Annu. Rev. Physiol. 1996. 58:329–48

LOW-THRESHOLD CALCIUM CURRENTS IN CENTRAL NERVOUS SYSTEM NEURONS

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KEY WORDS: LVA current, T current, low-threshold spike, calcium-dependent burst firing, oscillations

ABSTRACT

The low-threshold calcium current, or T current, has recently been demonstrated with voltage-clamp recordings in a variety of central nervous system (CNS) neurons. It is especially prominent in the soma and dendrites of neurons with robust calcium-dependent burst firing behaviors such as thalamic relay neurons and cerebellar Purkinje cells. Single-channel and macroscopic current behavior have been carefully investigated and kinetic schemes devised to completely describe the activation and inactivation processes. The kinetic properties of T current lead to activation of low-threshold spikes subsequent to transient membrane hyperpolarizations. Putative functional roles for T current include generation of low-threshold spikes that lead to burst firing, promotion of intrinsic oscillatory behavior, boosting of calcium entry, and synaptic potentiation.

INTRODUCTION AND HISTORY

In an elegant series of in vitro intracellular studies in cat thalamus, Eccles and collaborators (3) discovered that some central neurons displayed a form of paradoxical excitation. In contrast to the typical responses in most cells where depolarized membrane potentials are normally associated with enhanced excitability, hyperpolarizations such as those produced by inhibitory synaptic potentials resulted in increased responsiveness. This period of enhanced excitability following membrane hyperpolarizations was termed post-anodal exaltation. Llinás and colleagues carefully examined this property using intracellular recordings with in vitro slice preparations of inferior olive (65, 66) and thalamus (55, 56, 64). They noted that intracellular current injections, which hyperpolarized the membrane to levels more negative than rest (around

0066-4278/96/0315-0329$08.00

–65 to –70 mV), resulted in a rebound plateau excitation. The rebound potential exceeded the threshold for Na^+-dependent action potentials with the result that a burst of Na^+ spikes rode the crest of the plateau.

Further studies identified the likely mechanisms for the burst response. Blockade of Na^+ channels by tetrodotoxin revealed an underlying plateau potential. The activation threshold was around –55 mV, approximately 15 mV more negative than the threshold for Na^+ spikes. Therefore, the plateau was described as a low-threshold spike or LTS. The LTS was dramatically reduced by removing Ca^{2+} from the extracellular solution or by adding inorganic Ca^{2+} antagonists such as Co^{2+}. Substitution of Ba^{2+} for Ca^{2+} in the perfusate did not alter the time course of the LTS, thus indicating a lack of Ca^{2+}-dependent inactivation. These findings led to the suggestion that a specialized type of Ca^{2+} current, the low-threshold Ca^{2+} current (LTCC), was responsible for rebound burst firing in these neurons.

The pioneering current-clamp studies have been followed in detail over the last ten years with the direct identification of such a low-threshold, inactivating Ca^{2+} current in several central neuronal types. The low-threshold calcium current was first fully described in cultured sensory neurons from rat and chick (12, 29, 79). In these neurons, it was clear that the current was not due to an alternative form of gating of a high-threshold channel. Evidence for an independent entity included metabolic stability compared with the lability of high-voltage-activated (HVA) Ca^{2+} currents (14, 32, 63, 77), differential pharmacological sensitivity of the I_T as opposed to HVA currents (13, 32, 77), and identification of a unique single-channel entity with activation properties complementary to those expected for macroscopic low-threshold Ca^{2+} currents (12, 79).

Various nomenclatures have been devised to describe the multiple types of Ca^{2+} currents in excitable cells, but complete classification will depend on identification of the molecular structure of the channels (94). In the most common usage, LTCC is equivalent to T (for tiny or transient) current (79). Other synonyms are the low-voltage activated (LVA) current (12), type I current (77), or the low-threshold-inactivating (LTI) current (63). In this review we restrict ourselves to the common terminology: T current or I_T.

Since the early intracellular studies that revealed a role for a specialized Ca^{2+}-dependent conductance in burst firing, subsequent reports have provided information regarding other functional roles of I_T channels. Here we review several aspects of T current in a variety of central neurons (and a few other cell types where comparison is appropriate), with emphasis on biophysical properties, localization, modulation, heterogeneity, and proposed function(s).

BIOPHYSICS

The voltage dependence of activation and inactivation of I_T has been described in a number of preparations. Comparison of these studies is complicated by

the different recording conditions used in each study. Voltage-dependent membrane conductances are dramatically affected by membrane-screening charges, especially those resulting from extracellular divalent cations (13, 29, 34, 44, 97, 98). An e-fold increase in extracellular [Ca^{2+}] will shift gating curves by approximately +5 – +12 mV. These differences in screening charges must be accounted for when comparing the results of studies performed with various concentrations of Ca^{2+} or when the charge carrier is Ba^{2+}, which is less effective at charge screening than Ca^{2+} (13, 29, 52). The results from selected voltage-clamp studies that have provided relatively complete biophysical characterization of I_T in a number of cell types are presented in Table 1. These studies were performed mostly at room temperature (near 22°C). Both the kinetics and amplitude of I_T are highly dependent, with Q_{10} values of 2 to 3 (21, 29, 78). The time constants of activation and inactivation would be approximately three to four times shorter at physiological temperatures (37°C).

Activation

Voltage dependence of activation has been determined by a variety of methods including plotting the normalized peak current vs membrane potential (e.g. 24, 35, 43, 57) or by converting peak current to peak conductance by dividing by the driving force ($E-E_{Ca}$) (e.g. 40, 110). However, because I_T has non-instantaneous activation and inactivation kinetics, these methods do not provide an independent measure of the macroscopic activation process. Two alternatives have been used. One, based on the original methods of Hodgkin & Huxley (47), involves fitting kinetic functions to whole-cell currents. Some assumptions underlying the original theory have been disproved by modern single-channel recordings, most notably the lack of independence between activation and inactivation (e.g. 1). Thus although the results do not provide complete information about microscopic gating mechanisms (see Single-Channel Studies below), these methods provide an excellent means of completely describing the time- and voltage-dependent activation and inactivation of macroscopic currents. The equations thus generated can be used in simulations of neuronal behavior (51, 72).

The generic Hodgkin-Huxley equation for an inactivating current is

$$g_t = g' [1-\exp(-t/\tau_m)]^n \exp(-t/\tau_h), \qquad 1.$$

where g_t is the conductance at time t; $g' = \bar{g} (m)_\infty^n h_o$; $\bar{g}$ is the total conductance available; τ_m and τ_h are the time constants of activation and inactivation, respectively; *n* is the power of the activation function (equivalent to the number of closed states through which a channel must traverse before opening); m_∞ is the relative steady-state activation at a given membrane potential; and h_o is the relative level of inactivation at the initial holding potential. With a holding

Table 1 Voltage-dependent kinetics for T current in a variety of neurons

Cell Type	Charge Carrier	Inactivation				Activation			Reference
		$V_{1/2}$[a]	k[b]	τ_h[c]	$\tau_{recovery}$[c]	$V_{1/2}$[2]	k[b]	τ_m[c]	
Isolated hippocampal L-M cells	2 Ca	−94	6.3	25–10	~90 ms/−100 mV	−47	6	ttp	(35)
Isolated rat VB	3 Ca	−81	4.0	130–30	250 ms/−100mV	−57	6	15–2	(51, 52)
Isolated rat nRt	3 Ca	−80	5.3	100–80	500ms/−100mV	−50	7	11–3	(52)
Isolated rat dLGN	5 Ca	−64	7.8	70–20	750ms/−98mV	−45	6	ttp	(43)
Cat and rat dLGN in slice	1 Ca	−87	3.9	100–25	~300ms/−95mV	−60	2		(24)
Rat spinal dorsal horn in slice	2 Ba	−86	8.0	80–10		−45	7		(86)
Isolated rat basal forebrain	2.5 Ca	−49	3.9	82–16		−40	4.8	ttp	(2)
Isolated rat lateral habenula	3 Ca	−81	4.4	150, 50–30[d]	510ms/−90mV	−58	3.4	8–2	(50)
Isolated rat dorsal horn neurons	5 Ca	−82	3.7	43–16		−50	6		(49)
Isolated rat neostriatum	5 Ca	−88	6.1		288ms/–100mV	−53	6	ttp	(48)
Isolated rat Purkinje cells	5 Ba	−93	8.2	100–25		−46	9		(84)
Xenopus neurons in culture	2 Ca	−79	6.9	55–20		−49	6	ttp	(40)
Neuroblastoma	50 Ba	−51	4.0	400–20	~150ms/−80mV	−20	11	8–2	(110)
GH3 cells	10 Ca	−71		100–20	250, 1000ms[d]/−100mV	−33	7	10–2	(44)
Chick drg	10 Ca	−78	5.0	50–20		−51	7	ttp	(32)

Charge carrier concentrations are in mM. [a]: half-activation or inactivation voltage; [b]: slope of activation/inactivation curve, mV/efold; [c]: all values for τ (time constant) in ms. $\tau_{recovery}$ is the time constant for recovery at the indicated potential; [d]: Two exponential components; ttp: time to peak is voltage dependent.

potential sufficiently negative that $h_o \approx 0$, g' is determined primarily by m_∞. From Ohms law $g = I/E$; therefore, g_t can be obtained by dividing the current by the driving force ($E-E_{Ca}$) or by the constant field equation (21, 44, 46, 51). Relative values for m_∞ at a series of command potentials can then be obtained. Alternatively, activation can be approximated by measuring tail current amplitudes after a brief activating voltage step (e.g. 50–52, 84, 104). If an appropriate step duration is chosen, activation will be nearly complete while inactivation has not yet become significant. Thus tail current amplitude will closely reflect the maximum activation $[(m_\infty)^n]$ and has the advantage that the driving force is the same for each step.

Under physiological recording conditions, the apparent activation threshold for I_T is near resting membrane potential, −50 to −60 mV, with activation normally complete at −20 to −30 mV. Activation is relatively gradual in most cases, with an e-fold increase in conductance normally requiring about 6–7 mV depolarization (Table 1). Exceptions include cat and rat thalamic relay (24) and rat lateral habenular cells (50), which have very steep activation curves (2–3.4 mV/efold) that would promote rapid regenerative Ca^{2+}-dependent responses. However, one of these studies was performed in slices where neurons retain extensive dendritic trees, and as indicated by the authors, voltage-clamp control was probably compromised (24). Thus T current activation slope is probably a relatively constant feature in neurons from several brain areas. The voltage at which I_T is half-activated ($V_{1/2}$) is also comparable in many cell types, with values ranging between −45 and −60 mV in most cases. The differences in half-activation voltage between cell types (Table 1) cannot be completely explained by methodological differences. In a few experiments, direct comparison of activation properties between cell types was obtained with the same recording conditions (50, 52). In these cases, clear differences in $V_{1/2}$ were obtained, with thalamic reticular neurons showing half-activation 9 mV more depolarized than thalamic relay cells or lateral habenular neurons.

The rate of I_T activation is highly voltage dependent. In every case where it has been measured (Table 1), the time to peak (ttp) current becomes shorter with depolarization. Furthermore, the time constant of activation (τ_m) has been directly measured in many cases by fitting Equation 1 to whole-cell current traces. At threshold, τ_m is relatively slow (8–15 ms) and decreases to around 2 ms at maximal activation (Table 1). Comparison between cell types reveals that differences in the rate of activation are largely accounted for by shifts in the voltage dependence. For example, the relationship between τ_m and voltage is similar for thalamic relay and reticular neurons, but it is shifted about 20 mV in the positive direction for the latter (52). Functionally this means that at LTS threshold, ~ −50 mV, the rate of onset of T current is approximately twice as fast in relay cells compared with reticular cells. This slow onset of

I_T in reticular neurons may help explain the gradually accelerating Na^+ spike frequency found on the rising phase of the LTS (26, 53).

There is a significant delay to the onset of the current, indicating that I_T channels must traverse several closed states before opening (44). The sigmoid onset kinetics of macroscopic records can be best described by Equation 1, with the power factor n set to 2 or 3. Studies in thalamus (21) and GH3 cells (44) have shown that a power factor of 3 is most appropriate to describe T current activation. However, in most other studies (29, 51, 77, 81, 110), including a follow-up study in thalamic neurons performed under slightly different experimental conditions than the original (51, 52), a value of 2 provided a better fit to the data.

The reverse activation process—deactivation—is relatively fast and becomes more rapid with hyperpolarization. The time constant of this process is on the order of 2–12 ms (50–52, 84). Deactivation can become physiologically significant following brief depolarizations that activate I_T. Upon repolarization, the T channels remain open for a finite time governed by τ_m. The driving force at deactivation potentials (mainly –60 mV and below) is large so that significant Ca^{2+} entry can occur until the channels are completely deactivated. Thus I_T may serve to promote Ca^{2+} influx during the repolarization phase of action potentials (71, 104).

Inactivation

Inactivation is one of the main features that distinguishes I_T from the various components of HVA. Inactivation of Ca^{2+} currents are normally complete with voltage-clamp commands that are subthreshold for HVA activation. Three properties related to inactivation have significant functional impact on neurons containing I_T: time-dependent inactivation, steady-state inactivation, and recovery from inactivation. Membrane depolarizations into the activation range evoke a current that is slowly inactivating at threshold (time constant, τ_h, around 50–100 ms) (Table 1). Currents activated by stronger depolarizations decay more rapidly, with τ_h approaching values of 10–20 ms. This feature promotes the self-termination of the LTS (see below). In most cells inactivation can be described by a single, exponential decay process that is highly voltage dependent. By contrast, neurons from the thalamic reticular nucleus exhibit a T current whose inactivation is nearly voltage independent (52), with values between 80 and 100 ms across a wide voltage range. Similarly, cells from the lateral habenula are characterized by a slowly inactivating I_T, but in this case the decay is biexponential, with a fast voltage-dependent phase and a slow voltage-independent phase (50).

Steady-state inactivation approximates the availability of T channels as a function of resting membrane potential. Experimentally, it is determined by

using long voltage-clamp conditioning pulses that approach steady state, followed by test pulses of fixed amplitude. There is considerably more cell-type heterogeneity of the inactivation process compared with the activation functions described above. Half-inactivation values vary between −50 and −100 mV, although several types of cells have $V_{1/2}$ values near −80 mV (Table 1). The slope of steady-state inactivation is also quite variable, ranging from a low of 3.7 in dorsal horn neurons (49) to a high of 8.2 in cerebellar Purkinje cells (84). Thus weak hyperpolarizations to −60 mV can remove inactivation of a large fraction of I_T in cholinergic forebrain neurons, for example (2), while having little effect on hippocampal interneurons (35) or Purkinje cells (84). Thus the differences in I_T among neurons result in very different operational ranges of membrane potential in which burst firing can be generated. T currents in thalamic neurons have been carefully examined in a number of studies (21, 24, 43, 52, 96). These results indicate that with physiological levels of $[Ca^{2+}]_o$ T channels begin to become available around resting potential and more negative (−60 to −65 mV), reaching maximal levels around −100 mV.

The process of removal of inactivation is highly voltage dependent in almost all cell types (13, 16, 21, 43, 52, 58, 98, 110, but see 44). In some cases, the recovery process has been described as biphasic, with a slow phase up to several seconds in duration (21, 43, 44, 98). The rate of recovery, or deinactivation, determines the absolute and relative refractory periods for LTS generation. Some cell types exhibit very slow recovery processes, with time constants over 1 s (13, 98), whereas others are characterized by very rapid recovery, on the order of 90 ms (35). Deinactivation is expected to have a strong influence on whether a cell is capable of I_T-dependent rhythmic oscillatory behavior (see below).

Permeation

Under normal conditions, I_T channels are selectively permeable to Ca^{2+} and other divalent ions, including Ba^{2+} and Sr^{2+}. Peak current amplitude is a saturable function of $[Ca^{2+}]$. Concentration-response curves can be fitted by a single-site model with an apparent K_d of 3.3–10 mM (9, 13, 44, 98). Whole-cell voltage-clamp recordings demonstrate that, in general, Ba^{2+} permeates about the same (29, 59, 84), or not quite as well, as Ca^{2+} (9, 13, 43, 52, 76, 80, 87, 108), whereas Sr^{2+} current amplitudes are comparable to those obtained with Ba^{2+} (29, 110) or slightly larger (98). One exception to this rule is in thalamic reticular neurons, where macroscopic I_T amplitude is increased by about 50% when extracellular Ca^{2+} (3 mM) is replaced by Ba^{2+} (52). Whether this reflects differences in the permeation of single I_T channels or alteration in gating properties will require single-channel studies or nonstationary fluctuation analysis (see below).

Single-Channel Studies

T current channels have a very low conductance (5–9 pS) compared with HVA channels (14, 33, 63). In most studies, isotonic $BaCl_2$ was used as the charge carrier to maximize the conductance. Reported values of single-channel conductance include 8 pS in rat sensory neurons (79); 7.2 pS (60 mM Ba^{2+}) in mouse sensory neurons (63); 8 pS in rat retinal ganglion cells (59); 8 pS in rat and guinea pig hippocampal neurons (80); 9 pS (20 mM Ba^{2+}) in rat CA1 pyramidal cells (68); 8 pS (95 $BaCl_2$) in guinea pig hippocampal CA1, CA3, and dentate gyrus neurons (31); 5.2 pS, with a subconductance state of 3.6 pS (50 mM Ca^{2+}) in rat and chick dorsal root ganglion neurons (14); 7 pS in rat motoneurons (105); 9 pS in cerebellar Purkinje cells (8); and 8 pS in guinea pig basal forebrain neurons (39). I_T channels in sensory neurons are approximately equally permeable to Ca^{2+}, Ba^{2+}, and Sr^{2+} (14) or slightly less for Sr^{2+} compared with Ba^{2+} (63). Single-channel conductance was dependent on $[Ca^{2+}]_o$, with a value of K_d around 10 mM and a maximum permeability of 5.7 pS (14). At physiological $[Ca^{2+}]_o$ near 2 mM, the expected conductance would be about 1 pS, yielding single-channel currents on the order of 0.1 pA at –40 mV. Estimates of single-channel current amplitudes (0.13–0.15 pA) from nonstationary fluctuation analysis in thalamic relay neurons (23) and cranial sensory neurons (9) are consistent with this value. Interestingly, when $[Ca^{2+}]_o$ is reduced to less than 100 μM (67), I_T channels become permeable to monovalent cations including Na^+ and Li^+. Single-channel conductance is approximately two to four times larger (12–20 pS) under these conditions (14, 80).

Single-channel gating has been characterized in rat (14) and mouse (63) sensory neurons and in transformed 3T3 fibroblasts (16), but little information is available concerning gating of these channels in central neurons. In preliminary studies it appears that some features of I_T gating are common in a number of cell types. In each case, the channels tend to open in bursts with several intraburst closures before final inactivation (8, 14, 16, 63, 68, 80). The open time distributions of I_T channels are exponentially distributed with mean open times on the order of 1–2 ms (16, 33, 39, 63). In sensory neurons, the distribution of first latencies peaks significantly earlier than the macroscopic current (14). The time course of macroscopic activation and inactivation could be reproduced by evaluating the convolution integral of first latency distribution with the burst open probability. From these results it was concluded that activation and inactivation are only weakly coupled. A kinetic model was developed with two open, two closed, and one inactivated state that assumed to be absorbing (1). The open states were based on the two conductance states of the channel. At least two closed states were required based on the biexponential distribution of closed times and the first opening latency distribution,

which was consistent with multiple closed states. Similar results were obtained in 3T3 cells (16). Macroscopic currents could be described by convolving first opening latencies with burst duration. A cyclical Markov model with two closed, one open, and two inactivated states was developed in which inactivation was not voltage dependent. The only transitions that required voltage dependence were between the two closed states, and one of the steps between the inactivated states and the closed state. This model provided a good fit to macroscopic currents in 3T3 cells, but was inadequate to describe I_T in neuronal cells, even with modified rate constants. What is clear from these studies is that, in spite of relatively brief openings, slow inactivation of macroscopic I_T can be explained by delayed opening and multiple reopenings of I_T channels.

PHARMACOLOGY

Both up- and down-modulation of I_T has been demonstrated with a variety of neurotransmitters and peptides. Furthermore, T current is susceptible to blockade by organic and inorganic antagonists, many of which have some selectivity for I_T over other Ca^{2+} currents. However, in general there are not highly specific antagonists or toxins for T current, and thus there are few pharmacological tools available to demonstrate a functional role for I_T in neuronal behaviors. There is general agreement that specific toxins such as ω-conotoxin GVIA and agatoxin IIIa have no effect on T currents (e.g. 2, 27, 28, 32, 52).

Antagonists

Divalent and trivalent cations, including La^{3+}, Ni^{2+}, Cd^{2+}, and Zn^{2+}, are effective blockers of I_T (e.g. 58, 74, 77). Further evidence for heterogeneity of I_T channels among various neuronal types is provided by different potency series. For example, in rat frontal cortical neurons, the potency series was $La^{3+}>Cd^{2+}>Zn^{2+}>Ni^{2+}$ (109), whereas in rat amygdaloid neurons it was $La^{3+}>Ni^{2+}>Zn^{2+}=Cd^{2+}$ (57). A selective block of I_T was observed with low doses (<100 μM) of Ni^{2+} in rat sensory neurons (32), whereas 20–50 μM Cd^{2+} strongly depressed HVA Ca^{2+} currents with little effect on I_T. In general, this selectivity has not been observed in central neurons (Table 2). The concentration of Ni^{2+}, which blocks 50% of the current (EC_{50}), varies between 30 and 780 μM; the corresponding value for Cd^{2+} ranges from 15 to 650 μM. Therefore, a voltage-clamp analysis of Ca^{2+} current antagonism (obtained under similar ionic conditions) should be performed before a low concentration of Cd^{2+} or Ni^{2+} can be used as a probe for HVA or I_T function in a cellular response.

Dihydropyridines and related compounds can also block I_T. Nicardipine and flunarizine are especially potent in this regard with EC_{50}s of 1–3 μM in

Table 2 Blockade of T current by Cd^{2+} and Ni^{2+}

Cell type	Charge carrier	Ni^{2+}	Cd^{2+}	Reference
Rat hippocampal L-M	2 Ca	400	260	(35)
Rat Purkinje	10 Ca	110	70	(58)
Rat Purkinje	5 Ba	52		(84)
Rat amygdala	10 Ca	30	650	(57)
Rat frontal cortex pyramids	10 Ca	260	15	(109)
Rat CA1 pyramids	10 Ca	230	80	(97)
Rat dorsal horn	5 Ca	230	240	(49)
Neuroblastoma	50 Ba	47	160	(77)
GH3	10 Ca	777	188	(44)

Charge carrier concentrations are in mM. Values for Ni^{2+} and Cd^{2+} are EC_{50} in μM.

hippocampal CA1 neurons (97), cerebellar Purkinje cells (58), amygdaloid neurons (57), and in mouse sensory neurons (85). Other organic Ca^{2+} channel antagonists, including D-600 and diltiazem, block I_T at 100-fold higher concentrations (57, 58). An experimental diphenylmethylpiperazine derivative, U-92032, has recently been shown to be a more potent blocker of I_T than flunarizine and is ineffective in reducing HVA in a neuronal cell line (54).

Succinimides and related compounds include a class of antiepileptic drugs that are specifically effective in the treatment of absence-type epilepsy (19). Ethosuximide, or 2-ethyl-2-methylsuccinimide, effectively controls absence seizures when blood levels are between 200 and 700 μM. In this same concentration range, ethosuximide reduces I_T in thalamic relay (19, 20, 53) and reticular (53) neurons, without having any effect on activation or inactivation kinetics. At these concentrations, ethosuximide has no effect on HVA (19, 20) or on other voltage-dependent conductances (53). Two related compounds, methyl-phenylsuccinimide and dimethadione (active metabolites of anti-absences drug methsuximide and tridione), also reduce I_T in thalamic neurons (19, 22), but these drugs are not as selective as ethosuximide in that they also reduce HVA current. Furthermore, the unsubstituted succinimide ring compound is not active in either I_T current blockade or absence seizure reduction. The mechanism of block by methylphenylsuccinimide, as tested by nonstationary fluctuation analysis methods, was a reduction in the number of channels without a change in single-channel conductance (23), which suggests that succinimides block I_T channels without affecting their gating or permeation. Taken together, these results indicate that T current blockade in thalamic neurons is a likely mechanism for the antiepileptic action of this class of drugs. Consistent with this theory is the finding that in an animal model of absence

epilepsy the amplitude of I_T in thalamic reticular neurons is increased compared with that in nonepileptic controls (103). Additionally, an unrelated antiabsence compound, valproic acid, has also been shown to exert weak antagonistic effects on I_T (61).

Amiloride is a relatively specific blocker of I_T in neuroblastoma cells (101), with an EC_{50} of ~50 μM. In central neurons, however, the effects are highly variable. For example, in hippocampal CA1 cells, 300 μM amiloride reduces I_T by ~40% but also significantly reduces some components of HVA (99). In other studies of hippocampal cells, the EC_{50}s were ~250–500 μM (60, 102). By contrast, in amphibian spinal (40) and basal forebrain (2) neurons, the EC_{50} was ~100 μM, whereas in rat spinal motoneurons, 1 mM amiloride produced only 27% block (104). Octanol has been reported to be a specific antagonist of I_T (92). In cultured rat sensory neurons, 1 μM 1-octanol strongly inhibits I_T without affecting HVA (90). However, in hippocampal neurons, 300 μM octanol reduced all components of Ca^{2+} current (99), and in GH3 cells, the EC_{50} for I_T reduction was ~250 μM (44). Volatile anesthetics (45, 100) and neuroleptics (81) have all been shown to reduce the amplitude of I_T in various preparations.

Modulators

A prominent and common difference between I_T and HVA Ca^{2+} currents is metabolic stability. In contrast to HVA currents, I_T is stable during whole-cell dialysis (6, 13, 21, 29, 32, 35, 77, 82), persists with intracellular F^- (13, 35, 44, 98) or Ca^{2+} (13, 52) perfusion, without intracellular ATP or GTP (29), and in cell-free patches (14, 63). Given the relatively stable metabolic state of I_T channels, this may explain why there are fewer reports of I_T modulation than for HVA currents.

Examples of modulatory actions include cholinergic and serotonergic increases, as well as baclofen-dependent blockade, of I_T in hippocampal interneurons (35). Muscarine and carbachol, but not the β-adrenergic agonist isoproterenol, increase channel open probability in cell-attached patch recordings of hippocampal CA3 neurons (30). Substance P enhances I_T in dorsal horn neurons (86). Dopamine and norepinephrine slightly decrease I_T in chick sensory and sympathetic neurons (70). Angiotensin II causes a small (20%) depression of I_T in a neuronal cell line through a G protein-dependent process (10, 11). An activator of protein kinase C (1-oleoyl-2-acetyl-*sn*-glycerol, OAG) reduces both I_T and HVA currents in GH3 cells, with half-maximal effects near 25 μM (69). In sensory neurons, I_T is selectively downregulated by another protein kinase C activator, phorbol 12-myristate-13-acetate (88), but only at temperatures of 29°C and higher, whereas I_T and the inactivating components of HVA are both reduced by opiates acting at the μ receptor (89). The general

rule in each of these cases of T current modulation is a reduction in peak current with little effect on kinetics. One possible explanation for this result is that modulation alters the number of available channels but does not affect their time- and voltage-dependent gating.

LOCALIZATION

The specific location of I_T channels within the somadendritic membrane has significant influence on neuronal function. As far as LTS generation in thalamic relay neurons is concerned, it is clear that I_T channels are present in the somatic membrane at high density because large T currents are recorded in acutely isolated relay cells that have had most of their dendritic tree truncated (21, 43, 96). By contrast, thalamic reticular cells are capable of generating robust LTSs in vitro (53) and in vivo (75), yet only a relatively small conductance is observed in isolated and truncated neurons (52). This is consistent with a putative concentration of I_T channels in dendrites of thalamic reticular cells (75, 91). Dendritic localization in hippocampal CA1 cells has recently been directly demonstrated by dendrite-attached recordings up to 300 μm from the soma (68). Furthermore, a calcium-imaging study demonstrated that spike trains produced a Ni^{2+}-sensitive increase in $[Ca^{2+}]_i$ that was more pronounced in dendritic than somatic regions, which indicates that I_T channels may be somewhat restricted to dendritic membranes (17). Recordings of Ca^{2+} current from intact hippocampal CA1 neurons in slices demonstrated a transient Ca^{2+} current that resembles I_T, but the voltage-dependence of steady-state inactivation was very hyperpolarized with a $V_{1/2}$ value around −106 mV (60). This was interpreted as being the result of dendritic I_T channels that could not be adequately voltage clamped from a somatic site. In support of this idea was the finding that the amplitude of I_T became progressively smaller with cuts that removed increasing amounts of the apical dendritic tree. Intradendritic recording of rat cerebellar Purkinje cells in culture reveal a low-threshold, inactivating Ca^{2+} current present at moderate densities (7).

FUNCTION

Besides promoting Ca^{2+}-dependent burst firing, several additional functional roles for I_T have been proposed. These include intrinsic neuronal oscillations, promotion of Ca^{2+} entry, boosting of synaptic signals, and lowering threshold for high-threshold spike generation. By contrast, one role for T channels that appears unlikely is Ca^{2+} entry at synaptic terminals leading to synaptic release. A voltage-clamp study of excitatory synaptic connections in cultured thalamic neurons demonstrated that Cd^{2+}-dependent block of excitatory synapses was correlated with the level of HVA current blockade (83). For example, 10 μM

Cd^{2+} reduced HVA and evoked synaptic currents by greater than 60%, but only reduced I_T by 20%. Furthermore, 50 μM Cd^{2+} completely blocked synaptic transmission and HVA currents while leaving more than 50% of I_T unblocked. It appears that I_T channels cannot by themselves support excitatory neurotransmission, at least in thalamic cells.

Perhaps the most obvious functional role of T channels is to promote LTS generation, which can lead to burst firing in several cell types that include thalamic reticular (75) and relay cells (25, 64), inferior olive cells (65), hippocampal interneurons (35), lateral habenular neurons (107), a subpopulation of pontine reticular formation cells (37), and neocortical neurons (36). Within the neocortex, T channels seem to be found mainly in pyramidal neurons but not in interneurons (38, 42).

Several biophysical features of T current kinetics promote regenerative LTSs. Activation of I_T begins approximately at rest, around –65 mV and more positive, so that brief hyperpolarizing sojourns can result in return of the membrane potential to the activation range. The relatively hyperpolarized activation region for this current means that when I_T is deinactivated, the threshold for regenerative responses becomes much closer to the resting potential (~ –60 mV), compared with the normal threshold for Na^+-spike generation (~ –45 mV). Another feature is the voltage-dependent activation rate (Table 1) that contributes to robust regenerative responses in a manner similar to, but slower than, that which occurs with fast Na^+ spikes. When the threshold for LTS generation is crossed, the activation rate is slow but becomes progressively faster, leading to more and more depolarization (21).

Inactivation in general, and specifically a voltage-dependent inactivation rate, leads to a LTS that is self limiting in time (21). During the LTS, the rate of macroscopic inactivation becomes progressively faster, largely as a result of shortening of the time to first opening. Thus a separate repolarization mechanism may not be necessary for the LTS. This explains why LTS duration is not affected by Ba^{2+} substitution for Ca^{2+} (55). An exception occurs in thalamic reticular neurons (52), where the rate of inactivation is relatively slow and not very dependent on voltage. Along with dendritic localization of I_T, this may be one factor that promotes relatively long duration bursts in nRt cells (75, 91).

The steady-state inactivation function will determine the necessary hyperpolarization for repriming or deinactivation of sufficient I_T channels to lead to subsequent activation of an LTS. Given the variability in the position and steepness of this function among different cell types (Table 1), it appears that some neurons are poised to fire LTSs with minimal provocation, whereas others require substantial hyperpolarization. Interestingly, thalamic neurons have a large reserve of T channels, more than would be necessary to produce a full-fledged LTS. Specific blockade of approximately 40% of T channels by

succinimides does not reduce the size or duration of Ca^{2+}-dependent bursts in thalamic neurons, even though the probability of obtaining a LTS from a given stimulus is reduced (53).

One other feature of inactivation pertinent to burst generation is recovery from inactivation or deinactivation. This process describes the voltage- and time-dependence of the repriming process. Corrected for temperature, the time constant governing this process in somatosensory thalamic relay cells would be on the order of 60–80 ms at approximately –100 mV (21). This time is much shorter than the duration of inhibitory synaptic potentials mediated by $GABA_B$ receptors in thalamic neurons (200–300 ms), thus ensuring that synaptic inhibitory responses are effective in producing rebound LTSs (53).

As a secondary consequence of burst generation, the presence of significant I_T can promote intrinsic single-cell oscillatory activity (4, 5, 41, 107). The 15–25 mV depolarization and relatively long duration (20–150 ms) of the LTS can lead to activation or inactivation of other voltage- or Ca^{2+}-dependent conductances that can interact with I_T to produce repetitive bursts. For example, the depolarization associated with an LTS in thalamic relay cells can deactivate a hyperpolarization-activated inward current (I_H) that normally contributes to resting conductance (72, 73, 93). Following the LTS, the membrane hyperpolarizes because of the deactivated I_H, and this leads to deinactivation of I_T, followed by reactivation of I_H so that the cycle repeats (72). Similarly, LTS generation in thalamic reticular cells leads to Ca^{2+} entry, a Ca^{2+}-dependent burst after hyperpolarization (4, 5) that deinactivates I_T, and a Ca^{2+}-activated nonspecific cation conductance (5), which can return the membrane potential to the activation threshold for LTS generation and continue the cycle. Relatively slow inactivation of I_T in thalamic reticular and lateral habenular cells should lead to long duration LTSs, which would be especially powerful in promoting these types of secondary conductance changes and oscillatory behaviors (41, 50).

Another putative function for I_T in central neurons is boosting of synaptic potentials. As mentioned above, T channels have been shown by several methods to exist in the dendrites of hippocampal CA1 neurons. Therefore, these channels are present at the major site of synaptic input. Dendrite-attached patch recordings have been used to demonstrate that the depolarization associated with a dendritic synaptic input is sufficient to activate I_T channels (68). This would lead to an increase in the local depolarizing potential and potentially insure the active propagation of the synaptic potential to the soma. A similar boosting role has been proposed for I_T in neocortical neurons (95).

Significant Ca^{2+} entry may be promoted by the presence of I_T channels in neuronal membranes, which would lead to Ca^{2+}-dependent secondary responses. Voltage-clamped spike waveforms have been used to assess the contribution of various Ca^{2+} channels to total Ca^{2+} entry during action poten-

tials in sensory neurons (71). Selective blockade by Cd^{2+} or amiloride was used to demonstrate that entry through I_T channels is relatively independent of the duration of the spike. This is largely a result of the slow deactivation kinetics of I_T, which leads to a large fraction of Ca^{2+} entry occurring during the repolarizing phase of the action potential. A depolarizing after-potential (DAP), which follows single Na^+ spikes in dentate gyrus (111) and neocortical neurons (62), is thought to result from I_T in these neurons, based on its sensitivity to holding potential and Ni^{2+} and Co^{2+}. Interestingly, it has been postulated that Ca^{2+} entry resulting from the DAP is responsible for long-term potentiation (LTP) in kitten neocortical neurons (62) because manipulations that block the DAP, such as alteration of the membrane potential (either hyperpolarization or depolarization) or addition of Ni^{2+}, also block the induction of LTP. Finally, in amphibian spinal neurons in culture, I_T appears to promote spontaneous fluctuations in intracellular Ca^{2+}, possibly by lowering the threshold for spontaneous high-threshold spikes (40). Concentrations of amiloride and Ni^{2+}, which selectively block I_T in these neurons, reduce the number of cells with spontaneous Ca^{2+} fluctuations by about one third.

CONCLUSIONS

T currents in central neurons are heterogeneous among different neuronal types, with different antagonist profiles, voltage-dependent kinetics, and modulation. A common feature of T current is that if present in neuronal membranes at sufficient density, robust rebound burst firing is insured. The localization of I_T channels in dendrites will likely boost input or lead to burst generation during synaptic input (68, 91).

Important future directions in T channel research include identification of the molecular structure, including subunit composition (15, 106), and identification and development of specific pharmacological blockers or toxins. Furthermore, because neuronal T channel densities are upregulated by acute injury (18), investigation of regulatory mechanisms that control expression and trafficking of the channel protein is warranted.

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