Evolutionary Convergence and Shared Computational Principles in the Auditory System

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Abstract

Precise temporal coding is a hallmark of the auditory system. Selective pressures to improve accuracy or encode more rapid changes have produced a suite of convergent physiological and morphological features that contribute to temporal coding. Comparative studies of temporal coding also point to shared computational strategies, and suggest how selection acts to improve coding. Both the avian cochlear nucleus angularis and the mammalian cochlear nuclei have heterogeneous cell populations, and similar responses to sound. These shared characteristics may represent convergent responses to similar selective pressures to encode features of airborne sound.

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Introduction

In the auditory system, precise encoding of temporal information has direct behavioral relevance for sound localization and communication [Heffner and Heffner, 1992; Hafter and Trahiotis, 1997]. One might therefore expect selection to improve accuracy or encode the more rapid changes associated with sensitivity to higher frequency sounds. In fact, similar physiological and morphological features that might improve temporal coding characterize the auditory brainstem of both birds and mammals. We will make two points about the evolution of the amniote auditory brainstem in this review. First, the similarities among brainstem circuits that encode sound in birds and mammals may be the result of convergence. Second, the existence of convergent circuits allows us to identify algorithms shared by the auditory system of birds and mammals, and to argue that these are suited to extracting the stimulus variables relevant for auditory coding; thus, studies of evolution can inform computational neurobiology.

The fossil record provides evidence that some of the similarities in auditory structures in birds and mammals may be the result of convergence. Tetrapod tympanic ears are not homologs, and recent work has shown that tympanic ears may have evolved independently at least five times, in synapsids, lepidosauromorph diapsids, archosauromorph diapsids, probably turtles, and amphibians [Clack, 1997]. Wilczynski [1984] has argued that these peripheral changes would have different reorganizing effects upon the ancestral population of brainstem auditory

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neurons, leading to the parallel evolution of the central targets of the auditory nerve. Further developments in ancestral mammals, such as moveable ears and multiple ossicles, might have had additional reorganizing effects. In this paper, we will argue that similar features in birds and mammals represent convergence.

Convergence is a plausible outcome of auditory system evolution, because animals with tympanic ears should experience similar constraints in detecting sounds. Indeed, the essential features of auditory coding, and temporal coding in particular, are very similar in birds and mammals. Understanding the evolutionary and developmental events behind the similar form and function of temporal coding cells in birds and mammals will require a detailed knowledge of multiple species under study, and of their phylogenetic relationships. This requires deliberate concentration on the differences among animals. When we know more about the neural circuits in different groups, we can construct scenarios about how they evolved. In this review we compare similar coding strategies in the time coding neurons of birds and mammals, and use these comparative studies to argue that natural selection has produced suitable, convergent solutions to the problems of temporal coding (sections 'Encoding Temporal Information' and 'Coincidence Detection and ITD Coding', below). In the section 'Encoding Sound: ...', we will compare avian and mammalian auditory brainstem processing of other aspects of the auditory stimulus in order to identify shared features.

Encoding Temporal Information

Barn owls are 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 behavior. Auditory nerve fibers encode temporal information by phase-locking to the waveform of the acoustic stimulus, and this temporal information is preserved in projections to the primary auditory nuclei, nucleus magnocellularis (NM), and nucleus angularis (NA). Three lines of evidence show 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 [Köppl, 1997]. Second, models of coincidence detection perform better when the vector strength of the inputs improves [Colburn et al., 1990; Simon et al.,

1999]. Third, inactivation of NM neurons with lidocaine removes sensitivity to interaural time differences (ITDs) from the responses of midbrain space-mapped neurons [Takahashi et al., 1984]. We will review the features associated with preserving temporal cues up to the point where ITDs are detected in the nucleus laminaris (NL).

There are several shared features of temporal coding circuits in birds and mammals. These include high quality inputs, presynaptic specializations to make neurotransmitter release both precise and modifiable, and postsynaptic specializations, including specific glutamate receptors, potassium conductances and characteristic neuronal morphology.

Precise Synaptic Transmission

The task of accurately representing the stimulus phase becomes more difficult with increasing stimulus frequency because temporal dispersion decreases [Hill et al., 1989]. This is because the absolute temporal precision required for phase-locking to high frequencies is greater than that needed for low frequencies, i.e., the same variation in temporal jitter of spikes translates to greater variation in terms of degrees of phase for high frequencies. Hill et al. [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 [Köppl, 1997]. The upper frequency limit of phase-locking therefore appears to depend primarily upon the ability of auditory hair cells to encode stimulus phase, and on irreducible jitter in the timing of spikes [Carr and Amagai, 1996]. It is about 8 kHz for barn owls, and between 4–6 kHz for most other birds and mammals studied [Köppl, 1997].

Endbulb terminals may have emerged as an adaptation for accurate transmission of phase information for frequencies above 500 Hz, perhaps associated with the development of hearing in land vertebrates (fig. 1). Large somatic terminals have been found in all amniote groups examined. There are no data on turtles, but large somatic terminals and smaller boutons are found in all NM of the alligator lizard [Szpir et al., 1990]. In crocodilian NM, the rostral high best frequency NM neurons receive endbulb-like projections, whereas lower best frequency NM neurons receive bouton terminals [Soares, unpublished]. Elaborate endbulb terminals are found in both birds and mammals [Ryugo, 1991]. Thus it is possible that a large somatic terminal may have been present in the amniote common
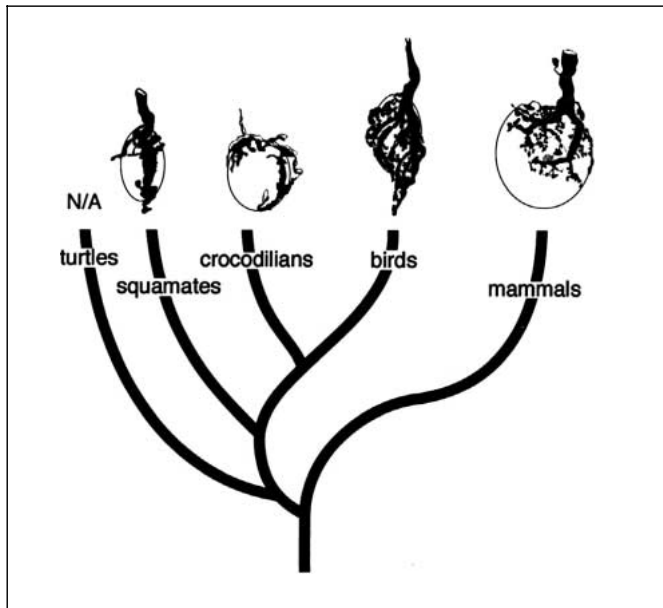
Fig. 1. Large somatic terminals appear in NM of birds, crocodilians and in the alligator lizard, as well as the mammalian ventral cochlear nucleus. These terminals are similarly elaborate in birds and mammals, and fractal analysis reveals similar morphological complexity [Ryugo et al., 1996; Carr et al., 1997]. This complexity appears to have developed in parallel in both birds and mammals. For example, although the terminals are similar, the mechanisms by which transmitter release is modulated are not the same. Activation of presynaptic glycine receptors enhances transmitter release in mammalian MNTB endbulbs by triggering a weakly depolarizing Cl^- current in the terminal. This depolarization enhances release by activating Ca^{2+} channels and increasing resting intraterminal Ca^{2+} concentrations [Brenowitz and Trussell, 2001]. In birds, activation of presynaptic $GABA_B$ receptors affects the endbulb to NM synapse by minimizing AMPA receptor desensitization and therefore enhancing synaptic strength during high-frequency activity [Turecek and Trussell, 2000].

ancestor, and have developed in parallel in lizards, archosaurs, and mammals to mediate accurate transmission of temporal information at higher sound frequencies. Support for the hypothesis that endbulbs developed to facilitate transmission of high best frequency phase-locking comes from comparisons of low and high best frequency regions of NM. 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 phase-lock to frequencies below ~ 1 kHz [Köppl, 1997], whereas in crocodilian NM, only the rostral high best frequency NM neurons receive endbulb-like projections [Soares, unpublished].

The advantages of the endbulb are that synaptic currents are injected into the cell body, not the dendrites.

Furthermore, 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, 1996]. The invading presynaptic action potential is extremely narrow (<200 μs at room temperature in 14-day-old rats and ~ 250 μs at 35 °C in postnatal day 8–10 animals) [Borst et al., 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 down stroke 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].

Large Neurons

The requirement of temporal accuracy at the synapse, particularly for high frequency inputs, may have driven the evolution of pathways that process precise temporal information. Improvement in intrinsic accuracy of neurons can be achieved through anatomical and physiological specializations of both presynaptic and postsynaptic structures that maximize the signal while minimizing the noise. One general strategy is to make everything large. Larger somata and axons are less vulnerable to noise caused by stray currents, as their low input resistance and large current generating ability would keep the influence of voltage fluctuations to a minimum. Many of the known time-coding pathways include large cells [Carr and Amagai, 1996].

Enlarged size must be accompanied by an increase in synaptic current, as observed (see below). Further, the currents also should have a fast rise time to minimize the influence of ambient voltage fluctuations on the timing of spikes. One solution is to have large terminals that partially engulf the postsynaptic cell, presumably translating into massive release of neurotransmitter [Zhang and Trussell, 1994; Trussell, 1997]. Fast rise times can be enhanced by reducing the electrotonic distance between the synapse and the site of integration, minimizing the attenuation of synaptic current. This occurs in time-coding electric fish neurons and in the cells of the nucleus magnocellularis and the nucleus laminaris in birds [Smith and Rubel, 1979; Jhaveri and Morest, 1982; Bell and Sza-
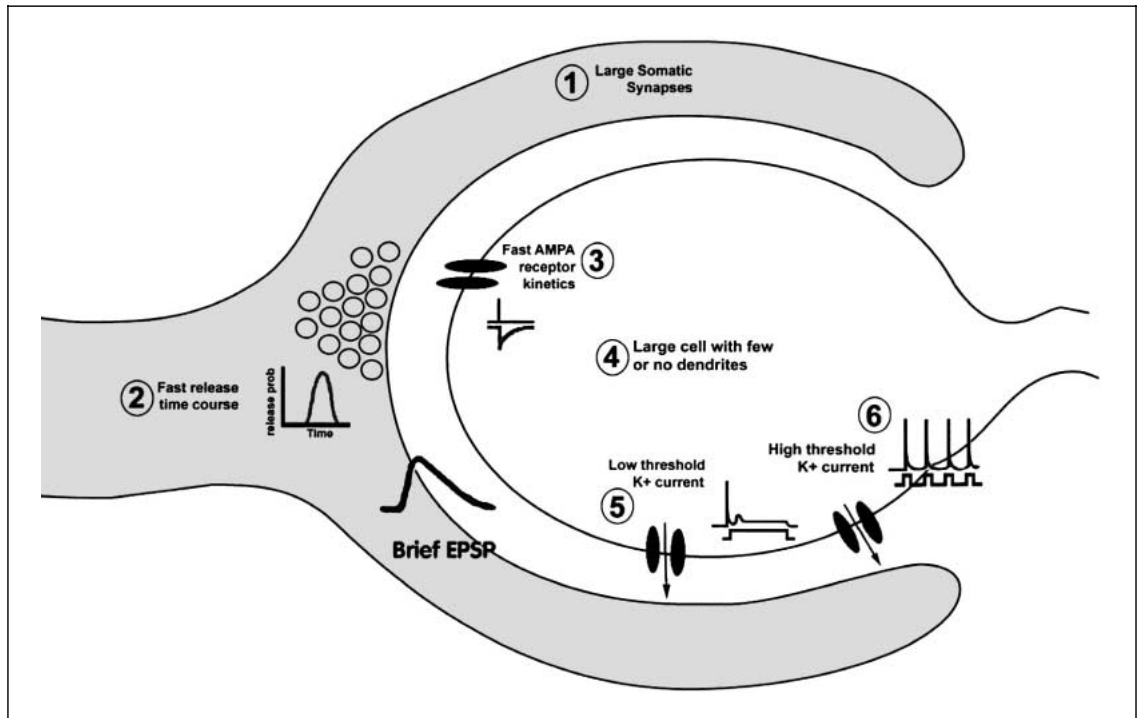
Fig. 2. Summary of physiological and morphological features that characterize time coding neurons. Diagram of endbulb terminal on NM neuron that identifies pre- and postsynaptic specializations including **1** large somatic synapse, **2** fast time course of release, **3** AMPA receptors with rapid kinetics, **4** large postsynaptic cell with few or no dendrites, **5** low threshold K⁺ conductances and **6** high threshold K⁺ conductances [redrawn from Trussell, 1999].

bo, 1986; Carr and Boudreau, 1993; Kawasaki and Guo, 1996; Amagai et al., 1998].

Behavioral evidence makes it clear that phase-coding systems can extract precise temporal information despite variability (jitter) in the phase-locking of neural spikes to the electrical or auditory stimulus. Large numbers of inputs are often invoked as a mechanism for reducing temporal jitter [Carr, 1986; Kawasaki et al., 1988; Heiligenberg, 1989]. In the simplest model, the averaging of n presynaptic units should reduce the jitter in the postsynaptic neuron by $1/\sqrt{n}$. An important requirement for this convergence to be effective is that the synapse and the spike-generating mechanism in the postsynaptic neuron not themselves contribute significant additional jitter [Carr and Amagai, 1996].

'Auditory' AMPA Receptors

Activation of AMPA type glutamate receptors at endbulb synapses generates brief, large synaptic currents that are suited to the transfer of temporally precise information from pre- to postsynaptic cell [fig. 2; Raman and Trussell, 1992; Zhang and Trussell, 1994]. 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 receptors. AMPA receptors are made up of GluR splice variants, and the GluR3 and 4_{flop} isoforms found 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 [Gardner et al., 1999; Trussell, 1999]. These fortunate kinetics result from a characteristic 'auditory' pattern of expression [Parks, 2000]. In the chicken NM, where a homogeneous population of neurons makes this possible, mRNA analysis has revealed the relative abundance of the four AMPA receptor subunits [Ravindranathan et al., 1996]. These receptors have very low levels of GluR2, and higher levels of the 'fast' flop splice variants of GluR 3 and 4 [Ravindranathan et al., 1996; Parks, 2000]. Similar splice variants characterize mammalian bushy cells [Gardner et al., 2001].

Low and High Threshold Potassium Conductances

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) [fig. 2; Manis and Marx, 1991; Reyes et al., 1994; Brew and Forsythe, 1995; Rathouz and Trussell, 1998; Wang et al., 1998].

The LTC activates at potentials near rest and is largely responsible for the outward rectification and non-linear current voltage relationship around the resting potential seen in a number of auditory neurons [for review, see Oertel, 1999, and fig. 5]. 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 [Wu and Oertel, 1984]. Only large EPSPs reaching threshold before significant activation of the LTC would produce spikes with short latencies, whereas small EPSPs that 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 Trussell, 1998] or synaptic activation [Brew and Forsythe, 1995]. It is believed that K⁺ channels underlying the LTC are composed of Kv1.1 and Kv1.2 subunits. Both subunits are expressed in auditory neurons, although the subcellular distribution is unknown [Grigg et al., 2000].

The HTC is characterized by an activation threshold around –20 mV and fast kinetics [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 after-hyperpolarization without influencing input resistance, threshold, or action potential rise time. Thus, the HTC can keep action potentials brief without affecting action potential generation. In addition, the HTC minimizes Na⁺ channel inactivation, allowing cells to reach firing threshold sooner and thereby facilitating high frequency firing. Relatively specific pharmaco-logical blockade of the HTC broadens action potentials and reduces the fast after-hyperpolarization [Brew and Forsythe, 1995]. Furthermore, blockade of the HTC diminishes the ability of the medial nucleus of the trapezoid body (MNTB) neurons to follow high frequency stimuli in the range of 300–400 Hz, but has little effect on responses to low frequency (<200 Hz) stimulation [Wang et al., 1998].

Currents produced by Kv3 channels share many characteristics of the HTC, including a positive activation range, rapid deactivation kinetics, and pharmacological sensitivity, and most likely underlie the HTC. Neurons that fire fast, including many auditory neurons, express high levels of Kv3 mRNA and protein [Perney and Kaczmarek, 1997; Li et al., 2001; Parameshwaran et al., 2001]. Interestingly, in several auditory nuclei including avian NM and nucleus laminaris (NL) [Parameshwaran et al., 2001], and rat MNTB [Li et al., 2001], Kv3.1 protein expression varies along the tonotopic map such that mid to high best frequency neurons are most strongly immunopositive, whereas 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 lobes 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. Because 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 et al., 2001; Parameshwaran et al., 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 NL in the owl, but not in the chicken [Parameshwaran et al., 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 suggests that an increase in the width of the input EPSC could impair ITD coding [Simon et al., 1999; see below]. Thus, the selective increase of Kv3.1-like currents in the NM delay line axons

in owl might contribute to the temporal synchrony necessary for accurate phase-locking.

There are differences among various temporal coding circuits. Examples from potassium channel expression include the coincidence detector neurons in birds and mammals. Neurons of the medial superior olive (MSO) do not express either Kv3.1 mRNA or protein, unlike NL neurons. They do, however, express high levels of Kv3.3 message [Perney and Kaczmarek, 1997; Grigg et al., 2000]. Thus, differences in Kv3 expression between NL and MSO structures may reflect species differences in the expression of Kv3 subfamily members, or this variation might represent a significant physiological difference. Other examples are the differences in the subcellular localization of Kv3.1 protein in chick and owl NM axons described above. In both the owl and the chicken, Kv3.1 is targeted postsynaptically in NM and NL. The major difference in localization of Kv3.1 protein between the two birds is that Kv3.1 protein is expressed in the NM axons and terminals that act as delay lines in the barn owl NL. The presynaptic localization of Kv3.1 in owl might be a specialization enabling neurons in owl NM to transmit high frequency temporal information with little jitter. Nishikawa [1997] has proposed that these types of interspecific differences could occur as small changes superimposed upon a basic developmental plan.

Similar potassium conductances characterize other time coding cells. There are numerous examples, many discussed in Oertel's 1999 review. In addition to the NM and mammalian cochlear nucleus bushy cells discussed above, the coincidence detectors in the avian NL and mammalian medial superior olive also express similar conductances and respond with temporal precision to the auditory stimulus (see below). The reasons for temporal precision are clear for the circuit that detects interaural time differences (ITDs). There are also other aspects of the auditory stimulus that require temporal precision. In particular, the mammalian cochlear nucleus octopus cells form the origin of a circuit that encodes timing of events, especially broadband transients. Octopus cells produce the briefest, most sharply timed synaptic responses in the mouse cochlear nucleus [Golding et al., 1995]. Octopus cells are characterized by both a large low threshold conductance and a high threshold conductance [Bal and Oertel, 2000]. Type II cells in the ventral nucleus of the lateral lemniscus produce sharply timed responses and receive endbulb input from octopus cells [Wu, 1999]. Thus selection for temporal accuracy might in each case drive the expression of conductances that improve neuronal performance and behavioral accuracy.

Coincidence Detection and ITD Coding

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 NL and the mammalian medial superior olive (MSO) [Young and Rubel, 1983; Carr and Konishi, 1990; Joris et al., 1998; fig. 3]. The projections from the NM to NL and from mammalian spherical bushy cells to MSO resemble the Jeffress model for encoding ITD [Jeffress, 1948]. The Jeffress model describes a circuit composed of two elements: delay lines and coincidence detectors. The coincidence detectors are arranged in an array, 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 cancel out the acoustic ITD [for reviews, see Konishi, 1991; Joris et al., 1998]. 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, i.e., when the difference in the conduction delays compensates for the ITD [Goldberg and Brown, 1969; Carr and Konishi, 1990; Yin and Chan, 1990; Overholt et al., 1992; Peña 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 bi-tufted neurons with inputs from each ear segregated on the dendrites (fig. 4). Modeling studies suggest this dendritic organization improves coincidence detection [Agmon-Snir et al., 1998]. Thus the cell morphology and the spatial distribution of the inputs enrich 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].

Two dendritic non-linearities aid coincidence detection. First, synaptic inputs arriving at the same dendritic
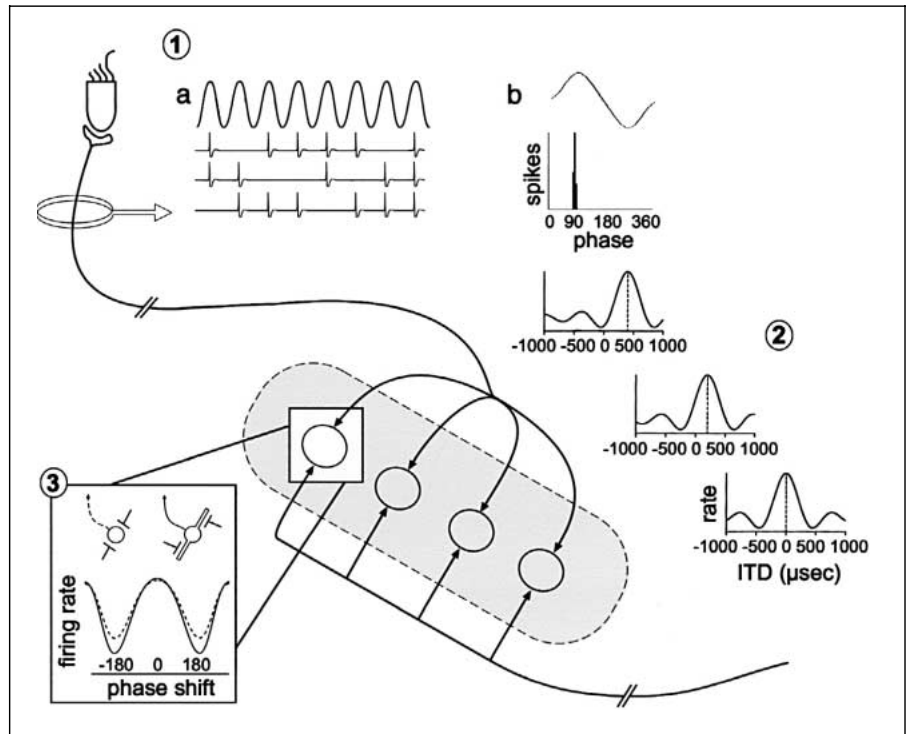
Fig. 3. Summary of ITD detection circuits. **1** Temporal code is maintained from hair cell to cochlear nucleus to site of ITD detection. **a** Phase-locking, with multiple input channels all encoding the phase of the auditory signal. **b** Period histogram whereby the timing of the spikes in **a** are plotted with respect to stimulus phase. **2** Place code for ITD achieved by Jeffress-like circuit. Monaural channels act as delay lines and project to an array of coincidence detectors that each tap the signal at a different ITD. The cells for which the internal (axonal) delay is equal but opposite to the acoustic ITD are maximally active [from Joris et al., 1998]. The delay lines create a map of ITD whereby the temporal code is transformed into a place code. The best evidence for this is in the cat [for review, see Joris et al., 1998]. **3** Coincidence detectors respond maximally to simultaneous inputs from each ear. Their firing rate drops to a minimum when these inputs are 180° out of phase. Models of coincidence detectors suggest that segregation of inputs from each ear onto bitufted dendrites improves coincidence detection by reducing the possibility of a response to a non-synchronous input [Agmon-Snir et al., 1998].

compartment sum non-linearly because the driving force decreases with depolarization [Agmon-Snir et al., 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 [Simon et al., 2000]. With only monaural input, the LTC in the opposite dendrite is somewhat activated, producing a mild current sink. However, when 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; Carr and Konishi, 1990; Yin and Chan, 1990] that the monaural firing rate, although lower than 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, sub-linear summation in the dendrites only improves coincidence detection below 2 kHz, after which discrimination between in-phase and out-of-phase inputs
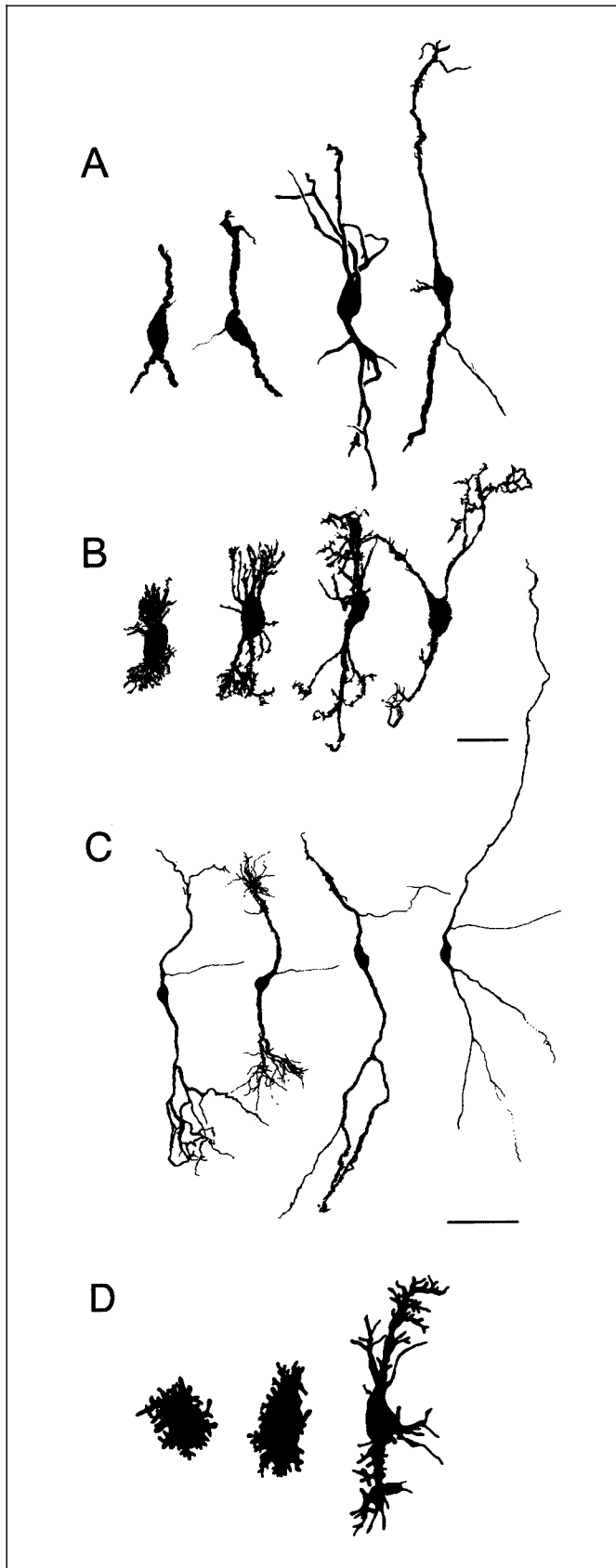
is poor [Agmon-Snir et al., 1998]. This is consistent with observations from rabbit MSO neurons, where ITD sensitivity has only been observed for sounds at or below 2 kHz [Batra et al., 1997]. The second dendritic non-linearity, subtractive inhibition of out-of-phase inputs, improves coincidence detection at all frequencies [Simon et al., 2000] and might therefore be most significant in avian coincidence detectors between 2–8 kHz. 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 [Simon et al., 2000]. The benefits conveyed by the neuronal structure of the coincidence detectors allow us to argue that selective forces have directed the convergent evolution of coincidence detectors in the bird NL and mammalian MSO.

Convergent Aspects of ITD Coding in Amniote Auditory Systems

ITD detection is a common feature of avian and mammalian auditory systems, although the resolving ability of the discrimination task varies among different species [Heffner, 1997]. The ability of the auditory system to use ITD cues to localize sounds requires accurate encoding of temporal information. An important feature of both avian and mammalian coincidence detectors is that they share physiological features with time coding neurons in the cochlear nuclei. Coincidence detectors exhibit specific K^+ conductances that lead to a single or few well-timed spikes in response to a depolarizing stimulus in vitro. The

Fig. 4. Coincidence detectors share bitufted morphology. **A** Alligator NL neurons labeled with Golgi technique, from presumed high to low best frequency regions of NL [left to right; Soares, unpublished]. **B** Chicken NL neurons labeled with Golgi technique, from high to low best frequency regions of NL [Jhaveri and Morest, 1982]. Bar for **A** and **B** = 40 μm, for **D** = 20 μm. **C** Guinea pig MSO neurons [Smith, 1995]. Bar = 100 μm. **D** Barn owl NL labeled with Golgi technique [Carr et al., 1997]. Dendritic length increases from left to right except in the principal cells of the medial superior olive (MSO) from the guinea pig, where a frequency gradient is not apparent [adapted from Smith, 1995]. The bipolar architecture and the segregation of the inputs arriving from both ears is common to both mammalian and avian coincidence detectors. In the barn owl, coincidence detectors have lost this bipolar organization (except in low best frequency regions), and their short dendrites radiate around the cell body.

LTC should decrease the effective membrane time constant. Modeling studies suggest that these fast conductances are instrumental in keeping the firing rate near zero when the inputs are completely out of phase while allowing non-zero firing rate when the inputs are monaural [Agmon-Snir et al., 1998; Simon et al., 1999].

Both avian and mammalian coincidence detectors share physiological features with NM neurons and mammalian bushy cells. Coincidence detectors exhibit specific K^+ conductances that lead to a single or few well-timed spikes in response to a depolarizing stimulus in vitro [Smith, 1995; Reyes et al., 1996]. The low threshold K^+ 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 should be shorter than the passive membrane time constant [Mainen and Sejnowski, 1995, 1996; Gerstner et al., 1996]. These fast conductances may be critical to coincidence detection.

Although coincidence detector neurons in birds and mammals display similar conductances and bipolar morphologies (fig. 4) they are not identical. At the cellular level, mammalian MSO neurons do not express Kv3.1 [Grigg et al., 2000; Li et al., 2001; see section on 'Potassium Conductances', above]. They do express high levels of Kv3.3 message [Grigg et al., 2000; Li et al., 2001]. We do not know whether this variation in expression represents a significant physiological difference. With regard to morphology, avian, crocodilian, and mammalian coincidence detectors all have a bitufted dendritic organization, but mammals do not show an appreciable change in dendritic length with best frequency [Cant, 1992; Smith, 1995] (fig. 4). We do not know whether the biophysical or synaptic properties change with best frequency because there are no data comparing the responses of MSO neurons with their best frequency.

At the circuit level, a second substantial difference between bird and mammal coincidence detectors 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; Kapfer et al., 2002]. In the gerbil, these inhibitory inputs enhance coincidence detection by shifting the peak of the ITD function so as to place the slope within the biological range [Brand et al., 2002]. In birds, inhibitory inputs in NL are more diffuse, and appear to decrease excitability through a gain control mechanism [Funabiki et al., 1998; Yang et al., 1999; Monsivais et al., 2000; Peña et al., 1996].

Because the bitufted structure can improve ITD detection, it is parsimonious to suppose that ITD detection in birds and mammals evolved independently, and that their similarity is due to convergence. Evolutionary and developmental studies will be needed to determine whether or not the coincidence detector neurons in the NL and MSO shared a common bitufted ancestor, or whether this morphology arose independently in the two groups.

Encoding Sound: Similar Strategies in Birds and Mammals

Both birds and mammals encode phase and detect ITD in a similar way. Do they also use similar strategies for encoding the rest of the auditory scene? When comparing the avian NA with the mammalian cochlear nuclei, we have found that both structures have heterogeneous cell populations, and similar responses to sound [Köppl et al., 2001; Soares and Carr, 2001; Soares et al., 2002]. We do not know whether these shared characteristics evolved from heterogeneous ancestral populations, or if they have evolved in parallel as a response to similar selective pressures to encode airborne sound. There are two possible reasons why similarities might be due to convergence. (1) True tympanic ears arose independently in birds and mammals [Clack, 1997; see Introduction]. These peripheral changes would have had different reorganizing effects upon the ancestral population of brainstem auditory neurons. (2) The cell types of the avian and mammalian cochlear nuclei are similar but not identical. We describe these similarities in this section. A satisfactory study will, however, require detailed analyses of the morphology and physiology of cell types in the cochlear nucleus in all amniote groups, including turtles, basal lizards, and crocodilians. We also note that the divisions of the cochlear column in birds and mammals do not appear to be the same. There are two avian cochlear nuclei, with NM containing essentially a single cell type, where as NA has heterogeneous cell types distributed throughout the nucleus. The mammalian cochlear nuclei contain groupings of cells and three adjacent divisions termed dorsal, anteroventral, and posteroventral. We and others have attempted to determine the relationship between NA and the mammalian cochlear nuclei. At present, no scheme can satisfactorily account for the observed similarities and differences.

Nucleus angularis and the Mammalian Dorsal Cochlear Nucleus

There are no true morphological correspondences between NA and the DCN, despite superficial similarity [Boord, 1969; Sachs and Sinnot, 1978; Sachs et al., 1980]. Historically, there were two main reasons for thinking NA and DCN were homologous: (1) the existence of type IV (complex non-monotonic) physiological responses in both NA and DCN [Sachs and Sinnott, 1978; Sachs et al., 1980; for review of DCN see Young et al., 1988]. (2) Boord [1969] proposed that medial NA and NM corresponded to the mammalian ventral cochlear nucleus and that lateral NA was comparable to the DCN. Boord's supposition was supported by the increased cell density and small cell size of lateral NA and by the presence of the lateral afferent tract. These anatomical features created a superficial resemblance to the fusiform and molecular layers of the DCN. We now know that NA is a unitary structure, with the same cell types distributed along the tonotopic axis [Soares and Carr, 2001]. Parsimony would therefore suggest that the type IV responses observed by Sachs and Sinnot [1978] might have emerged in parallel with similar responses in mammalian DCN. The DCN appears to be a unique feature of the mammalian auditory system, associated possibly with the development of motile external ears. Furthermore, unlike the case with the NA, the DCN shares many common features with the cerebellum, including unique cell types and cortical circuitry [Mugnaini et al., 1987, 1997; Wright and Ryugo, 1996]. It can be inferred therefore that at least some parts of DCN have a distinct embryological origin, different than the other cochlear nuclei.

Similar Organization of Multipolar Cell Types with Respect to the Tonotopic Axis in Birds and Mammals

Doucet and Ryugo [1997] described ventral cochlear nucleus neurons that project to the dorsal cochlear nucleus of the rat. They divided these multipolar neurons into two distinct groups: planar and radiate. Planar neurons have dendrites oriented within the isofrequency plane, and Doucet and Ryugo [1997] suggest that these neurons might respond best to a narrow range of frequencies. Radiate multipolar neurons, on the other hand, have long dendrites oriented perpendicular to the isofrequency contours, and might be sensitive to a broader range of frequencies. A third group of multipolar cells is present on the margins of the ventral cochlear nucleus.

Although the radiate neurons in the bird NA do not span as large a portion of the tonotopic axis as the radiate neurons described by Doucet and Ryugo [1997] the basic pattern of planar and radiate cells observed in the rat applies to NA. NA cells can be divided into classes on the basis of their dendritic organization with respect to the tonotopic axis, and with respect to their electrophysiological properties [Soares and Carr, 2001; Soares et al., 2002] (fig. 5). NA contains four major morphological classes of neurons: planar, radiate, vertical, and stubby. Planar neurons are confined to an isofrequency band, whereas radiate neurons have dendrites that could extend across an isofrequency band. Vertical cells have long dendrites oriented perpendicularly to isofrequency bands. Stubby cells are confined to an isofrequency band because of their short dendrites. Representatives of all cell classes can be found throughout NA. Thus, a similar pattern of organization appears to have evolved in parallel in the cochlear nuclei of both birds and mammals, in which one population (planar, stubby, bushy) remains within an isofrequency band, another (radiate) extends across the isofrequency axis, and a third (vertical, marginal, octopus) has a dendritic orientation orthogonal to the isofrequency axis.

Although there is a similar organization in the ventral cochlear nucleus and NA, there are significant differences between the two structures. First, the majority of NA cells are stubby neurons that have no obvious counterpart within the multipolar cell types of the mammalian ventral cochlear nucleus. Second, there are many cell types within the mammalian ventral cochlear nucleus that are not included in Doucet and Ryugo's classification scheme, principally bushy cells, octopus cells, and small cell types [for review see Brawer and Morest, 1974; Cant and Morest, 1979; Rouiller and Ryugo, 1984; Cant, 1992; Rhode and Greenberg, 1992]. Bushy cells might be homologous to the cells of NM [Sullivan and Konishi, 1984], but we find no obvious morphological counterpart to octopus cells in NA. These neurons are located in the posterior part of the ventral cochlear nucleus and encode rapid transients [Oertel et al., 2000] (fig. 5). This is significant because both octopus cells and cells in NA respond to sound with onset responses [Sullivan, 1985; Warchol and Dallos, 1990]. Nevertheless, Golgi analyses of barn owl NA neurons and intracellular labeling of cells in chicken NA have not revealed cells with the characteristic octopus cell morphology – thick dendrites that extend across the incoming auditory nerve inputs [Oertel et al., 2000; Soares and Carr, 2001; Soares et al., 2002]. Thus, evolution of onset coding might not necessarily have produced identical solutions. Finally, avian cochlear nuclei do not show the small cell cap that characterizes mammals, just as they lack the cerebellar-like organization of the DCN. Only two small cells were found in NA [Soares and Carr,
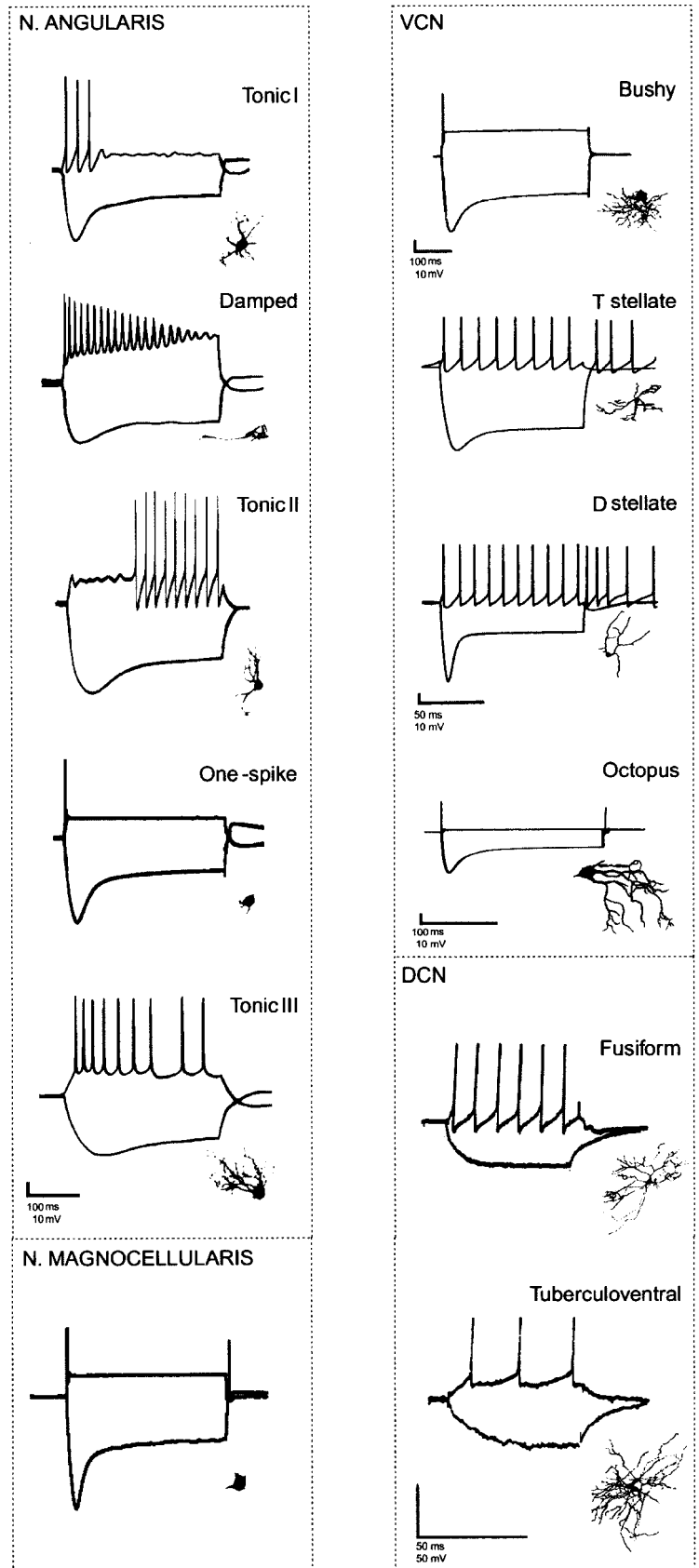
Fig. 5. Summary of current clamp responses in labeled cochlear nucleus neurons in chicken (**left**) and mammal (**right**). Avian NA data are taken from Soares et al. [2002], and NM data are from K. Macleod [unpublished data]. All avian scales: 100 ms and 10 mV. Currents injected: Tonic I, 150 and –500 pA; Damped, 150 and –500; Tonic II, 150 and –500; One spike, 200 and –500; Tonic III, 150 and –500; NM, 150 and –500. Mammalian information (right): Bushy cell: 100 ms, 10mV, 350 to –350 pA [physiology, Schwarz and Puil, 1997; anatomy, Cant, 1992]. T and D stellate: 50 ms and 10 mV, 100 to –600 pA [physiology, Fujino and Oertel, 2001; anatomy, T-stellate, Cant, 1992; anatomy, D-stellate, Doucet and Ryugo, 1997]. Octopus: 100 ms and 10 mV, 400 to –400 pA [physiology, Oertel et al., 2000; anatomy, Cant, 1992]. Tuberculoventral: 50 ms and 10 mV, 200 and –400 pA [physiology and anatomy, Zhang and Oertel, 1993]. Fusiform: 50 ms and 10 mV, 200 and –400 pA [physiology and anatomy, Zhang and Oertel, 1994]. Note that although responses from spherical bushy cells and NM neurons are similar, and both receive endbulb inputs from the auditory nerve, we have not placed them in adjacent rows because it is not clear whether they are homologous. Scales: 100 ms and 10 mV.

2001], and it appears that small cell types are not as various or numerous in NA as in the mammalian cochlear nucleus.

Heterogeneous Intracellular Physiological Responses

Neuronal responses to current injection in the cochlear nucleus show a heterogeneous repertoire of membrane characteristics in both birds and mammals (fig. 5). There is, however, no direct one-to-one correspondence between these traits, i.e., no single group of traits characterizes a cell type in both classes. The only exceptions are the features associated with temporal coding (see below). Because this suite of features characterizes temporal coding neurons in many auditory nuclei, including lemniscal nuclei [Wu, 1999], and is also found in temporal coding neurons in electric fish [Carr, 1986; Rashid et al., 2001], we cannot use their presence to argue for homology among cochlear nucleus neurons in birds and mammals.

In birds, stubby neurons respond with only one spike. Planar neurons show a damped response in the amplitude of their action potentials. Vertical neurons show a delayed response (tonic II) and radiate neurons show tonic responses to current injection (tonic I, III). The responses of stubby NA neurons are similar to those exhibited by both bushy and octopus cells in mammalian ventral cochlear nucleus [Wu and Oertel, 1984; Manis and Marx, 1991; Golding et al., 1999]. These cell types exhibit the depolarization-activated, dendrotoxin-sensitive, low-threshold K^+ conductance (LTC) that is activated at rest [see section 'Coincidence Detection ...', above, and Manis and Marx, 1991; Brew and Forsythe, 1995; Bal and Oertel, 2000]. A similar low threshold conductance could underlie the responses of NA one spike neurons, because it is also found in both NM and NL neurons [Reyes et al., 1994, 1996; Rathouz and Trussell, 1998] and in the irregularly firing principal cells of the tangential nucleus [Gamkrelidze et al., 1998, 2000]. These similarities suggest that stubby neurons, like bushy, octopus, NM and NL neurons, might mediate accurate transmission of temporal information [Oertel, 1999; Trussell, 1999].

There are no other NA neurons with direct one-to-one correspondence with mammalian cochlear nucleus neurons. The physiological characteristics that define planar neurons in birds are not seen in the cochlear nucleus neuron in mammals. A decrease in spike amplitude from the onset of depolarization is first seen in the mammalian inferior colliculus [Sivaramakrishnan and Oliver, 2001]. It is possible that similar computations could take place at different levels in the auditory system, or that different membrane properties might mediate the same physiological responses.

Radiate (tonic II) and pyramidal neurons in the mammalian DCN share two defining properties: fast inward rectification in response to hyperpolarizing current and delayed spike response to depolarizing current. Both produce subthreshold oscillations during depolarization pulses, similar to those in the pyramidal cells in the DCN [Manis and Molitor, 2001]. These low-frequency oscillations were blocked by tetrodotoxin in pyramidal cells (TTX, 500 nM). Voltage-gated Na^+ channels are therefore required to generate membrane oscillations, and Manis and Molitor suggest that they play a role in controlling spike timing in neurons when the membrane potential slowly approaches, or hovers near, spike threshold. Tonic II cells further resemble DCN pyramidal cells in that both exhibit similar delayed firing patterns in vitro [Kanold and Manis, 1999; Soares et al., 2002]. In vivo recordings will show whether these similar intracellular responses mediate similar responses to sound. Despite their similarities, tonic II and DCN pyramidal neurons have distinctly different projections [Young et al., 1988; Soares and Carr, 2001].

Radiate (tonic I and III) cells in NA share features with both D- and T-stellate neurons in the ventral cochlear nucleus. T- and D-stellates are physiologically differentiated in vitro by the shape of the action potential undershoot, which is rapidly repolarizing in D-stellates and scalloped in T-stellates (fig. 5). T- and D-stellates are further differentiated by differences in inward rectification, which is more prominent and more rapid in D-stellates [Fujino and Oertel, 2001]. Tonic I and III radiates are similarly distinguished. Tonic I neurons have prominent, rapid inward rectification, whereas Tonic III neurons have a scalloped undershoot and weak rectification. Despite these similarities, tonic cells in NA and neurons in the VCN differ in their transmitter phenotype and projections. They are unlikely to be homologous because T-stellates are excitatory neurons that project to the contralateral VCN, and D-stellate neurons are inhibitory glycinergic neurons that suppress activity in T-stellate cells [Wu and Oertel, 1984; Oertel et al., 1990; Saint Marie et al., 1991; Zhang and Oertel, 1993; Wickesberg et al., 1994; Gates et al., 1996; Moore et al., 1996; Ferragamo et al., 1998; Davis and Young, 2000]. In the barn owl, all NA neurons project to the midbrain [Soares and Carr, 2001] and none appear to be glycinergic. In these examples, there is again no direct one-to-one correspondence between the traits expressed in any cell type in birds and mammals.
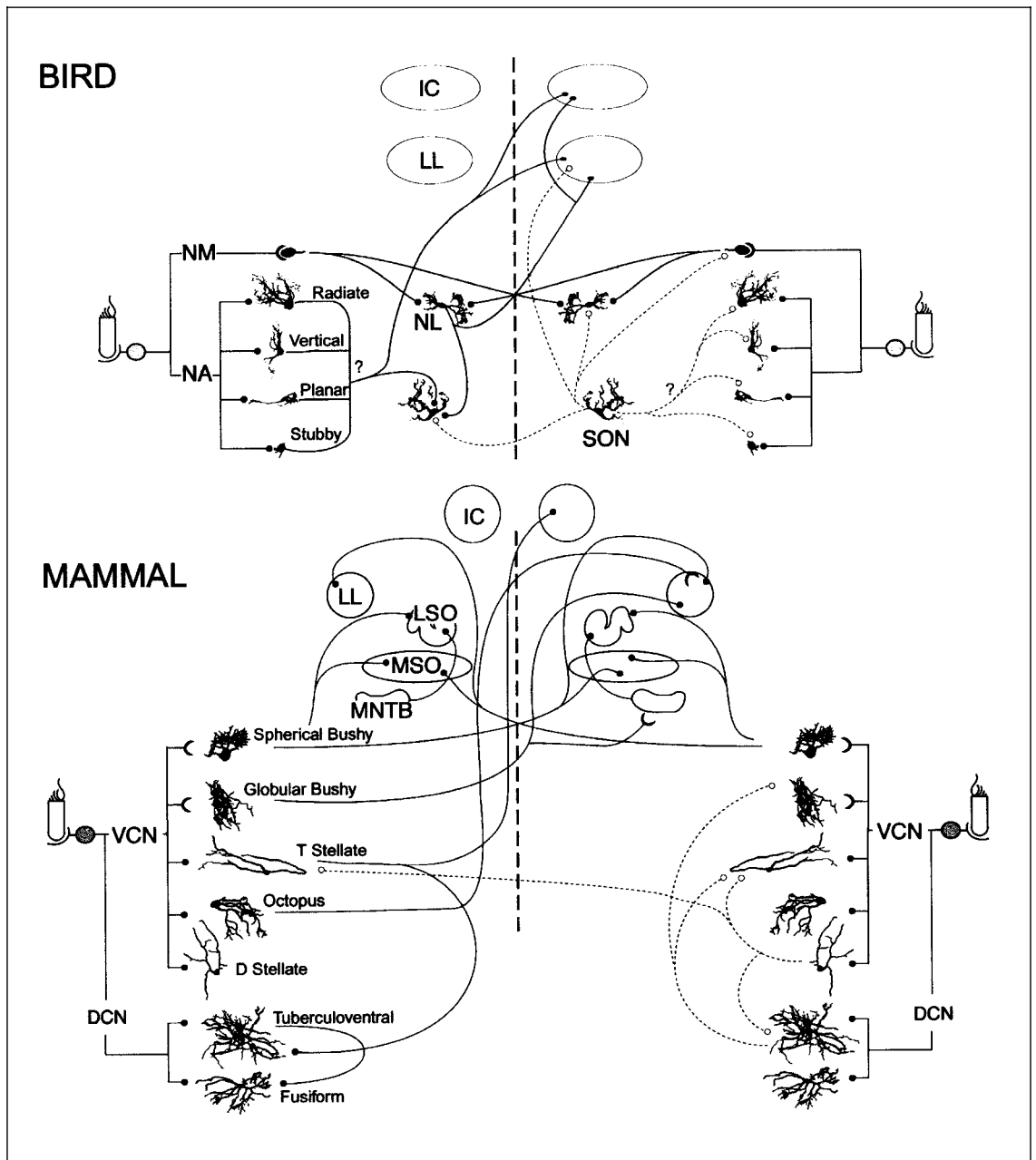
Fig. 6. Schematic summary of ascending connections and cell types of the avian and mammalian cochlear nuclei. Each connection displays a labeled cell body and shows the principal projections of each cell type. See text for citations. **Top:** Connections of the avian auditory system. NA (nucleus angularis) projections from Conlee and Parks [1986] and Yang et al. [1999]. **Bottom:** Connections of the mammalian cochlear nuclei. VCN (ventral cochlear nucleus) projections based on Oertel [1999], and DCN (dorsal cochlear nucleus) based on Wickesberg et al. [1991] and Zhang and Oertel [1994]. IC = Inferior colliculus; LL = lateral lemniscus; LSO = lateral superior olive; MNTB = medial nucleus of the trapezoid body; MSO = medial superior olive; NL = nucleus laminaris; NM = nucleus magnocellularis; SON = superior olivary nucleus. Note: It is not known whether the same SON cells project to both hindbrain and midbrain.

Ascending Lemniscal Projections

Avian and mammalian cochlear nuclei both share ascending lemniscal projections, but these differ in many respects (fig. 6). In birds and crocodilians, the NA projects to the contralateral posterior portion of the dorsal nucleus of the lateral lemniscus (LLDp, formerly VLVp) [Takahashi and Konishi, 1988a, b; Wild et al., 2001] and the inferior colliculus, while receiving GABAergic projections from the superior olivary nucleus (SON) [Conlee and Parks, 1986; Takahashi and Konishi 1988b; Yang et al., 1999]. The posterior division of the LLDp is the first site of binaural interactions in the intensity pathway of the barn owl and is where sensitivity to interaural level differences (ILDs) first appears [Moiseff and Konishi, 1983; Manley et al., 1988]. The pathways encoding ITDs and ILDs ultimately converge in the external nucleus of the inferior colliculus, where neurons are selective for combination of ITDs and ILDs [for review see Konishi, 2000]. In birds, the lemniscal projections of NA resemble octavolateralis projections in other vertebrates more than they resemble the lemniscal projections of the cells of the mammalian cochlear nucleus [for review see McCormick, 1992]. The projections of the mammalian cochlear nucleus are more variable [for reviews see Young et al., 1988; Cant, 1992; Romand and Avan, 1997; fig. 6].

At present it is not clear whether the features of the avian and mammalian cochlea nuclei described above mediate coding of some specific aspect of the auditory stimulus and are convergent, whether the similarities arose by chance, or whether they represent homologous features found in the common ancestor. Every neuron must be distinguished by a particular morphology and physiology, by embryological origins, location, and connections. Analysis of these characters in well-chosen species will be required to determine homology. It is not clear which characters should be given the most weight: projections can arborize and retract widely during development [Stanfield et al., 1982]; multiple transmitters can be expressed by any one neuron [Sato et al., 2000]; and patterns of channel expression appear to be driven by computational requirements. Furthermore, Turrigiano et al. [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, and retain the ability to modify these over time [Desai et al., 1999].

Embryological studies are possible in chicken and quail, and recent studies have described the cell fate of chicken auditory brainstem neurons [Marin and Puelles, 1995; Cramer et al., 2000]. Similar descriptions of embryological origins are needed in other amniotes.

Conclusions

Birds and mammals share a common ancestor in the Carboniferous [Carroll, 1988]. Many amniote synapomorphies are widely interpreted as adaptations of these ancestors to life on land. We propose that some features we have described in the avian and mammalian auditory systems are apomorphic, or derived and different from the ancestral condition, and not homologous. The principal reason for arguing for the lack of homology is the separate development of true tympanic ears in their ancestors [Clack, 1997]. A second reason is that close comparisons of bird and mammal cochlear nuclei reveal many differences. A third is that the observed convergence of morphology and physiology of cochlear neurons is a plausible outcome of convergent evolution, because neurons in both birds and mammals experience similar constraints in detecting sound. Thus, although a common population of brainstem auditory neurons existed in the tetrapod ancestor, we propose that distinct evolutionary forces acted on these two groups allowing for the emergence of different ears and in turn, dissimilar organization in the brainstem. Some elements are likely to be homologous (such as large somatic terminals), but at present it is difficult to separate homology from convergence without careful analyses of all amniote groups.

Comparisons of temporal coding reveal shared computational principles. 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. In fact, the essential features of auditory coding are very similar in birds and mammals (and probably in other animals as well). Comparative studies of temporal coding can therefore add to the discussion of whether neuronal function follows form. A case can be made for this in time coding neurons of the auditory brainstem of birds and mammals, and for phase coding neurons in weakly electric fish [Kawasaki, 2000].

If there are computational advantages to particular neuronal architectures, convergence should be expected. For example, we argue that the bitufted structure of coincidence detector neurons in birds and mammals is computationally advantageous. Therefore, morphological similarities might not support homology, but rather similar computational demands, and we can argue that the neurons of nucleus laminaris and MSO might have converged upon their similar form. In another example, it appears that large somatic terminals on NM or bushy cells are an ancestral feature of amniote auditory nerve. A

shared pressure to encode higher frequency sounds might have driven the convergent appearance of complex endbulbs in archosaurs and mammals.

Finally, phenotypically different neurons can produce similar computations. Neurons can differ in the expression and/or distribution of their ionic channels and still behave similarly. Thus, there might be numerous acceptable ways to carry out a particular computation. These could be revealed by comparative studies.

Differences between classes, such as those documented in the avian and mammalian cochlear nuclei, might result from lack of homology, a long separation over evolutionary time, and/or different selective pressures. Differences within a group can reveal how neural circuits evolve. The nervous system is evolutionarily conservative and small changes in structure can lead to profound changes in function and behavior [Nishikawa, 1997]. Within birds, there are differences in the subcellular distribution of potassium channels in chick and owl delay lines. The changes in presynaptic localization might be a specialization for enabling neurons in owl NM to transmit high frequency temporal information with little jitter [Parameshwaran et al., 2001]. Nishikawa [1997] has proposed that these types of interspecific differences could occur as small changes superimposed upon a basic developmental plan. Understanding how this type of change take place in the context of increased behavioral function should illuminate mechanisms by which neural circuits evolve.

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