Morphological and functional diversity of first-order somatosensory neurons

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Abstract First-order somatosensory neurons transduce and convey information about the external or internal environment of the body to the central nervous system. They are pseudo unipolar neurons with cell bodies residing in one of several ganglia located near the central nervous system, with the short branch of the axon connecting to the spinal cord or the brain stem and the long branch extending towards the peripheral organ they innervate. Besides their sensory transducer and conductive role, somatosensory neurons also have trophic functions in the tissue they innervate and participate in local reflexes in the periphery. The cell bodies of these neurons are remarkably diverse in terms of size, molecular constitution, and electrophysiological properties. These parameters have provided criteria for classification that have proved useful to establish and study their functions. In this review, we discuss ways to measure and classify populations of neurons based on their size and action potential firing pattern. We also discuss attempts to relate the different populations to specific sensory modalities.

Keywords Somatosensory neurons · Phasic neurons · Tonic neurons · Neuronal size · Firing pattern

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Introduction

First-order somatosensory neurons transduce an adequate stimulus related to the internal or external environment and carry this information into the central nervous system (Sherrington 1920). In addition to this role, these neurons are also involved in trophic functions of the tissues they innervate and in axonal reflexes that do not require communication with the central nervous system (Scott 1992; Carlton 2014). As a general rule, the cell bodies that give rise to primary sensory nerve fibers are located in one of several sensory ganglia, such as the nodose, trigeminal, petrosal, and the dorsal root [spinal] ganglia (DRG). Proprioceptors of the trigeminal nerve are an exception, as these cells reside within the brain stem (Cody et al. 1972; Connor et al. 2005).

More than a century of anatomical, biochemical, and electrophysiological studies reveal marked differences between individual sensory neurons. These differences are found not only when comparing between different ganglia but, principally, for neurons found within the same ganglion. Considering the many types and dimensions of sensory information to which the organism must respond, differences in the properties of sensory neurons is perhaps not surprising. Nonetheless, this diversity of form and function indicates a level of complexity in the primary processing of sensory information that is still incompletely understood.

Histological studies beginning in the nineteenth century documented different types of cell bodies within sensory ganglia. Later, immunohistochemistry revealed the presence of many different biochemical markers that define different populations of sensory neurons. When paired with electrophysiological measurements of conduction velocity, and specific stimuli (heat, cold, pressure, etc.) in intact preparations, these studies also permit association of sizes and histochemical markers with axon fiber type and sensory modality. This rich

literature has been the subject of many excellent reviews (Scott 1992; Carr and Nagy 1993; Le Pichon and Chesler 2014; Djouhri 2016).

More recently, the discovery of molecular mechanisms of sensory signal transduction have permitted classifications based on the selective expression of certain ion channels, especially TRP channels, ASIC channels, P2X receptors, certain isoforms of Na_v channels, among others (McCleskey and Gold 1999; Petruska et al. 2000; Le Pichon and Chesler 2014; Moraes et al. 2014). Retrograde labeling allows characterization of the neurons that innervate specific organs. In some special cases, where the sensory modality is known a priori, this approach allows the study of a functionally defined population (Benson et al. 1999; Silbert et al. 2003; Connor et al. 2005; Freisinger et al. 2013; Kanda et al. 2016). In addition, genetically modified animals that express a marker (for example, a fluorescent protein) under the control of a gene of interest are useful tools to study the properties of neurons that express that gene (Dussor et al. 2008; Tang et al. 2016; Le Pichon and Chesler 2014). Generally, these studies have been carried out using the whole-cell patch clamp technique on dissociated neuronal cell bodies in short-term culture. Here, we review the diversity of sensory neurons under these conditions as seen in their action potential firing patterns. We will provide examples where the above strategies identify neurons with specific firing patterns (tonic versus phasic). When appropriate, we will refer to the literature on recordings of sensory nerve fibers, as well as non-sensory sympathetic ganglia. We also revisit the question of differences in cell size and discuss statistical methods to determine the minimum number of subpopulations required to adequately describe the size distribution.

Classifying DRG neurons based on cell size

The diversity of neurons found within a single sensory ganglion has long been appreciated and many attempts have been made at classification. One striking difference between individual sensory neurons is the size of the cell body. Using light microscopy, Hatai (1901) measured the cell diameters of cell bodies in rat spinal DRG and identified three classes of neurons that he described as larger and lightly staining, smaller and deeply staining, and intermediate. Further light microscopy classification based on cell diameter size and the distribution and structure of Nissl bodies identified up to seven types of cell bodies (Clark 1926). Two major classes of neurons, with large and light or small and dark cell bodies, can also be observed in the electron microscope (Andres 1961; Lawson 1979; Lawson et al. 1984). Andres (1961) further subdivided each group (which he termed Type A and Type B) into subtypes (A1, A2, etc.), resulting in six populations with overlapping cell diameter ranges. Statistical analysis of

the distribution of cell size for mouse L5 DRG was undertaken by Lawson (1979). The results, based on a maximum likelihood approach (see below), indicated that two normally distributed size populations were necessary and sufficient to describe the cell size histogram. Unbiased estimates of cell number and volume also indicated two populations of neurons (Tandrup 2004). In cultured DRG neurons, three size populations have been reported (Study and Kral 1996; Abdulla and Smith 2001; Moraes et al. 2014). Statistical methods to determine the number of subpopulations in the distribution of cell sizes will be described below.

Developmental studies show that at least some aspects of neuronal phenotype are defined at the time of cell “birth”. DRG sensory neurons develop from neural crest cells that migrate out of the dorsal neural tube (reviewed by Scott 1987; Marmigère and Ernfors 2007; Liu and Ma 2011). Measurements of cellular birthdate indicate that DRG neurons in rats are born between embryonic days 12 to 16 (Lawson et al. 1974; Kitao et al. 1996). The first cells to be born are the larger lighter neurons, followed by the small dark neurons. The former will develop fast myelinated A-fibers and become proprioceptors and mechanoreceptors, whereas the latter will develop A δ - and C-fibers with more diverse functional properties, including nociceptors and thermoreceptors (reviewed by Marmigère and Ernfors 2007 and Liu and Ma 2011). The expression of tropomyosin receptor kinases TrkA, TrkB, and TrkC, which are receptors for specific growth factors, correlates with cell body size, the degree of myelination, and function. Cells with A δ - and C-fibers express TrkA, mechanoreceptors express TrkB, and proprioceptors express TrkC (Liu and Ma 2011; Bailey et al. 2017).

The relationship between cell size and sensory function can be inferred in some cases based on recordings from functionally and morphologically defined neurons. In general, cell size correlates positively with conduction velocity, so sensory modalities associated with fast A $\alpha\beta$ conduction velocities are likely mediated by neurons with large cell bodies, whereas slowly conducting A δ - and C-fibers are associated with small cells. Physiological data indicate that proprioceptors and many mechanoreceptors have fast A-fibers (Angel and Alston 1964; Appelberg et al. 1966; Knibestöl 1973), as do the large light populations of DRG neurons (Lawson and Waddell 1991). This leads to the inference that these neurons have large cell bodies. By similar logic, thermoreceptors have C-fibers (Darian-Smith et al. 1979), as do most small dark cells (Sugiura et al. 1988; Lawson and Waddell 1991), leading to an association of thermoreceptors with small diameter neurons.

As for nociceptors, although they are often associated with neurons with small cell bodies (and, by inference, A δ - and C-fibers), it is well documented that there are nociceptors with A $\alpha\beta$ -, A δ -, and C-fibers (reviewed by Djouhri and Lawson 2004). Retrograde labeling of dental pulp afferents permitted

the identification of a population of nociceptors which was found to contain small, medium, and large diameter cell bodies (Silbert et al. 2003). In other studies, expression of ASIC3, a putative nociceptive marker (McCleskey and Gold 1999; Naves and McCleskey 2005), was found in larger neurons that did not express P2X3 currents (Molliver et al. 2005; Moraes et al. 2014). These large neurons, which respond to reduced pH, lactate, and ATP released during ischemia, may correspond to muscle metaboreceptors or nociceptors (Naves and McCleskey 2005; Yagi et al. 2006; Birdsong et al. 2010; Light et al. 2008).

Using likelihood functions for describing subpopulations of DRG neurons

When attempting to relate sensory function with the cell body size of sensory neurons, it is worthwhile considering to what extent cell sizes fall into statistically distinct populations. The null hypothesis in this case would be that the size distribution is a single broad continuum. To distinguish these possibilities,

it is useful to apply curve fitting to the population distributions followed by model selection techniques to determine into how many subpopulations the data can be separated. Here, we describe one approach that has proven useful for the description of the distribution of cell body sizes found in DRG cultures (Moraes et al. 2014). For display and curve fitting, we feel the cumulative distribution function (CDF) has advantages over histograms in that it displays all the data points and, thus, avoids the necessity to choose arbitrary bin sizes. For comparison, we also present the histogram drawn below the CDF (Fig. 1).

As a first example, let us assume that samples are drawn from a single normal population with mean = μ and s.d. = σ . In this case, the theoretical CDF for the underlying population is given by:

$$CDF(x) = \frac{1 + \operatorname{Erf}\left(\frac{x-\mu}{\sqrt{2}\sigma}\right)}{2} \quad (1)$$

where $\operatorname{Erf}(x)$ is the error function. Note that Eq. 1 has two free parameters, mean (μ) and s.d. (σ). The number of free

Fig. 1 Use of least-square curve fitting and the Akaike information criterion (Akaike 1974) to select the optimal models of dorsal root ganglia (DRG) cell size distribution. Top: simulated data drawn from a population of one normal distribution (a) or the sum of three normal distributions (b). In the cumulative distribution function (CDF), data are shown as *black points* and the *blue line* represents the optimal model (one population in a and three populations in b, see text). In b, the *red lines* are for models containing one or two normal populations. In the histogram, the *smooth line* represents the best-fit model. Bottom: cell size data taken from Moraes et al. (2014). For panel c, as in panel c, the *blue line* represents the optimal model (three populations) and the *red lines* represent the best-fit for models containing one or two populations. Panel d shows the same data as in panel c, but with the three normal populations plotted individually

parameters will be important for the issue of model selection discussed below.

Figure 1a shows a simulated population of independent samples drawn from a normal distribution with mean $\mu = 1$ and s.d. $\sigma = 0.1$. The smooth blue line through the data was obtained from Eq. 1 using the best-fit parameters obtained through a standard Levenberg–Marquardt search algorithm (Press et al. 1992) to find coefficient values that minimize the sum squared error. As the number of samples increases, the estimated best-fit parameter estimates converge to the true population parameters.

In many cases, inspection of the population distribution reveals what appear to be subpopulations. For a made-up example, see Fig. 1b. In this case, a compound CDF (cCDF) can be written as:

$$cCDF(x) = \sum_N \left(f_i \frac{1 + \operatorname{Erf} \left(\frac{x - \mu_i}{\sqrt{2} \sigma_i} \right)}{2} \right) \quad (2)$$

where the sum is taken over all N subpopulations. Equation 2 simply states that the CDF for a model containing two or more subpopulations is the sum of the CDF for each of the individual subpopulations, each weighted by the fraction (f) of the population that they contain. As such, Eq. 2 can be used for curve fitting to obtain estimates of the mean and s.d. values for each of the subpopulations. The model is constrained by the fact that the sum of the $f_i = 1$, resulting in $3N - 1$ free parameters (N values of mean, N values of standard deviations, and $N - 1$ values of f).

The issue we wish to address is the number of subpopulations that can be statistically identified in the data. When the compound population consists of well-separated subpopulations, the best choice can sometimes be made “by eye”. In Fig. 1b, we show simulated data drawn from a population containing three normal subpopulations, with mean values of $\mu_1 = 1$, $\mu_2 = 2$, and $\mu_3 = 3$, and standard deviations $\sigma_1 = \sigma_2 = \sigma_3 = 0.1$. In this example, most readers would probably agree that the data fall into three distinct subpopulations. Indeed, Eq. 2 can be adjusted to fit the data when we include three populations (blue line), whereas if only one or two populations are included, it fails to fit the data badly (red lines). Thus, for the case illustrated in Fig. 1b, a model with three subpopulations appears both necessary and sufficient.

To make a more quantitative statement, we use the Akaike information criterion (AIC) to evaluate different models:

$$AIC = -2 \ln(L) + 2K \quad (3)$$

where L is the maximized value of the likelihood function (i.e., the likelihood of observing the data given the model and its best-fit parameters) and K is the number of model parameters (Akaike 1974). The first step is to use standard

curve fitting procedures to search for parameters that minimize the squared sum difference between Eq. 2 and the empirical cCDF of the data. This step is then repeated for each of the models (one population, two populations, and so forth). Using these best-fit parameters, one then calculates the maximized value of the likelihood function, L , which is the likelihood of observing the data given the model and the best-fit model parameters.

The likelihood function for a distribution composed of the sum of normal distributions can be calculated as follows. The samples are assumed to be independent, and, therefore, the probability of observing the data is the product of the probabilities of observing each individual datum. To calculate the probability of observing each individual datum, we sum the probabilities of observing that value from each of the N normal populations in the model. Thus:

$$L = \prod_i \sum_j p_j(y_i) \quad (4)$$

where $p_j(y_i)$ is the contribution of the j th subpopulation to the probability of observing the i th data value, assuming that p_j is a normal distribution with mean μ_j and s.d. σ_j . In Eq. 4, the sum is taken over all subpopulations included in the model and the product in Eq. 4 is taken over all recorded data values.

To choose the best model for the data, the maximized likelihood calculated by Eq. 4 for each model is then used in Eq. 3 to calculate the corresponding AIC for that model. According to Akaike (1974), the model with the lowest value of AIC is optimal in the sense of balancing the goodness of fit and the number of free parameters. Using this procedure for the data and fits shown in Fig. 1b, the calculated AIC value is much less for the model that includes three populations compared to one or two populations, as expected based on visual inspection of the data.

The situation just described and illustrated in Fig. 1b is highly idealized in that the three populations are well separated (in this case, the separation between mean values was ten times the s.d.). The choice of the number of subpopulations becomes much less obvious, and the need for statistical methods more critical, when the subpopulations are less well separated. Figure 1c shows the distribution of DRG neuron cell sizes (expressed as membrane capacitance, pF) taken from a recent publication (Moraes et al. 2014). The presence of subpopulations can be inferred from the inflection points in the CDF, but it is not clear by inspection how many subpopulations should be considered. Indeed, the best-fit results for one, two, three, or four populations all give reasonable fits to the data (although close inspection reveals that the model with three populations is better able to fit the data than one or two populations). To determine if the improvement in fit by the model with three populations compared to two populations justifies the addition of three free parameters (see above), we apply the AIC as just described. This analysis reveals that the

model with three populations is significantly better than models with one or two populations. The data in Fig. 1d could also be fit as the sum of four or more normally distributed populations (not shown). For each additional population added, the fit is somewhat improved (i.e., the residual sum-square error is slightly reduced), but three free parameters are added (see above). According to the AIC, any further improvement in the fit obtained by including four subpopulations is insufficient to justify the inclusion of three additional free parameters.

Note that the model selection procedure described above does not penalize overlap of the populations. For the data analyzed in Fig. 1d, the best-fit parameters for three populations predict about 12% total overlap (shaded areas in Fig. 1d), resulting in ambiguity for the classification of cells that fall into this region of the distribution. However, in this regard the three-population model still outperformed either the two- or four-population models, which each had 13% overlap. In conclusion, these results show that, for the sample studied, three size populations are both necessary and sufficient to adequately describe the distribution of DRG neuronal sizes in this preparation, and that 88% of the DRG neurons studied could be uniquely classified into one of three populations: small, medium, or large (Moraes et al. 2014).

Action potential firing patterns

Sensory information in the nervous system initiates with the transduction of chemical or physical stimuli into a change in transmembrane voltage, a phenomenon called the receptor generator potential. In the somatosensory receptor, if this potential reaches threshold, the signal is propagated to the central nervous system by action potentials (APs). The frequency of AP firing encodes the intensity of the stimuli (Werner and Mountcastle 1965). The shape of the AP and the neuronal firing pattern are determined by the passive and active electrical properties of the cell membrane (Bretag and Stämpfli 1975). AP shape can be characterized in terms of half-width, amplitude (measured from resting potential to peak), overshoot (measured from 0 mV to peak), amplitude and duration of the afterhyperpolarization (Djouhri et al. 1998; Moraes et al. 2014; Payne et al. 2015; Tang et al. 2016). For sensory neurons, an additional feature is the presence in some cells of an inflection or “hump” on the repolarization limb of the AP, best seen as a local maximum in the first derivative of V_m (Belmonte and Gallego 1983; Koerber et al. 1988). Firing patterns, as used here, are classifications based on the number of APs which a neuron fires and the degree of adaptation (a gradual decrease in firing frequency) upon sustained stimulation.

Recordings on sympathetic ganglia neurons led to the classification of cells as either phasic or tonic based on the firing

pattern they exhibit during prolonged stimulation. Cassell et al. (1986) defined phasic neurons as those neurons that fired one AP or a brief burst of APs at the onset of long depolarizing current injection, whereas tonic neurons fired “rhythmically and continuously”, often with some delay. Similar ideas have been employed for the classification of DRG neurons, although the classification criteria vary considerably between authors. In some cases, authors have adopted the same criteria described above for sympathetic neurons (e.g., Ditting et al. 2009; Yu et al. 2014). Other authors used a more strict criteria for phasic neurons based on the number of APs fired during a continuous suprathreshold stimulation, with phasic neurons firing exactly one (Chen et al. 1987) or, at most, four APs (Sculptoreanu and de Groat 2007; Freisinger et al. 2013). Neurons that fired more than these limits were classified as tonic cells. A subdivision of trigeminal ganglion tonic cells has been proposed by Catacuzzeno et al. (2008) based on the onset of the AP train, which, in some cells, was instantaneous and, in other cells, occurred after a delay. The classification criteria described above are based on the response to a prolonged depolarizing current injection. It is important to note that differences in firing patterns (phasic versus tonic) are also observed in the cell bodies of DRG neurons in response to sustained natural stimuli, such as reduced pH (Immke and McCleskey 2001; Ditting et al. 2009), changes in temperature (Greffrath et al. 2009), and mechanical stimulus (Viatchenko-Karpinski and Gu 2016).

Functional relationships associated with tonic and phasic firing patterns

Many studies have addressed the question of correlations of action potential shape with sensory receptor functions (reviewed by Scott 1992; Lawson 2002). Although it has been suggested that differences in AP shape correlates with conduction velocity, evidence suggests a more important correlation with sensory function. Across fiber types, the differences in AP shape correlate less with fiber type than with functional differences such as between different functional classes of C-fiber neurons (Gee et al. 1999) or between nociceptors and mechanoreceptors or between subtypes of mechanoreceptors (Djouhri et al. 1998).

Much less is known about the correlation of AP discharge pattern and sensory function. One consistent finding is that phasic and tonic neurons respond differently to certain modulators. For example, the effects of substance P on capsaicin-sensitive DRG neurons is stronger in phasic neurons (Sculptoreanu et al. 2009). Similarly, the effects of inflammatory modulators are different for phasic and tonic neurons and also for different size populations. In recordings from small and medium DRG neurons, inflammation induced by complete Freund’s adjuvant or by bee venom caused more changes

in the excitability of tonic neurons than phasic neurons (Yu et al. 2014). For large neurons, the inflammation induced by bee venom increased cellular excitability specifically in phasic neurons, as it increased the proportion of neurons with tonic responses (Sun et al. 2017). It is interesting to note that different size populations respond differently to substance P (Abdulla et al. 2001). Under normal conditions, substance P increases the excitability of small cells more than large cells, and, after axotomy, this relationship changes. Differences between phasic and tonic neurons in their sensitivity to modulators are also seen in the sensory nodose ganglion (Moreira et al. 2009) and in the sympathetic nervous system (Zhao et al. 1995).

Tonic and phasic neurons seem to contribute differently to specific sensory modalities. For example, 90% of DRG neurons innervating the bladder are phasic (Kanda et al. 2016), and capsaicin-sensitive bladder afferents change their firing pattern from phasic to tonic after spinal transection (Takahashi et al. 2013). Similarly, Freisinger et al. (2013) showed that a higher percentage of renal afferents are tonic (56%) compared to non-renal afferents (12%). In mechanosensitive DRG neurons, neurons with “nociceptive-like” APs were equally likely to have tonic or phasic responses, while neurons with “non-nociceptive-like” APs are almost all phasic (Viatchenko-Karpinski and Gu 2016). The putative itch sensing neurons are mostly phasic, while other afferents from the skin are tonic (Tang et al. 2016). The specificity of firing pattern with function is also seen in the autonomic nervous system. For example, the most caudal lumbar sympathetic ganglia neurons, whose activation causes vasoconstriction, are phasic, whereas most inferior mesenteric ganglia neurons, which are involved with visceral mobility and secretion, are tonic (Cassell et al. 1986).

In addition to the binary classification of phasic/tonic, firing patterns can also be classified on the basis of the degree and time course of adaptation. Adaptation is present in all sensory modalities and it happens at all levels of the neural pathways (Ganmor et al. 2010). At the first-order neuron, the discharge patterns of the cell bodies vary with the functional properties of the receptors. For example, since the earliest studies determining the coding of stimulus intensity by AP frequency (Werner and Mountcastle 1965), it is known that skin mechanoreceptors can have adapting or non-adapting axons. Although viscoelastic structures at the nerve endings play a role in adaptation, adaptation can still be observed after microdissection that leaves the sensory terminal almost bare, which implies that adaptation is an intrinsic electrical property of the neuronal membrane (Loewenstein and Mendelson 1965). Harper (1991) has shown that these adaptive properties of the distal nerve fibers are qualitatively the same in the cell bodies, regardless of whether they are stimulated by direct current injection or by stimulating the skin. He suggested that the adaptation properties may be due

to the presence of specific types of ion channels in the membrane of the soma and nerve endings.

Membrane properties associated with tonic and phasic firing patterns

The biophysical basis for the different firing patterns encountered in DRG neurons is incompletely understood. One plausible hypothesis is that differences in the properties of the action potential waveform promote one or the other firing pattern. Table 1 presents a comparison of several parameters related to the action potential recorded from tonic and phasic neurons. The parameter that most consistently distinguishes tonic and phasic neurons is that tonic neurons have a lower current threshold (rheobase). This may reflect expression of different isoforms of Na^+ or K^+ channels between these two types of neurons (see below).

Another approach to classify neurons is based on the specific types of ion channels that they express. It is difficult to measure the firing pattern and isolate ionic currents in the same cell, because isolating different currents generally requires ionic substitutions and the use of channel blocking drugs that are incompatible with AP generation (Cummins et al. 2009). One way to circumvent this problem is to record currents from subpopulations of previously defined phasic or tonic neurons. This approach has allowed some progress on defining the classes of ion channels involved in controlling firing frequency in sensory neurons. However, as described below, sensory neurons express many different ion channels, and it has been difficult to determine specific combinations that will lead to tonic or phasic firing.

Since before the recognition of the molecular identities of the ion channels, the depolarizing upstroke of the action potentials has been attributed to Na^+ influx (Hodgkin and Huxley 1952). Sensory neurons are endowed with multiple isoforms of voltage-gated sodium (Na_V) channels that differ in their kinetics and voltage dependence, and make distinct contributions to the depolarization and repolarization phases of the action potential (reviewed by Rush et al. 2007). Different Na_V subunits can be distinguished based on their sensitivity to tetrodotoxin and scorpion toxins (Moraes et al. 2011). In sensory neurons, $\text{Na}_V1.7$ channels, and in some subpopulations also $\text{Na}_V1.8$ and $\text{Na}_V1.9$, determine the upstroke. $\text{Na}_V1.8$ channels are required for repetitive firing (reviewed by Han et al. 2016). Indeed, slow inactivation of $\text{Na}_V1.8$ is one of the causes of spike rate adaptation in DRG neurons (Blair and Bean 2003). $\text{Na}_V1.6$ and $\text{Na}_V1.2$ are responsible for a resurgent current that produces afterdepolarization and increases firing rate (Do and Bean 2004; Grieco et al. 2005). In DRG, $\text{Na}_V1.6$ solely perform this role (Cummins et al. 2005). Different types of sensory neurons express different proportions of these Na_V channels (Schild and Kunze 1997; McCleskey and Gold 1999),

Table 1 Differences in action potential properties of sensory neurons classified according to their firing pattern (tonic versus phasic) in dorsal root or trigeminal (*) ganglia

Parameter	Differences observed in tonic versus phasic neurons	References
Rheobase	Lower	Catacuzzeno et al. (2008)*; Yu et al. (2014); Freisinger et al. (2013); Tang et al. (2016)
Membrane resistance	No difference	Sculptoreanu and de Groat (2007); Tang et al. (2016)
	Higher	Catacuzzeno et al. (2008)*
Action potential threshold	More depolarized	Freisinger et al. (2013)
	No difference	Tang et al. (2016)
Resting membrane potential	Less negative	Catacuzzeno et al. (2008)*; Tang et al. (2016)
	No difference	Sculptoreanu and de Groat (2007); Yu et al. (2014)
Membrane capacitance	Larger	Sculptoreanu and de Groat (2007)
	Smaller	Catacuzzeno et al. (2008)*
	No difference	Yu et al. (2014)
Overshoot	Higher	Freisinger et al. (2013)
	No difference	Tang et al. (2016)
AP duration	No difference	Tang et al. (2016)
	Longer	Catacuzzeno et al. (2008)*; Freisinger et al. (2013)
AP height	No difference	Catacuzzeno et al. (2008)*
AHP amplitude	Larger	Catacuzzeno et al. (2008)*
	Smaller	Yu et al. (2014)
	No difference	Tang et al. (2016)
AHP duration	Longer	Freisinger et al. (2013)
	Shorter	Catacuzzeno et al. (2008)*; Tang et al. (2016)

which contributes to the diversity of action potential shape and firing patterns encountered in these cells.

In DRG neurons, voltage-gated Ca^{2+} channels (Ca_V) can also participate in DRG action potential generation (Blair and Bean 2003). In the absence of functional voltage-gated sodium channels, Ca_V channels are capable of regenerative depolarization (Chen et al. 1987). There are multiple isoforms of Ca_V channels (reviewed by Simms and Zamponi 2014), and sensory neurons express several types. One interesting example of calcium channels directly controlling the firing rate was demonstrated for the Ca_V regulatory subunit $\alpha 2\delta$ -1 (Margas et al. 2016). The deletion of this subunit induced reduced mechanical and cold sensitivity, and reduced I_{Ca} and AP number in DRG neurons. This seems to be a direct effect of Ca_V , since calcium-activated potassium channels were not involved in these phenomena.

Potassium channels counteract depolarization and reduce excitation. They belong to the most diverse class of voltage-gated ion channels and different populations of DRG neurons express distinct subunits (reviewed by Moldovan et al. 2013). Most neurons express one or more types of delayed rectifier K^+ channels that provide sustained K^+ current during a depolarization. Many sensory neurons are sensitive to the dendrotoxins that inhibit K_V1 delayed rectifying K^+ channels (Harvey 2001), resulting in increased excitability. In some cases, dendrotoxin converts phasic neurons to tonic (Glazebrook et al. 2002; Catacuzzeno et al.

2008), indicating that $\text{K}_V1.1$ and $\text{K}_V1.2$ channels are essential to keep phasic neurons phasic. Reduction in the level of dendrotoxin-sensitive K^+ current is associated with the increase in excitability after nerve damage (Song et al. 2012).

In addition to the delayed rectifier, neurons with graded discharge rates express a distinctively fast activating and inactivating potassium current. This current, termed I_A , is selectively blocked by 4-aminopyridine (reviewed by Carrasquillo and Nerbonne 2014). The initial descriptions of this current (Connor and Stevens 1971) demonstrated its importance in determining the firing frequency of tonic neurons. After a spike, the afterhyperpolarization removes inactivation from I_A channels. As the neuron depolarizes towards threshold, I_A activates, thus prolonging the interspike interval. In DRG neurons, $\text{K}_V1.4$ (Rasband et al. 2001; Vydyanathan et al. 2005), $\text{K}_V3.4$ (Ritter et al. 2015), $\text{K}_V4.1$ (Yunoki et al. 2014), and $\text{K}_V4.3$ (Yunoki et al. 2014; Kuo et al. 2017) contribute to I_A . Catacuzzeno et al. (2008) have shown that 4-aminopyridine eliminated a delay to the first AP in a subtype of tonic neurons. These data suggest that I_A is responsible for the delay in those neurons. Other studies indicate that a decrease in I_A mediates increased excitability produced by angiotensin (Moreira et al. 2009) or diabetic neuropathy (Cao et al. 2010). Conversely, increased I_A by activation of serotonin 1D receptors decreases excitability (Zhao et al. 2016). Given its well established role in controlling graded AP frequency, it is,

therefore, surprising that no difference was found in the level of I_A when comparing phasic or tonic neurons (Tang et al. 2016).

KCNQ ($K_{V7.X}$) channels (reviewed by Brown and Passmore 2009), that are responsible for the slowly activating and non-inactivating M currents, are present in DRG neurons. Retigabine, which activates K_{V7} , raises the action potential threshold and decreases the firing rate of sensory fibers (Rivera-Arconada and Lopez-Garcia 2006; Lang et al. 2008). The K_{V7} blockers XE991 and linopirdine, in sympathetic neurons, switch phasic neurons to tonic (Brown and Passmore 2009).

Ca-activated K channels, K_{Ca} , also contribute to repolarization and adaptation. Zhang et al. (2010) have shown that 90% of the small IB4-positive DRG neurons from the skin have K_{Ca} currents and RT-PCR of mRNA from these neurons shows the expression of multiple splice variants. Yu et al. (2015) have shown that CaMKII blockage increases sensory sensitivity and DRG neurons firing rate. K_{Ca} blockers, apamin and iberotoxin, have the same effect as CaMKII blockage and occluded its effect on membrane excitability.

Chloride channels form a large family of anion-selective channels (reviewed by Duran et al. 2010). The reversal potential for Cl^- is variable from cell to cell, so the opening of channels selective for Cl^- can lead to either reduced excitation or depolarization. In DRG neurons, the calcium-activated chloride channels promote depolarization (Mayer 1985) and their activation by inflammatory mediators induces repetitive firing (Salzer et al. 2016).

HCN channels are cyclic nucleotide modulated mixed cation channels. In DRG neurons, they have been implicated in the activation of spontaneous firing (reviewed by Moldovan et al. 2013). It was demonstrated that HCN channels promote the transformation of phasic firing neurons into tonic (Sun et al. 2017).

It thus appears that no single channel type, or group of channel types, uniquely endows a neuron with a particular firing pattern. Rather, it seems that interplay of a number of different channel isoforms generating multiple types of ionic currents perform this role.

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Compliance with ethical standards

Conflict of interest Eder Ricardo de Moraes declares that he has no conflicts of interest. Christopher Kushmerick declares that he has no conflicts of interest. Lígia Araujo Naves declares that she has no conflicts of interest.

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