Published in final edited form as:

Trends Neurosci. 2017 October ; 40(10): 613–624. doi:10.1016/j.tins.2017.08.001.

Cellular Computations Underlying Detection of Gaps in Sounds and Lateralizing Sound Sources

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Abstract

In mammals, acoustic information arises in the cochlea and is transmitted to the ventral cochlear nuclei (VCN). Three groups of VCN neurons extract different features from the firing of auditory nerve fibers, and convey that information along separate pathways through the brainstem. Two of these pathways process temporal information: octopus cells detect coincident firing among auditory nerve fibers, and transmit signals along monaural pathways; and bushy cells sharpen the encoding of fine structure and feed binaural pathways. The ability of these cells to signal with temporal precision depends on a low-voltage-activated K^+ conductance (g_{KL}) and a hyperpolarization-activated conductance (g_h). This ‘tale of two conductances’ traces gap detection and sound lateralization to their cellular and biophysical origins.

Keywords

ion channels; hearing; sound localization; gap detection; Kv1; HCN; potassium channel

Timing information in the processing of sound

In mammals, acoustic information arises in the cochlea and is transmitted to the ventral cochlear nuclei (VCN). Three groups of VCN neurons extract different features from the firing of auditory nerve fibers: octopus, stellate, and bushy cells, which in turn convey that information along separate pathways through the brainstem. Two of these pathways process temporal information: octopus cells detect coincident firing among auditory nerve fibers, and transmit signals along monaural pathways; and bushy cells sharpen the encoding of fine

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structure and feed binaural pathways. The ability of these cells to signal with temporal precision depends on a low-voltage-activated K⁺ conductance (g_{KL}) and a hyperpolarization-activated conductance (g_h). Mice with genetically altered g_h and g_{KL} have deficits in detecting temporal gaps and in lateralizing sounds, and these sensory deficits parallel the slowing of electrical events in octopus and bushy cells, respectively.

Processing of temporally-precise auditory information underlies both monaural and binaural functions. For instance, the ability of mammals to detect temporal gaps in sounds is a monaural function. The detection of gaps is critical for mammals to determine the biological significance or meaning of sounds. In humans it is required for understanding speech [1–5]. People with auditory neuropathy whose gap detection thresholds are elevated have difficulty understanding speech even when their hearing thresholds are near normal. The ability to detect a gap of 3 msec [3] requires that neurons encode offsets and onsets of sounds with a temporal precision of at least 1 msec.

Localizing the azimuthal direction of sound origin, in contrast, is a binaural function. This function relies on comparisons of timing and intensity between the two ears [6]. The computation of interaural time and intensity requires that the delays in the neuronal pathways from the two sides are matched in the superior olivary complex [7, 8]. The temporal precision in the computation of interaural time requires, in addition, the ability to measure the magnitude of tiny temporal disparities. Differences in the relative time of arrival of sounds at the two ears are small even in animals with large heads, <0.5 msec in humans. Under optimal conditions human subjects can resolve differences in location of 1° that correspond to interaural time differences of ~10 µsec [9, 10].

In this review, we discuss progress in understanding processing of temporally precise auditory information, with emphasis on how two cellular conductances in VCN neurons make temporal processing possible. Genetic tools have made it possible to pin-point specific links between these cellular conductances and the perceptual functions of gap detection and sound localization. We conclude with a discussion of some of the open questions in field, including how the detection of synchronous firing in response to broadband transient sounds by octopus cells could help to bind together the spectral components of individual sound sources into a single percept.

Ascending pathways from the ventral cochlear nucleus convey timing cues

Type I spiral ganglion cells in the cochlea receive input from inner hair cells through their peripheral process and transmit signals through their central processes, the auditory nerve fibers, to the VCN. These myelinated auditory nerve fibers convey acoustic information to three groups of principal cells in the VCN—octopus, stellate, and bushy, cells—each of which form separate, parallel pathways through the brain stem (Fig. 1).

Octopus cells extract information from many (>60 in mice) fibers tuned to a broad range of frequencies [11, 12], each of which activates only a small conductance (<2 nS in mice) and produces a very small (<3 mV in mice) EPSP. They signal the presence of the onset of

broadband sounds with extraordinary temporal precision [13–15], projecting to the contralateral SPON [16, 17] and to the columnar area of the VNLL [16, 18, 19] (Fig. 1A).

Bushy cells extract information gleaned from the timing of firing of few auditory nerve fiber inputs. They receive few (in mice 2–6) large, somatic, end bulb terminals of auditory nerve fibers [20]. These terminals activate large conductances (in mice 22 ± 15 nS) that can deliver large synaptic currents that produce large EPSPs. All three subtypes of bushy cells are involved in binaural pathways. Large spherical bushy cells feed timing information to the MSO on both sides, globular bushy cells project to the MNTB which in turn signals the timing of contralateral sounds to the LSO. Small spherical bushy cells excite neurons in the ipsilateral LSO [21]. All subtypes of bushy cells also innervate parts of the VNLL [22–25] (Fig. 1A, B).

Lastly, stellate cells (also called T stellate [26], type I multipolar [27], chopper [28], or planar multipolar [29]), largely jettison timing information. These sharply tuned neurons receive input from only few auditory nerve fibers (5–6 in mice) that activate conductances of modest amplitude (4.6 ± 3 nS) [20]. Stellate cells project broadly, including to the ipsilateral (LSO) [30], possibly to the SPON [22, 31], and to the VNLL [19, 32–34] (Fig. 1B).

Monaural and binaural pathways through the brainstem are largely separate. Within target areas of the VNC – the superior olivary complex and the lemniscal nuclei – the superior paraolivary nucleus (SPON) and ventral nucleus of the lateral lemniscus (VNLL) process acoustic information that comes from only one ear (Fig. 1, top) whereas the medial (MSO) and lateral superior olivary (LSO) nuclei compare acoustic features from the two ears (Fig. 1, bottom).

g_h and g_{KL} are differentially expressed in principal cells of the VCN

The three groups of principal cells of the VCN differ in their biophysical properties, as is revealed in their differing responses to depolarizing current pulses (Fig. 2, upper panels) [11, 35–37]. Octopus and bushy cells fire transiently, reflecting the activation of g_{KL} whereas stellate cells do not have g_{KL} and fire tonically. Octopus cells require about ten times more depolarizing current than bushy cells reflecting their lower input resistances. The voltage returns to rest very rapidly in octopus cells, less rapidly in bushy cells and most slowly in stellate cells. Responses to hyperpolarizing current sag back toward rest, resulting from the activation of g_h .

Integrative roles of g_{KL} and g_h in the VCN

The presence of g_{KL} and g_h has three functional consequences. First, in octopus and bushy cells, g_{KL} and g_h are partially activated at the resting potential, thereby reducing the input resistance. Accordingly, they shorten the membrane time constants and accelerate voltage changes. The speed of depolarizing voltage changes in octopus cells and bushy cells indicates that synaptic currents, too, will produce rapid and brief voltage changes that enable temporally precise signaling [11, 38, 39]. Second, g_{KL} truncates EPSPs. The ion channels that mediate g_h open and close so slowly that their activation is affected little by the brief voltage deflections of EPSPs (Fig. 2). In contrast to g_h , g_{KL} activates rapidly in response to

the depolarization of EPSPs so that it actively repolarizes EPSPs, making them brief and giving them sharp peaks whose timing stays constant over a wide range of amplitudes [11]. Third, the presence of g_{KL} makes octopus and bushy cells sensitive to the rate at which they are depolarized [36, 40] (Fig. 3, left). If bushy or octopus cells are depolarized too slowly by insufficiently synchronous EPSPs (Fig. 3, bottom right), the activation of g_{KL} prevents firing. They fire only if the rate of depolarization exceeds a threshold level. The threshold rate-of-depolarization provides a measure of the duration of the integration window over which synaptic depolarization can sum (Fig. 3, gray bands) [40]. The magnitude of g_{KL} governs the temporal precision of coincidence detection (Fig. 3, top right).

Octopus cells have large g_{KL} and g_h that profoundly affect synaptic integration. Many small synaptic inputs must sum to generate the large synaptic current required to evoke action potentials in octopus cells [11]. Octopus cells have large g_{KL} and g_h that profoundly affect synaptic integration. Many small synaptic inputs must sum to generate the large synaptic current required to evoke action potentials in octopus cells [12]. These cellular properties account for the exceptional precision in the timing of firing of octopus cells in responses to sounds [13–15].

Bushy cells detect the coincident firing of small numbers of similarly tuned auditory nerve fibers. A small number of inputs each deliver substantial currents through large synaptic conductances [20]. The presence of g_{KL} and g_h enables bushy cells to sharpen the information contained in the timing of firing of their inputs by sharpening the averaged EPSP [41].

The expression of the subunits that form g_{KL} and g_h differ in the three groups of principal cells of the VCN. The tetrameric voltage-gated ion channels that mediate g_{KL} and g_h are formed from Kv1 and HCN α subunits respectively.

Most Kv1 channels in the brainstem, whose α subunits are encoded by the family of *Kcna* genes, are formed from Kv1.1, Kv1.2, Kv1.4 and Kv1.6 subunits [42–44]. The presence of Kv1.1 gives Kv1 channels a low activation voltage [45–48]. Kv1.1 subunits are prominent in the somatic and dendritic membranes of octopus cells. They are also present in the neuropil around bushy cells and are least prominent in the multipolar cell area that houses stellate cells [49].

Electrophysiological measurements parallel these immunohistochemical observations in relation to Kv1 channels. In octopus and bushy cells depolarizing pulses to between -70 and -40 mV activate a K^+ current that is sensitive to pharmacological blockers specific for Kv1 subunits [50, 51]. Maximal g_{KL} is greatest in octopus cells (~ 500 nS), smaller in bushy cells (~ 80 nS), and stellate cells have little or no g_{KL} [36].

Three HCN subunits are expressed in the brain, of which two, HCN1 and HCN2, are prominent in the VCN [52, 53]. Homomeric HCN1 channels have rapid kinetics whereas HCN2 channels are slower [54, 55]. Heteromeric channels have intermediate kinetics [56–59]. The voltage-sensitivity of g_h is regulated by cAMP [60]. HCN1 subunits are strongly expressed in somatic and dendritic membranes of octopus cells, and they are present less prominently in bushy and stellate cells [49, 53].

Again, electrophysiological measurements complement these immunohistochemical observations. Octopus [61], bushy [51], and stellate [62] cells have hyperpolarization-activated cation currents. Maximal g_h is largest and fastest in octopus cells (~150 nS) and smaller in bushy cells (~30 nS). In stellate cells, maximal conductances were smaller (~20 nS) and slower and the voltage range of activation was more hyperpolarized so that the resting I_h in stellate cells is smaller than in bushy or octopus cells.

g_h and g_{KL} are prominent in neuronal pathways fed by bushy and octopus cells

Since the ability of neurons to signal with temporal precision depends on g_h and g_{KL} , and since hearing requires temporal precision, one could expect to find expression of these conductances not only in VCN neurons but also in their inputs and their targets (Fig. 1, blue). Neurons that receive well-timed input but do not themselves fire with temporal precision presumably re-encode features that depend on signaling with temporal precision.

The type I spiral ganglion cells whose axons are the auditory nerve fibers have g_h and g_{KL} . In spiral ganglion cells g_{KL} is formed from Kv1 channels [63, 64] and g_h is formed from HCN1, HCN2, and HCN4 subunits [65]. Spiral ganglion cells in *Hcn1*^{-/-} mice were hyperpolarized relative to wild type controls by similar amounts as by the application of ZD7288, a specific blocker of g_h [65].

Octopus cells feed monaural pathways that have g_h and g_{KL} (Fig. 1, blue). Targets of octopus cells in the VNLL have g_h and g_{KL} and reflect the precise timing of firing of octopus cells [18, 47, 66–68]. Cells in the SPON also harbor the combination of g_h and g_{KL} although their firing patterns differ from those of their octopus cell inputs [69, 70].

All subtypes of bushy cells feed binaural pathways in which g_h and g_{KL} are prominent (Fig. 1, blue). Large spherical bushy cells project to the ipsilateral and contralateral MSO, whose principal neurons have exceptionally large g_h and g_{KL} [71–76]. Globular bushy cells project to the ipsilateral and contralateral lateral nucleus of the trapezoid body (LNTB) that have g_h and likely also g_{KL} [77]. Globular bushy cells contact the principal cells of the contralateral MNTB that have g_h and g_{KL} that depends on Kv1.1 and HCN1 subunits [78–84]. Targets of small spherical bushy cells in the LSO may also have the combination of g_h and g_{KL} [85]. Some, but not all, of the responses of LSO cells themselves convey the fine structure of sounds [86].

Genetic perturbations change g_h and g_{KL} in octopus and bushy cells

Mice that lack Kv1.1 [87] or HCN1 [88] subunits are viable and they hear [89, 90]. As expected, however, the biophysical properties of VCN neurons differed from wild type controls. Several observations are noteworthy in that regard.

The loss of HCN1 subunits not only reduces the magnitude and slows I_h in all three groups of VCN cells but, unexpectedly, also reduces g_{KL} in octopus and bushy cells (Fig. 2, middle

panels) [91]. In contrast, the loss of Kv1.1 is compensated in steady-state currents so that only the peak I_{KL} differed between mutants and wild type [92].

Wild type strains of mice differ from one another in the magnitudes of g_{KL} and g_h . They are largest in outbred ICR mice [50, 61], smaller in HCN1^{+/+} that are a mixed C57BL/6 and 129S strain [88, 91], and smallest in Kv1.1^{+/+} mice that are on a C3HeB/FeJ background [87, 92].

The magnitude of g_h and g_{KL} in differing strains of wild type and mutant mice across octopus and bushy cells is roughly correlated. The relative magnitude of g_h and g_{KL} , when examined in different strains of both wild type and mutant mice, and across octopus and bushy cells, is roughly preserved. This suggests that the regulation of g_h and g_{KL} is linked (Fig. 2, lower panels) [91–93]. The finding that both g_h and g_{KL} were diminished in HCN1^{-/-} octopus cells and that neither the steady state g_{KL} or g_h were diminished in Kv1.1^{-/-} mice suggests that g_h governs g_{KL} .

Differences in the expression of g_h and g_{KL} leads to differences in the rate-of-depolarization thresholds and of the duration of integration windows (Fig. 3). The rate-of-depolarization thresholds are correlated with g_{KL} in octopus and bushy cells across strains of mice. There is a significant difference in rate-of-depolarization thresholds between HCN1^{-/-} and HCN1^{+/+} mice and also between the wild type HCN1^{+/+} and Kv1.1^{+/+} mice.

Interactions between g_h and g_{KL} and the resting potential

There was the possibility that altering g_h and g_{KL} genetically might alter resting potentials because blocking g_{KL} acutely depolarizes and blocking g_h acutely hyperpolarizes cells. However, altering g_h and g_{KL} did not affect the resting potentials of octopus cells [92].

Conversely, in octopus cells the resting potential may affect g_h and g_{KL} . The large magnitude makes it possible to resolve I_h and I_{KL} at the resting potential. In wild-type octopus cells the ZD7288-sensitive I_h and α -dendrotoxin-sensitive I_{KL} are opposite and almost equal at the resting potential [13, 91, 92]. In *Kcna1*^{-/-} mice, however, the α -dendrotoxin-sensitive component of I_{KL} balances only about half of I_h . In these mutants, and in all other cells tested, the α -dendrotoxin-insensitive current was sensitive to 10 mM tetraethylammonium chloride (TEA). In *Kcna1*^{-/-} mice, therefore, K⁺ channels with a different subunit composition that are insensitive to α -dendrotoxin and that generally comprise only a minor component, compensated for the loss of Kv1.1 subunits. The finding that the voltage-sensitive I_{KL} equals the voltage-sensitive I_h equal even when resting potentials vary over a 9 mV range, suggests that the resting potential plays a role in matching the expression of g_{KL} to balance I_{KL} with I_h at rest [92]. Our inability to resolve the small resting I_h and I_{KL} in bushy cells leaves open the question whether this rule applies beyond octopus cells.

Genetic perturbation of g_h and g_{KL} affects the ability to detect features of sounds

Both *Hcn1*^{-/-} and *Kcna1*^{-/-} mice differ from wild type controls in their abilities to process acoustic information [90, 94, 95]. Ison and his colleagues have used inhibition of the acoustic startle reflex (ASR) to measure the detection of a wide range of acoustic stimuli in mice. Detection of a change in the sound field immediately prior to a brief but intense sound reduces the startle that is evoked by that intense sound. Inhibition of the acoustic startle response (ASR) is thus a measure of what features of acoustic stimuli mice are able to detect.

The loss of HCN1 results in a distinct deficit in the ability of mice to detect gaps in sound (Fig. 4A) [90]. Wild type control mice, *Hcn1*^{+/+}, can detect gaps of 1 msec in noise whereas *Hcn1*^{-/-} mice require gaps to be at least 2 msec to be detected (Fig. 4B) [90]. There was no measurable difference in gap detection between *Kcna1*^{-/-} mice and their wild type controls (Fig. 4C) [89].

The loss of HCN1 or Kv1.1 also results in a deficit in the ability of mice to lateralize sounds (Fig. 4D) [94]. When mice detect a symmetrical shift of a noise source from one side of the midline to the other, the startle evoked by a subsequent loud sound is depressed. Depression of the ASR was greatest when the interval (ISI) between the shift and the startle stimulus was between 30 and 60 msec. This task is a binaural task because performance is weak when mice are tested in monaural listening [96]. In contrast to wild type controls, shifts of up to 22° were almost undetectable to *Hcn1*^{-/-} and *Kcna1*^{-/-} mice (Fig. 4E, F). In contrast with the pattern of deficits for gap detection, deficits in lateralization of *Kcna1*^{-/-} mice were roughly equally severe as those of *Hcn1*^{-/-} mice.

Concluding remarks

The detection of gaps in noise and lateralization of sounds requires that neurons convey information in the timing of firing. Because the computations that involve the encoding of timing occur at the early stages of the auditory pathway in a few, well understood pathways, it becomes possible, at least tentatively, to assign functions to cell groups. The patterns of biophysical and behavioral deficits after genetic perturbation of g_h and g_{KL} (see Outstanding Questions box) suggest that octopus cells are involved in gap detection and support the conclusion by many others that bushy cells are involved in sound lateralization.

Stellate cells could participate in lateralization of sound but are unlikely to be involved in gap detection. Stellate cells provide excitation to at least some of the principal cells of the ipsilateral LSO (Fig. 1) that detect interaural intensity differences by balancing ipsilateral excitation with contralateral inhibition [30, 97, 98]. Their biophysical properties are not detectably different in *Kcna1*^{-/-} and *Hcn1*^{-/-} mice relative to wild type controls and thus cannot account for the differences in lateralization in different strains of mice. Stellate cells are unlikely to play a role in gap detection because the jitter in the timing of responses to sound is similar to the duration of detectable gaps (and 50 times greater than that of octopus cells) [15].

Bushy cells use g_h and g_{KL} to sharpen the temporal firing patterns of few similarly tuned inputs, sharpening the encoding of the fine structure of sounds [14, 41]. They convey that sharpened information to the binaural pathways, as excitation and inhibition [71, 99], whose interaural time and intensity comparisons underlie sound localization [6]. Precise timing information carried by bushy cells is required because the timing of excitation and inhibition from the two ears must be matched to assure that interaural comparisons are made of the same sound and not of an earlier with a later sound [7, 8, 100]. The finding that deficits in lateralization in *Hcn1*^{-/-} were greater than those in *Kcna1*^{-/-} mice relative to wild type controls parallels the changes in g_h and g_{KL} in bushy cells (Fig. 2). However, as several brainstem nuclei involved in these binaural pathways contain g_h and g_{KL} (Fig. 1B), it is unclear whether behavioral deficits in mutant mice result from deficits in bushy cells or their targets [83, 101]. Altogether many converging lines of evidence indicate that bushy cells play an essential role in sound localization.

Several lines of evidence support the conclusion that octopus cells play a role in gap detection. First, octopus cells form monaural pathways and gap detection is a monaural function (Fig. 1). Second, octopus cells use their large g_h and g_{KL} to convey when the firing among auditory nerve inputs is synchronous and they do so with exquisite precision [14, 15] as do their targets in the VNLL (Figs. 2, 3) [18, 66]. Third, their targets in the SPON could contribute to gap detection by signaling the offsets of sounds [70, 102–105]. Fourth, the finding that the reduction in g_h is compounded by a reduction in g_{KL} in octopus cells of *Hcn1*^{-/-} mice whereas the deficit in g_{KL} is compensated in *Kcna*^{-/-} mice could account for why there is a deficit in gap detection in *Hcn1*^{-/-} mice while there is no detectable deficit in *Kcna*^{-/-} mice (Fig. 4). How these mutations affect the targets of octopus cells in the VNLL or SPON neurons is not known. There remains a possibility that a pathway through bushy cells and the VNLL is involved in gap detection (Fig. 1). Not enough is known about the temporal resolution of this pathway to exclude it completely.

The association of octopus cells with gap detection suggests that octopus cells play a role in understanding environmental sounds, including understanding speech by humans. People who lose hearing in one ear can understand speech, indicating that this is a monaural function. People with auditory neuropathy who cannot detect brief gaps cannot understand speech [1–5]. This link between gap detection and speech comprehension is logical, given that it is the difference in gaps, specifically the voice-onset times after the consonant, that distinguish for instance “do” from “to” and “beer” from “peer.” Octopus cells are also uniquely suited to mark the onset of syllables and thus to mark the harmonic components associated with a single voice. In fact, human cochlear nuclei have the same types of neurons as other mammals, including prominent octopus cells [106] (see Outstanding Questions box). While progress has been made in understanding the integrative functions of neuronal circuits in the brainstem but the understanding of neuronal circuits at higher levels of the auditory pathway remains incomplete.

Acknowledgments

Philip H. Smith and Lin Lin carefully read and reread our manuscript and we received a particularly thoughtful anonymous review. We are grateful for the excellent suggestions from all these colleagues. The work was supported by a grant from the NIH DC00176 and by the UW Medical Foundation.

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Trends Box

- Two conductances enable auditory brainstem neurons to carry acoustic information in the timing of firing: a hyperpolarization-activated mixed-cation conductance (g_h) that is mediated through HCN channels, and a low-voltage-activated K^+ conductance (g_{KL}) that is mediated through Kv1 channels.
- Deletion of critical subunits of those ion channels differentially alters the biophysical properties of auditory neurons and also alters the ability of mice to detect gaps in sounds and to lateralize sound sources.
- Biophysical changes in the binaural pathways through bushy cells of the ventral cochlear nucleus parallel deficits in sound lateralization.
- Biophysical changes in octopus cells of the ventral cochlear nucleus, which form a disynaptic, monaural pathway through the brainstem to the inferior colliculus, parallel, and can account for, deficits in gap detection.

Outstanding Questions

1. What links the regulation of Kv1 channels with the regulation of HCN channels in auditory neurons?
2. How do the pathways through the brainstem converge in the inferior colliculus?
3. Humans have the same types of principal neurons in the ventral cochlear nucleus (VCN) as other mammals. But how similar functionally are the human VCN neurons to the corresponding neurons in mice?
4. How do the three types of principal cells of the VCN contribute to understanding speech in humans?
5. How do the three types of VCN neurons contribute to hearing music?
6. How do cochlear implants drive VCN neurons in humans?

Figure 1.

Schematic representations of the monaural and binaural auditory pathways through the brainstem. Auditory nerve fibers carry acoustic information from the cochlea to the ventral (VCN) and dorsal (DCN) cochlear nuclei. The targets of auditory nerve fibers include stellate (S), bushy (B) and octopus (O) cells in the VCN. **Monaural** pathways (top) convey input from only one ear through the superior paraolivary nucleus (SPON) and the ventral nucleus of the lateral lemniscus (VNLL) to the contralateral inferior colliculus. **Binaural** pathways (bottom) through the medial (MSO) and lateral (LSO) superior olivary nuclei combine direct excitatory and indirect inhibitory inputs from the contralateral and ipsilateral VCN. In the binaural pathways schematic, **thickness** of lines denotes side. Blue shading: Cells and nuclei that contain cells which express g_h and g_{KL} and which encode timing with

temporal precision. Tan shading: Cells and nuclei whose firing contains little temporal information. Red labels: Nuclei that contain mainly or solely inhibitory neurons.

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Figure 2.

Electrophysiological differences between the three cell classes of the VNC, and across mouse strains. **V_m**: Voltage changes in responses to depolarizing and hyperpolarizing current pulses, superimposed, reveal biophysical differences between octopus, bushy and stellate cells in HCN^{+/+} mice. Currents used to polarize octopus cells are larger than those used to polarize bushy and stellate cells. **I_{KL}**: Membrane currents evoked by depolarizing voltage pulses from -90 mV to -40 mV in the presence of a blocker of I_h are smaller in octopus cells of mice that lack HCN1 (red) than those in wild type control (blue). Currents are larger in octopus than in bushy cells and are absent in stellate cells. **I_h**: Membrane

currents evoked by hyperpolarizing voltage pulses from -57 mV to -112 mV in the presence of a blocker of I_{KL} are smaller and slower in mice that lack HCN1 than those recorded from wild type controls in all three cell types. **g_{KL}/g_h :** Conductances, g , were calculated by dividing the maximal I_h and I_{KL} by the driving force. In octopus and bushy cells of four strains of mice there was a positive correlation between the magnitudes of g_{KL} and g_h in four strains of mice. The wild type control strains, HCN1^{+/+} and Kv1.1^{+/+} differed from one another. This figure includes data published previously [91, 92].

Figure 3.

g_{KL} sharpens coincidence detection. **Left panels:** Depolarizing current ramps of varying durations to 1 nA reveal a threshold rate-of-depolarization (dV/dt_{thresh}). In an octopus cell from a Kv1.1^{+/+} mouse, the rate of depolarization had to be greater than 4.6 mV/msec to evoke action potentials. In an octopus cell from a Kv1.1^{-/-} mouse, slower depolarizations could evoke action potentials. The time window over which depolarization can sum (gray bar) is briefer in the wild type than in the Kv1.1^{-/-} octopus cell. **Top right:** Plot shows that dV/dt_{thresh} is positively correlated to g_{KL} . The relationship is more clearly resolved in octopus cells that have larger g_{KL} but was also present in the bushy cells that were tested. **Bottom right:** Models of summation of EPSPs illustrate the significance of the sensitivity to dV/dt . The sum of four asynchronous EPSPs rose less steeply than the sum of four synchronous EPSPs. The higher the dV/dt threshold, the more sharply timed is the coincidence detection performed by the cell. (The plot of comparisons between strains includes data from Fig. 7 [92].)

Figure 4.

The ability to detect features of sounds is compromised by the loss of HCN1 and of Kv1.1.

A. Detection by mice of gaps was monitored by inhibition of the startle reflex. The acoustic startle reflex (ASR), measured as the integral of the rectified output of an accelerometer over 100 msec, is reduced by detection of sound stimuli that occur shortly before the startle stimulus. In these experiments gaps of varying duration were presented to mice 60 msec before the startle stimulus, as illustrated schematically. **B.** There is a significant difference between gap detection in *Hcn1*^{-/-} mice and their wild type controls. *Hcn1*^{-/-} mice cannot detect gaps less than about 2 msec whereas wild type mice detect gaps of about 1 msec. Inhibition of the ASR, assessed as $(1 - \text{ASR}_{\text{test}} / \text{ASR}_{\text{control}})$, (This panel was adapted from Fig. 6 [90].) **C.** There is no difference in the duration of gaps detected by *Kcna1*^{-/-} mice and their wild type controls. (This panel is adapted from Figure 3 [89].) **D.** Lateralization of sounds was also measured by inhibition of the startle reflex. A mouse sat on the platform of the accelerometer, surrounded by an array of speakers, as illustrated, and with another speaker for the presentation of the startle stimulus mounted overhead. 30–60 msec before the startle stimulus, the source of noise was switched to a matched speaker placed symmetrically on the opposite side of the midline. **E, F.** Mutant mice showed less sensitivity to changing sides of sound sources than did their wild type controls. Symbols indicate means $\pm$ standard error; ** denotes significant differences $p < 0.01$, * denotes differences $p < 0.05$. (The figure is adapted from Figs. 6 and 7 [90], Fig. 3 [94], and Fig. 3 [89].)