow electroencephalographic waves [27], rhythms related to motor coordination [6, 10], to learning [100], and hyper-synchronous oscillations during epilepsy [59, 96]. Additionally, T-type Ca^{2+} currents are involved in sensory

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transmission [64], in dendritic integration [72, 76, 80], neurotransmitter release [18], neural development [68], mechanosensation [45], and pain [51]. The $[Ca^{2+}]_i$ dynamics resulting from T-type Ca^{2+} channel activation are now being measured using advanced optical techniques and will shed light on Ca^{2+} signaling related to important physiological conditions. This review discusses recent insights into neuronal Ca^{2+} signaling mediated through T-type Ca^{2+} channels. It focuses on studies in which the corresponding $[Ca^{2+}]_i$ dynamics have been optically resolved and associated with specific neuronal functions. The review will also discuss strong evidence for intracellular signaling events initiated through Ca^{2+} entry via T-type Ca^{2+} channels, as obtained from electrophysiological studies.

Basic principles of T-type Ca^{2+} channel function

T-type Ca^{2+} channels are distinct from other classes of VGCCs in terms of their gating characteristics and kinetics (Fig. 1a). T-type Ca^{2+} channels are activated by subthreshold membrane depolarizations between −65 and −50 mV. By virtue of their rapid and mostly complete inactivation at moderately depolarized membrane potentials, T-type Ca^{2+} channels can generate spike-like membrane depolarizations [47, 89, 105]. Depending on the specific Ca_v3 channel subtype, the time courses of activation, inactivation, deactivation, and recovery from inactivation vary [63, 66, 111]. T-type Ca^{2+} channels require a preceding period of hyperpolarization to recover from inactivation and to become primed to open. Therefore, in many instances, T-type Ca^{2+} channel activation occurs as a rebound to inhibitory input. Accordingly, in neurons expressing T-type Ca^{2+} channels, $[Ca^{2+}]_i$ increases will typically follow periods of hyperpolarization (Fig. 1b).

There are a number of reasons why our understanding of the $[Ca^{2+}]_i$ signals generated by T-type Ca^{2+} channels lags behind that of the HVA Ca^{2+} channels. First, the contribution of T-type Ca^{2+} channels to $[Ca^{2+}]_i$ is often masked by a more robust Ca^{2+} entry through HVA Ca^{2+} channels (see, e.g., [49, 75, 76, 113]). Second, the lack of potent and selective T-type Ca^{2+} channel blockers has hampered progress in dissecting their physiological contributions. Low concentrations of Ni^{2+} (50–100 μM) or mibefradil (10–100 μM) are commonly used to block T-type Ca^{2+} channels, but both of these affect other ion channels [84, 92]. T-type Ca^{2+} channels also have a comparatively low single-channel conductance, which, together with their rapid inactivation [47, 105], inherently limits Ca^{2+} influx. Third, in many neurons, T-type Ca^{2+} channels are predominantly expressed in the dendrites [26, 32, 57, 72], often in distal portions [26, 31, 73], which make resolving fluorescent signals arising from T-type Ca^{2+} channel activity difficult. Finally, in some cell types, Ca^{2+} currents resistant to HVA channel blockers contain a large contribution from the Ca_v2-channels of the R-type, which resemble T-type Ca^{2+} currents in their comparatively hyperpolarized voltage range of activation and recovery from inactivation, and in overlapping pharmacological profiles, including mibefradil sensitivity [92]. Extended pharmacological and biophysical analyses, sometimes combined with genetic ablation techniques, have been applied recently to convincingly distinguish between the two Ca^{2+} channel types (see, e.g., [99, 108]).

Despite these obstacles, there is considerable evidence implicating T-type Ca^{2+} currents in important Ca^{2+} signaling roles (see also [88]). First, in several types of bursting neurons, Ca^{2+} entering during a burst discharge is important for the temporal patterning of oscillations [4, 6, 10, 14, 43, 70, 88, 104], although, in most cases, the Ca^{2+} current subtypes dominating Ca^{2+} entry during bursting have not yet been defined. Second, T-type Ca^{2+} channels expressed in non-bursting neurons contribute to Ca^{2+}-dependent ionic currents accompanying action potentials (APs) [77, 116]. Third, several forms of long-term synaptic plasticity depend on T-type Ca^{2+} currents [1, 12, 83, 85, 91]. Finally, pathological oscillations, such as those found during epileptic activity, are accompanied by enhanced T-type Ca^{2+} channel function [65, 103, 109, 117].

Ca^{2+} entry determined by the unique voltage-gating of T-type Ca^{2+} channels

Three distinct voltage-gating characteristics endow Ca_v3 channels with a unique identity as a Ca^{2+} source (Fig. 2). First, T-type Ca^{2+} currents are activated close to resting membrane potentials [47, 89, 105] and produce $[Ca^{2+}]_i$ elevations at subthreshold potentials (Fig. 2a). For example, a Ni^{2+}-sensitive low-threshold Ca^{2+} signal accompanies subthreshold excitatory input in hippocampal CA1 and cortical layer V dendrites [72, 76]. In contrast, these channels typically make a minor contribution to Ca^{2+} entry resulting from a single AP [75, 77]. Through their low-threshold of activation, T-type Ca^{2+} channels can thus boost weak depolarizing inputs [41, 58, 110] and facilitate dendritic Ca^{2+} spikes [55, 117].

Second, T-type Ca^{2+} channels, while activating rapidly, deactivate comparatively slowly upon repolarization (Fig. 1a). During an AP lasting a few milliseconds, T-type Ca^{2+} channels may be activated but undergo little inactivation. Therefore, T-type Ca^{2+} channels remain open after the downstroke of the AP, permitting large Ca^{2+} influx due to the high driving force for Ca^{2+} ions (Fig. 2b) [77]. The dynamics of Ca^{2+} entry during AP repolarization, important for the timing of Ca^{2+}-dependent after-hyperpolarizing K^+ currents [113], vary considerably

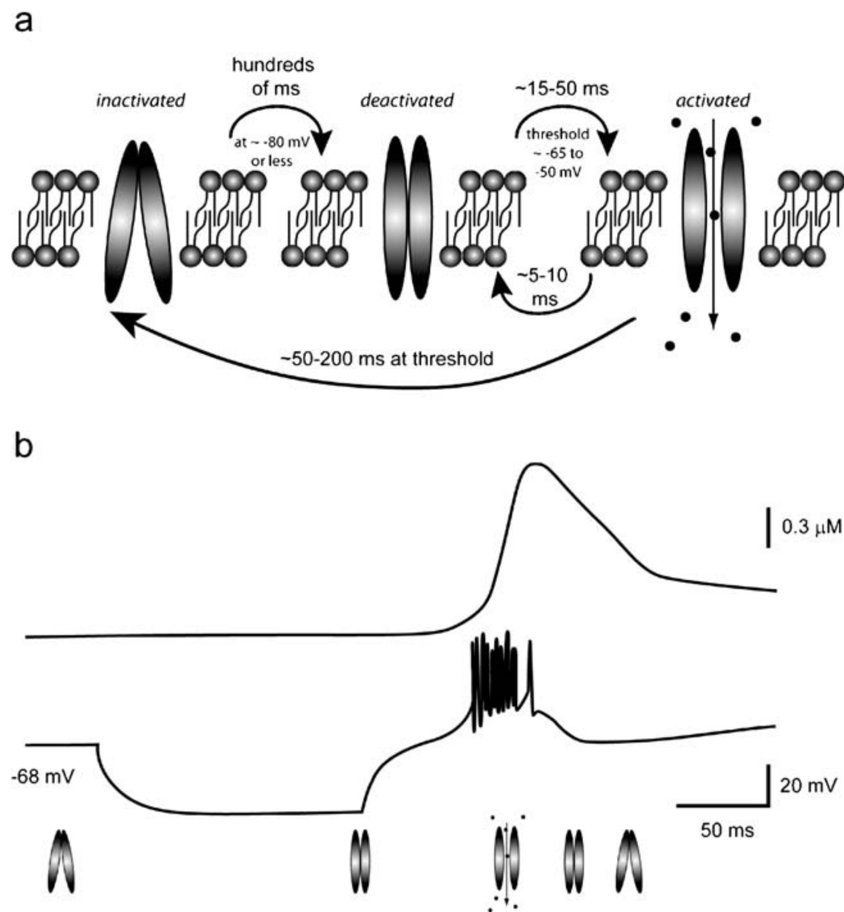

Fig. 1 Schematic representation of T-type Ca^{2+} channel gating and the $[Ca^{2+}]_i$ signals generated during a low-threshold burst. **a** A channel is depicted as two associated transmembrane proteins in a membrane bilayer in three different configurations (inactivated, deactivated, activated). *Arrows* point to the transitions between these three states of the channel. Next to the arrows, a *range of time constants* is indicated that is derived from work on heterologously expressed [63] and on native channels [47]. **b** Schematic traces presenting $[Ca^{2+}]_i$ signals (*top trace*) obtained by a single low-threshold burst (*bottom trace*). This burst was evoked by a brief negative current injection to hyperpolarize membrane potential such that channels could recover from inactivation. Typical channel configurations accompanying these electrical events are schematically depicted below the traces. The $[Ca^{2+}]_i$ signal is slightly delayed with respect to burst onset because it was derived from a recording with the low-affinity Ca^{2+} dye magfura-2 [29]

among the Ca_v3 channel subtypes [63]. In cerebellar Purkinje cells, the time course of activation of Ca^{2+}-dependent afterhyperpolarizing K^+ currents overlaps with that of T-type Ca^{2+} current deactivation [104], suggesting that the gating of the Ca^{2+}-activated K^+ channels activated in between APs may be mediated via Ca^{2+} entering through T-type Ca^{2+} channels.

Third, although well-known for their prominent inactivation, all three T-type Ca^{2+} channel isoforms show a window current [66]. Window currents result from a small fraction of channels that remain open and lead to a stationary Ca^{2+} influx and a persistent enhancement of $[Ca^{2+}]_i$ [28, 53] (Fig. 2c, left). The $Ca_v3.3$ channel subtype gives rise to a comparatively large window current [66], which results in a steadily elevated basal $[Ca^{2+}]_i$ and a propensity to generate oscillatory $[Ca^{2+}]_i$ signals [25]. A standing inward Ca^{2+} current in thalamocortical neurons underlies a membrane potential bi-stability [115] and the capability of switching abruptly between activated and silent states, such as those accompanying a slow (< 1 Hz) sleep rhythm [46]. During the up-states of these rhythms, the window current additionally recruits Ca^{2+}-dependent cationic currents and permits a plateau-like up-state that may last for periods of seconds, whereas Ca^{2+}-activated K^+ channels initiate the down state [14]. Window currents ensure a steady, yet comparatively small, Ca^{2+} influx for prolonged periods of time around the resting membrane potentials of typical neurons and could thus promote cellular differentiation ([68], see also the "Ca^{2+} signaling through developmentally regulated expression of T-type Ca^{2+} channels" section), but also lead to abnormal cell growth and tumor proliferation [87].

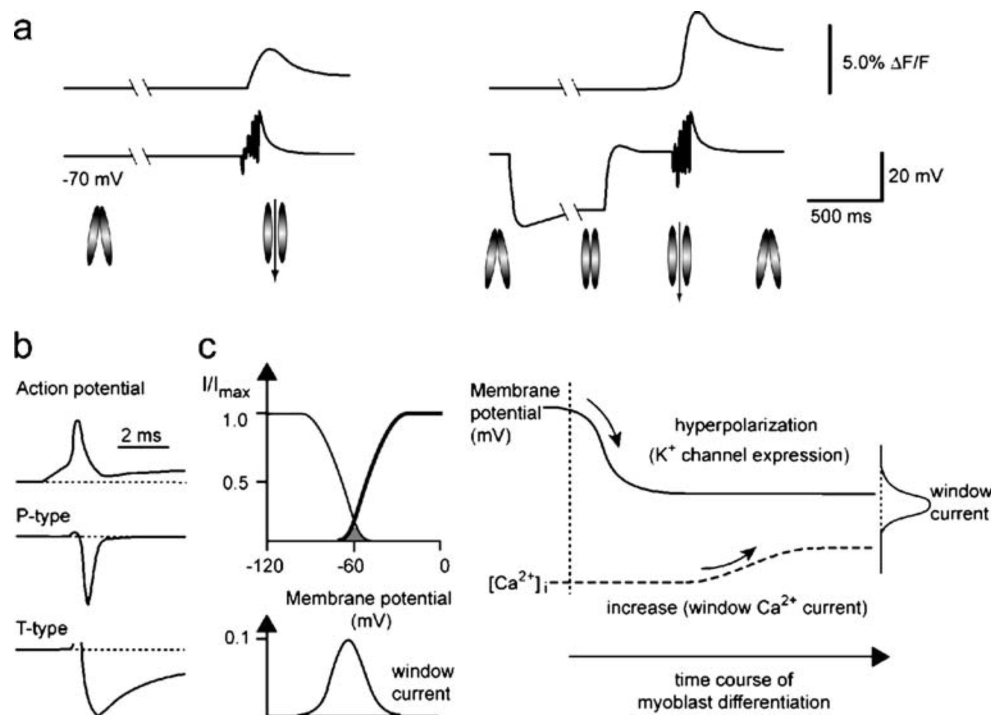

Fig. 2 $[Ca^{2+}]_i$ signals generated through the unique voltage-gating characteristics of T-type Ca^{2+} channels. **a** *Left*, membrane potential showing a subthreshold response to repetitive stimulation (*bottom trace*) which is accompanied by a small $[Ca^{2+}]_i$ increase (*top trace*). *Right*, this increase is boosted when synaptic stimulation is preceded by a short membrane hyperpolarization to allow for recovery from inactivation. Typical channel configurations introduced in Fig. 1a are shown *below the traces*. Traces adapted from [72]. **b** Time courses of the HVA P-type and T-type Ca^{2+} currents during an AP. Note the slow deactivation time course of the T-type Ca^{2+} current, leading to substantial Ca^{2+} influx during the postspike hyperpolarization. Traces adapted from [104]. **c** *Left*, generation of a window Ca^{2+} current due to overlapping steady-state activation (*thick line*) and inactivation (*thin line*) curves. Voltage region covered by both curves is *shaded*. An expanded portion of this graph is shown below to highlight the amplitude and voltage dependence of the window current. *Right*, qualitative graphic representation of changes in membrane potential (*continuous line*) and $[Ca^{2+}]_i$ (*dashed line*) during myoblast differentiation. Voltage range of window current is indicated to the right to illustrate that the hyperpolarization of membrane potential into this voltage range is a prerequisite for $[Ca^{2+}]_i$ increases. Traces adapted from [11]

Ca^{2+} signaling due to spatially defined expression of T-type Ca^{2+} channels

Electrophysiological recordings, Ca^{2+} imaging, and modeling studies support a nonuniform expression of T-type Ca^{2+} channels in diverse neuronal cell types. Ca^{2+} imaging of hippocampal dendrites of young adult rats revealed a graded expression profile for T-type Ca^{2+} channel-dependent signals, increasing with dendritic distance from the soma and reaching highest levels in distal dendrites [26, 56, 57, 73], in which T-type Ca^{2+} channel-mediated boosting of subthreshold potentials will facilitate dendrosomatic communication [71]. In thalamic neurons, T-type Ca^{2+} channels are heavily expressed in the dendrites, as shown by Ca^{2+} imaging [29, 81, 118], computational modeling [31], and cell-attached dendritic recordings [52]. In thalamocortical neurons of the paraventricular thalamic nucleus, T-type Ca^{2+} channels, predominantly formed by $Ca_v3.1$ subunits, are concentrated in proximal dendrites and lead to numerous, closely spaced hotspots of increased $[Ca^{2+}]_i$ [94], suggesting channel clustering, whereas in the *nucleus reticularis thalami* (nRT), both $Ca_v3.2$ and 3.3 subtypes are expressed and found along the somatodendritic axis [29, 52], but might be most strongly expressed in distal dendrites [31]. The dendritic localization of T-type Ca^{2+} channels underlies the robust bursting propensity of many neurons and enables the dendrites to be highly responsive to synaptic input [31]. T-type Ca^{2+} channels are also expressed on dendritic membranes of cerebellar Purkinje neurons [80] and contribute to the climbing fiber-evoked complex spikes observed in culture [20, 37]. Notably, two-photon imaging in Purkinje cell dendritic trees revealed expression of T-type Ca^{2+} channels at the level of single spines [49]. Therefore, these channels likely contribute to compartmentalized Ca^{2+} signaling in Purkinje cells in response to subthreshold input [36] and may influence the Ca^{2+} dependence of cerebellar synaptic plasticity [54].

The spatial compartmentalization of T-type Ca^{2+} channels has two important consequences for dendritic processing. First, the amplification of distal inputs through T-type Ca^{2+} channels boosts the sensitivity of peripheral sensory perception. In olfactory receptor neurons, odor-induced Ca^{2+}

transients in the cilia-containing knobs are strongly boosted by Ca^{2+} entry through T-type Ca^{2+} channels. Blocking T-type Ca^{2+} currents with mibefradil reduces the knob $[Ca^{2+}]_i$, and transient and somatic signals are virtually absent [39]. Therefore, the local boosting of olfactory stimuli in the knob helps to propagate incoming olfactory signals to the soma, thereby ensuring AP generation [58]. Similarly, the high density of T-type Ca^{2+} channels in thalamic dendrites helps in the amplification of proximally impinging excitatory input and in securing robust burst discharge [29, 114]. Second, the non-uniform expression of T-type Ca^{2+} channels along the somatodendritic axis can lead to highly polarized $[Ca^{2+}]_i$ increments. In cells of the vestibulocerebellum, burst firing induces a strong $[Ca^{2+}]_i$ signal in the brush, which is predominantly carried through $Ca_v3.1$ channels, whereas tonic AP firing produces a homogeneous $[Ca^{2+}]_i$ increase throughout the cell [33]. Therefore, the bimodal activity pattern in these cells is accompanied by distinctly compartmentalized Ca^{2+} signaling.

Ca^{2+} signaling through developmentally regulated expression of T-type Ca^{2+} channels

T-type Ca^{2+} channel expression undergoes marked developmental regulation and, in some cases, coincides with periods of neuronal differentiation (see also [68]). In the mouse peripheral vestibular system, large $Ca_v3.2$-type currents are recorded during embryonic development but current amplitude sharply decreases, reaching a minimum at postnatal day P4, after neurite outgrowth and synapse formation is terminated [2, 21]. Similarly, development of cochlear hair cells is accompanied by a marked reduction of $Ca_v3.1$ channel mRNA and T-type Ca^{2+} currents [67]. In these cells, expression of T-type Ca^{2+} currents occurs during periods of elevated spontaneous AP generation, however, the signaling functions adopted by T-type Ca^{2+} channels during development remain to be specified. In *Xenopus* spinal neurons, the role of T-type Ca^{2+} currents is to facilitate rhythmic intracellular $[Ca^{2+}]_i$ transients by initiating membrane depolarization that recruits HVA Ca^{2+} currents [43]. There is also evidence that the neuronal cell-adhesion molecules that promote differentiation regulate $[Ca^{2+}]_i$ through mechanisms involving T-type Ca^{2+} channels [61].

Increased $[Ca^{2+}]_i$ through window currents mediated by T-type Ca^{2+} currents have been implicated in skeletal muscle development. Skeletal muscle differentiation is a Ca^{2+}-dependent process that involves the transcription of a network of muscle-specific genes, and the fusion of myoblasts into multinucleate myotubes. At the onset of the fusion process, a subpopulation of myoblasts hyperpolarizes due to the expression of an inward rectifier K^+ current [62], starts expressing $Ca_v3.2$ T-type Ca^{2+} channels, and shows elevated $[Ca^{2+}]_i$ levels prior to fusion [11] (Fig. 2c, right). Pharmacological inhibition of T-type Ca^{2+} channels prevents myotube fusion [11]. Therefore, in skeletal muscle, $Ca_v3.2$-type Ca^{2+} channels appear responsible for the augmentation of basal $[Ca^{2+}]_i$ in response to membrane hyperpolarization, consistent with the generation of a window current. Whether T-type Ca^{2+} window currents in neurons play similar roles in developmental processes remains an intriguing open question.

Ca^{2+} signaling through co-localization of T-type Ca^{2+} channels with Ca^{2+}-dependent ion channels

Ca^{2+} entering through T-type Ca^{2+} channels can provide selective signaling through coupling with Ca^{2+}-dependent ion channels. In several cases, T-type Ca^{2+} channels are selectively coupled to Ca^{2+}-activated small conductance-type K^+ (SK) channels [101] (Fig. 3a). In the nRT, the physiological relevance of T-type Ca^{2+} to SK channel coupling is apparent at the cellular as well as the large-scale network level. The nRT is a thin inhibitory shell of neurons that is important for sleep rhythm generation and for sensory information transfer [90]. During slow-wave sleep, nRT neurons generate complex oscillatory burst discharges [4, 14, 38]. These rhythmic bursting patterns are strongly dependent on the activation of SK2 channels in between low-threshold bursts [3, 4]. The activation of SK2 channels occurs via Ca^{2+} ions entering through T-type Ca^{2+} channels in the long and thin dendrites of nRT neurons [29]. The density of T-type Ca^{2+} channels is high enough such that a single low-threshold burst leads to an elevation of $[Ca^{2+}]_i$ approaching 1 μM, essentially saturating the nearby SK2 channels. The coupling is apparent as SK2 channel activity closely follows the time course of dendritically averaged $[Ca^{2+}]_i$ signals and leads to a burst-induced afterhyperpolarization. This silent period allows for the next oscillatory burst, thereby generating the robust oscillatory behavior that is typical of nRT neurons. Accordingly, mice lacking SK2 channels show strongly suppressed electroencephalographic sleep waves and interrupted deep sleep behavior, suggesting an important role for Ca^{2+} entry through T-type Ca^{2+} channels in boosting sleep oscillations and in stabilizing sleep [29].

In dopaminergic midbrain neurons, T-type Ca^{2+} channels are coupled to SK3 channels [116]. Here, T-type to SK3 channel coupling results in an outward K^+ current that underlies the hyperpolarization necessary for regular, pacemaker-like AP discharge. However, during neonatal development of dopaminergic neurons, T-type Ca^{2+} channels are dually coupled not only to SK3 channels, but also to ryanodine receptors (RyRs) [30] (Fig. 3b). Therefore, the $[Ca^{2+}]_i$ transient that occurs via spontaneous openings of single T-type Ca^{2+} channels is boosted by Ca^{2+}-induced Ca^{2+}

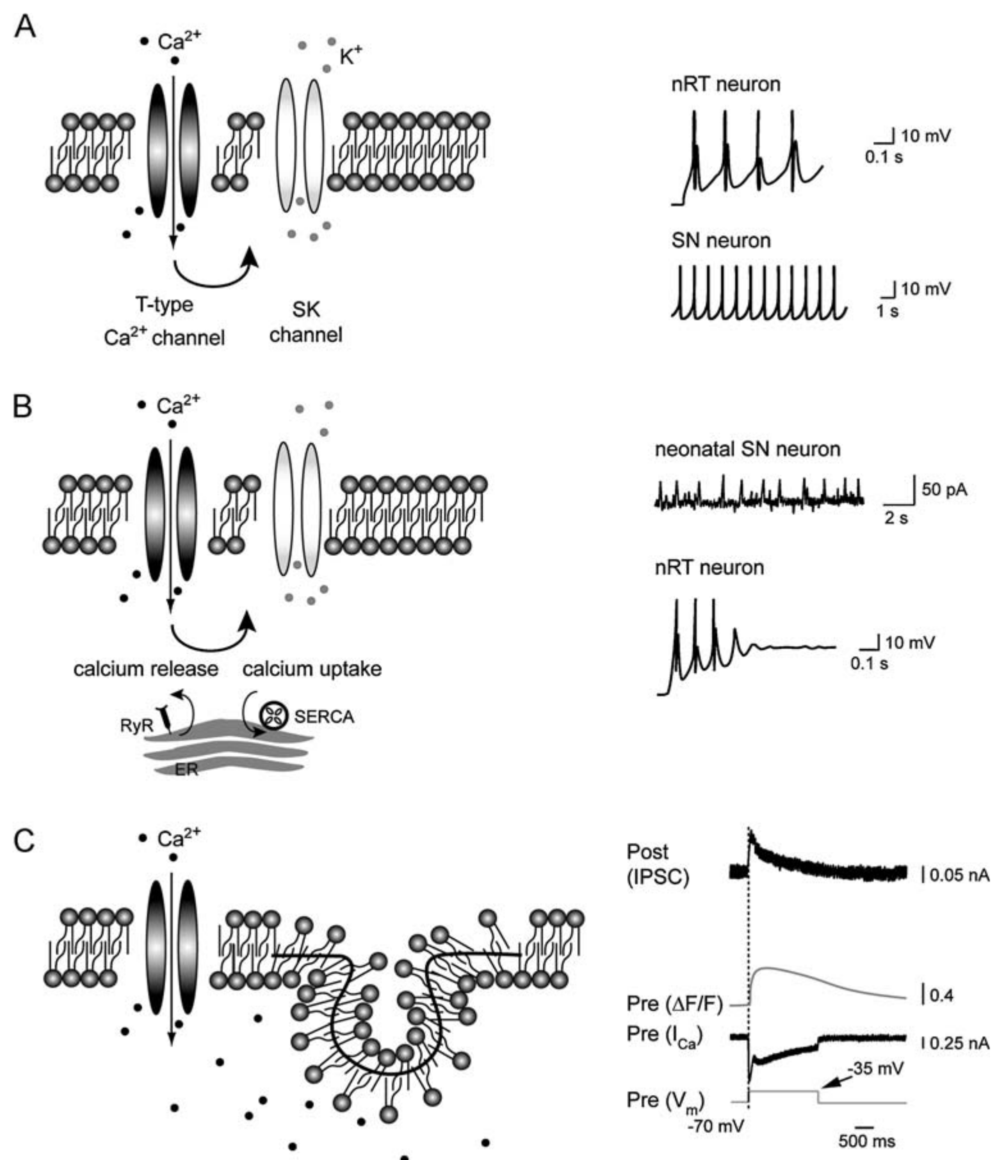

Fig. 3 Ca^{2+} signaling of T-type Ca^{2+} channels due to co-localization with Ca^{2+}-dependent effectors and with the intracellular Ca^{2+} handling machinery. **a** Schematic representation of co-localized T-type Ca^{2+} channels and SK channels in a membrane and representative oscillatory discharge patterns of nRT [29] and substantia nigra (SN) neurons [116]. **b** Co-localization of the T-type Ca^{2+}/SK channel pair with RyRs or SERCAs. In neonatal SN neurons, coupling to RyRs gives rise to spontaneous miniature outward currents [30]. In nRT neurons, coupling to SERCA induces oscillatory dampening [29]. *ER* Endoplasmic reticulum. **c** Ca^{2+}-induced synaptic transmission due to co-localization with the presynaptic release machinery (not shown). A single vesicle fused with the plasma membrane is depicted schematically. Representative pre- and postsynaptic recordings are shown to the right, as adapted from [50]. *IPSC* Inhibitory postsynaptic potential; *Pre (ΔF/F)* Presynaptic changes in fluorescent signal, *Pre* (I_{Ca}) presynaptic Ca^{2+} current, *Pre* (V_m) presynaptic voltage command

release (CICR, see also the "Coupling of T-type Ca^{2+} channels to intracellular CA^{2+} release and sequestration" section) and becomes large enough to gate SK3 channels. The resulting random SK3 channel-dependent miniature outward currents make the spontaneous AP discharge irregular, which is a characteristic signature of neonatal dopamine neurons [30] (Fig. 3b).

In thalamic and habenular neurons, T-type Ca^{2+} currents may also be coupled to Ca^{2+}-dependent cationic currents, thereby leading to afterdepolarizations following burst discharges [4, 14, 22, 70]. In thalamocortical neurons, the coupling of T-type Ca^{2+} channels to cation channels is not due to direct Ca^{2+}-mediated activation of the effector channels. Rather, coupling occurs through recruitment of Ca^{2+}-dependent adenylyl cyclase and synthesis of cAMP which increases the activity of hyperpolarization-activated cation-nonselective (HCN) channels [69]. The resulting membrane depolarization feeds back to limit the recruitment of T-type Ca^{2+} channels and causes thalamocortical neurons to fail in the generation of low-threshold bursts [5]. Such cell-intrinsic mechanisms of regulating oscillatory activity are thought to be critical in the periodicity of thalamic network oscillations in vitro, which reproduce fundamental aspects of sleep spindle-related activities [5]. Similar to the co-localization of T-type Ca^{2+} and SK2 channels in nRT dendrites, thalamocortical dendrites co-express T-type Ca^{2+} channels and HCN channels [102]. The mechanisms of activation of Ca^{2+}-dependent cationic currents, such as those in nRT and habenular neurons, remain to be determined [4, 14, 22].

Apart from the CNS, coupling of T-type Ca^{2+} channels to large-conductance-type Ca^{2+}-activated K^+ (BK) channels has

been suggested for the $Ca_v3.2$ isoform expressed in the vascular smooth muscle of coronary arteries in heart. Mice lacking the $Ca_v3.2$ isoform show constricted and malformed arteries, and impaired relaxation responses of arterial vessels [24]. This deficiency in arterial relaxation was proposed to be due to the loss of Ca^{2+} entering through $Ca_v3.2$ channels to antagonize contraction via activating BK channels. $Ca_v3.2$ channel and BK channel proteins from brain tissue co-immunoprecipitate, suggesting that they may co-localize in membranes through molecular interaction to translate Ca^{2+} entry rapidly into membrane hyperpolarization. In coronary arteries, Ca^{2+} transients due to T-type Ca^{2+} channels may mediate vasodilatation.

In addition, the coupling of T-type Ca^{2+} channels to BK and SK channels has been reported in a number of bursting neurons, such as cholinergic nucleus basalis neurons [113], intralaminar thalamic neurons [42], Purkinje neurons [104], and cartwheel cells of dorsal cochlear nucleus [60].

Coupling of T-type Ca^{2+} channels to intracellular Ca^{2+} release and sequestration

An emerging aspect of Ca^{2+} signaling via T-type Ca^{2+} channels is the coupling to intracellular Ca^{2+} release and sequestration (Fig. 3b). In addition to immature dopaminergic neurons (see the "Ca^{2+} signaling through co-localization of T-type Ca^{2+} channels with Ca^{2+}-dependent ion channels" section), T-type Ca^{2+} channel coupling to intracellular Ca^{2+} handling mechanisms has emerged principally from thalamic neurons (see also [88]). Thalamic nuclei are subdivided into first-order and higher-order nuclei depending on whether they receive their excitatory input from the periphery or from the cortex, respectively [95]. Accordingly, first-order nuclei are considered the classical relay stations of the thalamus, whereas higher-order nuclei are implicated in cortico-thalamo-cortical information transfer. These functionally defined thalamic subdivisions, are accompanied by a nucleus-specific relationship between $Ca_v3.1$ channels and CICR. In the visual and somatosensory first-order nuclei, activation of a low-threshold Ca^{2+} spike induces rapid Ca^{2+} entry and a $[Ca^{2+}]_i$ transient that decays on the time scales of the low-threshold current, without coupling to CICR [16, 93]. Tonic firing and HVA Ca^{2+} channel activation, however, leads to CICR in these cells [16]. Conversely, in higher-order neurons, a single low-threshold burst is sufficient to induce a tail in the corresponding intracellular $[Ca^{2+}]_i$ transient that persists for seconds and that is, at least in part, due to CICR [93]. In nRT neurons, Ca^{2+} entry is mediated through $Ca_v3.2$ and $Ca_v3.3$ channels and, rather than being boosted through CICR, is rapidly sequestered selectively into the endoplasmic reticulum. Thus, the coupling between T-type Ca^{2+} and SK2 channels is controlled through the sarco/endoplasmic reticulum Ca^{2+}–ATPases (SERCAs). SERCAs and SK2 channels compete for the same pool of Ca^{2+} ions entered through T-type Ca^{2+} channels, shaping and effectively limiting SK2 channel gating, thereby dampening nRT oscillations [29]. Notably, SERCAs specifically sequester Ca^{2+} ions entering through T-type but not through HVA Ca^{2+} channels, suggesting that the triad of T-type Ca^{2+} channels, SK2 channels, and SERCAs forms a signaling complex that is both self-triggering and self-limiting in rhythm generation.

T-type Ca^{2+} channel-induced CICR is also present in the heart. In addition to their major counterpart, the L-type Ca^{2+} channels, T-type Ca^{2+} channels act as Ca^{2+} sources and couple to the sarcoplasmic reticulum to induce CICR [98]. T-type Ca^{2+} channel density is highest in pacemaking structures, with a prominent expression of $Ca_v3.1$, whereas low levels are present in ventricular cells [112]. In pacemaking sinoatrial node and atrial cells, T-type Ca^{2+} channels contribute to the late phase of diastolic depolarization [44]. During this period, numerous and rapid (20–30 ms) localized $[Ca^{2+}]_i$ sparks appear at the sarcolemmal surface, which sum to a pedestal increase in $[Ca^{2+}]_i$ at subthreshold potentials that is further boosted by Ca^{2+} release from the sarcoplasmic reticulum [48]. Consistent with this finding, mice lacking the $Ca_v3.1$ Ca^{2+} channel subunit show no T-type Ca^{2+} currents in pacemaking cardiac tissue, a slowing of the late phase of diastolic depolarization, and bradycardia [74], whereas $Ca_v3.2$-deficient mice showed normal rhythms [24]. Thus, via the amplification of $[Ca^{2+}]_i$ through sarcolemmal Ca^{2+} release, $Ca_v3.1$ channels serve an important role in cardiac pacemaking.

Involvement of T-type Ca^{2+} channels in exocytosis

Presynaptic Ca^{2+} transients that underlie fast neurotransmitter release are among the largest and most highly localized $[Ca^{2+}]_i$ elevations, reaching levels of up to tens of micromolar within <1 ms, on spatial scales of 10–100 nm. While it is well established that presynaptic HVA Ca^{2+} channels contribute to fast excitatory neurotransmission, in some neurons, T-type Ca^{2+} channels are also involved in neurotransmitter release, engendering a low-threshold component of fast exocytosis [18]. A remarkable case is the graded transmission between reciprocally connected oscillator heart interneurons of leech, which inhibit each other through burst discharges in alternating sequence [50]. T-type Ca^{2+} current-dependent burst discharges lead to robust Ca^{2+} increases at the presynaptic sites of contact, whereas tonic APs produce comparatively minor $[Ca^{2+}]_i$ elevations. The amplitude of T-type Ca^{2+} currents correlates well with presynaptic $[Ca^{2+}]_i$ dynamics and with graded synaptic transmission (Fig. 3c) [50]. A role for T-type Ca^{2+} currents in graded neurotransmission has

also been shown for retinal bipolar cells. These cells transform light-evoked synaptic input from photoreceptor cells into a sustained response and use graded neurotransmitter release to communicate with postsynaptic retinal amacrine and ganglion neurons. Ca^{2+} imaging and membrane capacitance measurements, coupled with mibefradil application, identified a role for T-type Ca^{2+} currents in triggering vesicle fusion at the giant terminals of bipolar cells [86]. Based on its Ni^{2+} and mibefradil sensitivity, it was also proposed that AP-independent excitatory miniature synaptic currents in dorsal spinal chord are triggered by T-type Ca^{2+} channels [7].

T-type Ca^{2+} currents contribute to different forms of γ-aminobutyric acid (GABA) release in granule cells of the olfactory bulb [34]. These axonless inhibitory neurons exert a lateral inhibition via dendro-dendritic synapses formed with mitral cells, the major output cells of the bulb. Dendro-dendritic interactions may occur in a local mode, in which single synapses between granule and mitral cells enter into a reciprocal communication. Under these conditions, Ca^{2+} influx through *N*-methyl-D-aspartate receptors (NMDARs), VGCCs, and release from internal stores all contribute to trigger GABA release from granule cell dendrites [35]. Alternatively, release from GABA can be elicited via backpropagating APs initiated in the granule cell somata [34] or via strong subthreshold synaptic stimulation [35]. These stimuli provoke a global $[Ca^{2+}]_i$ increase in numerous distant spines, which is generated predominantly by T-type Ca^{2+} currents that evoke the release of GABA along large stretches of dendritic spines. These cells can thus release GABA in an AP-independent manner to exert global lateral inhibition of mitral cells.

Important forms of slow secretion, such as hormone release from neuroendocrine cells, are regulated by T-type Ca^{2+} channels [18]. An intriguing aspect is the recruitment of T-type Ca^{2+} channels for secretion in chromaffin cells. T-type Ca^{2+} channels are weakly expressed under control conditions, but the $Ca_v3.2$ subtype is strongly upregulated by day-long exposure to cAMP-producing stimuli or by hypoxia and functionally couples to catecholamine release [17]. Secretion controlled by T-type Ca^{2+} channels in these cells is initiated at more hyperpolarized potentials, but couples with equal efficacy and velocity to the release apparatus [40], thus permitting catecholamine release in response to subthreshold stimuli and after stressful conditions.

Involvement of T-type Ca^{2+} channels in synaptic plasticity

Ca^{2+} influx through T-type Ca^{2+} channels has been implicated in several forms of synaptic plasticity. In neonatal and young hippocampus, T-type Ca^{2+} channels have been implicated in long-term depression (LTD) induced by metabotropic glutamate receptors (mGluRs) [9, 12, 83, 85]. At least in one of these cases, T-type Ca^{2+} channels may also play a role in retrograde signaling mediated by endocannabinoids [83]. Conversely, in mature CA1 pyramidal cells, a contribution of T-type Ca^{2+} channels to NMDAR-dependent long-term potentiation (LTP) was reported [107]. T-type Ca^{2+} currents could facilitate the generation of dendritic Ca^{2+} spikes, thereby promoting the Mg^{2+} unblock from the external vestibule of the NMDAR, as shown for spike-timing-dependent plasticity between pairs of layer V cortical neurons [55].

Subthreshold Ca^{2+} signaling has been previously suggested to play a role in cerebellar synaptic plasticity [36, 49], and roles for rebound burst discharges generated by T-type Ca^{2+} channels have been recently discovered. Low-frequency stimulation of inhibitory afferents onto neurons of the deep cerebellar nuclei, each evoking a rebound burst discharge, lead to LTP or LTD, depending on the number of APs generated during the rebound bursting [1]. Furthermore, when mossy fiber activation was paired with a postsynaptic rebound current, LTP was generated that strongly depended on the relative timing of synaptic stimulation and the rebound current [91]. Possibly, Ca^{2+} entry through T-type Ca^{2+} channels potentiates a plasticity-promoting Ca^{2+} signal generated by the synaptic stimuli at individual contact sites. Such a mechanism would point to an important role of non-synaptic $[Ca^{2+}]_i$ signals generated by T-type Ca^{2+} channels in some forms of synaptic plasticity.

Conclusions and outlook

Recent work clearly shows that T-type Ca^{2+} currents, beyond their biophysical role as burst generators, produce marked $[Ca^{2+}]_i$ elevations that adopt intracellular signaling functions. To make use of this low-conductance, rapidly inactivating Ca^{2+} source active at subthreshold voltages, neurons have evolved specific strategies.

First, in a number of cases, T-type Ca^{2+} channels are highly expressed in subcellular compartments with comparatively weaker expression of other classes of VGCCs. $[Ca^{2+}]_i$ changes are then dominated by T-type Ca^{2+} channels in a spatially confined, yet highly efficient manner. Prominent examples are the thin dendrites of nRT neurons [29], the knobs of olfactory sensory neurons [39], and the brushes of vestibulocerebellar unipolar brush cells [33]. Dendrites and spines of olfactory granule neurons also express high densities of T-type Ca^{2+} channels, allowing for global subthreshold $[Ca^{2+}]_i$ increments in addition to local synaptic ones at single spines [35]. A relatively large T-type Ca^{2+} channel density is also present in the distal dendrites

of hippocampal [26, 57, 73] and cortical cells [76] and in dendritic spines of cerebellar Purkinje neurons [49].

Second, targets for Ca^{2+} ions entering through T-type Ca^{2+} channels are selectively co-expressed with T-type Ca^{2+} channels within these compartments. Particularly important are SK channels, BK channels, constituents of CICR, SERCAs, and dendritic vesicular release sites, but this list is likely to expand and may include additional types of ion channels, as well as proteins related to plasticity and development. The functional characteristics of their colocalization with T-type Ca^{2+} channels show remarkable cell type specificity. In the case of SK2 channels in nRT [29], the dendritic confinement of SK2 channels permits their selective activation upon a low-threshold Ca^{2+} burst. This activation is close to saturating, and SK2 currents are large and slow enough to allow for recovery of T-type Ca^{2+} channels. Conversely, in dopaminergic neurons, afterhyperpolarizations mediated by T-type–SK3 channel coupling are more rapid such that a full-fledged low-threshold burst is effectively prevented, and tonic discharge predominates [116]. This suggests that SK channel gating through T-type Ca^{2+} channels is tailored to control the deactivation/inactivation of Ca_v3 channels according to the neuronal function close to specific system. Additional targeting of T-type Ca^{2+} currents is found for ER membrane proteins. SERCA-mediated Ca^{2+} sequestration in nRT dendrites is selective for Ca^{2+} entry through T-type Ca^{2+} channels [29]. A preferential localization of SERCAs on dendritic ER protrusions could underlie its selectivity for T-type Ca^{2+}, whereas SERCAs may be rare in subcellular compartments expressing HVA Ca^{2+} channels. Consistent with this hypothesis, there is evidence for a functional distinction between Ca^{2+}-sequestering and non-sequestering elements of the ER [13]. Furthermore, in the case of dopaminergic neurons, developmental maturation of AP discharge regularity is likely accompanied by a reorganization of CICR elements, followed by uncoupling of RyRs from the T-type Ca^{2+} channel–SK3 channel pair [30].

Additional aspects of T-type Ca^{2+} channel signaling described here are just beginning to be recognized and will progress rapidly with new optical techniques, the availability of genetically modified animals lacking T-type Ca^{2+} channel subunits (for review, see [97]) and the advance of small interfering RNA technologies [87]. The distinct properties of channel subtypes are well established, and these shape cell-specific characteristics of low-threshold bursting [15, 47, 79, 82] and of $[Ca^{2+}]_i$ signals [63]. In keeping with this, the subcellular distribution of T-type Ca^{2+} channel subtypes [78], and subtype-specific Ca^{2+} signaling, including the generation of post-AP Ca^{2+} entry and window currents is an important aspect of future investigation. The prominent dendritic and spine expression of these channels in numerous cell types suggests that an assessment of their role in dendritic integration of synaptic inputs and in dendritic Ca^{2+} spikes is likely to be important. Depending on expression density and channel subtype, recruitment of T-type Ca^{2+} currents can confer local or global dendritic $[Ca^{2+}]_i$ signals and could hence contribute to various forms of synaptic plasticity. The rapidly expanding recognition of subtype-specific modulatory pathways on the short-term [23] and long-term ([8, 17]) provides an additional means for varying intracellular $[Ca^{2+}]_i$ dynamics. Moreover, T-type Ca^{2+} currents can contribute to neurotransmitter release, particularly in neurons with graded or dendritic forms of synaptic release. Such coupling may be more widespread in cells with dendrodendritic coupling in the CNS (see [33, 35]) and could be linked to retrograde signaling through dendritic neuropeptide and endocannabinoid release.

T-type Ca^{2+} currents appear to provide crucial signaling functions during developmental periods in which neurons undergo profound changes in morphology, electrophysiology, and synapse formation. Whether these channels facilitate neuronal excitability by providing a subthreshold depolarizing or window current, or whether Ca^{2+} entry through these channels carries specific signals remains to be determined. In the mature thalamus, sleep-related rhythmic $[Ca^{2+}]_i$ elevations are large and are handled in a cell-specific manner according to thalamocortical connectivity. It is thus tempting to speculate that these $[Ca^{2+}]_i$ oscillations may represent an analogue of developmental oscillations that drive plasticity. These may contribute to some of the subcellular mechanisms by which sleep affects neural functions related to synaptic remodeling and plasticity.

Gain-of-function mutations in Ca_v3 channel genes, or abnormal channel expression patterns, have been linked to states of chronic neuronal hyperexcitability and stress, such as chronic epilepsy, neuropathic pain, tumor formation, and hypoxia [8, 17, 59, 87], whereas genetic ablation confers resistance to seizures [96]. Abnormal $[Ca^{2+}]_i$ load in dendrites and perturbed Ca^{2+} homeostasis is a central theme in the affected cells. Understanding the contributions of T-type Ca^{2+} channels to these pathological states, in particular, how they alter excitability and how they impose or alter neurotransmission, may be important for determining their signaling profile and for identifying potential therapeutic targets to prevent the development of these diseases (see [87]).

As we learn more about the roles for T-type Ca^{2+} channels in neurons, we will find that they are important for the cytoplasmic, biochemical, and genetic consequences of particular behavioral states such as sleep, reward actions, learning and development, and for pathological states related to neuronal hyperexcitability.

Acknowledgements We acknowledge F. Longordo, Dr. L. Mapelli and Prof. K. Vogt for useful discussions and E. Bernardi for his help with figure preparation. The work of J.P.A. is supported by NIH grants. A.L. is supported by the Swiss National Science Foundation (Nr. 3100A0-116006).

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