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RESEARCH ARTICLE

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$GTP_{\gamma S}$ increases $Na_v1.8$ current in small-diameter dorsal root ganglia neurons

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Abstract Tetrodotoxin-resistant (TTX-R) sodium current in small-size dorsal root ganglia (DRG) neurons is upregulated by prostaglandin E_2 and serotonin through a protein kinase A (PKA)/protein kinase (PKC) pathway, suggesting G protein modulation of one or more TTX-R channels in these neurons. Recently, $GTP_{\gamma S}$, a hydrolysis-resistant analogue of GTP, was shown to increase the persistent current produced by the TTX-R $Na_v1.9$. In this study, we investigated the modulation of another TTX-R channel, $Na_v1.8$, by $GTP_{\gamma S}$ in small-diameter DRG neurons from rats using whole-cell voltage clamp recordings. Because it has been suggested that fluoride, often used in intracellular recording solutions, may bind to trace amounts of aluminum and activate G proteins, we recorded $Na_v1.8$ currents with and without intracellular fluoride, and with the addition of deferoxamine, an aluminum chelator, to prevent fluoride–aluminum binding. Our results show that $GTP_{\gamma S}$ (100 μM) caused a significant increase in $Na_v1.8$ current (67%) with a chloride-based intracellular solution. Although the inclusion of fluoride instead of chloride in the pipette solution increased the $Na_v1.8$ current by 177%, $GTP_{\gamma S}$ further increased $Na_v1.8$ current by 67% under these conditions. While the effect of $GTP_{\gamma S}$ was prevented by pretreatment with H7 (100 μM), a non-selective PKA/PKC inhibitor, the fluoride-induced increase in $Na_v1.8$ current was not sensitive to H7 (100 μM), or to inclusion of deferoxamine (1 mM) in the intracellular solution. We conclude that G protein activation by $GTP_{\gamma S}$ increases $Na_v1.8$ current through a PKA/PKC mechanism and that addition of fluoride to the pipette solution further enhances the current, but is not a confounding variable in the study of $Na_v1.8$ channel modulation by G proteins independent of a PKA/PKC pathway or binding to aluminum.

Keywords $Na_v1.8$ current · Tetrodotoxin-resistant sodium channels · G proteins · Protein kinase A · Protein kinase C · Fluoride

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Introduction

Voltage-gated sodium channels (VGSC) underlie the initiation and propagation of action potentials that are fundamental for communication between excitable cells. Intracellular signaling molecules can modulate VGSC and the sodium currents they produce, impacting on the biophysical properties of excitable cells and their responses to external and internal stimuli.

Many studies indicate that VGSC can be modulated by G proteins. For example, direct activation of G proteins causes an increase in the sodium current (I_{Na}) produced by the $Na_v1.2$ channel (Ma et al. 1994), whereas activation of muscarinic and dopamine D_1/D_2 receptors was also reported to modulate I_{Na} through G proteins (Cohen-Armon et al. 1988; Surmeier and Kitai 1993). In studies related to inflammatory pain, much effort has been invested in understanding the effects of inflammatory mediators and vasoactive neuropeptides on VGSC in primary afferent neurons. Serotonin, for example, which is an important neurotransmitter in pain processing, increases tetrodotoxin-resistant (TTX-R) sodium current through a cAMP-dependent pathway, and lowers the activation threshold of sensory neurons in dorsal root ganglia (DRG) (Cardenas et al. 2001). The pro-inflammatory mediator prostaglandin E_2 (PGE_2) increases the magnitude of TTX-R I_{Na} and induces a negative shift in the voltage-dependent activation of the slowly inactivat-

ing TTX-R I_{Na} through a cAMP–protein kinase A (PKA)/protein kinase C (PKC) pathway (England et al. 1996; Gold et al. 1998). Endothelin-1 (ET1), which evokes a nociceptive behavior, also amplifies the slowly inactivating I_{Na} and induces hyperpolarizing shifts in the voltage-dependent activation of TTX-R sodium channels (Zhou et al. 2002). Therefore, the modulation of VGSC in response to noxious stimuli or inflammation is arguably mediated, at least in part, through G proteins.

GTP-binding proteins represent a family of regulatory molecules. Binding of GTP to the G_α subunit leads to subsequent dissociation of the active G_αGTP and $G_{\beta\gamma}$ subunits. Both subunits can further regulate the activity of ion channels (Ca^{2+} and K^+ channels; for a review, refer to Dascal 2001) either directly or indirectly through second messenger systems (e.g., protein kinases). G proteins can thus function as active (G_αGTP) or inactive 'switches' in their GTP- or GDP-bound forms, respectively, due to an inherent GTPase activity (Brito et al. 2002). The hydrolysis-resistant analogue $GTP_{\gamma S}$ mimics the extended effects of GTP and persistently activates G proteins. On the other hand, the non-hydrolyzable $GDP_{\beta S}$ mimics GDP action by 'switching' G proteins to the inactive form. Recently, Baker et al. (2003) reported that $GTP_{\gamma S}$ increases the peak amplitude of the TTX-R $Na_v1.9$ persistent current by 3- to 8-fold, and results in a more negative threshold for the induction of action potentials. In this study, we investigated the modulation of $Na_v1.8$ channels by $GTP_{\gamma S}$ in rat small diameter DRG neurons using the whole-cell voltage-clamp technique. Because it was noted in previous reports that fluoride, a common component used in the pipette solution, might bind to trace amounts of aluminum and activate G proteins (Codina and Birnhaumer 1994; Matzel et al. 1996; Chen and Penington 2000), we used different pipette solutions with or without fluoride, or in the presence of an aluminum chelator.

In this study, we show that $GTP_{\gamma S}$ significantly increases $Na_v1.8$ current through a PKA/PKC-dependent mechanism to the same extent in the presence or absence of fluoride in the pipette solution. Moreover, the presence of fluoride in the pipette solution was also associated with a further increase in the current independent of a PKA/PKC activation.

Methods

DRG cultures from L4, L5 and L6 ganglia of male adult Sprague Dawley rats (250–350 g) were prepared as previously described (Rizzo et al. 1994). A class of relatively 'peptide poor' C-fiber nociceptors have been shown to express receptors for glial cell line-derived neurotrophic factor (GDNF), and a surface carbohydrate group that binds IB4 (Vulchanova et al. 2001; Dirajlal et al 2003). We used IB4 to identify this sub-population of C-fiber DRG neurons that were in the small-diameter range (15–25 μm). For co-localization of IB4-reactivity and the $Na_v1.8$ channel, IB4-FITC (40 μg/ml; Sigma, St. Louis, MO, USA) was added to the culture medium and incubated for 30 min at 37°C prior to beginning the immunostaining with anti-$Na_v1.8$ antibody as previously described (Black et al. 2000). Coverslips were mounted on glass slides and examined with a Nikon E800 light microscope equipped with epifluorescent optics. Digital images were captured with a Dage-MTI DC-330 color camera (Michigan City, IN, USA), and the $Na_v1.8$ immunofluorescent signal in IB4-positive DRG neurons was quantified with IPLab software (Scanalytics, Fairfax, VA, USA).

$Na_v1.8$ currents were recorded using standard whole-cell patch-clamp techniques from IB4-positive DRG neurons (15–25 μm) in the presence of TTX (500 nM) after short-term culture (6–24 h). All recordings were conducted at room temperature (~21°C) using an EPC-9 amplifier (HEKA Electronics) and the Pulse program (version 7.89). Fire-polished electrodes (0.7–1.4 MΩ) were made from 1.7-mm capillary glass using a Sutter P-97 puller, and voltage errors were minimized using series resistance compensation (~85%) with linear leak subtraction. The pipette solution contained (in mM): 1 EGTA, 10 NaCl, 10 HEPES, and either 140 CsF (fluoride solution), or 140 CsCl (chloride solution). The standard bathing solution contained (in mM): 140 NaCl, 3 KCl, 1 $MgCl_2$, 1 $CaCl_2$, 0.1 $CdCl_2$ (for blocking calcium currents), and 10 HEPES. The osmolarity of both solutions was adjusted to ~310 mOsm and the pH to 7.3. All cells were held at −60 mV and step pulses ranging from −50 to 40 mV by10-mV increments were applied for 100 ms to study current–voltage relationship (at −60 mV relatively few TTX-R $Na_v1.9$ channels are available for activation; Cummins et al. 1999). To study channel inactivation properties (H_{inf}), the membrane voltage was held at −100 mV and step prepulses ranging from −100 to 30 mV for 500 ms were followed by a step pulse to −10 mV for 20 ms. Activation curves were fitted with the Boltzmann function: $G_{Na}=1/(1+\exp[(V_a-V)/k])$, where G_{Na} is the peak sodium conductance, V_a is the midpoint of the curve, and k is the slope factor. G_{Na} is calculated from $G_{Na}=I_{Na}/(V-V_{rev})$, where I_{Na} is the peak sodium current during the test depolarization (V) and V_{rev} is the sodium reversal potential. Steady-state inactivation curves were fitted with the Boltzmann function: $I/I_{peak}=1/(1+\exp[(V-V_i)/k])$, where I_{peak} is the maximum peak current elicited with the depolarizing voltage steps during the activation protocol, V_i is the midpoint of the curve and k is the slope factor.

Data were generally collected 2–4 min after membrane rupture for whole-cell recording. In some experiments, $GTP_{\gamma S}$ (100 μM) and $GDP_{\beta S}$ (2 mM; Sigma) were added separately to the pipette solutions and kept on ice, whereas in other experiments, an aluminum chelator (deferoxamine 1 mM; Sigma) was added to the fluoride solution and kept on ice. Some DRG neurons were incubated for 24 h in a medium containing a non-selective isoquinoline sulfonamide protein kinase inhibitor (H7 100 μM; Sigma). A Student's two-tailed unpaired t-test was used to compute the significance level between the different groups of neuronal populations ($P<0.01$ was considered as significant, and results were reported as means ±SEM).

Results

In a previous study we found that 33 out of 33 IB4-positive small DRG neurons exhibited TTX-R sodium currents (Fjell et al. 1999). In order to determine what fraction of IB4-positive small DRG neurons express $Na_v1.8$ channels, we used a $Na_v1.8$-specific antibody for immunohistochemistry analysis. A total of 158 IB4-positive small-diameter (15–25 μm) DRG neurons were quantified for $Na_v1.8$ signal. Of the 158 neurons, 133 (84.2%) were $Na_v1.8$-positive (defined as signal intensity at least 30% greater than background level). Accordingly, IB4 was used as a reliable marker for $Na_v1.8$ expression in the DRG neurons studied, and only IB4-positive small-diameter (15–25 μm) DRG neurons were used for the voltage clamp experiments described below.

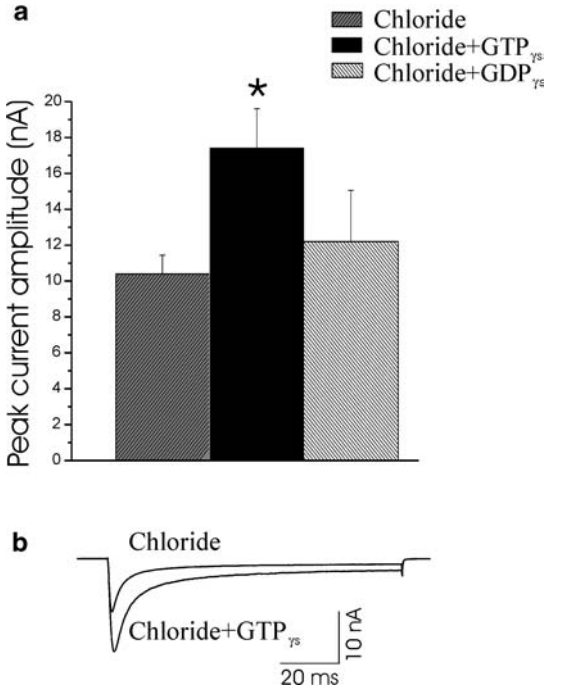

Fig. 1. a Bar histograms showing the average peak $Na_v1.8$ current amplitudes from IB4-labeled dorsal root ganglion neurons (±SEM) with either $GTP_{\gamma S}$ (100 μM) or $GDP_{\beta S}$ (2 mM) added to the chloride internal solution (*P<0.01 relative to Chloride). **b** Superimposed traces representing the peak $Na_v1.8$ currents recorded using the chloride internal solution or chloride and $GTP_{\gamma S}$

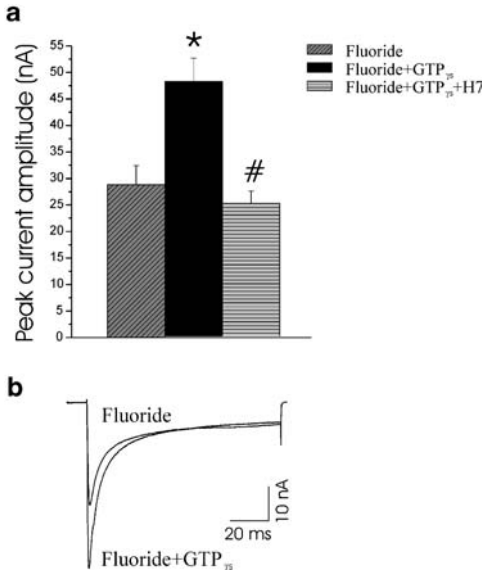

Fig. 2. a Bar histograms showing the average peak $Na_v1.8$ current amplitudes from IB4-labelled dorsal root ganglion neurons (±SEM) with either $GTP_{\gamma S}$ (100 μM) or $GTP_{\gamma S}$ (100 μM) plus the non-selective PKA/PKC inhibitor H7 (100 μM) added to the fluoride internal solution (*P<0.01 relative to fluoride, #P<0.01 relative to fluoride+$GTP_{\gamma S}$). **b** Superimposed traces representing the peak $Na_v1.8$ currents recorded using the fluoride internal solution or fluoride and $GTP_{\gamma S}$

Using the chloride intracellular solution, the average peak current amplitude ($\hat{I}_p$) was 10.4±1.0 nA (n=45). The addition of $GTP_{\gamma S}$ to the chloride solution was associated with an increase in $\hat{I}_p$ to 17.4±2.1 nA (n=18; Fig. 1). Furthermore, with $GTP_{\gamma S}$ present in the chloride solution, we noted a hyperpolarizing shift in the voltage-dependence of activation (V_a) and a depolarizing shift in the voltage-dependence of inactivation (V_i) of approximately 3 mV in either direction (Table 1, Fig. 3). However, addition of $GDP_{\beta S}$ to the chloride solution did not alter $\hat{I}_p$ significantly (12.2±2.8 nA, n=7) (Fig. 1), indicating that the basal activity level of G proteins affecting $Na_v1.8$ channels was presumably insignificant.

Using the fluoride intracellular solution, $\hat{I}_p$ was 28.8±3.6 nA (n=44). The addition of $GTP_{\gamma S}$ to the fluoride solution was associated with a further increase in $\hat{I}_p$ to 48.0±4.3 nA (n=15; Fig. 2). Furthermore, with $GTP_{\gamma S}$ present in the fluoride solution, we noted a hyperpolarizing shift in V_a and a depolarizing shift in V_i of approximately 4 mV in either direction, comparable to the effects observed using the chloride solution (Table 1, Fig. 3). However, this apparent shift in V_a should be carefully interpreted in light of the expected clamp restrictions imposed by such robust current amplitudes, which probably manifested as changes in the slope values derived from the current–voltage (I–V) curves (Table 1, compare the slope value $4.46x10^{-3}$ using the fluoride solution with $2.53x10^{-3}$ after the addition of $GTP_{\gamma S}$). On the other hand, when DRG neurons were incubated in the non-selective PKA/PKC inhibitor H7 for ~24 h, the $\hat{I}_p$ recorded using the fluoride solution containing $GTP_{\gamma S}$ was significantly reduced to 25.0±2.3 nA (n=9, not significantly different from $\hat{I}_p$ using the fluoride solution; Fig. 2).

Table 1 Values for the voltage of half-activation (V_a), slopes of individual curves (Sl), voltage of current reversal (V_{rev}), and voltage of inactivation (V_i) were derived from current–voltage (I–V) or steady-state inactivation (H_{inf}) curves in four different groups of rat dorsal root ganglion neurons (means ±SEM) using different internal solutions with chloride, fluoride, or with $GTP_{\gamma S}$ added to either the chloride or the fluoride internal solution (n=5 in each group)

Internal solution	I-V			H_{inf}	
	V_a (mV)	Sl ($\times10^{-3}$)	V_{rev} (mV)	V_i (mV)	Sl ($\times10^{-3}$)
Chloride	−17.08±2.38	3.99 ±0.59	42.20±1.48	−34.54±1.32	−4.56±0.23
Chloride+$GTP_{\gamma S}$	−20.14±4.08	4.17 ±0.86	55.36±3.66	−31.46±0.75	−5.35±0.51
Fluoride	−18.96±3.54	4.46 ±0.63	42.56±2.79	−35.26±0.59	−4.99±0.25
Fluoride+$GTP_{\gamma S}$	−22.56±5.11	2.53 ±1.00	49.24±4.38	−31.60±1.02	−4.38±0.29

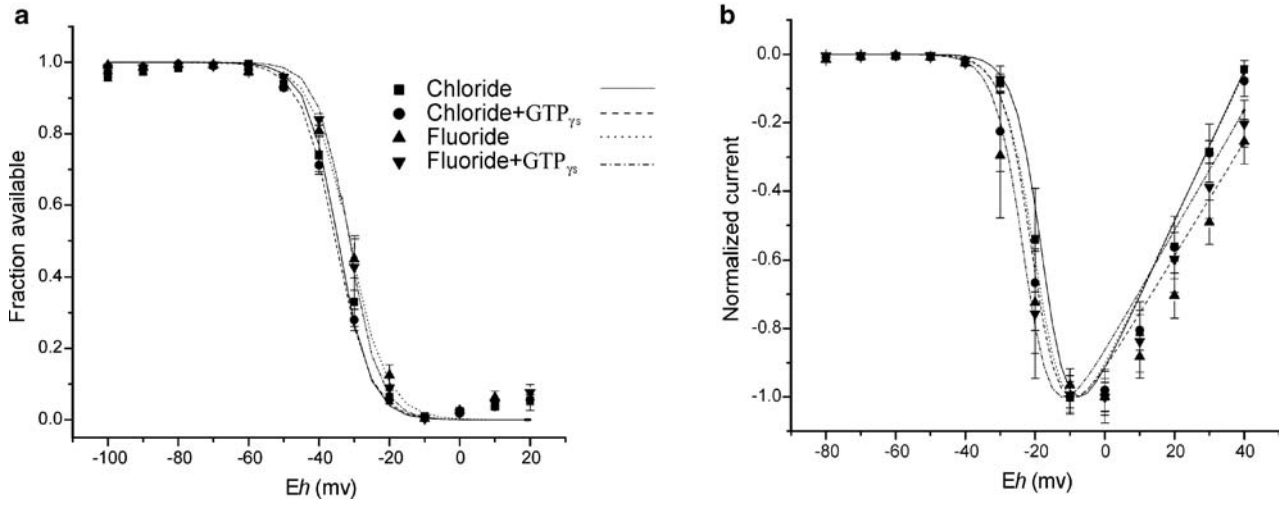

Fig. 3a,b Curves representing the voltage dependence of steady-state inactivation (**a**) or current activation (**b**) in four different groups of IB4-labelled dorsal root ganglion neurons (±SEM) using different internal solutions with chloride, fluoride, or with $GTP_{\gamma S}$ added to either the chloride or the fluoride internal solution (n=5 in each group)

Clearly, $\hat{I}_p$ is enhanced using the fluoride solution compared with that in the chloride solution. However, no associated changes were observed in the voltage-dependence of activation or inactivation (Table 1). To test whether the fluoride-induced enhancement of the $Na_v1.8$ current is also dependent on PKA/PKC activation, $\hat{I}_p$ was recorded using the fluoride solution in DRG neurons incubated in H7. While H7 prevented the $GTP_{\gamma S}$-induced increase, H7 did not prevent the effect of fluoride per se on $\hat{I}_p$ (27.9±4.6 nA, n=4, compare with $\hat{I}_p$ of 28.8±3.6 nA recorded using the fluoride solution in the absence of H7, see above).

Even though aluminum was not included in the fluoride solutions used, deferoxamine was added in one set of experiments to rule out possible binding of fluoride ions with trace amounts of aluminum and subsequent activation of G proteins by AlF_4^-. We did not detect a significant difference in $\hat{I}_p$ using the fluoride solution in the absence or presence of deferoxamine (P>0.9, n=8, data not shown).

Discussion

Although it can be inferred from previous studies that G proteins may be involved in the receptor-mediated modulation of VGSC, this study clearly shows that activation of G proteins is sufficient to increase $Na_v1.8$ current in small-diameter DRG neurons through a PKA/PKC-dependent mechanism. In fact, $GTP_{\gamma S}$ increased $Na_v1.8$ current to the same extent (67%) using intracellular solutions containing either chloride or fluoride. Cardenas et al. (2001) showed a comparable increase (64%) in TTX-R I_{Na} following activation of serotonin receptors that are presumably coupled to G proteins. On the other hand, Gold et al. (1998) described a 25% upregulation of TTX-R I_{Na} by PGE_2, whereas England et al. (1996) showed that PGE_2 'frequently' increased the current amplitude by only 13%. Apparently, activation of G proteins by $GTP_{\gamma S}$ or serotonin receptors is more effective for the modulation of $Na_v1.8$ channels than activation by the PGE_2 receptors. Baker et al. (2003) recently reported that $GTP_{\gamma S}$ led to >300% increase in the maximal peak current amplitude of $Na_v1.9$ channels, indicating differences in the extent to which $Na_v1.8$ and $Na_v1.9$ channels may be modulated by G proteins.

Hyperpolarizing shifts in the voltage-dependent activation of TTX-R I_{Na}, presumably due to the activation of G proteins, have been previously documented (England et al. 1996; Gold et al. 1998). Comparable changes in voltage-dependent properties in this study were associated with addition of $GTP_{\gamma S}$ to the pipette solutions. However, the hyperpolarizing shift noted when $GTP_{\gamma S}$ was added to the fluoride solution should be carefully interpreted in the light of the slope variance caused by robust currents in the range of nearly 40-60 nA. Such upregulation of $Na_v1.8$ current would be expected to attenuate the quality of the clamp, in spite of acceptable seal formation and high series resistance compensation.

The significant difference in $\hat{I}_p$ recorded using the chloride and the fluoride solutions point to an amplification of the $Na_v1.8$ current by fluoride independently of PKA/PKC. Furthermore, $\hat{I}_p$ was not significantly different in the absence or presence of deferoxamine (an aluminum chelator), indicating that the addition of fluoride to the pipette solution results in larger current amplitudes independent of the formation of AlF_4^-. Qu et al. (2000) observed that fluoride promoted the formation of good seals in their patch-clamp experiments but caused an 'obscure' increase in the current amplitude in olfactory receptor neurons. Our data indicate that the presence of fluoride in the pipette solution enhances TTX-R I_{Na} produced by the $Na_v1.8$ channel, but this does not seem to represent a confounding variable in the study of TTX-R

sodium channel modulation by G proteins. In fact, Zhou et al. (2000) were able to demonstrate the modulation of TTX-R I_{Na} by ET1 in the presence of 130 mM CsF in the pipette solution.

The rapid increase in current amplitude reported in our study may be due to increases in the probability of opening or conductance in single channels, or increase in the total number of functional channels, but it is unlikely to be related to de novo protein synthesis. Future experiments at a single channel level may help to identify the specific mechanisms involved in the modulation of the $Na_v1.8$ channel, whereas current-clamp experiments may determine the influence of such modulation on the excitability of peripheral nociceptors, where $Na_v1.8$ channels tend to be expressed (Akopian et al. 1996; Cummins et al. 1999). Interestingly, calcitonin gene-related peptide (CGRP), substance P, adenosine, γ-aminobutyric acid (GABA), serotonin, and other neurotransmitters that are released during inflammation may bind to receptors coupled to G proteins (Abdulla et al. 2001; Cardenas et al. 2001; Yang et al 2001), indicating that the potential effects of G proteins on VGSC of the TTX-R type may have important functional implications with regard to pain.

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