CHARACTERISTICS OF LATE Na⁺ CURRENT IN ADULT RAT SMALL SENSORY NEURONS

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Abstract—Na⁺ currents were recorded using patch-clamp techniques from small-diameter (<25 µm) dorsal root ganglion neurons, cultured from adult rats (>150 g). Late Na⁺ currents maintained throughout long-duration voltage-clamp steps (>200 ms) were of two types: a low-threshold, tetrodotoxin-sensitive (TTX-s) current that was largely blocked by 200 nM TTX, and a high-threshold, TTX-resistant (TTX-r) current. TTX-s late current was found in approximately 28% (10/36) of small-diameter neurons and was recorded only in neurons exhibiting TTX-s transient current. TTX-s transient current activation/inactivation gating overlap existed over a narrow potential range, centered between −30 and −40 mV, whereas late current occurred over a wider range. The kinetics associated with de-inactivation of TTX-s late current were slow (> approximately 37 ms at −50 mV), strongly suggesting that different subpopulations of TTX-s channel generate transient and late current. High-threshold TTX-r late current was only present in neurons generating TTX-r transient current. TTX-r late current operated over the same potential range as that for TTX-r transient current activation/inactivation gating overlap, and activation/inactivation gating overlap could be measured even after 1.5-s-duration pre-pulses. We suggest that TTX-s late sodium current results from channel openings different from those generating transient current. As in large-diameter sensory neurons, TTX-s channels generating late openings may play a key role in controlling membrane excitability. In contrast, a single population of high-threshold TTX-r channels may account for both transient and late TTX-r currents. © 2003 IBRO. Published by Elsevier Science Ltd. All rights reserved.

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Small-diameter (<25 µm) dorsal root ganglion (DRG) neurons generate heterogeneous Na⁺ currents (e.g. Elliott and Elliott, 1993; Rush et al., 1998; Cummins et al., 1999; reviewed by Baker and Wood, 2001). These currents can be pharmacologically discriminated by their sensitivity to tetrodotoxin (TTX), a marine toxin that blocks subtypes of Na⁺ channel over the single-nanomolar concentration range. Currents with distinctive electrophysiological properties have been defined as either TTX-sensitive (TTX-s) or TTX-resistant (TTX-r), and are differentially expressed in small and large neurons (e.g. Kostyuk et al., 1981; Roy and Narahashi, 1992; Caffery et al., 1992). High-threshold, TTX-r currents are preferentially expressed in small neurons, supporting the smallest-diameter fibers (Harper and Lawson, 1985; Villiere and McLachlan, 1996), many of which are involved in nociception. Small-diameter neurons also generate TTX-s Na⁺ currents either alone or in combination with TTX-r currents (e.g. Rush et al., 1998). High-threshold TTX-r Na⁺ current is generated by Na₈.₁₈ (sensory neuron specific sodium channel (SNS)) and is absent in neurons cultured from null-mutant mice (Akopian et al., 1999). A low-threshold, TTX-r current, attributed to Na₈.₁₉ (novel sodium channel α-subunit, Na₈, Dib-Haj et al., 1998; Cummins et al., 1999; Sleeper et al., 2000), has been described in small DRG neurons cultured from Na₈.₁₈ null-mutant and wild type mice, and also in rat. The current exhibits remarkably slow kinetics, and gives rise to large persistent currents over the most negative portion of its activation range. The Na₈.₁₉ current is reported to disappear rapidly in vitro, through loss of tropic factor support (Sleeper et al., 2000; Cummins et al., 2000).

We have previously described a TTX-s, low-threshold, late Na⁺ current in rat large DRG neurons (Baker and Bostock 1997, 1998). Over the most negative portion of its potential range of activation, inactivation is minimal, giving rise to persistent current. Because the current exhibits fast activation, and is regenerative and partially activated at the resting potential, it was expected to contribute to the control of peripheral nerve excitability (Baker and Bostock, 1997). Experiments involving selective block of the late current with local anesthetics (Baker, 2000a) have supported this hypothesis. TTX-s late current plays a role in generating pathological activity in the peripheral nervous system by driving the membrane potential oscillations that give rise to spontaneous activity in demyelinated axons (Baker and Bostock, 1992; Kapoor et al., 1997; Baker, 2000b). It is also likely that late Na⁺ channels contribute to the steady-state TTX-s Na⁺ conductance in normal optic nerve axons (Stys et al., 1993), and permit resting Na⁺ fluxes across nerve membrane.

Although the presence and importance of TTX-s low-
threshold, late Na\(^+\) current in neurons with myelinated axons is now established, the nature of late current in small DRG neurons has been less certain: recordings of very slowly and partially inactivating TTX-s currents in small DRG neurons have been reported briefly (Elliott and Elliott, 1993). Given the present incomplete understanding of C-fiber function, the possibility arises that late currents may play a role in pain states. The aims of the present study were first, to determine whether small DRG neurons generate late Na\(^+\) current, and secondly, to compare the TTX-s and TTX-r component of late Na\(^+\) current (reported in abstract form by Kiernan et al., 2001).

**Experimental procedures**

**Cell culture**

Primary cultures of neurons were prepared from the lumbar DRGs of male Wistar rats (150–350 g) using a technique previously described (Baker and Bostock, 1997) and in accordance with the UK Animals (Scientific Procedures) Act 1986 and associated guidelines. The number of animals used was kept to a minimum and suffering was minimized by removing tissue under terminal anaesthesia. Dissociated neurons were plated on coverslips coated with poly-L-lysine (Sigma, Poole, UK) in the culture wells of 12-well plates (Falcon, Becton Dickson and Co., NJ, USA). Neurons were maintained in a 37 °C incubator with a 5% CO\(_2\) atmosphere with a 95% O\(_2\) balance. Cultures were maintained in 12-well plates (Falcon, Becton Dickson and Co., NJ, USA). Neurons were blocked by either external Cd\(^{2+}\) (10), tetraethylammonium (TEA) Cl (10), KCl (5), CdCl\(_2\) (0.1); in abstract form by Kiernan et al., 2001).

**Electrophysiology**

Coverslips with adherent neurons were transferred to a 35-mm plastic Petri dish (which formed the recording chamber) and mounted on the stage of an inverted microscope. Experiments were carried out on neurons 10–25 mm in apparent diameter, measured using a scale within the microscope eyepiece. The recording solutions used were designed to eliminate all ionic currents apart from Na\(^+\) currents, using solutions similar to those described previously (Baker and Bostock, 1997). For whole-cell voltage clamp, the normal solutions contained the following (in mM): extracellular, NaCl (135.6), Na-HEPES (4.54), HEPES (5.46), CaCl\(_2\) (1.1), MgCl\(_2\) (1.2), 4-aminopyridine (4-AP) (5), CsCl (10), tetraethylammonium (TEA) CI (10), KCI (5), CdCl\(_2\) (0.1); intracellular, CsF (143), (Na) EGTA (3), Na-HEPES (6.04), HEPES (3.96), CaCl\(_2\) (1.21), MgCl\(_2\) (1.21). In some experiments internal CsF was replaced by CaCl\(_2\). High-threshold Ca\(^{2+}\) currents are blocked by either external Cd\(^{2+}\), or internal F\(^-\) (e.g., Kostyuk et al., 1981; Fox et al., 1987), and both these ions were present in order to eliminate the contribution of Ca\(^{2+}\) currents to the whole-cell current–membrane potential relation. In some whole-cell experiments external Na\(^+\) was lowered (to 31.5 mM Na\(^+\) with equimolar replacement by tetraethylammonium (TMA) ions) or to 43.3 mM Na\(^+\) (Fig. 2, Fig. 4A) with equimolar replacement by TEA ions in order to reduce the transient current amplitude and magnitude of the voltage errors attributable to series resistance. 4-AP base was neutralized using HCl, and the final pH of the solutions was 7.2–7.3. Superfusion of solutions was driven by gravity and all experiments were carried out at room temperature (20–22 °C). TTX was obtained from Sigma (Poole, Dorset, UK).

Recordings were made with the use of an Axopatch 200 amplifier (Axon Instruments, CA, USA). All electrodes were made from thin-wall glass (GC150TF-15, Harvard, Pangbourne, UK), coated with Sylgard (Dow Corning), and fire polished. The effect of the gluconate–Cl junction potential at the electrode tip was eliminated by applying a −10-mV offset to the holding potential (Baker and Bostock, 1997). The whole-cell capacity current transient generated on an imposed step in potential was routinely cancelled using the simple resistance-capacitance (RC) circuit within the amplifier. In whole-cell recordings, estimates of series resistance (R\(_s\)) and membrane capacity (C\(_m\)) were read from the front panel potentiometers for each cell. The mean R\(_s\) value at the start of whole-cell recording sessions was 2.17±0.13 M\(\Omega\) (mean±S.E.M., n=36). Feedback series-resistance compensation was always used, and was set to ≥60%. Control of command pulse protocols and data collection was carried out by a 486 personal computer running pClamp version 6 (Axon Instruments).

**Voltage-clamp protocols**

Whole-cell late currents were recorded using voltage-clamp steps from a negative pre-pulse potential (−100 mV) to a range of more positive membrane potentials in 10-mV increments. Cells were held at the pre-pulse potential between depolarizing increments. Families of membrane currents were elicited by long-duration clamp steps (i.e. 200 ms to 1 s). Whole-cell leakage currents were usually removed by subtracting appropriately scaled currents evoked by reversed polarity clamp steps, recorded over a range of negative potentials. Alternatively, a p/n pulse protocol was employed in pClamp6, with n=5, giving on-line leak subtraction. During stable experiments it was possible to record sufficient data to subsequently compute ‘difference currents’ from families of currents recorded before and after the superfusion of low Na\(^+\) or TTX. The steady-state inactivation curve for the TTX-r late current was obtained using a 500-ms pre-pulse to a range of potentials and then stepping the membrane potential to +5 mV (h protocol). Evoked currents were usually measured as the mean current over 10 ms at the end of a voltage-clamp test step, or as a peak current value. Pooled data are reported as mean±S.E.M. Voltage-clamp protocol repeat frequencies did not exceed 1 Hz.

**Data analysis**

Conductance-voltage (G–E\(_m\)) relationships were calculated from peak current values, according to the equation:

\[
G = \frac{I}{(E - E_r)}
\]

where I is the peak current at potential E\(_m\), and E\(_r\) is the reversal potential extrapolated from the linear portion of the I–E relationship.

Comparison of current amplitudes before and after the superfusion of TTX or following Na\(^+\) replacement was performed using a one-tailed, paired t-test, statistical significance being attributed where \(P<0.05\).

**Results**

In approximately 28% of neurons (10/36), the current–membrane potential (I–E\(_m\)) relation measured at the end of 200-ms-duration clamp steps exhibited a low-threshold late component, peaking close to −40 mV. In some of these neurons, a high-threshold component was also present, that peaked close to −10 mV. Where the low-threshold component was either absent or negligible, the I–E\(_m\) relationship was dominated by the high-threshold late component. TTX-s late current was only observed in neurons also generating TTX-s transient current, and TTX-r late current was found only in conjunction with TTX-r transient current.

**Low-threshold late current**

The low-threshold, late current operated at potentials more negative than transient Na\(^+\) current in the same neuron. Fig. 1A shows membrane currents evoked by
clamp steps from \(-100\) mV to a range of potentials between \(-80\) and \(-30\) mV. The low-threshold, late current began to activate at around \(-65\) mV and gave rise to a peak inward current around \(-40\) mV (Fig. 1B). The current activated within 10 ms, even when close to threshold. Both the transient and late current were blocked reversibly by the superfusion of 200 nM TTX (Fig. 1C). The effect of TTX on the steady-state \(I-E_m\) relation for neurons dominated by the low-threshold, late current was clearly similar to that described previously for large DRG neurons (Baker and Bostock, 1997), and is shown in Fig. 1D. The superfusion of 200 nM TTX did not always completely abolish the region of negative slope conductance. This suggests either that 200 nM TTX was just insufficient to fully block the late Na\(^+\) current or the remaining current may reflect residual TTX-resistant Na\(^+\) current. However, at \(-50\) mV, late-current amplitudes before and after exposure to TTX were significantly different (\(P=0.008;\) one-tailed, paired \(t\)-test, \(n=6\)).

In previous studies on large DRG neurons, it was not possible to adequately control the TTX-s transient current because of their large size (up to several tens of nanoamperes with a quasi-physiological Na\(^+\) gradient, Baker and Bostock, 1997, 1998). However, recording transient current from small neurons was less problematic (Fig. 2). The currents analyzed corresponded with the kinetically fast currents described by Caffrey et al. (1992) and those recorded in type A neurons by Rush et al. (1998). Low-threshold, late current was also present in these neurons, and the small contribution it made to the peak current–membrane potential relation was at least partially eliminated by baselining the currents at a latency of 50 ms. Activation/inactivation gating (\(mh\) overlap for the transient current) is shown in Fig. 2B and C, where peak current amplitude measurements have been converted to conductance values to generate the activation curve (equation 1). Deriving the \(h_m\) (current availability) curve unambiguously demonstrated that TTX-s transient currents exhibited substantial inactivation (greater than 50%) over the whole activation range, very similar to currents recorded at nodes of Ranvier (e.g. Neumcke and Stämpfli, 1982). Transient current can give rise to \(mh\) overlap only over a circumscribed potential range around \(-40\) and \(-30\) mV. In these experiments, the \(h_m\) curve was obtained using only 20-ms-duration pre-pulses, and longer pre-pulses would be expected to shift the \(h_m\) relation to the left, further reducing the membrane potential region of \(mh\) overlap (Roy and Narahashi, 1992; Ogata and Tatebayashi, 1993). TTX-s late current operated at potentials more negative than the
activation threshold for transient current, and at these potentials the late current was not noticeably subject to inactivation over 20 ms. These observations suggest that the late current was generated by a mechanism other than mh overlap. The inactivation time constants associated with transient Na\(^+\) currents in small DRG neurons are shown in Fig. 2D and are similar to values published previously (e.g. Kostyuk et al., 1981; Ogata and Tatebayashi, 1993).

In large neurons, the clear differences in inactivation kinetics between currents contributing to late Na\(^+\) currents and those generating transient current provided one strand of evidence indicating that transient and late current were generated by separate sub-populations of Na\(^+\) channel (Baker and Bostock, 1998). De-inactivation is a process clearly separable from the preceding inactivation of the much larger transient current, and the slow kinetics of late current de-inactivation, leading to an increase in steady-state Na\(^+\) current, provided strong evidence that steady-state Na\(^+\) currents were largely or wholly the result of late Na\(^+\) channel openings. Unitary current recordings revealed that the macroscopic de-inactivation time constants measured corresponded with different single-channel open-times (Baker and Bostock, 1998), none of which were appropriate for the channels underlying the TTX-s transient current. Low-threshold, late current in small DRG neurons behaved in a similar manner. After the late current was partially inactivated by a clamp step to −40 mV, stepping to −50 mV caused not only rapid deactivation but also an increase in late-current amplitude, attributable to the removal of inactivation (Fig. 3). De-inactivation was difficult to perceive on stepping to potentials more negative than −50 mV. The de-inactivation of late current at −50 mV exhibited a time constant close to 37 ms, longer than that found for late Na\(^+\) current in large DRG neurons (Baker and Bostock, 1998). The time constant of de-inactivation was over six times the longest time constant of transient current inactivation, and de-inactivation of late current occurred at potentials at which the transient current was not activated.

Unitary current recordings

Recordings of unitary currents indicate that TTX-s Na\(^+\) channel gating is heterogeneous. Subjecting an outside-
out patch to repeated depolarizing clamp steps elicits openings that rapidly inactivate. However, in 3% of recordings made during a single recording session (three of 100 sequential traces), channel openings occurred at least 60 ms following the onset of the clamp step, and exhibited long open times (Fig. 4). (The latency of 60 ms was previously chosen as a latency at which any transient current would be expected to be minimal or non-existent; Baker and Bostock, 1997.) Similar activity occurred over the first 50 ms in seven traces. The estimated chord conductance for openings throughout 80-ms clamp steps, 13.0±0.5 pS, is similar to values found for late channels in large-diameter sensory neurones (Baker and Bostock, 1998), and is consistent with these openings being due to Na⁺ channels.

Subsequent exposure of the patch to micromolar TTX rapidly eliminated all channel activity. An obvious possibility was that channels giving rise to transient openings could occasionally generate late openings by undergoing a switch in gating-mode (i.e. the Na⁺ channels exhibit 'modal gating' e.g. Patlak and Ortiz, 1986; Zhou et al., 1991; Alzheimer et al., 1993). The late openings are likely to be the unitary current correlate of the macroscopic TTX-s late current in small neurones. The late openings appear to be compatible with an inactivation time constant of several tens of milliseconds, perhaps intermediate between late-1 and late-2 current in large neurones (Baker and Bostock, 1998). Expecting a negative shift in the activation voltage dependence of Na⁺ channels in patches relative to those in whole-cell recordings (approximately 20 mV in large neurones; Baker and Bostock, 1998), the de-inactivation data presented in Fig. 3 are consistent with the late-channel open times depicted in Fig. 4.

**High-threshold late current**

A TTX-r inward current exhibiting a voltage dependence and kinetics similar to that described previously (Fig. 5A, B; c.f. Kostyuk et al., 1981; Roy and Narahashi, 1992; Elliott and Elliott, 1993), and attributable to Na⁺,1.8 (SNS) (Akopian et al., 1999), was associated with a high-threshold late current. The high-threshold TTX-r late current was only present in neurons generating TTX-r transient current. On recording the high-threshold TTX-r current in response to incrementing clamp steps (Fig. 5A), the current evoked by the most negative potentials appeared practically non-inactivating, and must form a part of the late current. However, this non-inactivating component is evoked only 10 mV or so more negative than currents undergoing the typical slow inactivation, and therefore a wide mh overlap may be all that is necessary to explain the TTX-r late current.

When measured at the end of 200-ms-duration clamp steps, the high-threshold, late current had an apparent threshold close to −30 mV and exhibited a peak inward current around −10 mV (Fig. 5C, D). The current was unaffected by exposure to 200 mM TTX (n=12). Although all recordings were made in the presence of both intracellular F⁻ and external Cd²⁺ ions, we tested the possibility that this TTX-r current represented residual high voltage-activated Ca²⁺ current by observing the effects of extracellular Na⁺ replacement. Superfusion of a solution in which Na⁺ was equimolurly replaced with TMA⁺ ions reversibly suppressed both the transient Na⁺ current and the high-threshold, late current, removing the TTX-r component of the steady-state I–Eₘ relation. Similar results were obtained in five other neurons each exhibiting a conspicuous high-threshold, late current (P=0.019 at −10 mV; one-tailed, paired t-test; Fig. 5D).

The voltage dependence for inactivation of the high-threshold TTX-r current was explored using h₃ protocols (see methods). Typical TTX-r transient currents are shown for a single neuron evoked by clamp steps increasing up to +5 mV following 500-ms-duration pre-pulses to a range of
potentials (Fig. 6A). Mean current availability data from six neurons are shown in Fig. 6B. For the same neurons, activation curves were constructed by measuring peak currents evoked by clamp steps preceded by a prepulse to \(-100\) mV and subsequently converting them to conductances (equation 1). The TTX-r transient current exhibited a wide gating overlap between activation and steady-state inactivation extending over 40 mV. This overlap existed even when pre-pulses of 1.5-s duration were used.

Fig. 6. Characteristics of high-threshold, late Na\(^+\) current. (A) TTX-r transient currents, evoked by incrementing clamp steps from \(-90\) mV to \(+20\) mV, recorded in the continuous presence of 200 nM TTX. (B) Peak \(I-E_m\) relationship for the neuron in A. TTX-r transient current activates close to \(-30\) mV. (C) Comparison of typical \(I-E_m\) relations for neurons generating TTX-s late current (○) and TTX-r late current (●), measured at the end of 200-ms clamp steps. TTX-s late current activates and peaks at more negative potentials than TTX-r current. (D) \(I-E_m\) relationships for neurons in the continuous presence of TTX obtained with a bath solution containing 136 mM Na\(^+\) (○) and after equimolar replacement of Na\(^+\) with TMA\(^+\) (●), mean±S.E.M., \(n=6\).

DISCUSSION

Origin of TTX-s low-threshold, late current

We have demonstrated the presence of a TTX-s low-threshold, late current in a sub-population of small-diameter sensory neurons. As in large DRG neurons, the current operates over a wide potential range and is larger than would be expected were the current to be generated by \(m_h\) overlap of the transient current. Late current activates at
more negative potentials than transient current and may attain its maximal amplitude before transient current is activated. Furthermore, the inactivation kinetics that we associate with TTX-s late current are different from those of transient current and suggest non-homogeneous channel gating. Many TTX-s transient Na⁺ currents recorded in small neurons are likely to be attributable to Naᵥ1.7 (hNE-Na, Black et al., 1996; PN1, Toledo-Aral et al., 1997), although the presence of other mRNAs in small neurons suggests the involvement of other subtypes, including Naᵥ1.6. Neurons are therefore likely to generate composite TTX-s Na⁺ currents. However, the absence of selective blockers in peripheral axons and the closely similar biophysical properties of TTX-s Na⁺ channels mean that they cannot convincingly be discriminated, although recent studies using µ-conotoxin in cortical neurones would argue in favor of a molecular difference to underlie transient and late TTX-s current (Nielsen et al., 2002).

Naᵥ1.6 is likely to generate most Na⁺ current in larger peripheral axons at nodes of Ranvier (Caldwell et al., 2000), and has also been strongly implicated in producing late currents in cerebellar Purkinje neurones (Raman et al., 1997). Bostock and Rothwell (1997) provided strong, although indirect, evidence for a resting, regenerative inward current at human nodes of Ranvier in sensory nerves, similar to late Na⁺ current in large-diameter DRG neurons. One possibility is that Naᵥ1.6 can generate both transient current and low-threshold, late currents at nodes of Ranvier by exhibiting non-homogeneous gating behavior, described for other Na⁺ channel subtypes as resulting from gating-mode switches (e.g. Patlak and Ortiz, 1986; Moorman et al., 1990; Zhou et al., 1991; Alzheime et al., 1993). In small neurons, TTX-s late current was only observed together with TTX-s transient current, consistent with late current being generated by a channel subtype also involved in generating transient current. The late current in small DRG neurons may differ kinetically from that in large neurons and exhibits a more positive activation voltage dependence (with an activation threshold of −60 or 65 mV, rather than −70 or 75 mV). It is therefore possible that late currents in small and large neurons are generated by different Na⁺ channel subtypes.

**Origin of the TTX-r, high-threshold late current**

TTX-r late current appears to be mainly explicable as mh overlap for the high-threshold, TTX-r transient Na⁺ current. In some records, TTX-r late current can seem to disappear during long-duration clamp steps, but this is because of the progressive activation of residual outward rectification. High-threshold TTX-r current has previously been shown to exhibit substantial mh overlap (Ogata and Tatebayashi, 1993) when studied using relatively short voltage-clamp protocols. However, the large mh overlap dramatically shrinks when pre-pulses longer than 500 ms are used (up to 5 min), because of slow inactivation (Ogata and Tatebayashi, 1993), and we would therefore predict a loss of high-threshold TTX-r current over many minutes by the slow-inactivation process. While our observations are consistent with the late current being due to mh overlap, we cannot exclude the possibility that TTX-r Na⁺ channels exhibit heterogeneous gating.

We did not record the idiosyncratic, slowly activating and inactivating current attributed to Naᵥ1.9, that would have been expected to generate a major low-threshold late component (e.g. Cummins et al., 1999). Although the holding potential utilized in the present experiments may not have been optimal to remove inactivation from this current, it seems safe to conclude that this current does not operate in many normal adult rat small sensory neurones maintained for 1–3 days in vitro.

**Functional roles of different Na⁺ current subtypes**

There is evidence for both TTX-s and TTX-r Na⁺ currents in C-fibers (reviewed by Baker and Wood, 2001). TTX-s Na⁺ channels are necessary for transmission in many C-fibers and in Aδ-fibers (e.g. Quasthoff et al., 1995; Grosskreutz et al., 1996; Strassman and Raymond, 1999). TTX-r currents operate in mechanically sensitive nerve endings in the cornea and cerebral dura (Brock et al., 1998; Strassman and Raymond, 1999) and are presumably necessary for initiating action potentials. The multiplicity of Na⁺ currents that operate in small-diameter sensory neurones may allow the maintenance of conduction over a range of membrane potentials, for example during the depolarization expected to result from K⁺ release due to tissue damage, or during the hyperpolarization expected to result from activity (Serra et al., 1999). At resting potentials more negative than −45 or −50 mV (i.e. more negative than the potential at which transient current is recruited), low-threshold late Na⁺ current should help to set the firing threshold by acting as an amplifier of the receptor potential, in the same way in which it appears to contribute to the control of firing threshold in large sensory neurones (Baker, 2000a). The functional role of mh overlap current, such as the high-threshold TTX-r late current, is rather different. It is expected to have little effect on voltage threshold but to reduce accommodation so that very slowly depolarizing stimuli (which would otherwise inactivate the transient sodium channels before they could be activated) may initiate impulses. This might be particularly important for nociceptors that have to be activated by chemicals released in response to tissue damage or inflammation.

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