a0005

3.32 Biophysical Specializations of Neurons that Encode Timing

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Glossary

g0005 ***action potential*** The action potential is a stereotyped electrical signal, consisting of a rapid, millisecond long, decrease in membrane potential, with a rapid return to the resting potential. Action potentials are typically 50–100 mV in amplitude. Action potentials serve to encode information as it is transmitted from one neuron to the next, and drive transmitter release from synapses.

g0010 ***anomalous rectifier*** Anomalous rectifier channels are those that are opened by hyperpolarization of the cell membrane as opposed to depolarization. They are anomalous because most channels are opened by depolarization.

g0015 ***brain slice*** The brain slice is a reduced preparation of the nervous system, in which a thin section of live brain tissue is obtained and maintained in an

artificial oxygenated balanced salt solution. Brain slices are typically between 0.25 and 0.5 mm thick. The slices have the advantages of mechanical stability and optical access, allowing careful biophysical analyses of individual cells and local neuronal circuits.

g0020 ***cation-selective channels*** Membrane proteins that are permeable to K, Na, and/or Ca are cation selective. Often this term is used for channels that do not have high selectivity, and so are permeable to more than one cation.

g0025 ***delayed rectifier*** Delayed rectifier is a term used to refer to the set of potassium conductances that repolarize the action potential. The term arises from the time-delayed activation of the membrane conductance, and because the membrane current–voltage relationship is nonlinear (nonohmic) when this conductance is active. Delayed rectifiers typically do not show significant inactivation.

g0030 ***depolarization*** Depolarization refers to movement of the membrane potential from its resting value, typically near −60 mV, toward more positive potentials, such as 0 mV. Depolarization of the neuronal membrane is often excitatory, in the sense that it increases the probability of triggering action potentials, or increasing the frequency of action potentials.

g0035 ***EPSC (excitatory postsynaptic current)*** EPSC refers to the current flow created when excitatory ligand-gated ion channels (such as glutamate and some acetylcholine receptors) are activated. The change in conductance, associated with a cation-selective channel, depolarizes the neuron and increases the probability of firing.

g0040 ***hyperpolarization*** Hyperpolarization refers to movement of the membrane potential from its resting value, typically near −60 mV, toward more negative potentials, such as −80 mV. Hyperpolarization of the neuronal membrane is often inhibitory, in the sense that it decreases the probability of triggering action potentials, or decreases the frequency of action potentials.

g0045 ***intrinsic firing pattern*** Intrinsic firing pattern refers to the temporal pattern of action potentials elicited by an extrinsic depolarization of the neuron membrane, in the absence of synaptic inputs. Typically, the pattern is defined with respect to simple rectangular current pulses injected into the cell.

g0055 ***node of Ranvier*** The node of Ranvier is a specialized region of the axon, where ion channels (sodium and potassium channels) are clustered. The nodes are located between the long stretches of the myelin sheath created by different myelinating glial cells (Schwann cells and oligodendrocytes).

g0060 ***pore loop*** The pore loop is the region of an ion channel protein that helps determine the selectivity of the channel, and plays a role in regulating the channel open or closed states. The pore loop often consists of a hairpin length of the protein inserted into the membrane, that begins and ends on the same side of the membrane.

g0065 ***tetrameric*** Tetrameric proteins have four subunits, often arising from the assembly of four distinct proteins encoded by different genes.

g0070 ***transient potassium current (or A current)*** The transient potassium currents are those that show inactivation, or an intrinsic closing, of the channels during a sustained change in membrane potential. This inactivation distinguishes these channels from delayed rectifiers. The time course of inactivation of transient potassium currents varies from about 10 ms to seconds, depending on the potassium channel subunits that make up the channel.

g0075 ***transmembrane domain*** Transmembrane domains are regions of a protein that are hydrophobic, so that they prefer to be inserted into the cell membrane such that the parts of the protein on either side of the domain are on opposite sides of the membrane.

s0005 3.32.1 Introduction

p0005 The auditory system faces unique challenges in processing the temporal and spectral features of sound, because sound contains biologically relevant information in timescales that are much faster than the capabilities of most common neuronal mechanisms. Most forebrain neurons have synaptic potentials that last tens of milliseconds and action potentials that are 2–5 ms wide. In comparison, the task of localizing sound in the azimuthal plane requires that the central auditory system compare spike trains with microsecond precision. Specializations of the standard neural processing mechanisms are thus necessary in the neurons and synapses of the auditory brainstem to meet these challenges (Oertel, D., 1999). Over the

past 15 years, these mechanisms have been identified and characterized in some detail. In particular, neurons in the auditory brainstem have phenotypes that result from the expression of specific patterns of ion channels and neurotransmitter receptors that produce temporal processing performance appropriate to the tasks of sound localization, sound identification, and sound perception for communication. In this chapter, the roles of voltage-gated potassium channels, which are highly expressed in auditory brainstem nuclei, and the role of cation-selective hyperpolarization-activated currents will be discussed. Equally important to the task of neural computation based on fine timing information are the synapses and their receptors; these too are specialized in the brainstem auditory system and are reviewed in 3.33.

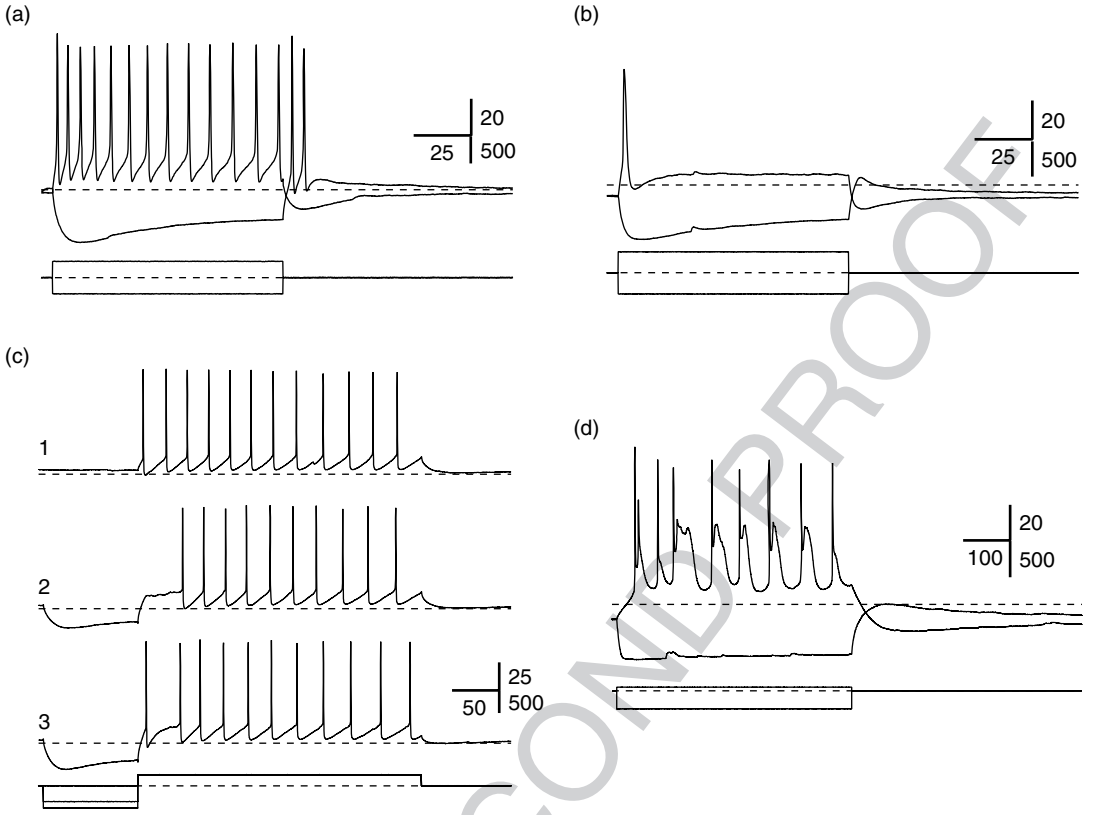
p0010 We will begin by discussing the four primary firing pattern motifs that are found in brainstem auditory neurons. Next, we will briefly review the biophysics and structure of potassium channels, as these are the critical elements that endow auditory neurons with their ability to encode timing information. We will then review the expression of these channels along the auditory pathway in specific cell types. In the last section, we will discuss specific roles for these channels from the perspective of synaptic integration.

s0010 3.32.2 Firing Patterns

p0015 There are four fundamental motifs of electrical excitability that predominate in the brainstem auditory system (Figure 1). The first intrinsic pattern is a simple regular spiking pattern that is common to many neurons in the nervous system. In this case, a step depolarization of the cell membrane leads to a train of evenly spaced action potentials that can be sustained indefinitely (Figure 1(a)). The interval between the action potentials decreases as the injected current increases, and the rate does not change over time (in other words, there is no adaptation or slowing of firing as seen in many other neurons). The action potentials are narrow, and even in the best recordings reach only to about +10 mV (as compared to +40 mV for cortical neurons). The firing pattern is not sensitive to the membrane potential of the cell before depolarization (this will be important later). The cells in the ventral cochlear nucleus (VCN) that have this pattern are multipolar (or stellate) neurons (Wu, S. H. and Oertel, D., 1984) that receive many small bouton synapses from the auditory nerve fibers (ANFs). In response to sound *in vivo*, multipolar neurons fire trains of evenly spaced action potentials, similar to what is seen in brain slices with current injection. Cells with this firing pattern do not convey fine timing information necessary for speech perception or some types of sound localization, but may encode information about sound intensity or slower modulation of sound amplitude with their firing rate (Sullivan, W. E. and Konishi, M., 1984; Rhode, W. S. and Smith, P. H., 1986; Frisina, R. D. *et al.*, 1990; Kim, D. O. *et al.*, 1990).

The second intrinsic pattern is characterized by p0020 the presence of only one or two action potentials (Figure 1(b)) at the beginning of a depolarizing current step (Oertel, D., 1983). After these initial action potentials, the membrane potential stays close to the resting potential, and the membrane conductance is high. The action potentials may be wider than those in multipolar cells, and are often quite short. *In vivo*, neurons with these electrical properties may respond with patterns of action potentials that are similar to their inputs, or may respond only at the onset of a sound, depending on the strength and convergence of the inputs. Some neurons with these intrinsic properties can actually improve the temporal precision of firing relative to their inputs (Joris, P. X. *et al.*, 1994; Paolini, A. G. *et al.*, 2001; Louage, D. H. *et al.*, 2005). Neurons with this intrinsic pattern are commonly found in cells that process fine timing information, and the mechanisms underlying this processing will be discussed in more detail below.

The third intrinsic pattern is uniquely character- p0025 ized by sensitivity of the cell's firing pattern to the membrane potential prior to a depolarization. Cells with this firing motif can fire a regular train of action potentials when the membrane potential has been at rest before current is injected (Figure 1(c), trace 1), but the timing of the first few spikes changes when the membrane potential is negative (hyperpolarized) to the resting potential before depolarization (Manis, P. B., 1990). Two different, related discharge patterns can occur. The first pattern has a first spike latency that is tens of milliseconds (Figure 1(c), trace 2), and the second pattern has a short first spike latency (Figure 1(c), trace 3), but long first interspike interval. The firing of subsequent spikes in these cells in response to depolarization is regular, and does not show adaptation, similar to the regular firing cells discussed above. A surprising feature is that these patterns closely resemble the patterns reported for



f0005 **Figure 1** Example recording from cells in the cochlear nucleus with different intrinsic firing patterns. (a) Regular firing pattern (type I) found in stellate–multiploar cells of the ventral cochlear nucleus. Note occasional anodal break spikes following a hyperpolarizing current injection. Data from P23 mouse (DBA) ventral cochlear nucleus. (b) Phasic firing pattern (type II) found in bushy cells (including spherical and globular bushy cells); a slightly modified version of this pattern is found in octopus cells. Data from P35 mouse (DBA) ventral cochlear nucleus. (c) Three different voltage-dependent discharge patterns of dorsal cochlear nucleus (DCN) pyramidal cells. Trace 1 shows the regular firing elicited when the membrane potential is at rest. Trace 2 shows the delay to the first spike following a hyperpolarization. Trace 3 shows the slightly longer first interspike interval that is seen with larger hyperpolarizations, or with different hyperpolarization–depolarization sequences. Data from P13 rat DCN pyramidal cell. (d) Complex spiking pattern seen in cartwheel cells of the DCN. Note the related complex bursts and broad after depolarization when only single spikes are generated. Data from P12 rat DCN cartwheel cell. Calibrations: horizontal bars indicate time in milliseconds. Upward vertical bars are voltage in millivolts. Downward vertical bars indicate current, in picoamperes. For voltage traces the dashed lines are at −60 mV, except in (d), where they are at −75 mV. For current traces, the dashed lines are at 0 pA. Recordings in (a) and (b) from Wang Y. and Manis P. B. (unpublished data). Recording in (c) from Manis P. B. (unpublished data) Recording in (d) from Mancilla J. and Manis P. B. (unpublished data)

the responses to tone bursts for these cells *in vivo*. While these cells are not normally thought of as being involved in precise timing circuits, their intrinsic mechanisms are capable of encoding timing information (Manis, P. B. *et al*., 2003; Kanold, P. O. and Manis, P. B., 2005) and so they are briefly discussed below.

p0030 The fourth motif is a bursting or complex spiking pattern, in which groups of action potentials occur closely together in time, with much longer intervals between the bursts (Figure 1(d)). This pattern is seen in cartwheel cells of the dorsal cochlear nucleus (DCN) (Zhang, S. and Oertel, D., 1993; Manis, P. B. *et al*., 1994). Because these cells do not seem to be involved in timing circuits *per se*, and little is known about their channels, they will not be discussed further.

p0035 Each of these patterns is generated by neurons that express different complements, densities and possibly distributions of ion channels in their membrane. While the discharge patterns result from the interplay between the membrane voltage and all of the time and voltage dependences of the ion conductances, the potassium conductances vary most between the cells with different patterns. Therefore, we will focus on the potassium channels in this chapter.

s0015 ## 3.32.3 Voltage-Gated Potassium Channels

p0040 Phylogenetically, the voltage-gated potassium channels are ancient, and homologous channels can be found in plants (Cherel, I., 2004). Even the ionotropic glutamate receptors have a pore domain that closely resembles an inverted pore from the voltage-gated potassium channels (Wo, Z. G. and Oswald, R. E., 1995; McFeeters, R. L. and Oswald, R. E., 2004). In mammals, voltage-gated potassium channels arise from several gene families with different properties (reviewed in Coetzee, W. A. *et al.*, 1999). The major known families include the Kv series, which are principally gated by membrane voltage, the KCNQ family (Robbins, J., 2001), some of which form the G-protein-gated channels associated with muscarinic receptors, the ether-a-go-go (ERG) channels that play a role in cardiac action potential repolarization (Schwarz, J. R. and Bauer, C. K., 2004), two calcium-dependent families (Sah, P. and Faber, E. S., 2002; Stocker, M., 2004), and a host of smaller two pore channels (O'Connell, A. D. *et al.*, 2002). In addition, cellular excitability is regulated by hyperpolarization-activated currents (HCN) (Robinson, R. B. and Siegelbaum, S. A., 2003). Each of these sets of channels performs different functions in regulating the excitability of neurons, and each exhibits a selective pattern of cellular expression in the nervous system. This review will focus on the Kv family; however, the HCN currents will also be discussed. Indeed, the principal regulation of electrical excitability in the brain seems to depend on the Kv, HCN, and K(Ca) currents, which together form the major voltage-dependent K^+ conductances in the cell membrane. The next best-studied group of channels, the calcium-activated potassium channels, are also important in some auditory neurons for regulating spike frequency and firing rate accommodation.

p0045 For the other classes of channels, much less is known about their distribution in the central auditory system or their contribution to electrical excitability. In particular, KCNQ4 channels have a very interesting pattern of expression in brainstem auditory nuclei, being prominent in the anterior ventral cochlear nucleus (AVCN), and ventral nucleus of the lateral lemniscus (Kharkovets, T. *et al.*, 2000). The pattern of expression is limited to just a few brainstem nuclei (not all of which are auditory). So far, no currents attributable to these channels have been identified. Two other sets of channels are also known to be expressed at high levels in some neurons of the auditory brainstem. Two-pore potassium channels are found throughout the nervous system, and some show high levels of expression in specific auditory brainstem nuclei (Karschin, C. *et al.*, 2001; Pal, B. *et al.*, 2005; Chen, W. C. and Davis, R. L., 2006; Holt, A. G. *et al.*, 2006). The TASK-5 channel is specifically highly expressed in cochlear nucleus and some nuclei of the superior olivary complex, but is notably not expressed in the medial nucleus of trapezoid body (MNTB) (Karschin, C. *et al.*, 2001). Potassium-dependent sodium channels, Slick and Slack (Bhattacharjee, A. and Kaczmarek, L. K., 2005) are also found widely, but have a particular pattern of expression in the auditory system. Slack has been localized to the calyces of Held in the MNTB (Bhattacharjee, A. *et al.*, 2002), while Slick is found in the VCN, lateral superior olive (LSO), and MNTB (Bhattacharjee, A. *et al.*, 2005). It is likely that these channels play an important role in regulating repetitive firing. While these and other channels are likely very important for some aspects of neural processing, and in setting the membrane potential, they are in need of further experimental analysis. This requires pharmacological and genetic tools that allow specific analysis of their contribution to the physiological functions of neurons.

3.32.3.1 The Kv Family

s0020

p0050 Voltage-gated potassium channels consist of tetrameric assemblies of proteins with six transmembrane domains, with a pore loop located between the fifth and sixth transmembrane spans. The specific assembly of the channel subunits is thought to be governed by C-terminal protein interactions such that all of the subunits of a given channel must belong to a single family. Thus, while there are specific rules regarding assembly, the number of different combinations of channel assemblies that can be produced is potentially quite large.

p0055 Several Kv genes are known to have splice variants (Kv1.5, Kv3.1, Kv3.2, Kv3.3, Kv3.4, and Kv4.3). However, there is no evidence for posttranslational editing of these channels in mammals. At least for Kv1, glycosylation can alter channel function (Thornhill, W. *et al.*, 1996). In addition, the biophysical behavior of the channels can vary considerably, even within a family, giving a wide range of potential channel function according to the rules of assembly. The details of channel assembly are not well understood, but are known to depend on both targeting motifs in the

protein that regulate channel trafficking to the membrane, and specific interactions among subunits at the level of the endoplasmic reticulum (Heusser, K. and Schwappach, B., 2005). In addition, auxiliary subunits (β subunits) have been shown to act as chaperones, and influence the targeting and assembly of the channels, as well as gating in assembled channels.

p0060 Ultimately, the pore-conducting portion of the Kv channels (referred to as the α subunits) are associated with β subunits in a 1:1 α–β stoichiometry. The β subunits play an important modulatory role in channel function, sometimes in conjunction with channel interacting proteins. Furthermore, the localization of Kv channels can be regulated by motifs that can target the channels to postsynaptic densities. Channel localization in the membrane is not random, but is, at least for some channels, quite focal. For example, Kv4.2 has been found to be targeted to postsynaptic densities in preoptic neurons (Alonso, G. and Widmer, H., 1997). This allows the channels to interact with other proteins, and may also facilitate local modulation by short-range messengers.

p0065 Because specific families of Kv channels have particular properties, it is useful to briefly review the families and the properties of the channels as expressed as homomers in heterologous systems. Such a description is useful in considering the potential functional contribution of the channels in auditory neurons.

s0025 #### 3.32.3.1.1 The Kv1 family

p0070 The Kv1 family of channels is homologous to the Drosophila *shaker* family. There are currently seven genes that are known to be associated with this family, and their functional conductance and kinetics in heterologous expression systems is somewhat diverse. All of these have been detected in at least some regions of the brain, although Kv1.7 is not highly expressed (Kalman, K. *et al.*, 1998). Kv1.1 and Kv1.2 channels are found principally in axons, terminals (such as cerebellar basket cells) and cell somata, although Kv1.2 can also be found in dendrites (Sheng, M. *et al.*, 1994). In the axon, they are localized in a juxtaparanodal position (Rasband, M. N. and Trimmer, J. S., 2001; Rasband, M. N., 2004). These channels play the role of a delayed rectifier, where they repolarize the axonal action potential. Kv1.1 and Kv1.2 are also highly expressed in the auditory brainstem, as will be discussed in detail below. Kv1.4 channels are also found principally in axons and axon terminals (Sheng, M. *et al.*, 1992), and form an inactivating current that is sensitive to tetraethylammonium (TEA) and 4-aminopyridine (4-AP) (however, a unique localization has been reported in the auditory system, as discussed below). Kv1.4 gating is strongly accelerated by β subunit association (Castellino, R. C. *et al.*, 1995). While Kv1.4 contributes to some A currents (inactivating or transient potassium currents) in brain, other channels, such as Kv3.4, Kv4.2, and Kv4.3 can also be responsible for these currents (see below). Simply taking into account the seven members of the Kv1 α family and their tetrameric assembly, and ignoring issues related to β subunits or other proteins, or assembly order (adjacency), it is obvious that there exists the potential for a large number of different subunit combinations. In practice, however, any given cell seems to express only a subset of the family, and so the potential heteromultimeric composition of membrane channels is far more limited. In brain, immunoprecipitation experiments have shown that heteromeric combinations of Kv1.1–Kv1.2, Kv1.1–Kv1.4, Kv1.1–Kv1.2–Kv1.6, and homomeric Kv1.2 predominate (Wang, H. *et al.*, 1999).

3.32.3.1.2 The Kv2 family

s0030

p0075 The Kv2 family of channels is homologous to the Drosophila *shab* family. There are two known members of this family, and both are widely expressed in brain. Kv2 channels are high-voltage-activated, TEA- and 4-AP-sensitive delayed rectifiers (Shi, G. *et al.*, 1994). Kv2 channels have not been extensively studied in the auditory system, although they are reported to be expressed in the cochlear nucleus (Fitzakerley, J. L. and Quale, M., 2005) and inferior colliculus (Hwang, P. M. *et al.*, 1993; Richardson, F. C. and Kaczmarek, L. K., 2000).

3.32.3.1.3 The Kv3 family

s0035

p0080 The Kv3 family of channels is homologous to the Drosophila *shaw* family. There are four known members of the family, and one member, Kv3.1 can exist as one of two splice variants, known as Kv3.1*a* and and Kv3.1*b* (Luneau, C. J. *et al.*, 1991). While Kv3.1 is especially found in the forebrain in gamma-aminobutyric acid (GABA)ergic interneurons, it is highly expressed in auditory brainstem neurons that are both glutamergic and glycinergic (Perney, T. M. *et al.*, 1992; Perney, T. M. and Kaczmarek, L. K., 1997), and thus is of significant interest in auditory processing. Kv3.1 channels form high-threshold delayed rectifiers, with activation near -10 mV and incomplete slow inactivation. Kv3.2 channels are also delayed rectifiers, and are expressed in many cells, including in the auditory brainstem (Weiser, M. *et al.*,

1994). Kv3.3 and Kv3.4, in contrast, show a relatively deep, slow inactivation.

s0040 ***3.32.3.1.4 The Kv4 family***

p0085 The Kv4 family of channels is homologous to the Drosophila *shal* family. There are three known members of the family, and one member, Kv4.3 can exist in multiple splice variants (Ohya, S. *et al.*, 1997). Kv4.1 is not expressed in the brain, but Kv4.2 and Kv4.3 are expressed in throughout the neural axis, but in specific populations of neurons (Serodio, P. and Rudy, B., 1998). Due to a particular targeting motif (Rivera, J. F. *et al.*, 2003), these channels are largely found in dendrites, and not in axons or synaptic terminals (Sheng, M. *et al.*, 1992). The channels are all rapidly and nearly completely inactivating, and their gating is subject to modulation by a number of factors, including arachidonic acid (Villarroel, A. and Schwartz, T. L., 1996) and phosphorylation by various kinases (Yuan, L. L. *et al.*, 2002; Varga, A. W. *et al.*, 2004). A particularly important set of regulatory proteins that interact with the Kv4 family of channels are the the KChip proteins (An, W. F. *et al.*, 2000). These proteins confer a calcium sensitivity, as well as modulate activation and inactivation voltage dependence and gating kinetics. A surprisingly linear relationship between Kv4 family mRNA (including Kv4.2, Kv4.3, and *shal*) and the rapidly inactivating transient potassium current has been demonstrated in several cell types (Baro, D. J. *et al.*, 1997; Tkatch, T. *et al.*, 2000; Liss, B. *et al.*, 2001).

s0045 ***3.32.3.1.5 Kv5–Kv9***

p0090 These are all accessory proteins that do not, on their own, form ion channels, but which can associate with other Kv channels (Coetzee, W. A. *et al.*, 1999). Their roles are less well defined, and their presence in auditory neurons has not been extensively explored. Kv9.1, which is present in the inferior colliculus, has been shown to modify Kv2.1 gating, so that cells may be able to fire more rapidly or entrain better (Richardson, F. C. and Kaczmarek, L. K., 2000).

s0050 3.32.4 Channel Specialization and Biophysical Characterization of the Channels in the Vertebrate Auditory Cental Nervous System

p0095 Since the initial work of Oertel D. (1983) it has been evident that neurons in the auditory brainstem could be differentiated by their intrinsic firing responses to rectangular current pulses. For many cell types, the intrinsic firing responses can be shown to be related or to underlie the acoustically evoked spike patterns, although this is not always a trivial relationship. The intrinsic firing patterns are regulated by three principal features of cells. First, and often most important, is the cell-specific selection of specific ion channels complexes; for example, which sets of Kv α and β subunits, in conjunction with any auxillary proteins such as the KChips, are expressed. Second, the firing patterns depend on the location and density of the channel proteins, which is a function of channel targeting. Finally, and to a lesser extent, the shape of the dendritic tree affects the patterns of current flow through the cell (Mainen, Z. F. and Sejnowski, T. J., 1996), so dendritic structure also influences the cell voltage at the spike initiation site, which is usually in the initial segment (Colbert, C. M. and Johnston, D., 1996; Stuart, G. *et al.*, 1997; Colbert, C. M. and Pan, E., 2002).

p0100 In this section, we will review the patterns of ion channel expression in a number of nuclei and cell types of the auditory brainstem. There are a number of caveats on the interpretation of data in the literature that should be recognized before we delve into this section. The first is that expression of channels in a single cell population can show differences among species; a prime example of this is in heart, where atrial I_{to} (the transient outward current) is mediated by Kv4.2 channels in rat (Bou-Abboud, E. and Nerbonne, J. M., 1999), but is mediated by heteromultimers of Kv4.2 and Kv4.3 channels in mice (Guo, W. *et al.*, 2002). While the intrinsic physiology of most auditory neurons seems comparable across species, the underlying channel composition may vary. Second, channel expression is regulated during development, sometimes in a nonmonotonic manner, and is not complete (in rodents) until late adolescence (e.g., ~30 days of age in rats and mice). Thus, the ages of animals used for physiological analyses is an important variable. Third, the technical limitations of message and protein localization studies should always be carefully considered. The presence of a particular mRNA in a cell does reveal the cellular localization of the presumptive protein(s); in most cases the level of mRNA is also not necessarily correlated with the level of functional protein in the membrane (an exception is for Kv4.2, as discussed above). Proteins can be localized by immunocytochemistry, but the limits on the specificity of the available antibodies suggest some caution is warranted in interpreting these results, and localization of proteins in relevant membrane compartments can be difficult to demonstrate, particularly in the auditory brainstem where the nuclei often have

a complex neuropil, multiple fiber systems, and nonlaminar organization. Physiological studies directly demonstrate the existence of different kinds of channels in specific cell types, but require the use of pharmacological or genetic manipulations to identify specific types of channels, and frequently cannot assay protein function in dendritic or axonal processes.

s0055 ### 3.32.4.1 Spiral Ganglion Cells

p0105 A recent discovery was the identification of a diversity of discharge characteristics in spiral ganglion cells (SGCs). SGCs are endowed with rapidly inactivating sodium channels, a low-voltage-activating potassium current, a transient potassium current, hyperpolarization-activated currents, and calcium channels (Yamaguchi, K. and Ohmori, H., 1990; Sheppard, D. N. *et al.*, 1992; Valverde, M. A. *et al.*, 1992; Santos-Sacchi, J., 1993; Garcia-Diaz, J. F., 1999; Adamson, C. L. *et al.*, 2002b; Mo, Z. L. *et al.*, 2002). Studies using cultured neurons showed that the transient current and the low-voltage-activating current could vary along the length of the modiolus (Adamson, C. L. *et al.*, 2002a; 2002b). In response to current pulses, high-frequency (cochlear base) cells showed shorter latency action potentials and phasic firing, and in older cultures, narrower action potentials, whereas low-frequency (cochlear apex) cells more frequently showed repetitive firing and longer latency action potentials to current pulses. These physiological features correlated with a higher expression (as assayed by a semiquantitive immunocytochemical method) of Kv1.1 and Kv3.1 in the base, whereas Kv4.2 was slightly more highly expressed in the apex. These results suggest that there may be differential processing of temporal information along the length of the cochlea. Given that the representation of the temporal structure of sound in SGCs varies with cochlear location (e.g., see Louage, D. H. *et al.*, 2004), perhaps this is not surprising. Nonetheless, the role of these channel configurations in temporal coding in the spiral ganglion cell (SGC) is still not well understood, although some clues may be derived from work in the central auditory system, as discussed next.

s0060 ### 3.32.4.2 Ventral Cochear Nucleus Bushy Cells

s0065 #### *3.32.4.2.1 The low voltage-activated potassium conductance*

p0110 Since the pioneering studies of Oertel (Oertel, D., 1983; Wu, S. H. and Oertel, D., 1984) in mouse cochlear nucleus brain slices, it has been evident that bushy neurons have specialized electrical excitability. The principal signature of these cells when recorded in current clamp is a strong outward rectification that opposes depolarizing currents, and limits the cell membrane potential to not move too far above the resting potential (Figure 1(b)). This rectification was associated with a significant increase in membrane conductance. Initial voltage clamp studies from acutely isolated guinea-pig VCN neurons showed that the rectification could be explained by the presence of a strong, low-voltage-activated (often called low-threshold, or I_{LTK}) potassium conductance (Manis, P. and Marx, S., 1991) that was partially blocked by 4-AP, but was not blocked by TEA. The cardinal characteristics of this conductance are that it is partially activated at rest, it shows modest, voltage-dependent inactivation, and that activation from potentials near rest (−60 mV) has a monoexponential time course. Subsequently, depolarization from more negative potentials revealed a sigmoidal activation time course (Rothman, J. S. and Manis, P. B., 2003a), consistent with cooperative gating of four subunits during channel opening. Estimates of the maximal conductance in isolated cells revealed a mean value of about 200 nS for a 12 pF cell, but the conductance varied over a wide range. In addition, the voltage at which the conductance yielded a current of 0.1 nA also showed wide variability (Rothman, J. S. and Manis, P.B., 2003c), suggesting that the voltage dependence of activation, and therefore the availability of the conductance to participate in synaptic integration, is not constant among VCN cells.

p0115 In both rat and guinea-pig, I_{LTK} has been shown to be sensitive to the mamba snake toxin, dendrotoxin (DTX)-I (Dodson, P. D. *et al.*, 2003; Rothman, J. S. and Manis, P.B., 2003a; 2003c; Pal, B. *et al.*, 2004), which blocks Kv1.1- and Kv1.2-containing channels (Hopkins, W. F., 1998). The low-voltage-activated conductance has been reported to be blocked in a subset of bushy cells by tityustoxin-Kα, which blocks only Kv1.2-containing channels (Dodson, P. D. *et al.*, 2003), suggesting that either bushy cells are heterogeneous in their channel expression, or that not all cells express Kv1.2-containing channels within the spatial reach of the voltage clamp, for example, on or near the soma. A very similar conductance is present in neurons of the chicken nucleus magnocellularis that are homologous to the mammalian bushy cells (Reyes, A. D. *et al.*, 1994; Zhang, S. and Trussell, L. O., 1994; Rathouz, M. and Trussell, L., 1998;

Fukui, I. and Ohmori, H., 2003; 2004; Lu, Y. *et al.*, 2004). The similarities of the conductance extend to the voltage dependence, apparent density (as estimated from currents recorded in somatic voltage clamp), sensitivity to 4-AP and DTXs, and the presence of partial inactivation with prolonged steps.

p0120 The pharmacological profile of block by 4-AP and DTXs suggests that the low-voltage-activated conductance in bushy neurons is mediated by channel complexes containing both Kv1.1 and Kv1.2. Three additional lines of evidence support this conclusion. First, the mRNA for both channel subunits is widely expressed in mouse VCN (Grigg, J. J. *et al.*, 2000), although colocalization of multiple messages has not been attempted. In addition, while it is clear that the major populations of bushy and octopus neurons have the message (see below), it is less clear whether the multipolar cell classes express the message. Neither immunocytochemical nor *in situ* hybridization studies have attempted to positively identify cell types using classical criteria. Second, preliminary single-cell PCR studies (Sonnenburg, R. *et al.*, 2002) have shown coexpression of Kv1.1 and Kv1.2 message in individual bushy neurons in the rat VCN, but surprisingly, these channels were also found in a subset of regular firing (stellate) neurons, suggesting that their expression is not limited to cells expressing a low-voltage-activated conductance. Third, positive immunostaining for Kv1.1 and Kv1.2 is widely apparent in the VCN, including in the bushy cell populations (Dodson, P. D. *et al.*, 2003; Caminos, E. *et al.*, 2005; Pal, B. *et al.*, 2005; Bortone, D. S. *et al.*, 2006), as might be expected from their expression of DTX-sensitive low-voltage-activated K^+ currents. However, it remains unclear as to whether the channels are coexpressed in individual cells, and if they are, whether the functional channels are actually coassembled in the membrane. In addition, a recent report of immunostaining for Kv1.3 and Kv1.6 in the rat VCN (Pal, B. *et al.*, 2005) raises additional questions about the composition of channel complexes. Thus, while Kv1.1 and Kv1.2 seem likely to be key components of the conductance, the pharmacological data, together with immunocytochemical observations and the variations in the activation threshold of the potassium conductance (Rothman, J. S. and Manis, P. B., 2003c), also support the idea that there is heterogeneity across cells in the function and molecular composition of the low-voltage-activated current in the VCN.

p0125 Hallows J. L. and Tempel B. L. (1998) examined the developmental profile of Kv1.1 message in whole brain. The mRNA for Kv1.1 showed a spike during embryonic development, and did not increase again until between P12 and P15, with levels remaining stable after P15. Using real-time PCR, message in cochlear nucleus increases from P3 until P28 (Manis, P. *et al.*, 2002; Bortone, D. S. *et al.*, 2006). The reason for the later maturation compared to whole brain is not clear; however, the results suggest regional differences in the development of potassium channels. Mechanisms related to the control of expression of these channels are not well understood. Transcriptional control of Kv1 channels has only partially been elucidated (Wymore, R. S. *et al.*, 1996; Jang, G. M. *et al.*, 2004).

3.32.4.2.2 The high voltage-activated potassium conductance

s0070

p0130 In the initial studies of guinea-pig VCN neurons (Manis, P. and Marx, S., 1991), a second potassium conductance was characterized. This conductance activated at more positive voltages, and was blocked both by TEA and 4-AP. It also showed slower activation kinetics, and only a small amount of inactivation. A similar conductance, which is also insensitive to DTXs, but which can be blocked by low concentrations of 4-AP, has been seen in all subsequent studies in both mammals and avians (Reyes, A. D. *et al.*, 1994; Rathouz, M. and Trussell, L., 1998; Rothman, J. S. and Manis, P. B., 2003a; 2003c; Pal, B. *et al.*, 2004). This high-threshold conductance (I_{HT}) is not as strong as the low-voltage-activated conductance, activates slightly more slowly, and appears to have two kinetically distinct activation components (Rothman, J. S. and Manis, P.B., 2003a). There is also evidence for heterogeneity in deactivation time constants (Manis, P. *et al.*, 1996) suggesting that there may be multiple channels contributing to the conductance. This conductance is thought to be mediated by channels containing Kv3.1, as this subunit is highly expressed in the auditory brainstem, and particularly in bushy neurons of the cochlear nucleus (Perney, T. M. *et al.*, 1992; Perney, T. M. and Kaczmarek, L. K., 1997; Grigg, J. J. *et al.*, 2000). The properties and pharmacology of the conductance are generally consistent with those of heterologously expressed channels.

p0135 In whole brain (Perney, T. M. *et al.*, 1992), in the cochlear nucleus (Bortone, D. S. *et al.*, 2006), and in the inferior colliculus (Liu, S. J. and Kaczmarek, L. K., 1998a; Liu, S. Q and Kaczmarek, L. K., 1998b), Kv3.1 mRNA increases through development. Kv3.1 transcription is regulated by a cAMP response element (Gan, L. *et al.*, 1996), and indirectly by electrical

activity (Liu, S. J. and Kaczmarek, L. K., 1998a; Liu, S. Q and Kaczmarek, L. K., 1998b; von Hehn, C. A. *et al.*, 2004). In DBA2/J mice, which undergo an age-related high-frequency hearing loss (Zheng, Q. Y. *et al.*, 1999), the expression pattern of Kv3.1 is disrupted in high-frequency regions of the VCN, suggesting an activity-dependent regulation (von Hehn, C. A. *et al.*, 2004).

s0075 #### 3.32.4.2.3 The transient potassium conductances

p0140 While rapidly inactivating potassium currents (I_A) are not a feature of bushy neurons in adult guinea-pig, even when conditions were optimized for their detection (Manis, P. and Marx, S., 1991; Rothman, J. S. and Manis, P. B., 2003a), they have been reported in embryonic chickens (Rathouz, M. and Trussell, L., 1998), and early postnatal rats and gerbils (Schwarz, D. W. and Puil, E., 1997; Pal, B. *et al.*, 2004). Consistent with their possible presence in bushy cells in rats and mice, Kv4.2 (but not Kv4.1 or Kv4.3) has been detected immunocytochemically in the VCN of P4-10 rats (Pal, B. *et al.*, 2005), and by *in situ* hybridization in the juvenile mouse cochlear nucleus (Fitzakerley, J. L. *et al.*, 2000). There are several possible explanations for the different expression patterns, including age or species differences.

s0080 #### 3.32.4.2.4 The hyperpolarization-activated conductances

p0145 VCN bushy neurons have a strong hyperpolarization-activated conductance (I_H), which has been partially characterized (Rusznak, Z. *et al.*, 1996). This conductance is effectively blocked by cesium, but not barium, shows half-activation at −95 mV, and reverses at −33 mV. It is not prominent in isolated cells, presumably because the enzymatic treatment inactivates the channels. HCN1 and HCN2 are both strongly expressed by VCN bushy neurons (Koch, U. *et al.*, 2004). The specific roles of HCN channels in the VCN are not known, although it is likely that they contribute to setting the membrane potential and thereby regulating the level of activation of I_{LTK}. As such, they may be served as a transducer of modulatory influences, as suggested in the MNTB (Banks, M. I. and Smith, P. H., 1992).

s0085 ### 3.32.4.3 Ventral Cochlear Nucleus Stellate/Multipolar Cells

p0150 Stellate neurons are not normally associated with the processing of high-frequency auditory events. They are characterized by having longer time constants as measured with small hyperpolarizing current pulses from rest, typically between 3 and 10 ms (White, J. A. *et al.*, 1994; Francis, H. W. and Manis, P. B., 2000), and regular firing (Figure 1(a)) upon depolarization (Oertel, D., 1983; Wu, S. H. and Oertel, D., 1984). Estimates of electrotonic structure suggest that these cells will significantly filter excitatory postsynaptic potentials (EPSPs) impinging on their dendrites (White, J. A. *et al.*, 1994). Voltage clamp studies show that stellate cells lack the low-voltage-activated conductance of bushy cells. However, they express a high-threshold K^+ current that is kinetically and pharmacologically indistinguishable from that in bushy neurons (Manis, P. and Marx, S., 1991; Rothman, J. S. and Manis, P.B., 2003a; 2003c).

p0155 Stellate cells can be distinguished along two different dimensions with respect to ion channel expression. The first is that the I_H currents show slower activation kinetics in T-stellate cells than in D-stellate cells (Fujino, K. and Oertel, D., 2001; Rodrigues, A. R. and Oertel, D., 2006). The second is that some cells (not classified as T- or D-stellate cells) exhibit a 4-AP-sensitive transient potassium current, whereas others do not (Manis, P. *et al.*, 1996; Rothman, J. S. and Manis, P. B., 2003c). The significance of these differences is not known.

3.32.4.4 Octopus Cells

s0090

p0160 Octopus cells are arguably one of the most interesting and perhaps extreme neurons in the cochlear nucleus. These cells have long dendrites that extend across the fascicles of ANFs in the posterior VCN, and so receive input from a broad region of the cochlea. In spite of this massive input, the cells fire only a single action potential at the beginning of tone bursts, with excellent precision (standard deviation 20–50 μs). They have also been reported to entrain, cycle by cycle, to tonal stimuli up to 1 kHz (Rhode, W. S. and Smith, P. H., 1986; Rhode, W. S. and Kettner, R. E., 1987). As such, they may also be among the most rapidly firing neurons in the brain.

p0165 Recordings from octopus cells show that they have very strong rectification around the resting potential, small action potentials at the soma (typically 10–20 mV), a low-input resistance of about 2.5 MΩ, and a short membrane time constant of 0.21 ms (Golding, N. L. *et al.*, 1999), which is close to the limit that can be measured with whole-cell recordings. These general properties arise from high levels of expression of both the low-voltage-activated

potassium current and I_H. I_{LTK} is similar to the current in bushy neurons. It is active at the resting potential, shows some inactivation over time in voltage clamp, and is variably blocked by DTX-I, DTX-K, α-DTX, δ-DTX, and tityustoxin (Bal, R. and Oertel, D., 2001). The selectivity of these toxins indicates that I_{LTK} in octopus cells includes Kv1.1, Kv1.2, and possibly Kv1.4 channels. The variability of block among cells by different toxins suggests that the pattern of channel expression varies among cells. The estimate of the total conductance in octopus cells is on the order of 500 nS, or roughly 2.5 times the conductance in bushy cells. While the low-voltage-activated current is so large that it is difficult to analyze across a wide voltage range under voltage clamp with patch pipettes, these estimates were obtained by partially blocking the current with α-DTX. However, it is quite possible that the conductance is even larger than this.

p0170 Octopus cells have DTX-resistant, TEA-sensitive current that activates at more positive voltages than the DTX-sensitive current (Bal, R. and Oertel, D., 2001). This I_{HT} is weak relative to the low-voltage-activated current, but is still substantial, with an estimated maximal conductance of about 115 nS (Bal, R. and Oertel, D., 2001). While there is a low level of Kv3.1 immunoreactivity in the octopus cell area (Perney, T. M. and Kaczmarek, L. K., 1997), Kv3.3 mRNA is clearly present in the octopus cells (Li, W. *et al.*, 2001) and could be the substrate for the I_{HT} current.

p0175 The I_H current in octopus cells has been more extensively characterized than in bushy cells (Bal, R. and Oertel, D., 2000), and it appears that I_H is much larger in these cells than any other cells in the brain. Similar to the current in bushy cells, it is blocked by extracellular cesium and ZD7288, but not by barium. The conductance is half-activated at -66 mV, and has a mixed cation (sodium and potassium) selectivity with a reversal potential of -38 mV. Perhaps most remarkable, the conductance is estimated to be 41% activated at rest, contributing about 62 nS of conductance to the cell membrane. Kinetics of activation showed two components at 44 and 180 ms, at -77 mV. This suggests a rapidly activating I_H. In terms of subunit composition, HCN1 is particularly clearly expressed in immunocytochemistry in octopus cells, whereas HCN2 is less clearly expressed in these cells, although it is found elsewhere (Koch, U. *et al.*, 2004). This conductance approximately balances the currents through the low-voltage-activated K channel at rest (Bal, R. and Oertel, D., 2001), so that subtle variations in voltage dependence or modulation by second messengers will affect the activation of the low-voltage-activated current (Cai, Y. *et al.*, 1997).

3.32.4.5 Dorsal Cochlear Nuclear Pyramidal Cells

s0095

DCN pyramidal cells can exhibit multiple discharge patterns in response to tones (Godfrey, D. A. *et al.*, 1975; Rhode, W. S. *et al.*, 1983) and in response to intracellular current steps (Manis, P. B., 1990). These discharge patterns (Figure 1(c)) are regulated by an interaction between transient potassium currents with different rates of inactivation (Kanold, P. O. and Manis, P. B., 1999) and subthreshold sodium conductances (Manis, P. B. *et al.*, 2003). One of the transient K^+ currents inactivates with a time constant between 11 and 20 ms, and shows a variable half-inactivation voltage. The other transient current inactivates with a time constant of about 200 ms, and activates at a more positive voltage. Following a hyperpolarization, depolarization activates the rapidly inactivating conductance, which can keep the membrane potential from reaching spike threshold. However, as this conductance inactivates, the membrane depolarizes. The depolarization is slowed by the slowly inactivating conductance, which continues to activate during the slow depolarization. The insensitivity of the rapidly inactivating current to 4-AP and TEA suggests that it is mediated by Kv4 family channels, of which Kv4.2 is most highly expressed in the DCN (Serodio, P. and Rudy, B., 1998; Fitzakerley, J. L. *et al.*, 2000). The slowly inactivating channel is sensitive to 4-AP and TEA, and may be mediated by a Kv3 or Kv1 family channel. A persistent (or slowly activating, relatively noninactivating) sodium current also provides the depolarizing drive necessary to produce long latency spikes in these cells. While pyramidal cells do not encode temporal information by phase locking, except at low frequencies, they may be able to encode a different kind of temporal information. Modeling based on the experimental measurements and range of kinetic parameters suggests that the relative timing of inhibitory and excitatory inputs can be reported by a small population of cells in which the half-inactivation (or magnitude) of the rapidly inactivating current varies (Kanold, P. O. and Manis, P. B., 2005). Thus, the cells may help analyze information about the relative timing of auditory and nonauditory events.

p0180

s0100 ### 3.32.4.6 Superior Olivary Complex

s0105 #### *3.32.4.6.1 Medial nucleus of trapezoid body*

p0185 Neurons of the MNTB are often compared to VCN bushy cells, because they share several features, including a strong, multisite, afferent synapse (the calyx of Held), and they have firing properties and voltage-dependent conductances that resemble those of bushy cells (Banks, M. I. and Smith, P. H., 1992; Forsythe, I. D. and Barnes-Davies,M., 1993; Brew, H. M. and Forsythe, I. D., 1995). However, there are notable differences also. For example, MNTB neurons rarely fire more than one action potential when depolarized (Banks, M. I. and Smith, P. H., 1992; Forsythe, I. D. and Barnes-Davies, M., 1993), whereas VCN bushy neurons usually fire one, but up to three action potentials to a depolarizing current step. However, in mice at 22–25 °C, multiple action potentials have been reported (Brew, H. M. *et al.*, 2003). Second, the action potential height, as measured in brain slices at 33–34 °C, is slightly larger in MNTB neurons (~50 mV; Banks, M. I. and Smith, P. H., 1992) than in bushy neurons, where it averages 30–40 mV (Oertel, D., 1983; Francis, H. W. and Manis, P.B., 2000).

p0190 As with the VCN bushy cells, MNTB principal neurons possess a low-voltage-activated, potassium current and a high-threshold delayed rectifier. The low-voltage-activated current is reduced by 4-AP, and is blocked by DTX-I (Banks, M. I. and Smith, P. H., 1992; Forsythe, I. D. and Barnes-Davies, M., 1993; Brew, H. M. and Forsythe, I. D., 1995; Dodson, P. D. *et al.*, 2002). A detailed pharmacological dissection of the currents in rats (Dodson, P. D. *et al.*, 2002) showed that block by DTX-I is relatively complete, implicating Kv1 channels in the generation of the conductance. The current is also largely blocked by DTX-K, which is selective for Kv1.1-containing channels. Tityustoxin-Kα blocks about half of the low-voltage-activated current, suggesting that only a subpopulation of the channels contain Kv1.2. Noxiustoxin, which also blocks Kv1.2, as well as Kv1.3- and Kv 1.7-containing channels, also blocked about half of the current. Taken together, these data suggest that the low-voltage-activated current in MNTB neurons may be composed of a roughly equal mixture of channels containing Kv1.1 and Kv1.2, or Kv1.1 without Kv1.2, but possibly Kv1.6 (Dodson, P. D. *et al.*, 2002). The presence of other channels is not clear, although a compound that blocks Kv1.3 channels did not affect the current. Consistent with these data, immunostaining revealed Kv1.1, Kv1.2, Kv1.6, but not Kv1.4 or Kv1.5, in the MNTB (Dodson, P. D. *et al.*, 2002), and the high levels of Kv1.1 and Kv1.2 mRNA present in the MNTB by *in situ* hybridization (Grigg, J. J. *et al.*, 2000).

p0195 Further evidence regarding the contribution of Kv1.1 to the low-voltage-activated currents in the MNTB was obtained in a study of Kv1.1 knockout mice by Brew H. M. *et al.* (2003). In these mice, the low-voltage-activated current, as measured near threshold, was reduced in the knockouts, but not eliminated. DTX-I blocked about half of the current in both normal and knockout mice; the remaining current activated with a different time course and was not identified (although as it was not blocked by DTX-I, it appears to not be generated by Kv1 family channels). Nonetheless, in the knockouts, there was a substantial increase in the number of action potentials evoked during a rectangular current pulse. These results support not only Kv1.1 in MNTB neurons, but also show that in the absence of Kv1.1, Kv1.2, and/or Kv1.6 remain and generate a low-voltage-activated current. In this study, a small transient, rapidly inactivating current was also identified, although it appeared to be largely inactivated at rest.

p0200 The most detailed studies of the high-threshold current have been done on MNTB neurons. Both Kv3.1 and Kv3.3 are present in these cells by immunocytochemistry (Perney, T. M. *et al.*, 1992; Li, W. *et al.*, 2001) and by *in situ* hybridization (Wang, L. Y. *et al.*, 1998). A comparison of I_{HT} in MNTB neurons and Kv3.1 homomultimers in CHO cells (Wang, L. Y. *et al.*, 1998) shows that the currents are very similar. The similarity extends to the voltage dependence of the activation kinetics, and the magnitude of sensitivity to block by TEA. In these cells, the Kv3.1-like current contributes to action potential repolarization, and allows the cells to fire rapidly in response to trains of depolarizing current pulses (Wang, L. Y. *et al.*, 1998).

3.32.4.7 Medial Superior Olive

s0110

p0205 In terms of temporal precision, the neurons of the medial superior olive (MSO) have one of the most daunting tasks. These cells are responsible for comparing information from the two ears and generating a representation that the rest of the nervous system can use to make judgments about differences in sound arrival times that are on the order of 10 µs. The ion channels of MSO neurons are central to analyzing synaptic events with this level of temporal precision. It is not surprising then, that their discharge patterns

under current clamp is similar to that of bushy or MNTB neurons (Smith, P. H., 1995) (also, similar excitability is seen in the avian homolog, n. laminaris; Reyes, A. D. *et al.*, 1996). The conductance underlying this behavior was found first to be blocked by 4-AP (Smith, P. H., 1995), and subsequently by DTX-I and DTX-K (Svirskis, G., 2002; Scott, L. L. *et al.*, 2005), again implicating Kv1.1 and/or Kv1.2 channels in its generation. Similar observations have been made in n. laminaris (Kuba, H. *et al.*, 2002; 2005). While the general features of the conductances have been examined, so far no detailed kinetic analyses of the currents in these cells have been reported. Immunocytochemical analyses in both the MSO and n. laminaris support the presence of Kv1.1 and Kv1.2 channels. These cells also possess a high-threshold conductance that is revealed in the presence of DTX or 4-AP. Immunocytochemical analyses and *in situ* studies suggest that Kv3.3, rather than Kv3.1, may be responsible for this conductance in mammalian MSO (Li, W. *et al.*, 2001), although Kv3.1 is present in n. laminaris (Parameshwaran, S. *et al.*, 2001).

p0210 The operation of MSO and n. laminaris neurons as coincidence detectors in the traditional model (Jeffress, L. A., 1948) requires that the cells have a narrow temporal integration window. The presence of the low-voltage-activated conductance allows these cells to function as coincidence detectors of subthreshold inputs (Reyes, A. D. *et al.*, 1996; Kuba, H. *et al.*, 2005).

s0115 3.32.4.8 Other Auditory Structures

p0215 The conductances present in the principal nuclei involved in the processing of rapid timing information are recapitulated in other auditory brainstem nuclei, although in general less is known from a functional standpoint. Because, in general, these have not been investigated as extensively as the regions just discussed, they will be discussed as a group.

s0120 *3.32.4.8.1 Superior olive*

p0220 Nuclei that show high expression of Kv1.1 include scattered neurons in the ventral and lateral periolivary nuclei (Grigg, J. J. *et al.*, 2000; Rosenberger, M. H. *et al.*, 2003) and a few neurons in the LSO (Barnes-Davies, M. *et al.*, 2004); however, in general, the superior olive shows low levels of Kv1.2 (Grigg, J. J. *et al.*, 2000). HCN1 is highly visible in all nuclei of the SOC except the MNTB, whereas HCN2 is principally seen in the MNTB and the LSO (Koch, U. *et al.*, 2004). Kv3.1 is not highly expressed except in some cells of the superior paraolivary nucleus, whereas Kv3.3 appears to be widely expressed in all the principal nuclei and in surrounding periolivary cells (but see Grigg, J. J. *et al.*, 2000; Li, W. *et al.*, 2001). Most neurons of the superior olivary complex fire in a regular discharge pattern (Wu, S. H. and Kelly, J. B., 1991; Fujino, K. *et al.*, 1997; Adam, T. J. *et al.*, 1999; 2001; Barnes-Davies, M. *et al.*, 2004), although some neurons in the LSO (Barnes-Davies, M. *et al.*, 2004) and the lateral nucleus of the trapezoid body (Spirou, G. A. *et al.*, 1995) exhibit phasic responses and rectification.

s0125 *3.32.4.8.2 Nuclei of the lateral lemniscus*

p0225 Some, but not all, neurons of the ventral nucleus of the lateral lemniscus have phasic responses to current pulses (Wu, S. H., 1999) that are similar to those of VCN bushy neurons. Kv1.1 immunoreactivity is evident in this nucleus (Rosenberger, M. H. *et al.*, 2003), as is message for Kv3.1 and Kv3.3, and light immunostaining for Kv3.1 (Li, W. *et al.*, 2001). HCN1 and HCN2 are both found in the ventral nucleus also (Koch, U. *et al.*, 2004). Neurons in this nucleus can exhibit accurate onset timing in bats (Covey, E. and Casseday, J. H., 1991). The GABAergic neurons of the dorsal nucleus of the lateral lemniscus, in contrast, fire regular trains of action potentials (Wu, S. H. and Kelly, J. B., 1995). Kv3.1 and Kv3.3 are highly expressed as assayed by *in situ* hybridization (Li, W. *et al.*, 2001), and in bat in some neurons are lightly immunoreactive for Kv1.1 (Rosenberger, M. H. *et al.*, 2003).

s0130 *3.32.4.8.3 Inferior colliculus*

p0230 Neurons of the inferior colliculus can show a variety of sustained firing patterns to depolarization (Peruzzi, D. *et al.*, 2000; Sivaramakrishnan, S. and Oliver, D., 2001). However, a subset of cells show an onset response to current steps and an associated outward rectification (Wagner, T., 1994; Peruzzi, D. *et al.*, 2000) that is generated by a 4-AP-sensitive current (Sivaramakrishnan, S. and Oliver, D., 2001), and which allows the cells to follow higher rates of stimulation than other collicular neurons (Peruzzi, D. *et al.*, 2000). IC neurons express Kv3.1 and Kv3.3 at fairly high levels (Perney, T. M. *et al.*, 1992; Grigg, J. J. *et al.*, 2000; Li, W. *et al.*, 2001). Kv1.1 and Kv1.2 are also present (Grigg, J. J. *et al.*, 2000; Rosenberger, M. H. *et al.*, 2003), although some regional variation in expression patterns are evident. HCN1 and HCN2 are also both present (Koch, U. *et al.*, 2004).

p0235 There are hints that upper levels of the auditory system may have some specializations to improve temporal processing relative to neurons in nonauditory pathways. For example, action potentials of

thalamocortical recipient neurons in cat auditory cortex are narrower than those in similar neurons of the visual cortex (Smith, P. H. and Populin, L. C., 2001). In addition, GABAergic IPSPs have a faster time course in layer V neurons (Hefti, B. J. and Smith, P. H., 2003). Finally, at least during postnatal development, some auditory cortical neurons may have rectifying current–voltage relationships and phasic firing similar to the auditory brainstem neurons that convey timing information (Metherate, R. and Aramakis, V., 1999). Kv3.1 is highly expressed in auditory cortical interneuorns, apparently at higher levels than in surrounding regions (Li, W. *et al.*, 2001). The significance of these specializations is not known.

s0135

3.32.5 Summary of Channel Expression

p0240 As can be seen from the above review, there are several themes in the patterns of ion channel expression and discharge patterns in the auditory brainstem. Cells expressing low-voltage-activated potassium channels are present in circuits involved in processing timing information. These cells tend to fire a single action potential (or sometimes just a few action potentials) with step depolarization. Cells lacking this conductance are present in those auditory brainstem circuits that are not involved in processing precise timing information, and these cells tend to fire regular trains of action potentials. It is not clear to what extent these two motifs truly exist as canonical forms. Some evidence is consistent with the hypothesis that the expression of channels is in fact a continuum, with a graded variation of total conductance, and this may vary along to tonotopic axis, or even across tonotopic sheets of cells. The idea that there is a tonotopic distribution of conductances is supported by several lines of recent evidence, and is discussed later.

p0245 Because of the bifurcation of the cell voltage trajectory that results from the nonlinear interactions of the sodium and potassium channels over time, cells with similar qualitative but quantitatively different channel expression can show different firing patterns. For example, expression of the low-voltage-activated K^+ currents is not sufficient to make a cell fire phasically at all current levels. If a cell has relatively weak low-voltage-activated potassium conductance, it might fire phasically only for weak current injections that are just suprathreshold for an AP, but larger current injections could be sufficient to counter the outward current and push the cell into a repetitive firing mode (Rothman, J. S. and Manis, P. B., 2003b). Current clamp recordings in the VCN and MNTB have consistently shown (in mice, rats, and guinea-pigs, e.g., see Oertel, D., 1983; Francis, H. W. and Manis, P. B., 2000) that some cells fire with a type II phasic pattern of a single action potential for weak currents can generate a short, although not sustained, train of repetitive spikes for larger currents. Thus, the simple expression of channel transcripts is not sufficient for the elaboration of a particular discharge pattern; both the density and distribution of the channels in the membrane play a critical role. These two factors are difficult to measure accurately.

s0140

3.32.6 The Role of Low-Voltage-Activated K^+ Channels in Temporal Integration

p0250 The low-voltage-activated K^+ channels play several roles in the temporal integration of synaptic inputs in auditory neurons (Trussell, L. O., 1999). Each of these roles serves to enhance the ability of the cells to fire precisely timed action potentials in response to afferent activity. The first role is as a conductance shunt. Because it is generally found that the low-voltage-activated channels are partially conducting at rest, they participate in both setting the resting potential and in setting the membrane conductance (and therefore, time constant). Estimates of the fraction of channels open at rest in cochlear nucleus neurons vary from 10% to 15%, based on calculations using Boltzman fits to the voltage dependence of the conductance in mammals (Manis, P. and Marx, S., 1991; Bal, R. and Oertel, D., 2001; Rothman, J. S and Manis, P. B., 2003a), to about 30% in avian n. magnocellularis (Rathouz, M. and Trussell, L., 1998). The conductance contributed by the low-voltage-activated channels at rest then corresponds to 20–60 nS, which can be nearly as large as the resting conductance of the cell. This conductance may also be balanced by the conductance of I_H channels, which are of similar magnitude at rest in octopus cells (Bal, R. and Oertel, D., 2000). This is also on the same order of magnitude as the conductance contributed by single endbulb of held synapses in mouse VCN (a typical single auditory nerve fibre (ANF) input generating a 5 nA excitatory postsynaptic currents (EPSCs) at −60 mV in mouse VCN bushy cells (Wang, Y. and Manis, P. B., 2005) would correspond to 83 nS). Because the membrane time constant is short, the synaptic conductance can charge and discharge the

cell membrane very rapidly; thus the excitatory postsynaptic potential (EPSP) is not much longer than the duration of the synaptic conductance, and the conductances themselves are very brief (Trussell, L. O., 1999). In addition, this shunting effect limits the window for temporal summation of subthreshold EPSPs, so that close temporal coincidence of subthreshold events is necessary to reach threshold; this can enhance temporal precision by averaging inputs to the cell and may be responsible for the ability of some cells to show greater phase locking than their inputs (Rothman, J. and Young, E., 1996).

p0255 Second, the low-voltage-activated channel limits extra action potentials that might be produced by strong excitatory inputs (Brew, H. M. and Forsythe, I. D., 1995; Gittelman, J. X. and Tempel, B. L., 2006). This occurs because the conductance activates during action potentials, and so contributes to action potential repolarization (Rothman, J. S. and Manis, P. B., 2003b; Klug, A. and Trussell, L. O., 2006). Limiting extraneous action potentials in response to a cyclical input (click train or tones) would improve temporal signaling, especially when this signaling is compared to that of other neurons responding to the same temporal pattern of input, and is analyzed by higher-order neurons receiving convergent input. Suppression of multiple action potentials would also maximize the opportunity for action potentials to be phase locked to subsequent cycles of a tonal stimulus, and would reduce the refractory period by providing additional hyperpolarization between cycles. A similar role for these channels in the presynaptic terminal has been shown (Dodson, P. D. *et al.*, 2003). In this context, the high- and low-voltage-activated currents are likely to interact during periods of high synaptic drive to promote sustained and temporally precise high rate firing (Fernandez, F. R. *et al.*, 2005; Klug, A. and Trussell, L. O., 2006).

p0260 Third, the low-voltage-activated channels makes the cells more sensitive to rapidly changing events than to slowly changing events; in other words, they become sensitive to the slope of the EPSP, such that rapidly rising EPSPs have a much higher probability of bringing the cell to threshold than slowly rising events (Ferragamo, M. J. and Oertel, D., 2002; McGinley, M. J. and Oertel, D., 2006). The slope sensitivity arises in part because activating the low-voltage-activated conductance can raise spike threshold (Brew, H. M. *et al.*, 2003; see also Fukui, I. and Ohmori, H., 2004), and in part because slowly rising EPSPs will allow the low-voltage-activated conductance to turn on before the peak of the EPSP, which reduces the amplitude of the EPSP. In contrast, rapidly rising events bring the cell to threshold before the low-voltage-activated currents become fully activated. In the case of octopus cells, this allows the cells to respond to synchronous synaptic inputs with precisely timed action potentials, but will tend to suppress responses to desynchronized inputs (Ferragamo, M. J. and Oertel, D., 2002; McGinley, M. J. and Oertel, D., 2006). The slope sensitivity varies among cells in the VCN that express different amounts of low-voltage-activated conductances (McGinley, M. J. and Oertel, D., 2006). The way in which these channels impart slope sensitivity will depend on their rates of activation. Although the low-voltage-activated channel activates with fourth-order kinetics, at a resting potential of -60 mV the energetics are such that the channels need only move through a single gating transition to achieve the open state (Rothman, J. S. and Manis, P. B., 2003a). Thus, at rest, they will open with first-order kinetics with no delay (Manis, P. and Marx, S., 1991; Rathouz, M. and Trussell, L., 1998; Rothman, J. S. and Manis, P. B., 2003a), so that they will be engaged at the first sign of depolarization. A covariance analysis of the membrane potential preceding spikes in n. magnocellularis was undertaken to examine the temporal nonlinearities present in these cells (Slee, S. J. *et al.*, 2005). Spike generation depended on two features of the input: a short-term (2 ms wide) smoothing function and a short-term (<5 ms wide) derivative-like function. Sensitivity to the derivative-like function was largely abolished with the low-voltage-activated conductance was blocked with α-DTX, whereas the short-term smoothing component remained. This analysis thus supports the contention that the low-voltage-activated conductance confers sensitivity to rapidly fluctuating voltage changes, rather than the time-averaged membrane potential.

p0265 Fourth, activation of the low-voltage-activated channels can improve the signal-to-noise ratio for detection of weak excitatory events against a background of uncorrelated activity (Svirskis, G., 2002; Svirskis, G. *et al.*, 2004). These authors used dynamic clamp to simulate synaptic conductances onto MSO neurons. The contribution of the low-voltage-activated channels to signal detection was found to be twofold. First, reducing the low-voltage-activated current with DTX reduced the synchrony of the response to specific, slightly larger, inputs, largely because decreasing the conductance permitted weaker, uncorrelated, inputs to generate extraneous spikes. Second, using reverse correlation (spike-triggered averaging), it was found that the average

synaptic current that brought the cell to threshold was rapidly rising (see also Slee, S. J. *et al.*, 2005), and that in the presence of DTX, more slowly rising events could also be effective. These properties are consistent with results described above for MNTB principal neurons, n. magnocellularis neurons, and cochlear nucleus octopus cells.

p0270 Together, these features suggest that low-voltage-activated potassium conductances optimize detection of rapidly changing synchronous synaptic input (whether from a few or many synapses), while simultaneously suppressing the contributions of asynchronous and slow inputs, and suppressing asynchronous postsynaptic spikes. Which contribution is most important for processing for a given cell type seems to depend on the pattern of afferent convergence, and perhaps the relative size of the low-voltage-activated conductance.

s0145 3.32.6.1 Tonotopic Channel Expression Patterns, and Relationship to Integrative Roles

p0275 The fundamental organizing principle of the auditory system is the representation of sound frequency as position (tonotopic organization). In many species, there are clear and well-established gradients of cellular mechanisms along the tonotopic axis in the auditory end organs (cochlea and basilar papilla) that support the temporal requirements for sensory processing of different frequency sounds (Fettiplace, R. and Fuchs, P. A., 1999). Such gradients make sense for peripheral processing. Perhaps not surprisingly, similar gradients have been described in central nuclei, even though their existence might not be predicted to be necessary. Because sound is converted into a train of action potentials at the level of the auditory nerve, the sound frequency itself is no longer represented in terms of a continuously variable signal. Instead, frequency is represented as the place of activity, and other attributes such as intensity or stimulus phase are encoded in action potential intervals in single fibers or as temporally correlated firing across fibers. The information represented by these action potentials is, in some senses, independent of acoustic stimulus frequency. However, both the tonotopic variation in ion channel expression in the SGCs (discussed above), and the variation in the precision of temporal structure in ANF responses to broadband noise suggests that ANFs represent other kinds of temporal information that do change with tonotopic position. For example, the temporal dispersion of spike times sufficient to attain a vector strength of 0.9 at 500 Hz is much greater than the dispersion necessary to attain a lower vector strength at 2 kHz (Koppl, C., 1997; Paolini, A. G. *et al.*, 2001); hence, the temporal requirements for detection of correlated afferent activity are more stringent for high-frequency cells. Finally, phase locking in the low-frequency tail of cat high characteristic frequency (CF) ANF response areas is better than the phase locking seen at the same frequencies, near CF, for low-frequency ANFs (Joris, P. X. *et al.*, 1994), which suggests that timing information in high CF fibers is more precise than in low CF fibers. This is also reflected in the temporal correlations in response to broadband noise. The interstimulus correlations of responses to noise in cat ANFs show a central peak whose width varies from about 1 ms for 4 kHz fibers to 400 μs for 12 kHz fibers (Louage, D. H. *et al.*, 2004). Translating this into the response of many fibers of a given CF to the same stimulus, it suggests that certain features of the stimulus generate correlations in synaptic input whose relative timing is in the 1–0.4 ms range, depending on CF. Postsynaptic cells that receive subthreshold inputs (globular bushy cells and octopus cells) could detect these coincident synaptic events and forward this information to higher-order nuclei.

p0280 Tonotopic gradients in cellular mechanisms of information processing are present in some central auditory nuclei. High levels of Kv3.1 immunostaining are seen in the high-frequency regions of the avian n. magnocellularis and n. laminaris (Parameshwaran, S. *et al.*, 2001). A similar gradient of Kv3.1 expression is present along the tonotopic axis of the rat and mouse MNTB (Li, W. *et al.*, 2001; von Hehn, C. A. *et al.*, 2004) and possibly VCN (von Hehn, C. A. *et al.*, 2004). Because Kv3.1 is a high-threshold delayed rectifier channel, it is largely involved in action potential repolarization (Rothman, J. S. and Manis, P. B., 2003b; Klug, A. and Trussell, L. O., 2006). Thus, the gradient suggests that the high-frequency cells might recover from a spike more rapidly and could have greater firing precision for high afferent rates. However it is unclear why the low-frequency cells do not have a similar expression level; it is possible that they utilize another channel. Physiological measurements in the MNTB are consistent with this, revealing a gradient in the low- and high-voltage-activated K^+ conductances (largest conductance in the high-frequency regions), whereas an unidentified K^+ conductance showed an opposing gradient (Brew, H. M. and Forsythe, I. D., 2005). In n. magnocellularis, there is higher Kv1.1 expression in the high-frequency regions, which correlates well with the intrinsic physiology of the cells

(Fukui, I. and Ohmori, H., 2004). The higher expression of Kv1.1 endows the high-frequency cells with shorter time constants, and a shorter window for coincidence detection. This kind of gradient is also consistent with the smaller timing dispersion for afferent synapses from high-frequency regions of the basilar papilla (Koppl, C., 1997). In n. laminaris, which expresses Kv1.1 at a lower level than Kv1.2, Kv1.2 is found to be maximal in the middle region, and lower at higher and lower frequencies (Kuba, H. *et al.*, 2005). This is also consistent with cells in the mid-frequency region having shorter time constants, lower input resistances, and more rapidly decaying EPSPs (however, cf. Reyes, A. D. *et al.*, 1996). In rat LSO, Kv1.1 protein and low-voltage-activated conductance expression are higher in the low-frequency regions (Barnes-Davies, M. *et al.*, 2004). With the exceptions of the LSO and n. laminaris, the central K^+ channel gradients follow a general pattern similar to that reported for the SGC: Kv1.1 (or Kv1.2) and Kv3.1 are more highly expressed in the higher-frequency neurons. Thus, it appears that the biophysical mechanisms that support fine temporal processing are optimized to match the tonotopic variation in the precision of afferent spikes.

s0150 3.32.7 Conclusion

p0285 Many neurons of the auditory system are specialized for rapid temporal processing. Although the specific mechanisms that participate in the analysis of timing information are most evident in the brainstem, there is also evidence that some specialization in terms of receptors and channels may be present even in primary auditory cortex. The key elements appear to be combinations of voltage-gated potassium and hyperpolarizatation-activated conductances that appear as repeated motifs in the cells involved in temporal processing. These include low-voltage-activated potassium channels that operate in a subthreshold voltage regime to determine the rules of synaptic integration as well as participate in dynamically regulating spike threshold, hyperpolarization-activated cation channels that presumably control the level of activation of the subthreshold potassium conductances and perhaps the availability of sodium conductances, and high-voltage-activated potassium channels that rapidly repolarize action potentials and support the ability of the cells to fire precisely timed spikes at high rates. These combinations are seen both in avians and mammals, attesting to their fundamental importance in auditory temporal processing. Many of the neurons with these channel combinations were once thought to operate as relays that forwarded temporal information with little modification. However, this is clearly not an accurate depiction of their operation, as the cells do not fire in response to all afferent spikes (Li, R.Y.-S. and Guinan, J. J., 1966; Kopp-Scheinpflug, C. *et al.*, 2002; 2003). Temporal processing in these cells is influenced by many additional processes, such as synaptic depression (Brenowitz, S. and Trussell, L., 1998; Cook, D. L. *et al.*, 2003), contributions from dendritic and electrotonic structure (Agmon-Snir, H. *et al.*, 1998; Zhou, Y. *et al.*, 2005), regulation by neuromodulators (Kossl, M. and Vater, M., 1989; Banks, M. I. *et al.*, 1993), and of course, inhibition (Caspary, D. M., *et al.*, 1994; Grothe, B. and Sanes, D. H., 1994; Brand, A. *et al.*, 2002; Kopp-Scheinpflug, C. *et al.*, 2002). It is the dynamic interaction between all of these influences and the different sets of ion channels that ultimately determines the exquisite temporal acuity of the auditory system.

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