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Are Neurons Adapted for Specific Computations? Examples from Temporal Coding in the Auditory System

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Introduction

Are neurons adapted for specific computations? Evolution has led to the appearance of specialized neurons, such as the neurons in the auditory system that encode temporal information with great precision (Trussell 1997; Oertel 1999). Nevertheless, it is not clear whether all neurons are adapted for particular computations or even whether specialized computational units are desirable under all circumstances. Some neurons may have more general responses. Other neuron types change their responses under the action of some modulator, but these might be regarded as being adapted for several computations, rather than for some general input-output function (see Golowasch et al. 1999; Stemmler and Koch 1999; Turrigiano, Abbot, and Marder 1994).

It is important to understand the functions of single neurons. Johnston et al (1996) wrote, ''Before one can hope to understand systems of neurons fully, one must be able to describe the function of the basic unit of the nervous system, that is, the single neuron and its associated dendritic tree.'' To make the case that neurons may be adapted for particular tasks, we will use the example of temporal coding cells in the vertebrate auditory system because their function is well known. This allows us to tie physiological and morphological observations to function.

Encoding Temporal Information

In the auditory system, precise encoding of temporal information has direct behavioral relevance. The timing of firing of auditory neurons carries information used for both localization and interpretation of sound. Psychophysical

studies support a role of a timing code for localization and pitch detection, and there is good evidence that localization of interaural phase differences falls off with frequency in the same way that temporal encoding falls off (see Hafter and Trahiotis 1997 for review). Therefore, those features of auditory neurons that lead to improved temporal processing should experience positive selection.

Cellular Specializations for Encoding Time: Quality of Input

Sound coming from one side of the body reaches one ear before the other, and the auditory system uses these time differences to localize the sound source. The auditory system encodes the phase of the auditory signal and then uses interaural phase differences to compute sound location (Heffner and Heffner 1992). Nocturnal predators such as the barn owl and mammals that use auditory information to direct their visual foveas towards a sound source all have well-developed abilities to localize sound (Heffner and Heffner 1992). The barn owl's ability to detect small phase or time differences is acute, and the owl is able to catch mice on the basis of auditory cues alone (Konishi 1973). Accurate and precise processing of the auditory stimulus is required for this detection. Auditory nerve fibers phase lock to the waveform of the acoustic stimulus, and this information is preserved and improved in the brain. Two lines of evidence support the idea that accurate temporal coding is important. First, measurements of the vector strength of the auditory nerve signal (calculated from the variability in the timing of action potentials with respect to the phase of the acoustic stimulus) show an improvement in high-frequency phase locking in the owl as compared to other animals by an octave or more (Koppl 1997). Second, models of coincidence detection perform better when the vector strength of the inputs improves (Simon, Carr, and Shamma 1999; Colburn, Han, and Culotta 1990; Grau-Serrat, Carr, and Simon 2003).

Presynaptic Specializations for Encoding Temporal Information

In the bird, auditory nerve afferents divide into two with one branch to the cochlear nucleus angularis (NA), a structure that codes for changes in sound level, and the other branch to the cochlear nucleus magnocellularis (NM) that codes for phase (Sullivan and Konishi 1984; Takahashi, Moiseff, and Konishi 1984). In mammals, similar cell types receiving auditory nerve input are contained in a single nucleus, the ventral cochlear nucleus (see Ryugo 1991). The termination of the auditory nerve onto the somas of avian NM neurons

and mammalian bushy cells take the form of a specialized calyceal or endbulb terminal while avian NA neurons and mammalian stellate cells are contacted through bouton-like synapses (figure 12-1A; Jhaveri and Morest 1982; Brawer and Morest 1974; Ryugo and Fekete 1982). The endbulb terminals envelop the postsynaptic cell body and are characterized by numerous release sites. They therefore form a secure and effective connection for the precise relay of the phase-locked discharges of the auditory nerve fibers to their postsynaptic targets. Physiological measures show that phase-locking abilities are correlated with the morphology of the nerve terminals so that phase locking is preserved in the neurons of the NM, and lost at higher frequencies in the noncalyceal projection to the NA (Koppl 1997). In the cat, there is a slight improvement in phase locking between the nerve and the bushy cells of the cochlear nucleus presumably due to monaural coincidence of auditory nerve fibers (Joris, Smith, and Yin 1994; Rothman, Young, and Manis 1993), while in the barn owl, there is a slight decrease (Koppl 1997).

Endbulb terminals are not essential for transmission of phase-locked spikes at low frequencies. The very low best frequency cells of the NM receive large bouton terminals from the auditory nerve and can also phase lock to frequencies below ~1 kHz (Koppl 1997). The task of encoding temporal information precisely becomes more difficult with increasing frequency. The

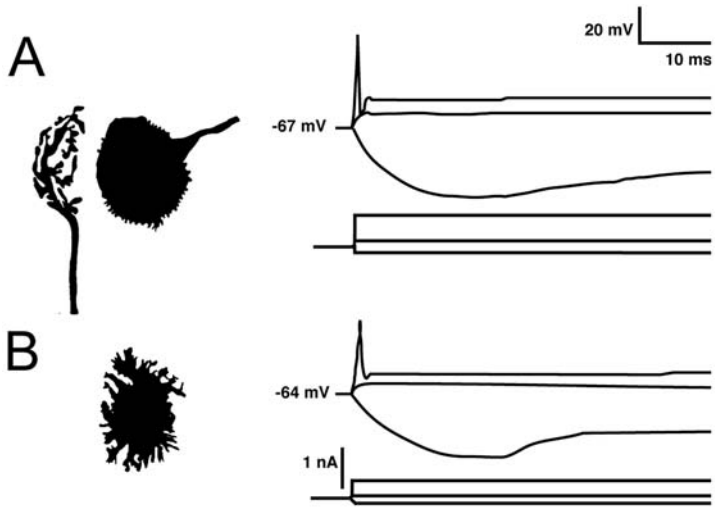

Figure 12-1. Time coding neurons in the bird brain exhibit a suite of physiological and morphological features suited to their function. (A) Auditory nerve endbulb terminals and magnocellular neurons in barn owl (*left*) and current clamp recordings from chicken NM neuron (*right*; from Reyes, Rubel, and Spain 1994). (B) Laminaris neuron in barn owl (*left*) and current clamp recordings from chicken NL (*right*; from Reyes, Rubel, and Spain 1996).

reason for this is clear when one considers that the absolute temporal precision required for phase locking to high frequencies is greater than that needed for low frequencies, that is, the same variation in temporal jitter of spikes translates to greater variation in terms of degrees of phase for high frequencies. Hill, Stange, and Mo (1989) estimated phase locking in the auditory fibers of the pigeon in terms of the commonly used synchronicity index (vector strength) as well as by measuring temporal dispersion. Vector strength of phase locking decreased for frequencies above 1 Khz. Temporal dispersion, however, also decreased with frequency, indicating enhanced temporal synchrony as frequency increased. The upper frequency limit of phase locking, therefore, appears to depend on irreducible jitter in the timing of spikes (see Carr and Friedman 1999). Thus, endbulb terminals may have emerged as an adaptation for transmission of phase information for frequencies above 1kHz, perhaps associated with the development of hearing in land vertebrates (Rubel and Fritzsch 2002). ◀ EDQ1

The invasion of the presynaptic action potential into the calyx leads to the synchronous release of quanta at many endbulb release sites giving this synapse a high safety factor of transmission (Isaacson and Walmsley 1995; Taschenberger et al. 2002). The invading presynaptic action potential is extremely narrow, being about 250 μsec at 35°C in postnatal day 8–10 animals (Borst, Egelhaff, and Haag 1995; Taschenberger and von Gersdorff 2000) probably due to rapid repolarization mediated by specific potassium conductances. Calcium influx into the presynaptic terminal is also brief and occurs only during the falling phase of the presynaptic action potential (Borst and Sakmann 1996). Because the action potential is narrow, its downstroke occurs quickly, as does calcium influx, reducing the synaptic delay. In addition, the brief period of calcium influx produces a confined and phasic period of neurotransmitter release, which also increases the temporal precision of transmission across the synapse (Sabatini and Regehr 1999). ◀ EDQ2

Transmitter release becomes more precise during development, which leads to less desensitization of the postsynaptic alpha amino-3-hydroxy-5-methylisooxazole-4-propionic acid (AMPA)-type glutamate receptors (Brenowitz and Trussell 2001, Taschenberger et al. 2002). In the MNTB, vesicle pool size, exocytotic efficiency, and the number of active zones increase with age. These changes lead to active zones that are less prone to multivesicular release, reducing AMPA receptor saturation and desensitization (Taschenberger et al. 2002). Similarly, endbulb synapses on chicken NM showed synaptic maturation around the time of hatching with an increased pool of synaptic vesicles, lower release probability, larger transmitter quanta, and reduced AMPA receptor desensitization (Brenowitz and Trussell 2001). These factors improve the ability of avian endbulb synapses and mammalian MNTB calyces to provide an accurate representation of high-frequency firing in mature synapses. ◀ EDQ3

Postsynaptic Specializations for Encoding Temporal Information

Both avian and mammalian time-coding cells possess a number of morphological and physiological specializations that make them well suited to preserve the temporal firing pattern of auditory nerve inputs. In addition to the specialized synaptic arrangement, large cell bodies and reduced dendritic arbors serve to keep the cells electrically compact. Time-coding neurons possess a particular combination of synaptic and intrinsic membrane properties, including fast AMPA receptors and specific K^+ conductances. These features lead to a single or a few well-timed spikes in response to a depolarizing stimulus (figure 12-1A; for reviews see Oertel 1999 and Trussell 1997, 1999). A similar suite of physiological and morphological features also characterizes the neurons of the medial nucleus of the trapezoid body and the type-II neurons of the ventral nucleus of the lateral lemniscus, both of which receive endbulb synapses (Brew and Forsythe 1995; Wu 1999).

Activation of AMPA receptors at endbulb synapses generates extremely brief but large synaptic currents (Raman and Trussell 1992; Zhang and Trussell 1994; Isaacson and Walmsley 1996). The brevity of EPSCs in these neurons depends not only on the time course of release but also on the specific properties of the postsynaptic AMPA receptors. AMPA receptors in time coding auditory neurons have fast kinetics and very rapid desensitization rates such that the duration of miniature EPSCs in auditory neurons are among the shortest recorded for any neuron (Raman and Trussell 1992; Geiger et al 1995; Gardner, Trussell, and Oertel 1999). These receptors are also characterized by high Ca^{2+} permeability (Otis, Raman, and Trussell 1995). AMPA receptors in auditory neurons have low levels of GluR1 and perhaps GluR2 subunits and high levels of GluR3 and GluR4 subunits with the majority being of the flop isoform (reviewed by Trussell 1999; Ravindranathan, Parks, and Rao 1996; Parks 2000). These results are consistent with expression studies showing that AMPA receptors containing GluR4 subunits gate rapidly and that flop variants desensitize most quickly (Mosbacher et al. 1994; Geiger et al. 1995).

Although brief EPSCs underlie the rapid synaptic potential changes seen in time coding neurons, the intrinsic electrical properties of these neurons also shape the synaptic response as well as the temporal firing pattern. Of particular interest are the voltage sensitive K^+ conductances. The importance of these conductances in sculpting the response properties of auditory neurons was first demonstrated by Manis and Marx (1991) who showed that differences in the electrical responses of bushy cells and stellate cells in the mammalian cochlear nucleus can be attributed to a distinct complement of outward K^+ currents in each cell type. At least two K^+ conductances underlie phase locked responses in auditory neurons: a low threshold conductance

(LTC) and a high threshold conductance (HTC) (Manis and Marx 1991; Brew and Forsythe 1995; Reyes, Rubel, and Spain 1994; Rathouz and Trussel 1998; Wang et al. 1998).

The LTC activates at potentials near rest and is largely responsible for the outward rectification and nonlinear current voltage relationship around the resting potential seen in a number of auditory neurons (figure 12-1A; see Oertel 1999 for review). Activation of the LTC leads to a short active time constant so that the effects of excitation are brief and do not summate in time (Oertel 1999). Only large EPSPs reaching threshold before significant activation of the LTC would produce spikes with short latencies, whereas small EPSPs which depolarize the membrane more slowly would allow time for LTC activation to shunt the synaptic current and prevent action potential generation and thus long latency action potentials. Blocking the LTC elicits multiple spiking in response to depolarizing current injection (Manis and Marx 1991; Rathouz and Trussel 1998) or synaptic activation (Brew and Forsythe 1995). K^+ channels underlying the LTC appear to be composed of Kv1.1 and Kv1.2 subunits. Both subunits are expressed in auditory neurons although the subcellular distribution is unknown (Grigg, Brew, and Tempel 2000). Consistent with a role for Kv1.1 subunits in the LTC, synaptic activation of MNTB neurons in Kv1.1 null mice produce action potentials with more jitter compared to wild type (Brew, Hallows, and Tempel 2003; Kopp-Scheinpflug et al. 2003).

The HTC is characterized by fast kinetics and an activation threshold around –20 mV (Brew and Forsythe 1995; Rathouz and Trussell 1998;Wang et al. 1998). These features of the HTC result in fast spike repolarization and a large but brief afterhyperpolarization without influencing input resistance, threshold, or action potential rise time. Thus, the HTC can keep action potentials brief without effecting action potential generation. In addition, the HTC minimizes Na^+ channel inactivation allowing cells to reach firing threshold sooner, facilitating high frequency firing. Relatively specific pharmacological blockade of the HTC broadens action potentials and reduces the fast afterhyperpolarization (Brew and Forsythe 1995). Furthermore, blockade of the HTC diminishes the ability of MNTB neurons to follow high-frequency stimuli in the range of 300–400 Hz but had little effect on responses to low frequency stimulation (<200 Hz; Wang et al. 1998).

Elimination of the Kv3.1 gene in mice results in the loss of the HTC and failure of MNTB neurons to follow high-frequency stimulation (Macica et al. 2003). Neurons that fire fast, including many auditory neurons, express high levels of Kv3 mRNA and protein, although it should be noted that not all neurons that express Kv3 subunits have fast firing abilities (Perney and Kaczmarek 1997; Parameshwaran, Carr, and Perney 2001; Li, Kaczmarek, and Perney 2001). Interestingly, in several auditory nuclei including avian NM and NL (Parameshwaran, Carr, and Perney 2001), rat MNTB (Li, Kaczmarek,

and Perney 2001), Kv3.1 protein expression varied along the tonotopic map such that mid to high best frequency neurons are most strongly immunopositive, while neurons with very low best frequencies are only weakly immunopositive. A high to low frequency gradient of Kv3.3 expression has also been observed in electrosensory lateral line lobe of a weakly electric fish (Rashid et al. 2001). These results suggest that the electrical properties of higher-order auditory neurons may vary with frequency tuning. Since no differences in either spontaneous or driven rates have been observed across the tonotopic axis, however, Kv3 channels may be functioning as more than just a facilitator of high frequency firing and may also enhance the temporal precision of spike discharges.

Distribution of Kv3.1 protein in auditory neurons is largely somatic and/or axonal, consistent with its role in spike repolarization (Perney and Kaczmarek 1997; Li, Kaczmarek, and Perney 2001; Parameshwaran, Carr, and Perney 2001). EM studies have shown that Kv3.1 is present in the membranes of endbulb terminals onto MNTB neurons suggesting that Kv3.1 channels may be at least partially responsible for the extremely brief action potential seen at this terminal. Kv3.1 protein is also present in the NM axons innervating the NL in owl but not chicken (Parameshwaran, Carr, and Perney 2001). The increased levels of HTC associated with Kv3.1 expression in owl NM axons would reduce the width of the action potential invading the NM terminals and thus the amount of neurotransmitter released. Modeling of coincidence detector neurons suggest that an increase in the width of the input EPSC could impair ITD coding (Simon, Carr, and Shamma 1999; Grau-Serrat, Carr, and Simon 2003). Thus, the selective increase of Kv3.1-like currents in the NM delay line axons in owl may contribute to the temporal synchrony necessary for accurate phase locking.

Coincidence Detection

In birds and mammals, precisely timed spikes encode the timing of acoustic stimuli, and interaural acoustic disparities propagate to binaural processing centers such as the avian nucleus laminaris (NL) and the mammalian medial superior olive (MSO; Young and Rubel 1983; Carr and Konishi 1990; Joris, Smith, and Yin 1998). The projections from the NM to NL and from mammalian spherical bushy cells to MSO resemble the Jeffress model for encoding interaural time differences (Jeffress 1948). The Jeffress model has two elements: delay lines and coincidence detectors. A Jeffress circuit is an array of coincidence detectors, every element of which has a different relative delay between its ipsilateral and contralateral excitatory inputs. Thus, ITD is encoded into the position (a *place code*) of the coincidence detector whose delay lines best cancels out the acoustic ITD (for reviews, see Joris, Smith, and Yin 1998 and Konishi

1991). Neurons of NL and MSO phase lock to both monaural and binaural stimuli but respond maximally when phase-locked spikes from each side arrive simultaneously, that is, when the difference in the conduction delays compensates for the ITD (Goldberg and Brown 1969; Yin and Chan 1990; Carr and Konishi 1990; Overholt, Rubel, and Hyson 1992; Pena et al. 1996).

Delay Line-Coincidence Detection Circuits

The barn owl is capable of great accuracy in detecting time differences, and its auditory system is hypertrophied in comparison to birds like the chicken whose auditory systems are less specialized. The details of delay line circuit organization vary between species (figure 12-2). In the chicken, NL is composed of a monolayer of bipolar neurons that receive input from ipsi- and contralateral cochlear nucleus onto their dorsal and ventral dendrites, respectively (Rubel and Parks 1975). These dendrites increase in length with decreasing best frequency. Only the projection from the contralateral cochlear nucleus acts as a delay line, while inputs from the ipsilateral cochlear nucleus arrive simultaneously at all neurons (Overholt, Rubel, and Hyson 1992). This pattern of inputs creates a single map of interaural time difference (ITD) in any tonotopic band in the mediolateral dimension of NL (Overholt, Rubel, and Hyson 1992). In the barn owl, magnocellular axons from both cochlear nuclei act as delay lines (Carr and Konishi 1988; Carr and Konishi 1990). They convey the phase of the auditory stimulus to NL such that axons from the ipsilateral NM enter NL from the dorsal side, while axons from the contralateral NM enter from the ventral side. Recordings from these interdigitating ipsilateral and contralateral axons show regular changes in delay with depth in NL (Carr and Konishi 1990). Thus these afferents interdigitate to innervate dorsoventral arrays of neurons in NL in a sequential fashion and

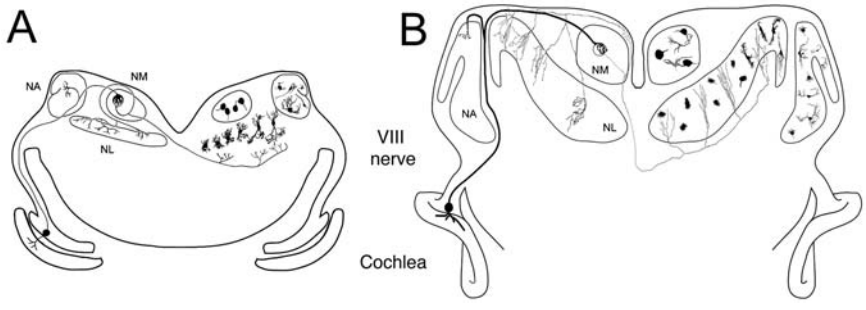

Figure 12-2. Schematic of a coronal section through the brainstem of (A) chicken and (B) owl. The medial branch of the auditory nerve innervates NM. NL receives bilateral projections from NM. The cells are not drawn to scale. (A) modified from Rubel and Parks (1988).

produce multiple representations of ITD within the nucleus. Despite the differences in organization of NL in owls and chickens, interaural time differences are detected by neurons that act as coincidence detectors in both species (Sullivan and Konishi 1984; Joseph and Hyson 1993; Pena et al 1996; Kubke, Massoglia, and Carr 2002). Very similar principles apply to the mammalian superior olive (Goldberg and Brown 1969; Yin and Chan 1990).

An important feature of both avian and mammalian coincidence detectors is that they share physiological features with NM neurons and mammalian bushy cells. Coincidence detectors exhibit specific K^+ conductances that lead to a single or a few well-timed spikes in response to a depolarizing stimulus in vitro (figure 12-1B; Reyes, Rubel, and Spain 1996; Smith 1995; Kuba, Koyano, and Ohmori 2002). The LTC channels should decrease the effective membrane time constant, that is, the average membrane time constant for a cell receiving and processing in vivo rates of EPSPs, which will be much shorter than the passive membrane time constant (Softky 1994; Mainen and Sejnowski 1995; Gerstner et al. 1996; Grau-Serrat, Carr, and Simon 2003). These fast conductances may be critical to coincidence detection—the models described in the next section of this chapter suggest that they are instrumental in keeping the firing rate near zero when the inputs are completely out of phase but allowing nonzero firing rate when the inputs are monaural.

Coincidence detector neurons in birds and mammals may display similar conductances and bipolar morphologies, but they are not identical. In mammals, MSO neurons do not express either Kv3.1 mRNA or protein (Grigg, Brew, and Tempel 2000; Li, Kaczmarek, and Perney 2001). They do, however, express high levels of Kv3.3 message (Grigg, Brew, and Tempel 2000; Li, Kaczmarek, and Perney 2001). Thus, differences in Kv3.1 expression between NL and MSO structures may reflect species differences in the expression of Kv3 subfamily members. We do not know whether this variation in expression also represents a significant physiological difference. A second substantial difference is in inhibitory inputs. In mammals the MSO receives well-timed inhibitory input from the medial and lateral nucleus of the trapezoid body (Cant and Hyson 1992; Kuwabara and Zook 1992; Grothe and Sanes 1994; Grothe 2003). These inhibitory inputs may enhance coincidence detection in several ways. First, by producing a somatic shunt during coincidence detection to decrease the membrane time constant (Brughera, Stutman, and Carney 1996; Thompson, Rowland, and Spirou 2004). Second, in the Mongolian gerbil, a small mammal with low frequency hearing, precisely timed glycine-controlled inhibition in the MSO appears to shift the ITD curve so that the peak change in firing rate falls within the physiologically relevant range of ITDs (Brand et al. 2002). In birds, inhibitory inputs in NL are more diffuse and appear to decrease excitability through a gain control mechanism (Monsivais, Yang, and Rubel 1999; Funabiki, Koyano, and Ohmori 1998; Yang, Monsivais, and Rubel 1999; Pena et al. 1996).

Models of Coincidence Detection Relate Dendritic Structure to Detection of Interaural Time Differences

A singular feature of the coincidence detectors in mammals and of low best frequency NL cells in birds is their common morphological organization. Both are bitufted neurons with inputs from each ear segregated on the dendrites (figure 12-3). Modeling studies have shown that this dendritic organization improves coincidence detection (Agmon-Snir, Carr, and Rinzel 1998; Grau-Serrat, Carr, and Simon 2003). Thus the cell morphology and the spatial distribution of the inputs enriches the computational power of these neurons beyond that expected from point neurons. How does the dendritic structure of the coincidence detectors enhance their computational ability? An ITD discriminator neuron should fire when inputs from two independent neural sources coincide (or almost coincide) but not when two inputs from the same neural source (almost) coincide. A neuron that sums its inputs linearly would not be able to distinguish between these two scenarios. To understand this mechanism, we constructed a biophysically detailed model of coincidence detector neurons using NEURON (Simon et al 1999; Grau-Serrat, Carr, and Simon 2003).

Two dendritic nonlinearities aid coincidence detection. First, synaptic inputs arriving at the same dendritic compartment sum non-linearly because the driving force decreases with depolarization (Agmon-Snir, Carr, and Rinzel 1998). Hence, the net synaptic current from several inputs arriving simultaneously at nearby sites on the same dendrite is smaller than the net current generated if these inputs are distributed on different dendrites. As a result, the conductance threshold, or minimum synaptic conductance needed to trigger a somatic action potential, is higher when the synaptic events are on the same dendrite compared to when they are split between the bipolar dendrites. Second, each dendrite acts as a current sink for inputs on the other dendrite, consequently increasing the voltage change needed to trigger a spike at the soma when inputs arrive only on one side. This effect is boosted by the presence of a low threshold K^+ conductance similar to that found in NM and bushy neurons so that out of phase inputs are subtractively inhibited (Grau-Serrat, Carr, and Simon 2003). With only monaural input, the LTC in the opposite dendrite is somewhat activated, producing a mild current sink. When, however, there are recent EPSPs in the opposite dendrite due to out-of-phase inputs, the LTC is strongly activated and acts as a large current sink suppressing spike initiation. Thus, the model predicts the experimental finding (Goldberg and Brown 1969; Yin and Chan 1990; Carr and Konishi 1990) that the monaural firing rate while lower that the binaural in-phase rate, is higher than the binaural out-of-phase rate.

One dendritic effect diminishes with increasing stimulus frequency. When typical chick-like parameters are used, sublinear summation in the dendrites only improves coincidence detection below 2kHz, after which discrimination

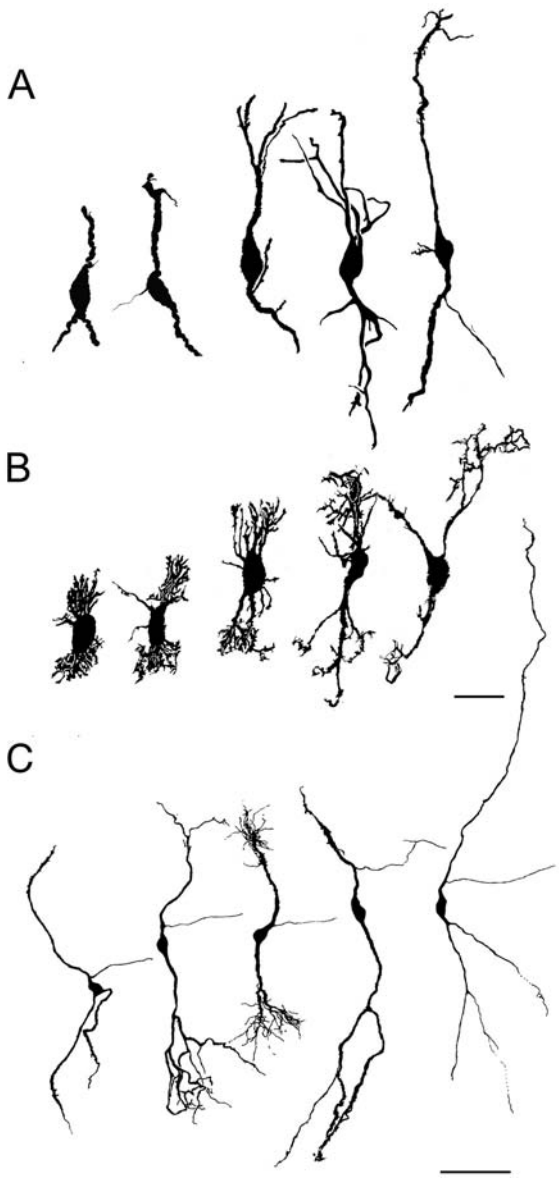

Figure 12-3. Coincidence detectors share bitufted morphology. Avian (*top*) and mammalian (*bottom*) low-frequency coincidence detector neurons. The stimulus frequency of the chicken nucleus laminaris (NL) cells increases from left to right (adapted from Smith and Rubel 1979). The dendritic morphology of the principal cells of the medial superior olive from the guinea pig (adapted from Smith 1995) differs somewhat from the chicken, and a frequency gradient is not apparent. Nevertheless, the bipolar architecture and the segregation of the inputs arriving from both ears is common to both mammalian and avian coincidence detectors with low best frequencies. In the barn owl, coincidence detectors have largely lost this bipolar organization, and their short dendrites radiate around the cell body.

◀ EDQ10

between in-phase and out-of-phase inputs is poor (Agmon-Snir, Carr, and Rinzel 1998). This is consistent with observation from rabbit MSO neurons, where ITD sensitivity has only been observed for sounds at or below 2kHz (Batra, Kuwada, and Fitzpatrick 1997). The second dendritic nonlinearity, subtractive inhibition of out-of-phase inputs, improves coincidence detection all frequencies (Grau-Serrat, Carr, and Simon 2003) and may therefore be most significant in avian coincidence detectors between 2 and 8kHz. It is also clear that the quality of phase-locked inputs has some bearing on coincidence detection: typical chick-like parameters but with barn owl–like phase locking allow ITD discrimination up to 4–6 kHz (Grau-Serrat, Carr, and Simon 2003). The benefits conveyed by the neuronal structure of the coincidence detectors allows us to argue that selective forces have directed the evolution of coincidence detectors in the bird NL and mammalian MSO, perhaps in parallel (Carr and Soares 2002).

Encoding Onsets

Both birds and mammals have neurons that respond preferentially to onsets, or transients in sound. Onsets play an important role in theories of speech perception (Stevens 1995), music perception, sound localization (Zurek 1987), and segregation and grouping of sound sources (Bregman 1990). The computational importance of encoding onsets may be also inferred by the parallel evolution of onset coding in bird cochlear nuclei (figure 12-4; Warchol and Dallos 1990; Sullivan and Konishi 1984; Koppl et al. 2001). ◀ EDQ4 Mammals differ from birds, however, in that they have a specialized *octopus cell* pathway for onset coding in addition to onset responses in other cell types (see Oertel et al. 2000 for review). Octopus cells integrate auditory nerve inputs across a range of frequencies and encode the time structure of stimuli with great precision (Kim, Rhode, and Greenberg 1986; Golding, Robertson, and Oertel 1995; Ferragamo and Oertel 2002; Oertel et al. 2000).

Octopus Cells Transform Auditory Nerve Inputs to Produce Onset Responses

How does the transformation of the auditory nerve response to onset code occur? Octopus cells have a few thick dendrites emanating from one end of the cell body (see Oertel et al. 2000). These dendrites are perpendicular to entering auditory nerve fibers, enabling them to sample nerve inputs spanning a broad range of frequencies (Kane 1973; Golding et al. 1995). The relatively broad tuning of octopus cells may be a reflection of this anatomy. Many of the electrical and anatomical properties of octopus cells resemble those that help bushy and magnocellular cells encode the time structure of stimuli. Like bushy cells, octopus cells appear to exhibit little dendritic filtering. They have

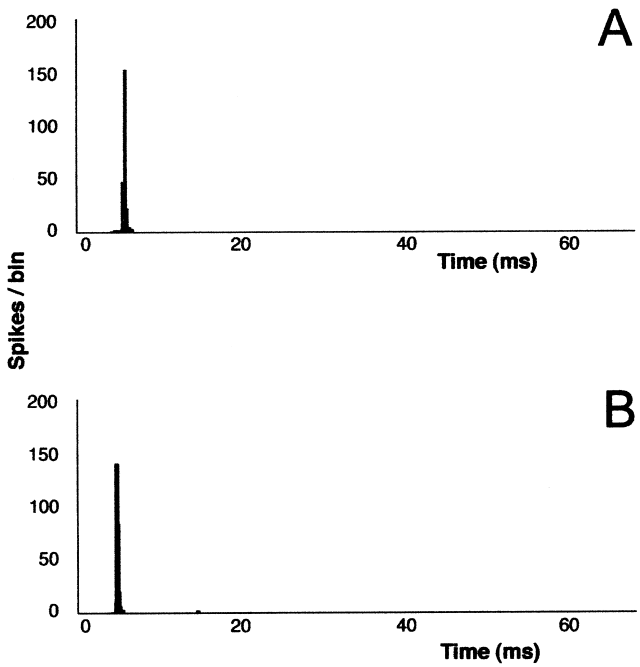

Figure 12-4. ▸Onset responses in birds and mammals can show a prominent response at the onset of a tonal stimulus, followed by little or no sustained activity. (A) Onset response from an octopus cell (from Winter and Palmer 1995). (B) Onset responses from the nucleus angularis in the barn owl (from Köppl and Carr 2003). EDQ11

large spherical cell bodies and even though their dendrites are fairly long (120 to 180 μm), they are also thick (Kane 1973; Brawer and Morest 1974; Golding, Robertson, and Oertel 1995; Golding, Ferragamo, and Oertel 1999). The spherical cell body and thick dendrites make the cell electrically compact (Kane 1973; Cai, Walsh, and McGee 1997). Moreover, the many weak auditory nerve inputs are on the soma and proximal dendritic surfaces (Kane 1973), and miniature synaptic currents measured in octopus cells are brief (Gardner, Trussell, and Oertel 1999). Such brief synaptic responses should preserve the time pattern of discharges in the corresponding presynaptic auditory nerve fibers (Kalluri and Delgutte 2003a).

The brevity of the small synaptic responses in octopus cells requires the coincident activation within one millisecond of enough auditory nerve inputs to produce sufficient depolarization to bring the cell to threshold (Golding, Robertson, and Oertel 1995; Oertel et al. 2000). The intrinsic biophysical properties of octopus cells support this coincidence detection role. Like other neurons in the auditory brainstem that preserve the time patterns of discharge in their inputs, octopus cells have a very low input resistance (2–7 MΩ just below resting voltage, and the membrane time constant is near 200 μs, the

smallest of any cochlear nucleus neuron (Golding, Ferragamo, and Oertel 1999). The low input resistance of octopus cells is determined in part by two voltage-dependent conductances that are active at rest: a hyperpolarization-activated, mixed-cation conductance, g_h, and a depolarization-activated, low-threshold potassium (K^+) conductance (see Oertel et al. 2000). Like the coincidence detectors in NL and MSO, the low-threshold K^+ conductance in octopus cells allows them to be sensitive to coincident activation of their inputs by making the membrane sensitive to fast transients in the synaptic input (Golding, Ferragamo, and Oertel 1999). A rapidly rising input, such as that arising from the synchronous activation of synapses, can depolarize the membrane to threshold before the relatively slow low-threshold K^+ conductance is activated (2–3 ms time constant). In contrast, a slower input would fail to drive the membrane voltage to threshold because it could not outpace this conductance (Cai, Walsh, and McGee 1997; Kalluri and Delgutte 2003a,b).

Onset Responses Have Evolved in Parallel in Birds

The computational importance of encoding onsets, or rapid fluctuations, may be inferred by the parallel evolution of onset coding in the bird cochlear nucleus angularis (NA). In the barn owl, the chicken, and the blackbird, some NA neurons exhibit onset responses, while others have primary-like, chopper, and Type IV responses (figure 12-4B; Warchol and Dallos 1990; Sullivan and Konishi 1984; Koppl and Carr 2003). Nevertheless, there does not seem to be an avian counterpart of the octopus cell. NA onset cells have relatively narrow frequency tuning curves, unlike the octopus cell (Rhode, Oertel, and Smith 1983; Koppl and Carr 2003) Furthermore, Golgi analyses of barn owl NA and intracellular labeling of chicken NA neurons in brain slices have not revealed cells with thick dendrites that extend across the incoming auditory nerve inputs (Soares and Carr 2001, Soares et al. 2002).

The presence of onset units argues for NA's involvement in temporal processing. In mammals, onset responses are found in several cell types in the cochlear nucleus and may encode temporal features such as broadband transients (Oertel et al. 2000; Kalluri and Delgutte 2003b). NA onset neurons may serve a similar function. Thus NM may mediate coding of the temporal information used for the computation of ITDs, while one of the cell types in NA may encode other temporal features of the stimulus (Koppl and Carr 2003).

Neuronal Structure and Function

When compared with a simple integrate-and-fire unit, the auditory neurons that phase lock, detect coincidences, and encode temporal patterns all exhibit a suite of physiological and morphological adaptations that suit them for their

task. Other neuronal systems exhibit similarly well-equipped neural circuits. The blowfly has an array of direction-selective, motion-sensitive cells that conform to the Reichardt model of motion detection (Borst, Helmchen, and Sakmann 1995). An array of Reichardt motion detectors projects onto the lobular plate tangential cell to create a response to both the direction and velocity of pattern motion. The geometry of the tangential cell dendrites supports this computational task in visual motion control because they are aligned with the direction of motion.

The question remains whether all neurons are adapted for specific computations. Neurons in the auditory brainstem and fly motion detectors appear to be, and a similar case may be made for phase coding neurons in weakly electric fish (Matsushita and Kawasaki 2004; for reviews see Friedman and Carr 1998; Kawasaki 2000). In other body tissues, cells appear to have a precise function, and it could be argued that the same should be true for brain, once its functions are understood. Nevertheless, the brain must be able to respond to changing and disparate stimuli, so it would be not be advantageous to have all cells and neural circuits restricted in their responses. Turrigiano, Abbott, and Marder (1994) have shown that there are activity-dependent changes in the intrinsic properties of cultured neurons, so neurons could be equipped with a suite of features suited for particular computations, but also retain the ability to modify these over time (Desai, Rutherford, and Turrigiano 1999).

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References

H. Agmon-Snir, C.E. Carr, J. Rinzel. (1998) The role of dendrites in auditory coincidence detection *Nature* 393: 268–272.

R. Batra, S. Kuwada, D.C. Fitzpatrick. (1997) Sensitivity to interaural temporal disparities of low- and high-frequency neurons in the superior olivary complex. I. Heterogeneity of responses. *J Neurophysiol* 78: 1222–1236.

A. Borst, M. Egelhaaf, J. Haag. (1995) Mechanisms of dendritic integration underlying gain control in fly motion-sensitive interneurons. *J Comput Neurosci* 2: 5–18.

J.G. Borst, F. Helmchen, B. Sakmann. (1995) Pre- and postsynaptic whole-cell recordings in the medial nucleus of the trapezoid body of the rat. *J Physiol* 489: 825–840.

J.G. Borst, B. Sakmann. (1996) Calcium influx and transmitter release in a fast CNS synapse. *Nature* 383: 431–434.

A. Brand, O. Behrend, T. Marquardt, D. McAlpine, B. Grothe. (2002) Precise inhibition is essential for microsecond interaural time difference coding. *Nature* 417: 543–547.

J.R. Brawer, D.K. Morest. (1974) Relations between auditory nerve endings and cell types in the cat's anteroventral cochlear nucleus seen with Golgi method and Nomarski optics. *J Comp Neurol* 160: 491–506.
S. Brenowitz, L.O. Trussell. (2001) Maturation of synaptic transmission at end-bulb synapses of the cochlear nucleus. *J Neurosci* 21: 9487–9498.
H.M. Brew, J.L. Hallows, B.L. Tempel. (2003) Hyperexcitability and reduced low threshold potassium currents in auditory neurons of mice lacking the channel subunit Kv1.1. *J Physiol* 548: 1–20.
A.S. Bregman. (1990) Auditory Scene Analysis. Cambridge, Mass.: MIT Press.
H.M. Brew, I.D. Forsythe. (1995) Two voltage-dependent K+ conductances with complementary functions in postsynaptic integration at a central auditory synapse. *J Neurosci* 15: 8011–8022.
A.R. Brughera, E.R. Stutman, L.H. Carney. (1996) A model with excitation and inhibition for cells in the medial superior olive. *Auditory Neurosci* 2: 219–233.
Y. Cai, E. J. Walsh, J. McGee. (1997) Mechanisms of onset responses in octopus cells of the cochlear nucleus: implications of a model. *J Neurophys* 78: 872–883.
N.B. Cant, R.L. Hyson. (1992) Projections from the lateral nucleus of the trapezoid body to the medial superior olivary nucleus in the gerbil. *Hear Res.* 58: 26–34.
C.E. Carr, M. Konishi. (1988) Axonal delay lines for time measurement in the owl's brainstem. *Proc Natl Acad Sci* 85: 8311–8315.
C.E. Carr, M. Konishi. (1990) A circuit for detection of interaural time differences in the brainstem of the barn owl. *J Neurosci* 10: 3227–3246.
C.E. Carr, D. Soares. (2002) Evolutionary convergence and shared computational principles in the auditory system. *Brain Behav Evol* 59: 294–311.
H.S. Colburn, Y. Han, C.P. Culotta. (1990) Coincidence model of MSO responses. *Hear Res.* 49: 335–355.
N.S. Desai, L.C. Rutherford, G.G. Turrigiano. (1999) Plasticity in the intrinsic excitability of cortical pyramidal neurons. *Nat Neurosci* 2: 515–520.
M.L. Ferragamo, D. Oertel. (2002) Octopus cells of the mammalian ventral cochlear nucleus sense the rate of depolarization. *J Neurophysiol* 87: 2262–2270.
K. Funabiki, K. Koyano, H. Ohmori. (1998) The role of GABAergic inputs for coincidence detection in the neurones of nucleus laminaris of the chick. *J Physiol* 508: 851–869.
S. Gardner, L. Trussell, D. Oertel. (1999) Time course and permeation of synaptic AMPA receptors in cochlear nucleus neurons correlate with input. *J Neurosci* 19: 8721–8729.
J. R. P. Geiger, T. Melcher, D.-S. Koh, B. Sakmann, P.H. Seeburg, P. Jonas, H. Monyer. (1995) Relative abundance of subunit mRNAs determines Gating and Ca^{2+} permeability of AMPA receptors in principal neurons and interneurons of rat CNS. *Neuron* 15: 193–204.
W. Gerstner, R. Kempter, J.L. van Hemmen, H. Wagner. (1996) A neuronal learning rule for sub-millisecond temporal coding. *Nature* 383: 76–81.
J.M. Goldberg, P.B. Brown. (1969) Response of binaural neurons of dog superior olivary complex to dichotic tonal stimuli: Some physiological mechanisms of sound localization. *J Neurophysiol* 32: 613–636.
N.L. Golding, M.J. Ferragamo, D. Oertel. (1999) Role of intrinsic conductances underlying responses to transients in octopus cells of the cochlear nucleus. *J Neurosci* 19: 2897–2905.

N.L. Golding, D. Robertson, D. Oertel. (1995) Recordings from slices indicate that octopus cells of the cochlear nucleus detect coincident firing of auditory nerve fibers with temporal precision. *J Neurosci* 15: 3138–3153.
J. Golowasch, M. Casey, L.F. Abbott, E. Marder. (1999) Network stability from activity-dependent regulation of neuronal conductances. *Neural Comput* 11: 1079–1096.
V. Grau-Serrat, C.E. Carr, J.Z. Simon. (2003) Modeling coincidence detection in nucleus laminaris. *Biol Cybern* 89: 388–396.
J.J. Grigg, H.M. Brew, B.L. Tempel. (2000) Differential expression of voltage-gated potassium channel genes in auditory nuclei of themouse brainstem. *Hear Res* 140: 77–90.
B. Grothe. (2003) New roles for synaptic inhibition in sound localization. *Nat Rev Neurosci* 4: 540–550.
B. Grothe, D.H. Sanes. (1994) Synaptic inhibition influences the temporal coding properties of medial superior olivary neurons: an *in vitro* study. *J Neurosci* 14: 1701–1709.
E.R. Hafter, C. Trahiotis. (1997) Functions of the binaural system. In: Handbook of Acoustics, edited by M. Crocker, 1461–1480. New York: Wiley.
R. S. Heffner, H.E. Heffner. (1992) Evolution of sound localization in mammals. In: The Evolutionary Biology of Hearing, edited by DB Webster, RR Fay, AN Popper, 691–716. New York: Springer-Verlag.
K.G. Hill, G. Stange, J. Mo. (1989) Temporal synchronization in the primary auditory response in the pigeon. *Hear Res* 39: 63–74.
J.S. Isaacson, B. Walmsley. (1996) Amplitude and time course of spontaneous and evoked excitatory postsynaptic currents in bushy cells of the anteroventral cochlear nucleus. *J Neurophysiol* 76: 1566–1571.
L.A. Jeffress. (1948) A place theory of sound localization. *J Comp Physiol Psych* 41: 35–39.
S. Jhaveri, K. Morest. (1982) Sequential alterations of neuronal architecture in nucleus magnocellularis of the developing chicken: A Golgi study. *Neurosci* 7: 837–853.
D. Johnston, J.C. Magee, C.M. Colbert, B.R. Christie. (1996) *Ann Rev Neurosci.* 19: 165–186. ◀ EDQ6
P.X. Joris, P.H. Smith, T.C.T. Yin. (1998) Coincidence detection in the auditory system: 50 years after Jeffress. *Neuron* 21: 1235–1238.
A.W. Joseph, R.L. Hyson. (1993) Coincidence detection by binaural neurons in the chick brain stem. *J Neurophysiol* 69: 1197–1211.
S. Kalluri, B. Delgutte. (2003a) Mathematical models of cochlear nucleus onset neurons: I. Point neuron with many weak synaptic inputs. *J Comput Neurosci* 14: 711–790.
S. Kalluri, B. Delgutte. (2003b) Mathematical models of cochlear nucleus onset neurons: II. Model with dynamic spike-blocking state. *J Comput Neurosci* 14: 91–110.
E.C. Kane. (1973) Octopus cells in the cochlear nucleus of the cat: Heterotypic synapses upon homeotypic neurons. *Intern J Neuroscience* 5: 251–279.
M. Kawasaki. (2000) Phylogenetic evolution of computational algorithms. *Nonparametric Approach to Knowledge Discovery* 8: 77–80.
D. Kim, W. Rhode, S. Greenberg. (1986) Responses of cochlear nucleus neurons to speech signals: neural encoding of pitch, intensity, and other parameters. In: Auditory Frequency Selectivity, edited by B. Moore and R. Patterson, 281–288. New York: Plenum Press.

C. Koppl. (1997) Phase locking to high frequencies in the auditory nerve and cochlear nucleus magnocellularis of the barn owl, *Tyto alba*. *J Neurosci* 17: 3312–3321.
C. Koppl, C.E. Carr. (2003) Computational diversity in the cochlear nucleus angularis of the barn owl. *J Neurophysiol* 89: 2313–2329.
C. Kopp-Scheinpflug, K. Fuchs, W.R. Lippe, B.L. Tempel, R. Rübsamen. (2003) Decreased temporal precision of auditory signaling in KCNA1-null mice: An electrophysiological study in vivo. *J Neurosci* 23: 9199–9207.
M. Konishi. (1973) How the owl tracks its prey. *Am Sci* 61: 414–424.
M. Konishi. (1991) Deciphering the brain's codes. *Neural Computation* 3: 1–18.
H. Kuba, K. Koyano, H. Ohmori. (2002) Development of membrane conductance improves coincidence detection in the nucleus laminaris of the chicken. *J Physiol* 540: 529–542.
M.F. Kubke, D.P. Massoglia, C.E. Carr. (2002) Developmental changes underlying the formation of the specialized time coding circuits in barn owls (*tyto alba*). *J Neurosci* 22: 7671–7679.
N. Kuwabara, J.M. Zook. (1992) Projections to the medial superior olive from the medial and lateral nuclei of the trapezoid body in rodents and bats. *J Comp Neurol* 324: 522–538.
W. Li, L.K. Kaczmarek, T.M. Perney. (2001) Localization of two high-threshold potassium channel subunits in the rat central auditory system. *J Comp Neurol* 437: 196–218.
C.M. Macica, C.A. von Hehn, L.Y. Wang, C.S. Ho, S. Yokoyama, R.H. Joho, L.K. Kaczmarek. (2003) Modulation of the kv3.1b potassium channel isoform adjusts the fidelity of the firing pattern of auditory neurons. *J Neurosci* 23: 1133–1141.
Z.F. Mainen, T.J. Sejnowski. (1995) Reliability of spike timing in neocortical neurons. *Science* 268:1503–6
P.B. Manis, S.O. Marx. (1991) Outward currents in isolated ventral cochlear nucleus neurons. *J. Neurosci* 11: 2865–2880.
A. Matsushita, M. Kawasaki. (2004) Unitary giant synapses embracing a single neuron at the convergent site of time-coding pathways of an electric fish, *Gymnarchus niloticus*. *J Comp Neurol* 472: 140–155.
P. Monsivais, L. Yang, E.W. Rubel. (2000) GABAergic inhibition in nucleus magnocellularis: implications for phase locking in the avian auditory brainstem. *J Neurosci* 20: 2954–2963.
J. Mosbacher, R. Schoeper, H. Monyer, N. Burnashev, P.H. Seeburg, J.P. Ruppersberg. (1994) A molecular determinant for submillisecond desensitization in glutamate receptors. *Science* 266: 1059–1062.
D. Oertel. (1999) The role of timing in the brainstem auditory nuclei. *Ann Rev Physiol* 61: 497–519.
D. Oertel, R. Bal, S. Gardner, P. Smith, P. Joris. (2000) Detection of synchrony in the activity of auditory nerve fibers by octopus cells of the mammalian cochlear nucleus. *Proc Nat Acad Sci* 97: 11773–11779.
T.S. Otis, I.M. Raman, L.O. Trussell. (1995) AMPA receptors with high Ca2+ permeability mediate synaptic transmission in the avian auditory pathway. *J Physiol (Lond)* 482: 309–315.
E.M. Overholt, E.W. Rubel, R.L. Hyson. (1992) A circuit for coding interaural time differences in the chick brain stem. *J Neurosci* 12: 1698–1708.
S. Parameshwaran, C.E. Carr, T.M. Perney. (2001) Expression of the Kv3.1 potassium channel in the avian auditory brainstem. *J Neurosci* 21: 485–494.

T.N. Parks. (2000) The AMPA receptors of auditory neurons. *Hear Res* 147: 77–91.
J.L. Pena, S. Viete, Y. Albeck, M. Konishi. (1996) Tolerance to sound intensity of binaural coincidence detection in the nucleus laminaris of the owl. *J Neurosci* 16: 7046–7054.
T.M. Perney, L.K. Kaczmarek. (1997) Localization of a high threshold potassium channel in the rat cochlear nucleus. *J Comp Neurol* 386: 178–202.
I.M. Raman, L.O. Trussell. (1992) The kinetics of the response to glutamate and kainate in neurons of the avian cochlear nucleus. *Neuron* 9: 173–186.
A.J. Rashid, E. Morales, R.W. Turner, R. J. Dunn. (2001) The contribution of dendritic Kv3 K+ channels to burst threshold in a sensory neuron. *J Neurosci* 21: 125–35.
M. Rathouz, L.O. Trussell. (1998) A characterization of outward currents in neurons of the nucleus magnocellularis. *J Neurophysiol* 80: 2824–2835.
A. Ravindranathan, T.N. Parks, M.S. Rao. (1996) Flip and flop isoforms of chick brain AMPA receptor subunits: cloning and analysis of expression patterns. *Neuroreport* 7: 2707–2711.
A.D. Reyes, E.W. Rubel, W.J. Spain. (1994) Membrane properties underlying the firing of neurons in the avian cochlear nucleus. *J Neurosci* 14: 5352–5364.
A.D. Reyes, E.W. Rubel, W.J. Spain. (1996) *In vitro* analysis of optimal stimuli for phase-locking and time-delayed modulation of firing in avian nucleus laminaris neurons. *J Neurosci* 16: 993–1007.
W.S. Rhode, D. Oertel, P.H. Smith (1983) Physiological response properties of cells labeled intracellularly with horseradish peroxidase in cat ventral cochlear nucleus. *J Comp Neurol* 213: 448–463.
J.S. Rothman, E.D. Young, P.B. Manis. (1993) Convergence of auditory nerve fibers onto bushy cells in the ventral cochlear nucleus: implications of a computational model. *J Neurophysiol* 70: 2562–83.
E.W. Rubel, T.N. Parks. (1975) Organization and development of brainstem auditory nuclei of the chicken: Tonotopic organization of N. magnocellularis and N. laminaris. *J Comp Neurol* 164: 411–434.
E.W. Rubel, T.N. Parks. (1988) Organization and development of the avian brainstem auditory system. In: Brain Function, edited by G.M. Edelman, W.E. Gall, M.W. Cowan, 3–92. New York: Wiley.
E.W. Rubel, B. Fritzsch. (2002) Auditory system development: Primary auditory neurons and their targets. *Ann Rev Neurosci* 25: 51–101.
D.K. Ryugo, D.M. Fekete. (1982) Morphology of primary axosomatic endings in the anteroventral cochlear nucleus of the cat: A study of the endbulbs of Held. *J Comp Neurol* 210: 239–257.
D.K. Ryugo. (1991) The auditory nerve: peripheral innervation, cell body morphology, and central projections. In: The Mammalian Auditory Pathway: Neuroanatomy, edited by D.B. Webster, A.N. Popper, R.R. Fay, 23–65. New York: Springer-Verlag.
B.L. Sabatini, W.G. Regehr. (1999) Timing of synaptic transmission. *Annu Rev Physiol* 61: 521–542.
J.Z. Simon, C.E. Carr, S.A. Shamma. (1999) A dendritic model of coincidence detection in the avian brainstem. *Neurocomputing* 26–27: 263–269.
P.H. Smith. (1995) Structural and functional differences distinguish principal from nonprincipal cells in the guinea pig MSO slice. *J Neurophysiol* 73: 1653–1667.

Z.D.J. Smith, E.W. Rubel. (1979) Organization and development of brainstem auditory nuclei of the chicken: Dendritic gradients in nucleus laminaris. *J Comp Neurol* 186: 213–239.
D. Soares, C.E. Carr. (2001) The cytoarchitecture of the nucleus angularis of the barn owl (*Tyto alba*). *J Comp Neurol* 429: 192–205.
D. Soares, R.A. Chitwood, R.L. Hyson, C.E. Carr. (2002) Intrinsic neuronal properties of the chick nucleus angularis. *J Neurophysiol* 88: 152–162.
W. Softky. (1994) Sub-millisecond coincidence detection in active dendritic trees. *Neuroscience* 58: 13–41.
M. Stemmler, C.K. Koch. (1999) How voltage-dependent conductances can adapt to maximize the information encoded by neuronal firing rate. *Nat Neurosci* 2: 521–527.
K.N. Stevens. (1995) Applying phonetic knowledge to lexical access. In: 4th European Conference on Speech Communication and Technology, vol. 1. Madrid, Spain, pp. 3–11.
W.E Sullivan, M. Konishi. (1984) Segregation of stimulus phase and intensity coding in the cochlear nucleus of the barn owl. *J Neurosci* 4: 1787–1799.
T. Takahashi, A. Moiseff, M. Konishi. (1984) Time and intensity cues are processed independently in the auditory system of the owl. *J Neurosci* 4: 1781–1786.
H. Taschenberger, R.M. Leao, K.C. Rowland, G.A. Spirou, H. von Gersdorff. (2002) Optimizing synaptic architecture and efficiency for high-frequency transmission. *Neuron* 36: 1127–1143.
H. Taschenberger, H. von Gersdorff. (2000) Fine-tuning an auditory synapse for speed and fidelity: developmental changes in presynaptic waveform, EPSC kinetics, and synaptic plasticity. *J Neurosci* 20: 9162–9173.
J.M. Thompson, K.C. Rowland, G.A. Spirou. (2004) Cellular basis for ITD sensitivity in the MSO. *ARO Abstract* 1169.
L.O. Trussell. (1997) Cellular mechanisms for preservation of timing in central auditory pathways. *Curr Opin Neurobiol* 7: 487–492.
L.O. Trussell. (1999) Synaptic mechanisms for coding timing in auditory neurons. *Annu Rev Physiol* 61: 477–496.
G. Turrigiano, L.F. Abbott, E. Marder. (1994) Activity-dependent changes in the intrinsic properties of cultured neurons. *Science* 264: 974–977.
L.Y. Wang, L. Gan, I.D. Forsythe, L.K. Kaczmarek. (1998) Contribution of the Kv3.1 potassium channel to high-frequency firing in mouse auditory neurones. *J Physiol (Lond)* 509: 183–194.
M.E. Warchol, P. Dallos. (1990) Neural coding in the chick cochlear nucleus. *J Comp Physiol* 166: 721–734.
I. Winter, A. Palmer. (1995) Level dependence of cochlear nucleus onset unit responses and facilitation by second tones or broadband noise. *J. Neurophysiol* 73: 141–159.
S.H. Wu. (1999) Physiological properties of neurons in the ventral nucleus of the lateral lemniscus of the rat: Intrinsic membrane properties and synaptic responses. *J Neurophysiol* 2872–2874.
L. Yang, P. Monsivais, E.W. Rubel. (1999) The superior olivary nucleus and its influence on nucleus laminaris: a source of inhibitory feedback for coincidence detection in the avian auditory brainstem. *J Neurosci* 19: 2313–2325.
T.C.T. Yin, J.C.K. Chan. (1990) Interaural time sensitivity in medial superior olive of cat. *J Neurophysiol* 64: 465–488.

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S.R.Young, E.W. Rubel. (1983) Frequency-specific projections of individual neurons in chick brainstem auditory nuclei. *J Neuroscience* 7: 1373–1378.
R. Yuste and D.W. Tank. (1996) Dendritic integration in mammalian neurons, a century after Cajal. *Neuron 16*: 701–716. ◀ EDQ8
S. Zhang, L.O. Trussell. (1994) A characterization of excitatory postsynaptic potentials in the avian nucleus magnocellularis. *J Neurophysiol. 72*:705–718.
P.M. Zurek. (1987) The precedence effect. In: Directional Hearing, edited by W.A. Yost and G. Gourevitch. New York: Springer-Verlag. ◀ EDQ9