

Dynamic firing properties of type I spiral ganglion neurons

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Received: 30 September 2014 / Accepted: 17 November 2014 / Published online: 8 January 2015
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Abstract Spiral ganglion neurons, the first neural element in the auditory system, possess complex intrinsic properties, possibly required to process frequency-specific sensory input that is integrated with extensive efferent regulation. Together with their tonotopically-graded sizes, the somata of these neurons reveal a sophisticated electrophysiological profile. Type I neurons, which make up ~95 % of the ganglion, have myriad voltage-gated ion channels that not only vary along the frequency contour of the cochlea, but also can be modulated by regulators such as voltage, calcium, and second messengers. The resultant developmentally- and tonotopically-regulated neuronal firing patterns conform to three distinct response modes (unitary, rapid, and slow) based on threshold and accommodation. This phenotype, however, is not static for any individual type I neuron. Recent observations have shown that, as neurons become less excitable with age, they demonstrate enhanced plasticity enabling them to change from one response mode to another depending upon resting membrane potential and the presence of neurotrophin-3. Thus, the primary auditory afferents utilized to encode dynamic acoustic stimuli possess the intrinsic specializations that allow them dynamically to alter their firing pattern.

Keywords Primary auditory afferent · Accommodation · Neurotrophins · Membrane kinetics · Threshold voltage

Introduction

Type I spiral ganglion neurons, which comprise ~95 % of the cochlear afferent innervation, are solely responsible for

transmitting synaptic input from inner hair cell (IHC) sensory receptors into the central nervous system (CNS) for further processing. Despite their central importance for electrogenic transmission, only relatively recently have their intrinsic properties and potential contribution to sensory encoding been examined. The morphological simplicity of bipolar type I spiral ganglion neurons, which innervate a single IHC and elaborate a uniform peripheral innervation pattern, belies a deceptively rich signaling capability. This sophistication arises from a vast array of endogenous voltage-gated ion channels that have the capacity for short-, intermediate- and long-term regulation.

The intrinsic response properties of spiral ganglion neurons are not only complex but dynamic. Studies have found that spiral ganglion neurons differ in the kinetics and sensitivity of their firing based on stage of development, tonotopic location, resting membrane potential (RMP) and neurotrophin exposure. Despite this wide diversity, however, these primary afferents conform to three clearly defined accommodation classes that establish a strict framework in which the proportion of cells within each category can be altered dynamically. Moreover, as spiral ganglion neurons mature and become more uniform, their responses to voltage and neurotrophin-3 (NT-3) reveal the potential for greater modulation. Because spiral ganglion neurons are critical for stimulus detection and subsequent processing, their electrophysiological complexity and plasticity reveals much about the way that spiral ganglion neurons control the flow of auditory information into the brain.

Electrophysiologically unique type I somata

The primary auditory afferents are responsible for encoding the full scope and spectrum of the acoustic signal. The bipolar type I neurons, the focus of this review, make one-to-one synaptic connections with IHC sensory receptors (Fig. 1a).

The work of the authors is supported by NIH NIDCD RO1 DC01856.

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Approximately 10–30 type I spiral ganglion neurons innervate each IHC (Spoendlin 1973), thus forming a divergent neural pathway suggestive of parallel processing. This organization is in contrast to the type II neurons that make up the remaining ~5 % of the spiral ganglion and that receive convergent input from up to 15–20 outer hair cells (Spoendlin 1973).

At first glance, the organization of the initial stage of acoustic processing appears to be straightforward. Synaptic input from a single sensory receptor assures that frequency-specific information is transmitted from IHCs to type I neurons (Fig. 1a, black arrow). Once received, the signal is then conveyed into the CNS in which three separate frequency maps are constructed in the anterior ventral cochlear nucleus, posterior ventral cochlear nucleus and dorsal cochlear nucleus (AVCN, PVCN, DCN, respectively; Fig. 1a), thus giving rise to distinct parallel pathways (Cant and Benson 2003; Carr et al. 2001).

An initial indication that sound encoding in the auditory periphery is more complex than one might expect, however, can be found in the bipolar morphology of the type I spiral ganglion neurons. Although seemingly simple, it is significant that the spike-initiation zone is localized distal to the soma (Fig. 1a, red action potential demarcates the first heminode

that serves as the distal site of action potential generation; Hossain et al. 2005). Thus, action potentials must travel through the soma before reaching their central targets (Fig. 1a, red dotted arrow). Distinct from typical CNS neurons, the spike-initiation zone in the spiral ganglion abuts the afferent and efferent synaptic input (Fig. 1a, arrow and double arrowhead, respectively) and is positioned before the soma rather than after it. This arrangement potentially places constraints on the size and membrane properties of the neuronal somata and might affect the initial states of neuronal processing in the auditory system.

A clear example of the importance of the morphological parameters is that somatic size varies systematically along the tonotopic contour. The largest neuronal somata are localized at the high-frequency basal region, whereas the smallest are localized at the low-frequency apical region (Echteler and Nofsinger 2000; Liberman and Oliver 1984; Nadol et al. 1990; Rosbe et al. 1996). These tonotopic-associated changes in soma size not only serve potentially to filter action potentials (Robertson 1976) but could also differentially regulate conduction time through the soma, since this parameter is dependent on membrane area, input resistance and the length constant (Johnston et al. 1995).

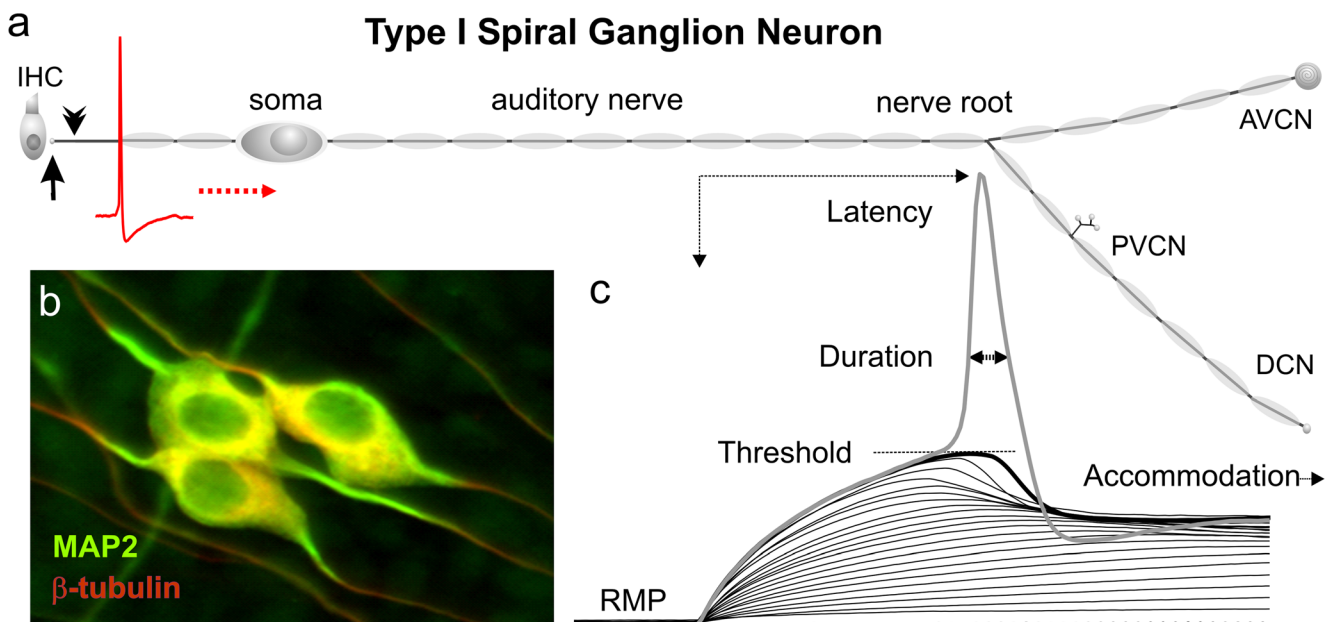


Fig. 1 Spiral ganglion somata interposed in the conduction pathway possess a chimeric phenotype displaying features of both axons and dendrites. **a** The simple bipolar morphology of the type I spiral ganglion neuron. The soma elaborates a distal process that innervates a single inner hair cell (IHC) and a proximal process that ultimately innervates the anterior ventral cochlear nucleus (AVCN), posterior ventral cochlear nucleus (PVCN) and dorsal cochlear nucleus (DCN). At the region of the afferent connection (black arrow), efferent fibers originating in the lateral superior olivary nucleus form synaptic connections on the postsynaptic membrane (double arrowhead). The distal spike-initiation zone is denoted by an action potential (red) that is conducted through the type I soma (dotted red arrow). The gray profiles

along the length of the distal and proximal processes represent compact myelin; the gray profile around the cell soma represents loose myelin. **b** Three bipolar spiral ganglion neurons labeled with anti-microtubule-associated protein 2 (MAP2, green) and anti-type III- β -tubulin (red) antibodies; regions of overlap are yellow. **c** Superimposed whole-cell current clamp sweeps from a single neuron are composed of subthreshold traces (thin black traces), the most depolarized of which (thick black trace) indicates the action potential threshold voltage (thick gray trace). Electrophysiological parameters that characterize the action potential at threshold are indicated (RMP resting membrane potential). **b** Re-published with permission (Chen et al. 2011)

Even the myelin sheath that wraps spiral ganglion somata is specialized. It is composed of a unique type of myelin, termed loose myelin, which differs from compact myelin not only in its structure (Romand and Romand 1987; Rosenbluth 1962) but also by likely permitting continuous electrogenic signaling of the underlying somatic membrane (Robertson 1976). In conjunction with this, a protein typically associated with the integrating membrane of dendrites, namely microtubule-associated protein 2 (MAP2), is localized to the somatic membrane and the processes that extend to either side (Fig. 1b, green/yellow) but is reduced or absent along the axonal membranes that extend further distally and proximally (Fig. 1b, red). Thus, the somatic membrane of spiral ganglion neurons, although separate from the postsynaptic region, appears to possess features that could independently affect signaling.

The impact of neuronal somata on signal transmission is not limited to cell structure but is also evident in the diversity of the voltage-gated ion currents that they contain (Chen 1997; Jagger and Housley 2002; Kim and Holt 2013; Liu et al. 2014b; Lv et al. 2012; Mo et al. 2002; Szabo et al. 2002; Wang et al. 2013). Direct analysis of the electrophysiological phenotype of spiral ganglion neurons via intracellular whole-cell current clamp recordings (Fig. 1c) has shown that parameters such as resting membrane potential, latency to the first spike, action potential duration, voltage threshold and accommodation (Fig. 1c) are all intimately controlled by intrinsic voltage-gated ion currents (Rusznak and Szucs 2009). Assessment of these firing features from spiral ganglion neurons throughout development and in various ganglionic regions has shown, further, that somatic recordings are quite diverse and can vary dramatically from cell to cell (Lin 1997; Lv et al. 2012; Marrs and Spirou 2012; Mo and Davis 1997a).

Multifaceted electrophysiological properties of spiral ganglion neurons

Consistent with the diversity of the underlying voltage-gated ion currents in the spiral ganglion, many studies have shown a wealth of heterogeneity in the neuronal firing patterns. For example, type I neurons are capable of firing with “fast” or “slow” features depending on their tonotopic location (Adamson et al. 2002b). As exemplified in Fig. 2a, two superimposed recordings from postnatal neurons with similar holding potentials and voltage thresholds show distinct differences in their timing. Electrophysiological parameters that are altered include onset time course (Fig. 2a, i), latency to peak voltage (Fig. 2a, ii), action potential duration (Fig. 2a, iii) and the time course of the afterhyperpolarization (Fig. 2a, iv). Interestingly, irrespective of whether they contribute directly

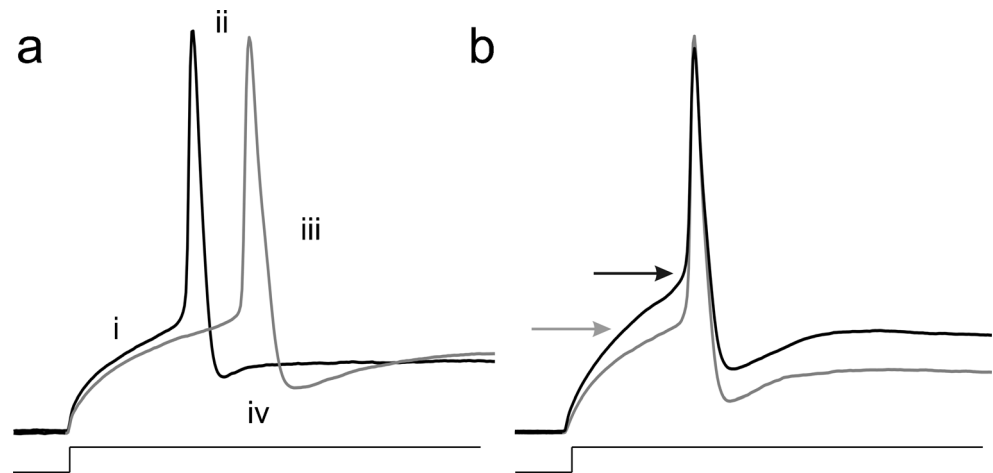
to frequency coding, these kinetic features are related to the tonotopic map. The slower firing features (Fig. 2a, gray trace) predominate in apical low-frequency neurons, whereas the faster firing features (Fig. 2a, black trace) typify basal high-frequency spiral ganglion neurons (Adamson et al. 2002a, b; Chen et al. 2011; Mo and Davis 1997a, b; Reid et al. 2004; Zhou et al. 2005).

Studies have also shown that spiral ganglion neurons differ in the voltage level of action potential threshold (Liu and Davis 2007; Mo and Davis 1997b). When neurons with similar kinetic features (action potential duration, peak voltage and afterhyperpolarization kinetics) are compared, for example, they can differ substantially in the voltage required to achieve threshold. This is exemplified by two recordings from different cells at action potential threshold (Fig. 2b). The recording from one neuron requires a much higher voltage to initiate an action potential (Fig. 2b, black trace, arrow) compared with another recording in which the voltage threshold level is significantly lower (Fig. 2b, gray trace, arrow). Whereas voltage thresholds can be remarkably heterogeneous throughout the ganglion, studies have shown that spiral ganglion neurons with the lowest thresholds are localized to the mid-ganglion region (Liu and Davis 2007; Liu et al. 2014b). Similarly, the RMP varies such that the highest voltage levels are found in mid-ganglion neurons (Liu et al. 2014a). This situation is comparable with neurons *in vivo* that have the greatest sensitivity in the mid-frequency region (Muller et al. 2005; Taberner and Liberman 2005) and thus might possess the same underlying endogenous electrophysiological features (hyperpolarized thresholds and depolarized RMPs) that possibly contribute to this characteristic.

Accommodation, which is a hallmark of other primary sensory afferents (Cleland et al. 1971; Loewenstein and Mendelson 1965), is also a feature of spiral ganglion neurons (Crozier and Davis 2014). Although a number of studies have reported differences in the way that accommodation relates to tonotopy, development, or neurotrophin effects, one thing is clear: spiral ganglion neurons are capable of firing to prolonged stimulation with a diversity of responses (Crozier and Davis 2014; Lin 1997; Lv et al. 2012; Mo and Davis 1997b). As shown in Fig. 3a, some spiral ganglion neurons fire only a single action potential irrespective of the level of depolarizing current injection, termed unitary accommodation (UA, Fig. 3a, gray square). Rapidly accommodating (RA) neurons are distinguished from UA neurons in that they are capable of firing more than one action potential but do not fire throughout a prolonged (240 ms) constant current injection (Fig. 3a, light gray circles). The third category, typified by repetitive firing throughout the duration of the step depolarization, is composed of slowly accommodating (SA) neurons (Fig. 3a, dark gray circles).

Neuronal characteristics within each of these accommodation classes are not all identical. For example, the number of

Fig. 2 Action potentials recorded from each spiral ganglion neuron have unique features. **a** Action potentials with “fast” (*black*) and “slow” (*gray*) characteristics recorded from two different postnatal spiral ganglion neurons show similar threshold voltages but different kinetics (*i* onset time course, *ii* latency, *iii*, action potential duration, *iv* afterhyperpolarization). **b** Action potentials with high (*black*) and low (*gray*) voltage thresholds (*arrows*) but essentially identical kinetic features



action potentials that are generated in response to a prolonged depolarization (APmax) is related to the interspike interval for neurons within the RA and SA response modes and they also display distinct firing frequencies ranging from 50 to >200 Hz (Crozier and Davis 2014). This feature can be most clearly observed for SA neurons (Fig. 3a, dark gray circles and three associated traces) in which the number of action potentials ranges from 11 to 40 and can be fitted with a single exponential (Fig. 3a, red line). The instantaneous firing rate for RA neurons, while not forming a specific function, also spans a similar range (Fig. 3a, light gray circles). RA and SA neurons are, thus, capable of displaying diverse firing rates that are distinct from one neuron to the next. This property highlights further the electrophysiological scope of the type I neurons that comprise the spiral ganglion.

Complex types and combinations of voltage-gated ion channels

The heterogeneous kinetics, threshold, RMP, accommodation and rate described above undoubtedly require a broad substrate of voltage-gated ion channels in order to orchestrate this wide complexity. Amongst the specializations observed in the spiral ganglion, the myriad types and classes of voltage-gated ion channel α -subunits that they possess are particularly striking (Table 1). Moreover, the distribution patterns of specific ion channel types explored with immunocytochemistry are remarkably diverse. As described in more detail below, some electrophysiologically relevant proteins are graded along the tonotopic contour of the ganglion, whereas others are differentially distributed along the scala tympani/scala vestibuli axis, which is associated with differing levels of spontaneous firing rates and yet others display heterogeneity throughout. In combination, this diverse set of ion channels has the capability of modulating the frequency of firing and of modifying action potential threshold, RMP, onset time course and action

potential duration (Child and Benarroch 2014; Jentsch et al. 2000; Rudy 1999; Rudy and McBain 2001), all of which have a profound impact on primary afferent encoding capabilities.

When considering the ways in which ion channels contribute to the endogenous membrane properties of the spiral ganglion neurons, one must first take the multifaceted interactions between the various classes of ion channels into account. The activation of voltage-gated calcium channels (VGCCs), for example, can either directly depolarize a cell or, conversely, hyperpolarize it when paired with calcium-activated potassium channels. Thus, VGCCs have a varied impact on neuronal firing patterns by underlying opposing effects, such as the broadening or truncation of action potential duration. Furthermore, by understanding the kinetics and voltage-dependence of the various ion channel classes, their potential roles can be inferred. For example, the role of low-voltage-activated ion channels can be contrasted to that of high-voltage-activated ion channels, since they differentially contribute to threshold and supra-threshold firing activity, respectively. The separation of the ion channels into non-voltage-activated, low-voltage-activated and high-voltage-activated for the spiral ganglion paints a picture of a highly regulated electrophysiological system.

Low-voltage-activated channels The hyperpolarizing leak currents identified in the spiral ganglion (Chen and Davis 2006) serve to drive the resting membrane potential towards the K^+ channel reversal potential (Plant et al. 2005). These two-pore domain K^+ channels are balanced by the abundance of low-voltage-activated cationic (hyperpolarization-activated cyclic nucleotide-gated channel, HCN), potassium (K_v1 , K_v4) and calcium (Ca_v3) channels, each contributing to spiral ganglion neuronal firing patterns (Fig. 1c). The I_h currents are carried by the α -subunits HCN1, -2 and -4 in ganglion neurons with HCN3 being expressed at extremely low levels in postnatal mice and either absent or below detection levels in adults (Kim and Holt 2013). Whereas these

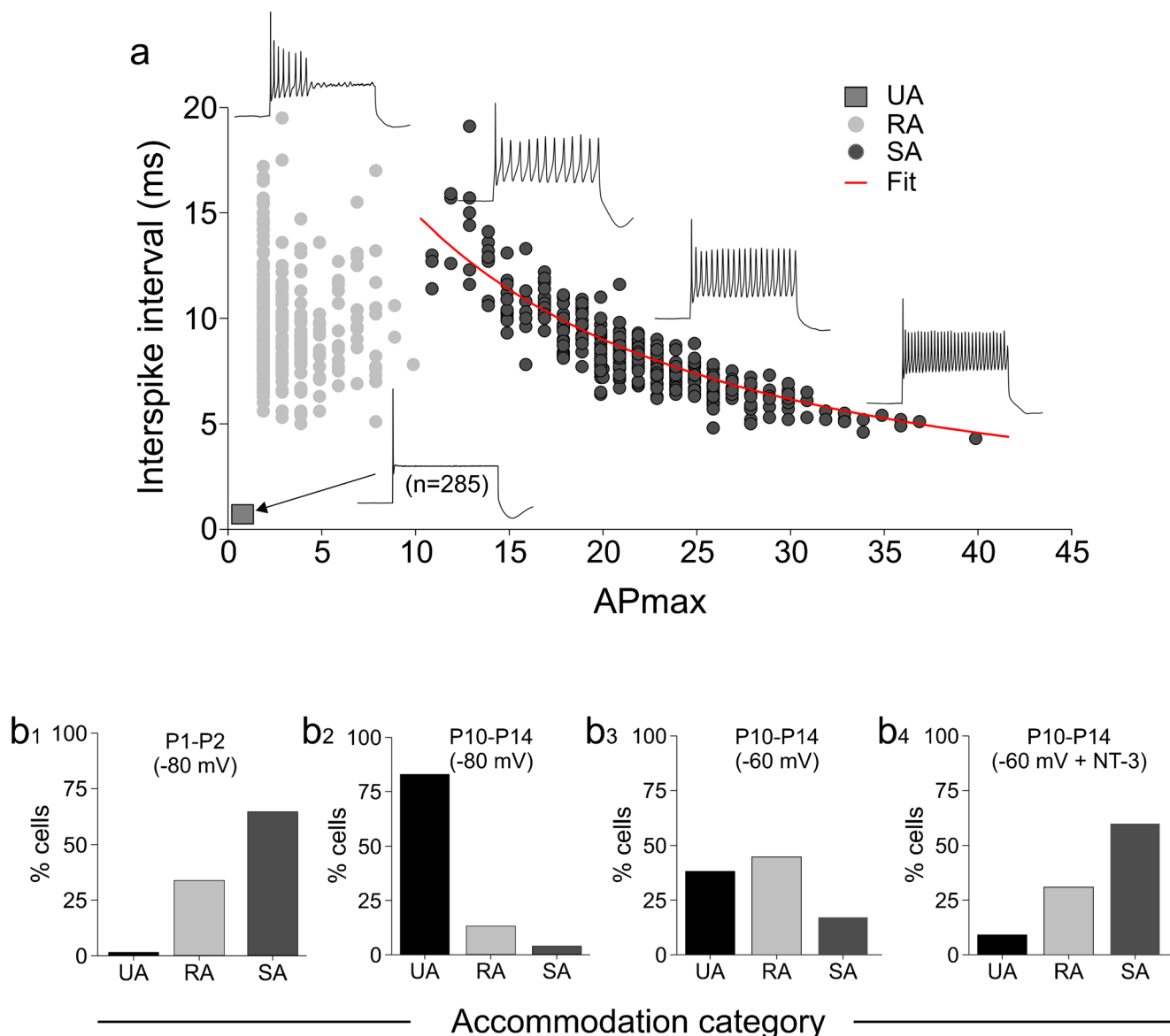


Fig. 3 Spiral ganglion neuron response properties can be categorized within a strict modal framework. **a** Interspike interval plotted against maximum number of action potentials at supra-threshold stimulation (APmax) for 972 experimental paradigms. Unitary accommodating (UA, gray square) neurons fire only one action potential (assigned an interspike interval of 1) during a 240 ms test pulse, rapidly accommodating (RA, light gray circles) neurons cease firing during the test pulse, whereas slowly accommodating (SA, dark gray circles) neurons fire throughout the test pulse. A single representative sweep is shown for UA and RA response modes, whereas three representative

sweeps are shown for the SA category to illustrate the range of firing rates displayed by individual neurons. A single exponential ($R^2=0.73$, red line) was fitted to the SA data. **b** Bar charts represent the percentage of cells in each accommodation category (UA, RA, and SA) with age (P postnatal day). P1-P2 at -80 mV (**b1**), P10-P14 at -80 mV (**b2**), P10-P14 at -60 mV (**b3**) and P10-P14 at -60 mV + NT-3 (**b4**). Note that P1-P2 and P10-P14 neurons show widely different response mode distributions when held at -80 mV but are remarkably similar when held at -60 mV and supplemented with neurotrophin-3 (NT-3). Data from Crozier and Davis (2014), re-published with permission

channel types affect the RMP in spiral ganglion neurons (Liu et al. 2014a), their specific contributions have the potential for additional fine control. Beyond their distinct voltage-dependence, each HCN α -subunit also displays differences in the time-course of activation and sensitivity to cAMP and cGMP (Pape 1996; Robinson and Siegelbaum 2003). Thus, the existence of multiple HCN α -subunits that combine in various

ratios suggests the potential for highly varied RMPs in spiral ganglion neurons, which could be dynamically modulated.

The threshold for firing and subsequent conduction of an action potential in a primary afferent has an obviously powerful impact on the detection of sensory stimuli. Therefore, expectedly, more than one class of channel might control neuronal excitability in the spiral ganglion. One prominent

Table 1 Ion channels in the spiral ganglion (*BK* large-conductance calcium-activated potassium channel, *HCN* hyperpolarization-activated cyclic nucleotide-gated channel, *SK* small conductance calcium-activated potassium channel, *TASK* two-pore-domain channel, *THIK* tandem pore domain halothane-inhibited K⁺ channel, *MAP* microtubule-associated

protein channel, *MBP* myelin basic protein, *SGN* neuronal soma, *Ax* axon, *M* myelin, *LM* loose myelin, *SC* satellite cells, *NSC* non-myelinating Schwann cells, *MSC* myelinating Schwann cells, *P* postnatal, *A* adult, *E* embryonic, *E* electrophysiology, *I* immunocytochemistry, *ISH* in situ hybridization, *R* polymerase chain reaction of RNA, *W* Western blot)

Ion channel	Localization	Age/species	Method	Reference
BK	SGN	E,P,A/Mouse; A/Guinea pig; P/Rat	E, I, ISH, R	Chen and Davis 2006; Hafidi et al. 2005; Langer et al. 2003; Skinner et al. 2003; Adamson et al. 2002a, b
BKβ1	SGN	P/Rat	ISH, R	Langer et al. (2003)
BKβ4	SGN	P/Rat	ISH, R	Langer et al. (2003)
Ca _v 1.2	SGN, NSC, MSC	P,A/Mouse; A/Chinchilla; A/Guinea pig	E, I, R	Chen et al. 2012, 2011; Layton et al. 2005; Lin 1997; Lopez et al. 2003; Xie et al. 2007; Zuccotti et al. 2013
Ca _v 1.3	SGN	P,A/Mouse; P,A/Rat	E, I, W, R	Chen et al. 2012, 2011; Lv et al. 2012, 2014
Ca _v 2.1	SGN, NSC, MSC	P,A/Mouse; A/Chinchilla	E, I, R	Chen et al. 2011; Lopez et al. 2003; Lv et al. 2012, 2014
Ca _v 2.2	SGN	P,A/Mouse; A/Chinchilla	E, I, R	Chen et al. 2011; Lopez et al. 2003; Lv et al. 2012
Ca _v 2.3	SGN, NSC, MSC	P,A/Mouse; A/Chinchilla	E, I, R	Chen et al. 2011; Lopez et al. 2003; Lv et al. 2012
Ca _v 3.1	SGN, NSC, MSC	P,A/Mouse	E, I, R	Chen et al. 2011; Lv et al. 2012
Ca _v 3.2	SGN	P,A/Mouse	E, I, R	Chen et al. 2011; Lv et al. 2012
Ca _v 3.3	SGN	P,A/Mouse	E, I, R	Chen et al. 2011; Lv et al. 2012
HCN1	SGN	P,A/Mouse	E, I	Kim and Holt 2013; Yi et al. 2010; Liu et al. 2014b
HCN2	SGN	P,A/Mouse	E, I, R	Kim and Holt 2013; Yi et al. 2010
HCN4	SGN	P,A/Mouse	E, I, R	Kim and Holt 2013; Yi et al. 2010; Liu et al. 2014b
K _v 1.1	SGN	P,A/Mouse; A/Guinea pig	E, I, R	Chen and Davis 2006; Adamson et al. 2002a, b; Liu et al. 2014a; Reid et al. 2004; Bakondi et al. 2008; Wang et al. 2013
K _v 1.2	SGN	P/Mouse; A/Guinea pig	E, I	Liu et al. 2014a; Bakondi et al. 2008; Wang et al. 2013
K _v 3.1	SGN	P,A/Mouse; A/Guinea pig	I, R	Chen and Davis 2006; Adamson et al. 2002a, b; Bakondi et al. 2008
K _v 3.3	SGN	P/Mouse	I, R	Chen and Davis 2006
K _v 4.2	SGN	P,A/Mouse; A/Guinea pig	I, R	Chen and Davis 2006; Adamson et al. 2002a, b; Bakondi et al. 2008
K _v 7	SGN	P,A/Mouse	E, I, R	Beisel et al. 2005; Lv et al. 2010
Kir	SC, NSC	P,A/Rat	I, R	Hibino et al. 1999
Na _v 1.1	SGN	A/Rat	I, R	Fryatt et al. 2009
Na _v 1.6	SGN	A/Mouse & Rat	I, R	Fryatt et al. 2009; Hossain et al. 2005
Na _v 1.7	SGN	A/Rat	I, R	Fryatt et al. 2009
SK1	Absent or below detection	P,A/Rat	ISH	Dulon et al. 1998
SK2	SGN	P,A/Rat	ISH	Dulon et al. 1998
SK3	SGN	P,A/Rat	ISH	Dulon et al. 1998
TASK-1		P/Mouse	R	Chen and Davis 2006
TASK-3		P/Mouse	R	Chen and Davis 2006
THIK-2		P/Mouse	R	Chen and Davis 2006
TRAAK		P/Mouse	R	Chen and Davis 2006
TREK-1		P/Mouse	R	Chen and Davis 2006
TWIK1	SGN	P/Mouse	I, R	Chen and Davis 2006
MAP2	SGN	P/Mouse; A/Human; P,A/Rat	I	Chen et al. 2011; Anniko et al. 1995; Hafidi et al. 1992
MBP	MSC	P,A/Rat; A/Guinea pig	I	Toesca 1996; Liu et al. 2014c

channel type is the low-voltage-activated, slowly inactivating $K_v1.1$ channel, which contributes to setting the RMP and consequently affects the voltage threshold at which an action potential is fired (Liu et al. 2014a). In the somatosensory system, $K_v1.1$ density is associated with each mechanoreceptor class of neuron and is intimately tied to sensitivity (Liu et al. 2014a; Weiss et al. 1999). In the spiral ganglion, $K_v1.1$ channels can determine whether a primary afferent will fire an action potential at a particular voltage and will also set its accommodation (Liu et al. 2014a). This association indicates a firing profile in which the most excitable cells, with the lowest thresholds, have a tendency to accommodate more slowly. When taken together, this behavior is consistent with the relationship between the spontaneous rate/level and threshold measured in vivo (Lieberman 1982).

The latency between stimulus onset and action potential firing is typically controlled by low-voltage-activated, rapidly-inactivating ion channels. Two such ion channels characterized within the spiral ganglion fit this description, yet each with opposite actions. The $K_v4.2$ channel serves to delay action potential firing, whereas the T-type calcium channels (Ca_v3) produce a more rapid threshold response. To date, little is known about the specific effects of $K_v4.2$ on the firing patterns of spiral ganglion neurons. Evidence is emerging that low-VGCCs can affect both the aforementioned action potential repolarization and also action potential latency at threshold (Chen et al. 2011), while having a minimal effect on threshold voltage (Suzuki and Rogawski 1989).

High-voltage-activated channels Once the threshold for action potential firing is reached, Na^+ influx through the $Na_v1.1$, $Na_v1.6$, or $Na_v1.7$ rapidly inactivating sodium channels quickly depolarizes the membrane potential (Hossain et al. 2005; Fryatt et al. 2009). Subsequently, the possibility increases for action potential waveform regulation. In this phase of the response, it is the high-voltage-activated ion channels that predominate. As described for neurons within the auditory central pathways, $K_v3.1$ and $K_v3.3$ are uniquely suited to rapidly repolarize the action potential in a system in which timing is of the utmost importance (Li et al. 2001). This is accomplished not by the classic delayed rectifier (Hodgkin and Huxley 1952) but rather by a rapidly activating ion channel, the delay of which is dependent directly on voltage (Kanemasa et al. 1995). Therefore, the kinetics of repolarization depend only upon the time that it takes to reach the activation voltage of the $K_v3.1/3.3$ channels, allowing for the maximum speed of repolarization, without affecting action potential amplitude. Counteracting these high-voltage-activated K^+ channels, are the high-voltage-activated VGCCs that can prolong the action potential duration (Chen et al. 2011). Following these are large-conductance calcium-activated potassium (BK) and small

conductance calcium-activated potassium (SK) channels that typically operate at more depolarized voltages and orchestrate longer-term effects, such as the regulation of the timing of interspike intervals and, along with K_v1 channels, accommodation.

Whereas ion channel contributions to the electrophysiological phenotype are relatively complex, additional levels of regulation must nonetheless also be taken into account. An example is whether some of these ion channel contributions are confined to specific developmental periods. Some ion channel types have been shown to be found exclusively in embryonic or early postnatal animals (Kim and Holt 2013), whereas others can be retained into adulthood. Some inroads have been made in determining the ion channel composition of adult spiral ganglion neurons by using approaches such as immunocytochemistry and in situ hybridization on cochlear sections. In addition to their tonotopic distribution (Adamson et al. 2002b; Langer et al. 2003), many of the ion channel types identified in young animals are also observed in adult tissues (Table 1). Thus, although their specific contributions remain to be determined in the fully functional auditory system, much of the electrophysiological complexity identified in postnatal ganglia is retained into adulthood.

Spiral ganglion neurons show location-dependent firing features

The voltage-gated ion channels described above have been shown to have corresponding tonotopic distribution patterns in both postnatal and adult ganglion paraffin-embedded tissue sections (Adamson et al. 2002b). The K^+ channels responsible for shaping rapid accommodation, abbreviated action potentials and short latencies ($K_v1.1$, $K_v3.1$, BK) have all been found at higher densities in basal neurons compared with apical ones. Conversely, one K^+ channel type known to increase latency ($K_v4.2$) has been localized in the opposite spatial gradient. Similarly, the presynaptic proteins synaptophysin and SNAP-25 have an apical-to-basal neuronal gradient, whereas the AMPA receptors $GluA_2$ and $GluA_3$ are distributed in the opposite spatial gradient (Flores-Otero and Davis 2011; Flores-Otero et al. 2007).

The basal-to-apical tonotopic contour representing a high-to-low frequency map is punctuated in the middle by the most sensitive region of hearing (Heffner et al. 1994; Koay et al. 2002; Ruggero and Temchin 2002). This frequency map is also transected by an orthogonal, scala vestibuli/scala tympani (SV/ST) organization of spontaneous rate and threshold level (Leake and Snyder 1989; Lieberman 1982). Interestingly, the lowest thresholds and highest RMP have been found in

neurons isolated from the mid-cochlear region (Liu and Davis 2007; Liu et al. 2014a), thus rendering the mid-ganglion neurons with endogenous properties that are potentially most sensitive and with greater ranges in excitability. In conjunction with this, $K_v1.1$, an ion channel type that increases voltage threshold and reduces RMP, is distributed in a predictable manner, such that its lowest levels have been found in the mid-cochlear region (Liu et al. 2014a). Patterns other than frequency-specific or tonotopic gradients might, in contrast, represent heretofore undiscovered organizational principles for the spiral ganglion. Thus, by mapping out the distribution patterns of a particular attribute at various stages of development, a better appreciation of its potential contribution can be gained.

Overlaid upon all of these observations, despite their clear and unique tonotopic-related distribution, is the marked heterogeneity displayed by spiral ganglion neurons. Although neurons between regions are significantly different, neurons within a tonotopic region are not identical. This integral aspect of the spiral ganglion neuron phenotype is a potentially compelling feature because it could underlie the early stages of parallel processing. Whereas some heterogeneous distributions are unpatterned, having no obvious morphological association, such as calcium-binding proteins (Liu and Davis 2014) and VGCCs (Chen et al. 2011; Lopez et al. 2003), synaptophysin has been found to be distributed in vivo as a dual gradient. Superimposed on its tonotopic gradient, this presynaptic vesicle-associated protein also displays an orthogonal gradient (Flores-Otero and Davis 2011). Thus, the local heterogeneity observed within each tonotopic region is graded; the highest immunolabeling density has been found in neurons closest to the ST, whereas the lowest density is present within neurons closest to the SV. This pattern is notable because it correlates not only with the representation of frequency along the tonotopic contour but also simultaneously with the spontaneous rate and threshold distributions that are aligned along the SV/ST axis (Leake and Snyder 1989).

The multidimensional response properties of type I spiral ganglion neurons and their underlying electrophysiological complexity revealed by the studies summarized above are consistent with electrophysiological observations of firing patterns in vivo. In addition to differences in characteristic frequency, spiral ganglion neurons in vivo show gradations in threshold (Lieberman 1978), differently shaped rate-intensity functions (Kiang 1965; Winter et al. 1990) and a wide range of spontaneous activity (Kiang 1965; Lieberman 1978; Schmiedt 1989) that can be placed into three groups (Lieberman 1978). These characteristics might arise from multiple sources, such as mechanical nonlinearities, synaptic regulation of neuronal firing (Evans 1992; Kiang 1990; Ruggero and Temchin 2002) and the endogenous electrical properties of the neurons themselves.

Spiral ganglion neuron response properties are dynamic

A salient feature of the voltage-gated ion channels listed in Table 1 is their ability to be dynamically regulated. For example, the voltage fluctuations that occur during ongoing activity are capable of altering the rapid inactivation of A-type potassium channels, such as $K_v4.2$. Alterations in internal Ca^{2+} concentration, through multiple mechanisms, can have effects either directly through depolarization or indirectly via activation of BK and SK channels, each having their own distinct time course of action (Adelman et al. 2012; Berkefeld et al. 2010). Furthermore, T- and L-type Ca^{2+} channels, HCN channels and select K^+ channel types can be modified by phosphorylation through multiple second messenger systems (Hille 2001). These posttranslational modifications can be initiated by extrinsic factors, such as efferent neurotransmitter receptors that are prevalent on the postsynaptic membrane of type I spiral ganglion neurons (Dulon et al. 2006). Lastly, long-term regulation by factors released by the target tissues, such as neurotrophins, can also change the subunit composition of many ion channel types through gene transcription (Lesser et al. 1997). Supporting this concept, studies have shown that the electrophysiological profile, ion channel α -subunits, presynaptic proteins and neurotransmitter receptor composition can be regulated by brain-derived neurotrophic factor (BDNF) and NT-3 (Adamson et al. 2002a; Crozier and Davis 2014; Flores-Otero et al. 2007; Sun and Salvi 2009; Zhou et al. 2005). Interestingly, neuron responses reflect the endogenous apex-to-base distribution of NT-3 and the base-to-apex distribution of BDNF at this stage of development (Farinas et al. 2001; Flores-Otero and Davis 2011; Fritzsche et al. 1997; Sugawara et al. 2007). Thus, although ion channel composition can be included into a manageable picture to improve our understanding of the firing capability of spiral ganglion neurons, the channels ultimately must be considered as a complex that includes modifying subunits together with other regulatory elements (e.g., Levitan 2006).

Whereas the complexity of the electrophysiological properties and their distributions are impressive, neurons within the spiral ganglion strictly conform to a defined framework of firing patterns best circumscribed by accommodation. From the very first recordings obtained from adult neurons (Santos-Sacchi 1993) to those characterized in embryonic and postnatal spiral ganglia (e.g., Marrs and Spirou 2012; Mo and Davis 1997a), these cells show levels of accommodation that fall into discrete groups (Fig. 3a). Although previous studies have included a UA response mode within the RA category, UA neurons have recently been shown to be distinguishable from RA neurons by their elevated thresholds (Crozier and Davis 2014). These same three response modes are observed whether neurons are isolated from early or late postnatal animals, exposed to NT-3, or maintained at differing holding potentials. However, it is the proportion of cells that display each of these

response modes that change predictably (Crozier and Davis 2014). Spiral ganglion neurons isolated from younger animals are more excitable, of which nearly 65 % display SA responses (Fig. 3b₁); by contrast, neurons from older animals at the same holding potential, particularly in the base, almost uniformly display UA responses (Fig. 3b₂).

Interestingly, these older neurons are not immutable; both voltage levels and NT-3 are capable of changing their response mode. Just by shifting the holding potential to a more depolarized level (Fig. 3b₃) or by exposing neurons to NT-3 (Adamson et al. 2002a; Zhou et al. 2005), the proportion of neurons that reside within each distinct response mode can be dramatically altered. A -60 mV holding potential in combination with NT-3 supplementation (10 ng/ml) shows that a high proportion of P10-P14 neurons (60 %) can once again be characterized predominately by the SA response mode (Fig. 3b₄). Thus, depending upon the conditions, the response properties of older postnatal animals can be made to resemble early postnatal ones (P1-P2; Fig. 3b₁). Surprisingly, spiral ganglion neuron intrinsic firing properties from older animals have the greatest capability to be dynamically regulated. This can occur within seconds by shifting RMP levels (Crozier and Davis 2014), over intermediate time periods by second messenger modulation (Mo and Davis 1997b), or over longer periods of time by neurotrophin regulation (Adamson et al. 2002a; Flores-Otero et al. 2007; Zhou et al. 2005).

Although the breadth of spiral ganglion neuron response properties appears to become more uniform as an animal ages (Fig. 4a, top), these same properties also become more dynamic over time (Fig. 4a, bottom). Whether neurons are originally isolated from the base or the apex of the ganglion, they all begin to display relatively similar, albeit not identical, “faster” firing properties. However, these same features become increasingly susceptible to differential regulation by voltage and NT-3. What remains constant is that the response profiles consistently fit within the UA, RA, and SA classes, and what changes is the percentage of neurons within these categories (Crozier and Davis 2014). Ultimately, the regulatory capability of NT-3 increases during development leading to a greater capacity for response mode plasticity (Fig. 4a, bottom).

In tandem with plasticity, it is interesting to note that not all response properties are subject to extrinsic regulation. Specifically, under these same conditions of depolarized RMP and NT-3 supplementation, the instantaneous firing rate remains constant, despite changes in accommodation and threshold. As shown in Fig. 4b, regardless of whether a particular neuron is held at either -80 mV or -60 mV, its instantaneous firing rate remains remarkably stable (Crozier and Davis 2014). This indicates a clear separation of mechanistic control over firing kinetics and neuronal excitability, a principle that has

also been observed in other circumstances. For example, the electrophysiologically assessed onset time course and latency that characterize firing kinetics are graded along the tonotopic contour, whereas threshold and RMP, which set neuronal excitability, display U-shaped and bell-shaped functions, respectively (Liu and Davis 2007; Liu et al. 2014a). Furthermore, developmental changes in action potential latency are accelerated relative to refinements in voltage threshold (Crozier and Davis 2014). Taken together, these observations present a compelling case that the timing and excitability features of spiral ganglion neurons are separately regulated.

The mechanisms underlying dynamic alterations in spiral ganglion neuron endogenous firing patterns and the differential regulation of timing and excitability features are undoubtedly derived from the modulation of the diverse set of low-voltage- and high-voltage-gated ion channels resident in these cells (Table 1). Because the dynamic response modes observed in spiral ganglion neurons are intimately associated with threshold, a straightforward expectation is that these plastic responses are predominately controlled by low-voltage-activated currents. Studies that have examined the functional impact of one low-voltage-activated K^+ channel, $K_v1.1$, are consistent with this hypothesis. As outlined above, $K_v1.1$ is capable of altering accommodation, RMP and threshold without affecting firing rate (Fig. 4c). Whereas other low-voltage-activated channel types likely contribute, this one α -subunit clearly displays all the attributes required to regulate neuronal response modes dynamically.

When speculating about the functional mediators of the stable instantaneous firing rate, it is clear that high-voltage activated ion channels must be involved since the alteration in plateau voltage has little impact on the first two action potentials (Fig. 4b, upper superimposed traces). One class of candidate ion channels that might contribute to this regulation are the high-voltage-activated VGCCs because they have been shown to alter action potential duration (Chen et al. 2011), a feature that is essential for setting the inter-spike interval. High-voltage-activated K^+ channel types probably play a similar role, since they are instrumental in regulating the hyperpolarizing phase of the action potential. Thus, a complex interaction between ion channels that prolong action potential duration and latency coupled with those that abbreviate it might contribute to the maintenance of constant timing for each neuron independent of its RMP.

Concluding remarks

Type I cells within the spiral ganglion are unusual neurons. Their somata are distant from the more peripherally

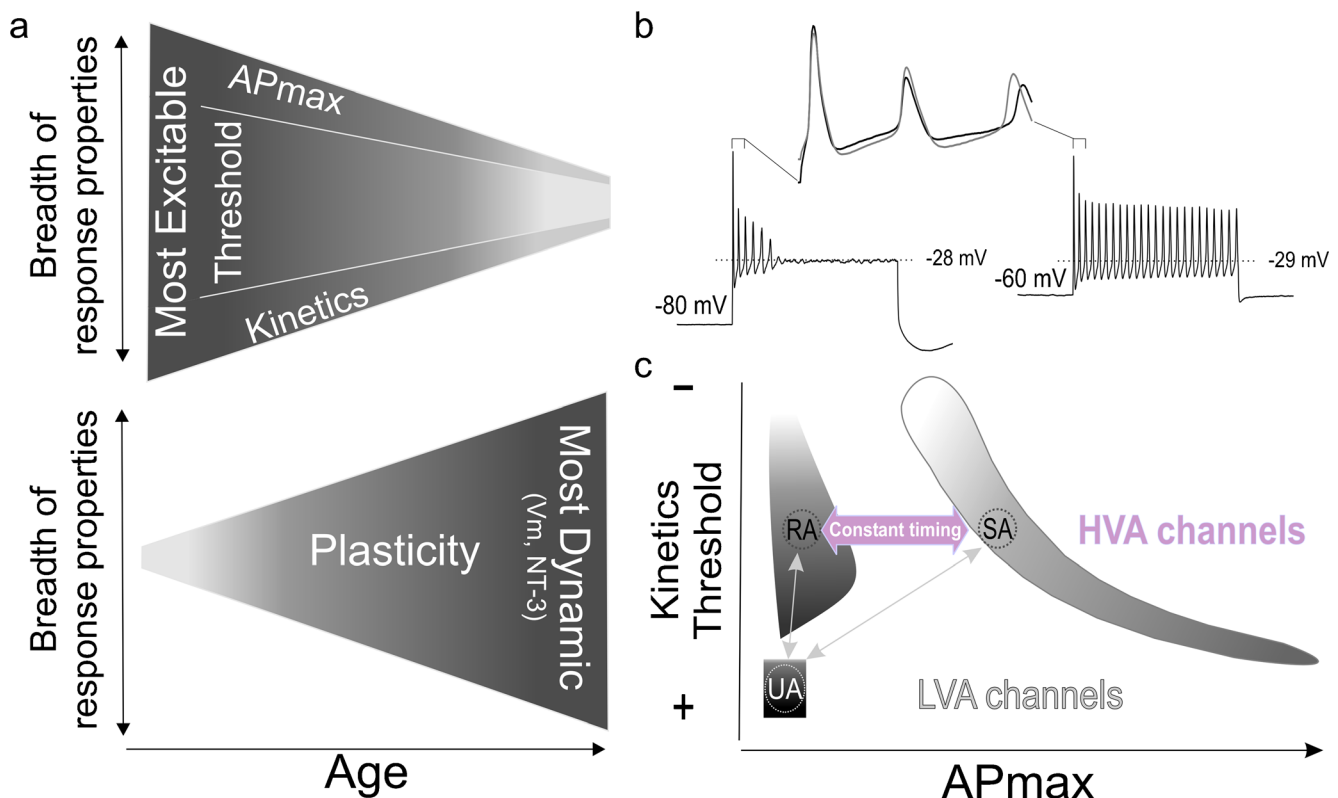


Fig. 4 Proposed contribution of low-voltage- and high-voltage-activated ion channels to response mode plasticity and firing rate stability. **a** With increasing age, the timing and excitability features become more uniform (*top*), whereas dynamic properties increase (*bottom*). At early postnatal ages, neurons are highly excitable, basal and apical neurons are equivalent and external factors such as membrane potential (V_m) and NT-3 have little effect. By P14, the neurons are faster, less excitable and similar in terms of kinetics and APmax, although tonotopic differences in threshold persist. However, at this later age, neurons manifest more dynamic regulation in terms of their responsiveness to V_m and NT-3. **b** Sweeps from the same neuron (P14) at similar depolarizing potentials were held at -80 mV (*left*) and then -60 mV (*right*). RMP level alters the response mode in this cell from RA at -80 mV to SA at -60 mV. However, as seen from the expanded scale *above*, the first two action potentials are essentially overlapping and, thus, are unaltered in their instantaneous firing frequency. **c** A mechanistic representation of dynamic changes in firing features and the impact on accommodation response mode. Displayed are the three accommodation categories (UA, RA and SA) and observed shifts in response mode. This model can slide

with age such that the percentage of neurons within each category can shift, whereas the framework remains stable. UA neurons (*bottom left*) possess the most hyperpolarized thresholds. Generally, as thresholds decrease, the likelihood of transitioning to RA or SA increases (*gray arrows* reversible transitions). Within each accommodation category are gradations in threshold (*gray scale*) indicating that those cells with more hyperpolarized thresholds are most likely to shift categories. Thresholds are regulated by low-voltage-activated (LVA) ion channel expression, which is highest in UA neurons and decreases both vertically and rightward giving rise to lower thresholds and an increase in APmax. The LVA expression profile is based on quantification of anti- $K_v1.1$ labeling (Liu et al. 2014a) and is highlighted because of its known role in regulating both threshold and accommodation but other channel types might also be involved. In contrast, neurons that shift from RA to SA categories manifest an increase in APmax but timing remains constant (*horizontal purple arrow*). This is consistent with the regulatory control of this feature by high-voltage-activated (HVA) ion channels. Data from Crozier and Davis (2014) re-published with permission

localized spike-initiation zone and yet, they are an obligatory part of the conduction pathway and display specializations that range from their tonotopically graded size to the myriad voltage-gated ion channels that they possess. Although additional studies are required to determine the manner in which type I cell somata specifically contribute to sensory processing in the initial stages of afferent coding, the sophistication of their electrophysiologically relevant phenotype is becoming more apparent. Recent studies have shown that type I spiral ganglion neurons not only are complex but can also be dynamically

regulated as they age. As a class of neuron, they no longer fit the view of being rigidly uniform in their response properties. Rather, they possess all the hallmarks necessary to contribute to the detection and analysis of auditory signals as they make their way to the brain.

Acknowledgments We thank Dr. Mark R. Plummer for discussions and critical reading of the manuscript.

Conflict of Interest No conflicts of interest, financial or otherwise, are declared by the authors.

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