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Beyond timing in the auditory brainstem: intensity coding in the avian cochlear nucleus angularis

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Introduction

Individual acoustic stimulus waveforms in the environment sum together to form a complex composite waveform that arrives at the ear as a single, time-varying pressure amplitude wave. The fundamental problem of hearing lies in how the brain decomposes that waveform into information useful for performing auditory tasks necessary for the survival of the animal such as sound localization and vocal communication. Many of the computational principles for sound localization have emerged from the study of avian brains, especially that of the barn owl, a specialized auditory predator (Konishi et al., 1988). Additional data from less specialized birds, such as the chicken, and from mammals have revealed a suite of cellular and synaptic specializations in common for the temporal coding of sound, necessary for the detection of one important cue for localization, interaural time difference (ITD): fast glutamatergic neurotransmission, calyceal synaptic morphology, low-threshold voltage-gated potassium conductances, bipolar dendritic structures, and axonal delay lines (Carr, 1993; Oertel, 1999; Trussell, 1999). Such commonalities of form arising in widely disparate animal clades suggest that there is a computational advantage to that form, whether it is dendritic structure, expression of a suite of ion channels, or the temporal patterning of activity. Brains in both birds and mammals experience similar constraints in detecting sound, and because hearing of airborne sound arose separately in these two groups, similarities in structure, function and coding between them suggest common coding principles at work, and common solutions arrived at through parallel evolution (Carr and Soares, 2002).

A similarly comprehensive answer to the question of coding non-ITD aspects of sound has lagged behind. Early work in the barn owl recognized a division of labor for the coding of interaural timing differences versus interaural intensity differences (also known as interaural level differences, or ILDs), beginning with the two divisions of the avian cochlear nucleus: nucleus magnocellularis (NM) as the origin of the ‘timing pathway’ and nucleus angularis (NA) as the origin of the ‘intensity pathway’ (Figure 1A)(Sullivan and Konishi, 1984; Takahashi et al., 1984); for review see. Both cochlear nuclei are monaural, and project to binaural targets which compare inputs from the two ears (Manley et al., 1988; Takahashi and Konishi, 1988). While NM neurons are similar to the mammalian cochlear nucleus bushy cells, NA is a heterogeneous nucleus with many properties similar to non-bushy cell components of the mammalian cochlear nucleus (CN) (Carr and Soares, 2002; Köppl and Carr, 2003; Oertel, 1999; Soares and Carr, 2001; Soares et al., 2002). This heterogeneity (described below) coupled with the extreme specialization of one pathway for timing cues beginning with NM, suggests that NA is largely responsible for encoding non-localization aspects of sound in addition to its role in the ILD pathway. A major challenge will be to

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determine how each component cell type contributes to different aspects of sound recognition.

In this chapter, we discuss the morphological and physiological cell types found in NA, their responses to auditory stimuli, and the commonalities and differences of these properties as compared to the mammalian cochlear nucleus. We review the synaptic properties of the neurons in NA and suggest that short-term synaptic plasticity may play a role in the division of intensity and timing information into parallel pathways. While many questions are yet unanswered, further comparative studies of auditory coding in the cochlear nuclei will increase our understanding of common principles of auditory coding. In the avian system especially, a better understanding of general sound coding at the brainstem level will contribute to our understanding of complex auditory function, such as birdsong recognition and learning.

Morphological and intrinsic physiological characteristics of the neurons of the cochlear nuclei

In both birds and mammals, the auditory nerve forms endbulb synapses on one cell type and bouton like terminals on all other cochlear nucleus targets (Ryugo and Parks, 2003). In mammals, endbulb of Held terminals are formed on the bushy cells of the ventral cochlear nucleus (VCN), and in birds, the auditory nerve forms endbulb terminals on the cells of the nucleus magnocellularis and bouton-like terminals on cell types of the cochlear nucleus angularis. These different terminal types are the origin of the ascending neural pathway that encodes timing information, and the parallel pathway for encoding sound level in nucleus angularis (Takahashi et al., 1984).

In addition to two types of auditory nerve terminals, the morphological and physiological characteristics of their target neurons contribute to the input-output functions of cochlear nucleus, and the encoding of different components of the auditory stimulus. NA is a heterogeneous nucleus, with at least 4 or 5 different cell types based on morphological and in vitro physiological criteria. Unlike the mammalian CN, there are no prominent subdivisions, and the cell types appear distributed throughout NA. Despite morphological and in vitro physiological similarities described below, there is no one-to-one correspondence between avian and mammalian cell types. Furthermore birds entirely lack an analog of the mammalian dorsal cochlear nucleus (DCN). Perhaps surprisingly then, there are both morphological similarities and overlap in the in vivo response classes.

One common theme between the cochlear nucleus neurons in birds and mammals is the orientation of dendritic arbors relative to the incoming nerve fibers, which form isofrequency bands. NA has a tonotopic mapping of frequency (Köppl, 2001b). There are 4 morphological types in barn owl NA, all of which bear multiple dendrites: planar, vertical, radiate and stubby (Soares and Carr, 2001). The planar neurons extend elongated dendrites oriented along the isofrequency axis, which presumably would limit their frequency tuning range. Stubby neurons have short dendrites, and thus limit their frequency input due to limited extent. Vertical neurons are elongated perpendicularly to the isofrequency axis, and radiate neurons have longer, radially oriented dendritic fields that also extend across the isofrequency axis. Thus, a similar pattern or organization may have evolved in parallel in which one population (planar and stubby in birds, bushy and planar/stellates in mammals) remains within an isofrequency band, another extends radially ('radiates' in both birds and mammals) across the isofrequency bands, and a third (vertical in birds, marginal and octopus) has a dendritic arbor orientation orthogonal to the isofrequency axis.

A second common theme is the characterization of the firing properties in vitro. Both NA neurons and mammalian CN neurons can be divided into two major classes based on firing properties recorded in brain slices: single-spiking and tonically-firing (for review see Cant and Benson (2003), (Grothe et al., 2005). Single-spiking neurons respond with only one action potential to injections of depolarizing current, and are characterized by a low-threshold voltage-gated, dendrotoxin-sensitive potassium conductance that is activated at rest, and consequently have a low input resistance and fast membrane time constant. In NA, single-spiking neurons correspond to stubby neurons, and thus these neurons have response properties similar to those found in NM and NL (Fukui and Ohmori, 2003; Soares et al., 2002). These biophysical similarities between single-spiking NA neurons and the timing pathway neurons suggest the stubby neurons may mediate transmission of temporal information. In mammalian VCN, bushy cells and octopus cells are single-spiking. Bushy cells are functionally similar to NM neurons (as they receive endbulb synaptic input from the nerve, are known to encode timing and project to ITD processing nuclei), but the octopus neurons are morphologically dissimilar to the stubby neurons, in that one of their primary features is that they extend across the isofrequency axis. Octopus neurons are thought to encode broadband onsets with high temporal accuracy; stubby neurons could conceivably encode onsets but would have limited frequency range.

The rest of the NA neurons fire tonically in response to current injection, and can be subdivided into 4 types on the basis of action potential size, adaptation, afterhyperpolarization and firing pattern (Soares et al., 2002). The vertical neurons are morphologically more similar to octopus cells, extending across frequencies, but fire tonically and have a higher input resistance. Thus the vertical cells may encode broadband noises, but lack the temporal precision of the octopus cells. The radiate and planar neurons in NA also fire tonically. In the mammalian VCN, multipolar neurons respond with tonic firing in the slice preparation (Manis and Marx, 1991; Oertel, 1983; Oertel et al., 1990; Wu and Oertel, 1984), and can also be subdivided on the basis of distinctions in the afterhyperpolarization (Oertel et al., 1990). It is thought that the tonic firing may contribute to the ‘chopping’ sound responses recorded in vivo (see below), and the reduced phase-locking at higher sound frequencies.

In vivo responses to auditory stimulation

The most striking similarities between avian and mammalian CN properties are found in the responses recorded in vivo to sound stimuli. In vivo studies in the barn owl, redwing blackbird and chicken show that NA is physiologically and morphologically much more heterogeneous than NM, with 5 major response types (Köppl and Carr, 2003; Sachs and Sinnott, 1978; Sullivan, 1985; Warchol and Dallos, 1990). The most common response pattern in the nucleus angularis is a primary-like poststimulus time histogram (a transient-sustained rate response similar to that of auditory nerve fibers; see Figure 2) that differs from auditory-nerve fibers in poorer phase locking to the auditory stimulus and often-lower spontaneous rates. There are two types of “chopper” responses, a transient chopper and a rare sustained chopper (“chop-T” and “chop-S” in Figure 2), which differ from primary-like in their poorer phaselocking, and instead show regular firing unrelated to the auditory stimulus phase. Angularis also contains onset units with characteristically low discharge rates (Figure 2, “onset”). NA also contains a complex response type with a pronounced inhibitory component, similar to the mammalian type IV found in the mammalian DCN. In both barn owls and a songbird, the redwing blackbird, Type IV neurons constitute around 10–15% of the neurons (Köppl and Carr, 2003; Sachs and Sinnott, 1978).

It is striking that all 5 physiological response types found in NA are similar to well-known types in the mammalian cochlear nucleus, which suggests parallel evolution of neurons

specialized for encoding different, behaviorally-relevant features of the auditory stimulus (Köppl and Carr, 2003). Although there are a similar number of cell types that have been identified in both in vivo and in vitro studies in birds, we do not know which in vivo type correlates with which in vitro type. This is not the case for the mammalian cochlear nucleus, where Rhode, Smith and Oertel (Rhode et al., 1983) and Rouiller and Ryugo (Rouiller and Ryugo, 1984), and later many others used in vivo intracellular labeling to correlate cell structure with in vivo physiological responses (for reviews, see (Rhode and Greenberg, 1992; Rouiller, 1997).

In the anterior VCN, bushy cells phase lock and respond in a primary like fashion to the auditory stimulus, and show similar responses to those in the avian nucleus magnocellularis. The posterior VCN contains octopus cells that respond to onsets or stimulus transients and two classes of multipolar neuron that respond principally with “chopper” firing patterns. Octopus cells precisely encode the time structure of stimuli and show onset responses to tonal stimuli (Oertel et al., 2000). Onsets play an important role in theories of speech perception, and segregation and grouping of sound sources (Bregman, 1990). Chopper units may primarily respond to the stimulus envelope. The great similarity of the physiological responses recorded in vivo in the cochlear nuclei of birds and mammals is particularly interesting given the morphological differences between the two, especially the absence of the DCN in birds.

In mammals, type IV responses in the DCN emerge from a circuit that receives direct projections from the auditory nerve, excitatory and inhibitory connections from other cochlear nucleus neurons, and proprioceptive input about pinna position (Young, 1998). It is thought that type IV DCN neurons are involved in the detection of spectral changes such as notches, characteristic nulls in the spectrum that are caused by the acoustic filtering properties of the pinna and provide reliable cues to sound direction (May, 2000; Young, 1998). The presence of Type IV cells in birds suggests that rapid changes in frequency are a behaviorally relevant auditory feature, at least in barn owls and songbirds (Köppl and Carr, 2003). Monaural spectral notches have been measured in the barn owl, created by the facial ruff, a specialized feather mask that effectively works like an immobile pinna (Keller et al., 1998). Most other birds, however, do not have an equivalent of the mammalian pinna, yet type IV responses were also seen in the blackbird and may be a typical feature of the avian NA.

The physiological similarities reviewed in this section raise the question of how and why birds acquired similar physiological types. One possibility may be that the cells and circuits in birds and mammals represent parallel evolution of neural processing streams, similar to the similarities in the visual response properties in the owl's visual Wulst and the cat and the monkey visual cortex. Both systems display precise topographic organization, binocular interactions, and selectivity for orientation and direction of movement (Pettigrew and Konishi, 1976).

Synaptic mechanisms in NA

Auditory nerve terminals make bouton-like synapses onto NA neurons (Carr and Boudreau, 1991; Köppl, 2001a) unlike the giant axosomatic endbulb, or calyceal, synapses seen in NM (Carr and Boudreau, 1991; Jhaveri and Morest, 1982b; Parks, 1981). The principal neurotransmitter of the auditory nerve at both types of terminals appears to be glutamate (MacLeod and Carr, 2005; Nemeth et al., 1983; Trussell et al., 1993; Zhou and Parks, 1992). Stimulation of the auditory nerve results in small to moderate amplitude, graded excitatory postsynaptic currents in NA neurons, in contrast to the all-or-none, very large synaptic currents evoked in NM neurons (Hackett et al., 1982; MacLeod and Carr, 2005; Zhang and

Trussell, 1994a). Each NA neuron receives input from multiple nerve fibers, and each auditory nerve fiber probably makes multiple contacts onto the postsynaptic NA neuron (MacLeod and Carr, 2005). Synaptic transmission from the nerve onto NA neurons is mediated entirely by AMPA- and NMDA-type glutamate receptors (MacLeod and Carr, 2005).

The AMPA-receptor (AMPA-R) mediated excitatory postsynaptic currents (EPSCs) recorded in NA neurons, both miniature EPSCs and those evoked by stimulation of the auditory nerve, have very fast decay kinetics, which speed up with age (MacLeod and Carr, 2005; Raman et al., 1994). As in NM, this is partially due to the fast desensitization kinetics of these receptors (Raman et al., 1994). The time course of these AMPA-R EPSCs is attributed to the presence of 'flop' splice variants of the glutamate ionotropic receptor subunits GluR3 and GluR4 and to the relative paucity of subunit GluR2, which together confer faster desensitization kinetics (Dingledine et al., 1999; Geiger et al., 1995; Parks, 2000; Sugden et al., 2002). The absence of GluR2 subunits results in auditory brainstem AMPA receptors that are calcium-permeable (Gardner et al., 1999; Lachica et al., 1998; Otis et al., 1995; Zhou et al., 1995). Immunohistochemical evidence from the barn owl suggests GluR3 and GluR4 are the most prominent AMPA-R subunits in NA (Kubke and Carr, 1998; Levin et al., 1997). Thus NA neurons, like NM neurons and mammalian VCN neurons, express a characteristic 'auditory' type of AMPA receptor (Parks, 2000). Despite heterogeneity in many other aspects, all cell types found in NA had similar AMPA-R EPSC decay times (MacLeod and Carr, 2005), as was also shown in an analysis of decay times across different mammalian VCN neurons (Gardner et al., 2001). In the mammalian DCN, however, a subset of neurons that receive both auditory and non-auditory inputs had a bimodal distribution of decay times (Gardner et al., 2001). The faster events in the distribution were attributed to the auditory inputs, and the slower events to the non-auditory. No bimodal distributions in kinetics were observed in the miniature EPSCs in NA neurons (MacLeod and Carr, 2005).

NMDA Component

Stimulation of the auditory nerve evoked a substantial NMDA receptor (NMDA-R) mediated component of the EPSC recorded in NA neurons in the late embryonic preparation (MacLeod and Carr, 2005). The NMDA-R mediated peak EPSC amplitude was as large as the AMPA-R mediated component, and was comparable to the NMDA-R EPSC component recorded in NM at the same age, although in NM this accounted for only a small fraction of the total peak current (Zhang and Trussell, 1994b). In other systems, a decline in the NMDA-R component, along with a speeding up of the AMPA-R EPSC kinetics, has been correlated with an improvement in temporal coding (Joshi et al., 2004; Taschenberger and von Gersdorff, 2000).

It is not known whether NMDA-R may contribute to neural coding in NA in more mature animals. A substantial NMDA-R input could help convert phase-locked inputs into a constant current stimulus, leading to the chopping responses and reduction of phase-locking. In mammalian VCN stellate neurons, an NMDA-R mediated EPSC contributes to long-lasting depolarizations (Ferragamo et al., 1998). In birds, immunohistochemical evidence showed that the NR1 subunit is expressed into adulthood in both cochlear nuclei (Tang and Carr, 2004). It is possible that the observed physiological decline in NMDA-R mediated responses may instead be due to changes in other subunit receptor components, a shift of NMDA receptor localization, or some other form of inactivation.

Calcium binding protein expression

Many NA neurons express calcium binding proteins (CaBPs), a ubiquitous feature of auditory brainstem areas (Celio et al., 1996; Kubke et al., 1999; MacLeod et al., 2006; Parks et al., 1997). Many species express only one or another of a family of calcium binding proteins: calretinin expression is present in the auditory brainstem of chick, owl, and zebra finch (Braun, 1990; Kubke et al., 1999; Parks et al., 1997; Rogers, 1987; Takahashi et al., 1987), parvalbumin in emu (MacLeod et al., 2006), and in the mammalian auditory brainstem three (calbindin, calretinin, and parvalbumin) are sequentially expressed during development (Friauf, 1994; Lohmann and Friauf, 1996). In NM and NL, CaBPs are highly expressed in the excitatory (glutamatergic) principal neurons. The staining in NA is heterogeneous, but it is unclear whether different cell types express CaBPs preferentially. In mammalian cortex, CaBPs are typically associated with fast spiking inhibitory interneurons (Kawaguchi and Kondo, 2002), but the presence of CaBPs in the excitatory neurons of the auditory brainstem would suggest that CaBP expression is a characteristic of neurons that have high firing rates and/or calcium-permeable AMPA-R, and not related to GABA production per se. It is intriguing to speculate that CaBPs might be preferentially expressed in the NM-like stubby neurons (under the hypothesis that CaBP expression would be highest in those NA neurons whose intrinsic properties most resemble those in NM or NL) or alternatively in the tonically-firing neurons (under the hypothesis that fast-spiking neurons need more calcium buffering), but further studies are needed to understand the role of CaBPs in auditory function.

Short term plasticity in auditory brainstem function: bug or feature?

Short-term synaptic plasticity has been proposed to contribute to neural coding by acting as a filter of the presynaptic spike train, determining what information is passed via the synapse (Abbott and Regehr, 2004; Markram et al., 1998; O'Donovan and Rinzel, 1997). While a beguiling idea, convincing evidence is still sparse that demonstrably shows that short-term synaptic plasticity is a functional component whose computational power is harnessed by the brain. An alternative argument suggests that short-term synaptic plasticity is simply a by-product of the inherent limitations of neurotransmission, a side effect to be mitigated or worked around. Thus remains an unanswered question: is short-term synaptic plasticity a 'bug' or a 'feature'? One of the difficulties in answering this question lies in the requirement for a good computational understanding of the circuit. It would be ideal to investigate the question in a brain area in which the 'code' or the input-output function, is well understood. In the auditory brainstem, the timing pathways meet this criterion, and the 'intensity' pathway has at least one well-defined function (that is, encoding intensity for the purposes of the ILD computation). Here we describe the short-term plasticity characteristics in the auditory brainstem system and their putative functions, and argue that the plasticity observed in at least two out of three cases appears to be well suited for a functional role in auditory processing.

Short-term depression at calyceal synapses

As described above, the auditory brainstem is characterized in part by large, calyceal-type synapses, not only in the NM of birds, but also by endbulbs of Held in the mammalian anterior VCN and calices of Held in the medial nucleus of the trapezoid body, the latter being one of the best studied synapses in the brain due to the physiological accessibility of the giant presynaptic terminal. The advantages of the calyceal synapse has led to a greater understanding of neurotransmission and the mechanisms of plasticity and are well reviewed by (Schneggenburger et al., 2002; Trussell, 2002; von Gersdorff and Borst, 2002). Here we will focus on the possible functional role of calyceal synapses rather than the details of the mechanism.

The axosomatic contact and the large number of active zones in the calyceal synapse result in very large postsynaptic currents, a specialization for the extremely precise encoding of timing information for sound localization (Carr et al., 2001; Jhaveri and Morest, 1982a; Parks, 2000; Trussell, 1999; Zhang and Trussell, 1994a; Zhang and Trussell, 1994b). These large currents nearly always result in a suprathreshold excitatory postsynaptic potential and a one-to-one relationship between a spike in the afferent and a spike in the postsynaptic neuron (Brenowitz and Trussell, 2001b; Taschenberger et al., 2002).

Calyceal synapses experience profound depression due to presynaptic vesicle depletion and postsynaptic AMPA receptor desensitization (Figure 3)(Barnes-Davies and Forsythe, 1995; Bellingham and Walmsley, 1999; Oleskevich et al., 2000; Schneggenburger et al., 2002; von Gersdorff and Borst, 2002; Wong et al., 2003; Zhang and Trussell, 1994a). At NM synapses, depletion and desensitization depend in part on the high probability of release; if release probability is reduced, there is a paradoxical enhancement of the steady state amplitude late in a train of stimuli (that is, a net reduction in depression leading to larger absolute EPSCs than in control), due to the relief of desensitization (Brenowitz et al., 1998; Brenowitz and Trussell, 2001b). One of the ways this might occur in vivo is by activation of metabotropic GABA_B-type receptors, which are located on both the presynaptic terminals and the postsynaptic cell membrane in NM (Brenowitz et al., 1998; Brenowitz and Trussell, 2001b; Burger et al., 2005b). Several other modulator systems (metabotropic glutamate receptors, glycine and GABA_A receptors, adenosine; for review see Trussell (2002)) may also affect release at the calyceal terminal, and thus this synapse appears exquisitely controlled. Yet, changes in synaptic amplitude (due to modulation or depression) appears to have little effect on whether the postsynaptic neuron fires except at very high rates, due to the excessive size of the conductance, which is suprathreshold even when reduced by nearly 90% by depression (Brenowitz et al., 1998; Brenowitz and Trussell, 2001b). While the degree of depression is reduced in more mature animals and at physiological temperatures, some depression still remains (Brenowitz and Trussell, 2001a; Taschenberger et al., 2002). Several views have developed as to why depression persists in this system: the 'epiphenomenon' view, in which synaptic depression is a side effect of the requirements of the synapse to maximize reliability and minimize delay, and thus is a consequence to be mitigated (such as modulation in order to maintain responses at very high rates); the metabolic view, in which depression reduces the load on the synapse at high firing rates, while maintaining a high safety factor at lower rate (von Gersdorff and Borst, 2002); and the fine-tuning view, in which depression reduces the size of the EPSP, introducing small delays in the onset of the spike, which could be useful for introducing small relative time shifts that are processed in higher areas (Trussell, 2002). A better understanding of short-term depression at this synapse might arise from in vivo studies of the effects of the various modulators, but at present synaptic depression does not appear to be computationally advantageous at this synapse.

Short-term plasticity differs at auditory brainstem bouton synapses in timing and intensity pathways: a role for differential filtering?

While depression appears to be the rule at calyceal synapses, what about at the smaller, bouton-like synapses that occur in NA, or in the third-order timing pathway brainstem area, nucleus laminaris? Nucleus laminaris (NL) receives input from both the ipsilateral and contralateral NM axons (Figure 1C), and is the first brain area to display sensitivity to ITD (Carr and Konishi, 1990; Moiseff and Konishi, 1983). Recordings of synaptic responses in NL to stimulation of the NM afferents demonstrate strong short-term depression (Cook et al., 2003; Kuba et al., 2002). The degree of depression is similar to that in NM, but because the inputs are smaller, decrements in EPSC amplitudes can reduce the drive on the postsynaptic neuron to the point where its firing is decreased. Like in NM, the depression is

simple, that is, the EPSC amplitudes decrease monotonically over the course of the train (see traces in Figure 3), and the amplitude of the final few EPSCs in the train also decrease monotonically with increasing stimulus rate (solid line in the cartoon in Figure 3). The inverse relationship of the EPSC amplitude with the input stimulus rate at 'steady state' means that short-term depression enacts a type of gain control, in which increases in the presynaptic fiber rate fail to drive the postsynaptic neuron further, due to proportional decrease in synaptic amplitudes (Abbott et al., 1997; Tsodyks and Markram, 1997).

What effect would a gain control mechanism have at the NM to NL synapse? Recent work on short-term depression and coincidence detection for ITD computation has provided an elegant hypothesis. Short-term depression may improve ITD tuning by scaling the incoming synaptic amplitudes to keep the inputs within a range suitable for coincidence detection (Cook et al., 2003; Kuba et al., 2002). If one ear were driven more strongly than the other, due to interaural intensity differences, synaptic depression would act to reduce the more strongly activated inputs relatively more, equalizing the input amplitudes, and favoring binaural coincidence detection. Thus, synaptic depression acts as an adaptive mechanism which maintains interaural timing information, removes interaural intensity information, and may account for the insensitivity of NL ITD tuning to sound intensity (Pena et al., 1996). An important next step would be to show that synaptic depression occurs in vivo and in mature animals. Despite the appeal of the depression hypothesis for enhanced coincidence detection in the face of unbalanced inputs, there are several alternative hypotheses, such as the inhibitory feedback from the superior olive (see below; Burger et al., 2005; Carr and Soares, 2002; Simon et al., 1999).

In contrast, auditory nerve fiber synapses in NA display a radically different short-term plasticity profile than the auditory nerve endbulbs in NM, or the bouton synapses in NL (MacLeod & Carr 2005). Synaptic responses recorded in NA neurons to stimulation of the auditory nerve inputs demonstrate a variety of complex short-term plasticity profiles. Typical responses included mixed facilitation and depression, which result in the maintenance of EPSC amplitude across the train and across a range of high frequencies (one example is shown in Figure 3). Some responses include a transient net facilitation, and sustained facilitation occurred in a minority of neurons. Most importantly, most NA neurons show a non-monotonic or flat function of the amplitude of the last EPSCs with stimulus rate (dashed line in the cartoon in Figure 3). This is critical, because it implies that increases in the firing rate of the auditory nerve inputs will cause increased drive to the postsynaptic NA neuron, and therefore a linear transmission of rate information contained in the auditory nerve fibers. Auditory nerve rate encodes information about sound intensity (Salvi et al., 1992; Saunders et al., 2002). Therefore, in a majority of synapses onto NA neurons, the short-term plasticity expressed appears suitable for its putative function of encoding intensity. This intensity information is important for binaural intensity comparisons (ILD) and for analysis of spectral cues, which may involve comparison of the intensity across frequency channels (Takahashi et al., 2003).

Interestingly, in a minority of NA neurons simple depression was observed, similar to synapses in NM and NL, suggesting that in some cases some rate (and therefore intensity) information is lost. Thus some NA neurons may mediate timing information, regardless of their location in the 'intensity' nucleus. It should be noted, however, that depressing synapses require several stimuli to reach their 'steady state' amplitudes, resulting in a transient change in synaptic drive before the gain control normalizes the response. This occurs when there are abrupt changes in input rate, suggesting these synapses can signal changes in intensity (which would be true in NL as well). As a result, depressing synapses are rather good at signaling changes in rate (Abbott et al., 1997), which would be useful for indicating changes in amplitude or onsets of sound, highly salient cues for sound recognition

tasks. It is intriguing to consider that different synapses in NA may transmit different aspects of the input stimulus, another form of parallel processing.

These data suggest that the short-term plasticity expressed at a synapse is correlated more strongly with functional role than with the size of the synapse. The effect on coincidence detection described above depends critically on NL synapses showing increased depression with input rate (with a nearly inversely proportional relationship), not the overall degree of depression. Thus it is the relationship with input rate that is the important difference between the NL and NA synaptic plasticity, not the overall degree of depression at any given input rate. Taken together, these data suggest that the short-term plasticity expressed at the synapses in NL and NA may be more of a feature than a bug, directly related to the computational tasks.

Functional roles for NA in coding sound intensity: a multi-faceted nucleus?

The idea that NA may play multiple roles in sound processing is reinforced by the fact that NA projects to multiple nuclei in the ascending pathway. These projection targets include the superior olivary nucleus (SON), two lemniscal nuclei, and a direct projection to the inferior colliculus (Figure 1A). Three of these targets are associated with different roles; the superior olive mediates descending control of gain (Monsivais et al., 2000; Pena et al., 1996; Takahashi and Konishi, 2002; for review see Hyson, 2005), the lemniscal nuclei encode sensitivity to ILDs (Adolphs, 1993; Manley et al., 1988; Mogdans and Knudsen, 1994; Takahashi et al., 1995), and the inferior colliculus mediates the emergence of responses to biologically relevant stimuli (for review see Konishi, 2003).

NA as the origination of the ILD pathway

The most established role for NA is as the origination of the ILD pathway. Takahashi et al. (1984) showed that injection of lidocaine into NA abolished sensitivity to changes in ILD in space specific neurons in the inferior colliculus. Thus, although most neurons in NA and NM show similar monotonic rate level curves, it appears likely that level information is largely processed in NA and its target nuclei. Processing of ILDs has been extensively examined in the barn owl, where the vertical asymmetry in ear directionality makes ILD a cue for sound source elevation (Keller et al., 1998; Knudsen and Konishi, 1980).

The current hypothesis proposes that level is encoded by neurons in NA (Köppl and Carr, 2003) and binaural level difference sensitivity then emerges in one of the lemniscal targets of NA, the nucleus ventralis lemnisci lateralis, pars posterior, or VLVp (also referred to as the dorsal nucleus of the lateral lemniscus, posterior portion, or LLDp; Figure 1B). VLVp neurons are excited by stimulation of the contralateral ear and inhibited by stimulation of the ipsilateral ear (Manley et al., 1988). The contralateral excitation emerges from the ascending projection of NA, and the ipsilateral inhibition from the opposite VLVp (Takahashi and Keller, 1992). VLVp neurons exhibit discharge rates that are sigmoidal functions of ILD (Adolphs, 1993; Manley et al., 1988; Takahashi et al., 1995). The neural responses in VLVp are similar to those in the mammalian lateral superior olive (LSO), except that in the LSO the excitatory inputs are ipsilateral and inhibitory inputs are contralateral (Takahashi and Keller, 1992; Tsuchitani, 1977). VLVp projects bilaterally to the inferior colliculus, specifically to the lateral shell of the central nucleus of the inferior colliculus, endowing the neurons there with sensitivity to ILD (Figure 1B)(Adolphs, 1993).

Which NA neurons encode the level information used to compute ILD? Tracing studies showed that all four morphological types of NA neurons project to both the VLVp and IC (Soares et al. 2001). At this time its unknown whether the different cell types in NA form parallel pathways, whether there are differences in their projection fields, and what role is

played by the direct projection from NA to IC. Further studies relating the in vivo response classes to in vitro and morphological types through intracellular recordings will be needed to clarify this question. Physiological responses in NA show that primary like, onset and chopper responses did not differ in dynamic range from the auditory nerve (Köppl and Carr, 2003), and thus any or all of these response types may encode changes in intensity. How intensity is represented remains an important issue in auditory neurobiology.

NA encodes intensity for gain control of the timing nuclei

NA projects to the SON, a heterogeneous nucleus populated by stellate-type neurons. Its heaviest projection is to the ipsilateral SON (Figure 1D), but NA also projects to the contralateral SON (not shown) (Conlee and Parks, 1986; Takahashi and Konishi, 1988). The SON also receives a lesser projection from the ipsilateral NL, forming a restricted terminal field that overlaps with NA terminations. Auditory responses in SON are biased toward ipsilateral excitation: neurons are either excited by ipsilateral stimulation, or by both contralateral and ipsilateral stimulation (Moiseff and Konishi, 1983). One class of SON neurons is GABAergic, and appears to be the major source of inhibitory feedback to NL, NA and also NM. GABAergic IPSPs can be elicited in NM and NL neurons in vitro (Yang et al., 1999). A separate population of SON neurons project contralaterally to the opposite SON (Burger et al., 2005a), although an inhibitory influence was not observed in physiological recording in vivo (Moiseff and Konishi, 1983).

Thus a model emerges that proposes that high sound intensity increases activity in NA, which excites the ipsilateral SON, which provides inhibitory feedback to the ipsilateral brainstem nuclei, especially NL, and a cross-disinhibition of the contralateral brainstem nuclei due to inhibition of the contralateral SON. This inhibitory feedback onto NL has been hypothesized to isolate the ITD response from differences in interaural level (Burger et al., 2005a; Fujita and Konishi, 1991; Pena et al., 1996; Viete et al., 1997). The projection to NM may have similar inhibitory effects (Monsivais et al., 2000), but the presence of GABA_B receptors suggests that SON inputs could modulate synaptic transmission at the endbulb synapses in addition to postsynaptic effects. However, the putatively inhibitory postsynaptic effects are complicated by the observation that ionotropic GABAergic currents are depolarizing, due to an altered chloride reversal potential in NM and NL neurons (Hyson et al., 1995; Lu and Trussell, 2001; Monsivais et al., 2000). Stimulating SON inputs evokes depolarizing responses in NM neurons that could be blocked by bicuculline (Monsivais et al., 2000). This inhibitory effect was attributable to a large reduction in input resistance caused by a combination of the opening of a GABAergic chloride conductance and the recruitment of a low-voltage activated potassium conductance. This large reduction of input resistance increased the amount of current necessary to drive NM neurons to threshold. Monsivais et al. (2000) proposed that GABAergic inhibition enhances phase-locking fidelity of NM neurons. In NA, the effects of a GABAergic feedback are unknown, but one hypothesis is that they are a potential source of the inhibitory component of the type IV auditory responses found in NA (the other being a relatively sparse population of local GABAergic neurons within NA).

Re-examination of the role of timing in NA

The standard model from the elegant experiments of Takahashi et al. says that NM/NL originates the 'timing' pathway for sound localization, and NA originates the 'intensity' pathway and therefore is not involved in 'timing'. This is clearly an oversimplification, because other temporal aspects of the auditory stimulus, such as onsets and envelopes, must also be encoded, perhaps by NA. Several lines of evidence suggest that neurons in NA encode temporal features of sound, although NA does not project to the ITD coding circuit in NL or the core division of the inferior colliculus. Temporal information may underlie

accurate encoding of onsets and pitch, and contribute to an ascending projection to dorsal thalamus and pallium. Evidence in favor of this hypothesis includes the presence in NA of fast glutamatergic receptors, single-spiking, NM-like physiology, primary-like poststimulus time histograms neurons that phase lock fairly well, and short-term synaptic depression. In the mammalian CN, bushy cells are not the sole purveyors of timing information: the octopus neurons have extremely fast membrane time constants, can frequency follow very high rates, and project to the lemniscal nucleus with endbulb like terminals. Globular bushy neurons receive endbulb-like input and provide phase locked output, but project to LSO, not the MSO. While these two cell types have no direct correspondence to any NA neurons, temporal information may be encoded by multiple neuronal types and project to non-ITD areas.

Conclusions

The study of auditory coding in birds provides an excellent opportunity to combine behavioral, systems-level and cellular analyses of hearing. The established behavioral paradigms in birds, particularly sound localization in the barn owl, and birdsong recognition in zebra finches and other songbirds, provide a rich context and framework for understanding the physiological, biophysical and synaptic properties of the auditory brainstem neurons. An understanding of the cochlear nucleus angularis, along with the organization of its outputs, is critically important to forming a more comprehensive theory of sound processing. This will necessary expand and blur the simplistic dualistic construct of 'timing' and 'intensity' pathways, localization and non-localization tasks. Comparative studies between avian and mammalian cochlear nucleus will furthermore highlight which features are conserved and perhaps may be computationally necessary, and which are species- or clade-specific details demonstrating either disparate environmental requirements or, alternatively, different solutions to similar problems.

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Abbreviations

NA	nucleus angularis
NM	nucleus magnocellularis
NL	nucleus laminaris
SON	superior olivary nucleus
VLVp	nucleus ventralis lemnisci lateralis, pars posterior
LLV	nucleus lemnisci lateralis, pars ventralis
IC	inferior colliculus (also referred to as MLD)
MLD	nucleus mesencephalicus lateralis, pars ventralis; (also referred to as IC)
ILD	interaural level difference
ITD	interaural time difference
CN	cochlear nucleus
VCN	ventral cochlear nucleus

AVCN	anterior ventral cochlear nucleus
DCN	dorsal cochlear nucleus
MNTB	medial nucleus of the trapezoid body
LSO	lateral superior olive
MSO	medial superior olive
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
NMDA	N-methyl-D-aspartate
GABA	gamma-aminobutyric acid
CaBP	calcium binding protein
EPSC	excitatory postsynaptic current
EPSP	excitatory postsynaptic potential
IPSP	inhibitory postsynaptic potential

Literature cited

- Abbott LF, Varela JA, Sen K, Nelson SB. Synaptic depression and cortical gain control. *Science*. 1997; 275:220–224. [PubMed: 8985017]
- Abbott LF, Regehr WG. Synaptic computation. *Nature*. 2004; 431:796–803. [PubMed: 15483601]
- Adolphs R. Bilateral inhibition generates neuronal response tuned to interaural level differences in the auditory brainstem of the barn owl. *J Neurosci*. 1993; 13:3647–3668. [PubMed: 7690063]
- Barnes-Davies M, Forsythe ID. Pre- and postsynaptic glutamate receptors at a giant excitatory synapse in rat auditory brainstem slices. *J Physiol*. 1995; 488 (Pt 2):387–406. [PubMed: 8568678]
- Bellingham MC, Walmsley B. A novel presynaptic inhibitory mechanism underlies paired pulse depression at a fast central synapse. *Neuron*. 1999; 23:159–70. [PubMed: 10402202]
- Braun K. Calcium-binding proteins in avian and mammalian central nervous system: Localization, development and possible functions. *Prog Histochem Cytochem*. 1990; 21:1–64. [PubMed: 2198609]
- Bregman, A. Auditory scene analysis. MIT Press; Cambridge: 1990.
- Brenowitz S, David J, Trussell L. Enhancement of synaptic efficacy by presynaptic GABA(b) receptors. *Neuron*. 1998; 20:135–41. [PubMed: 9459449]
- Brenowitz S, Trussell LO. Maturation of synaptic transmission at end-bulb synapses of the cochlear nucleus. *J Neurosci*. 2001a; 21:9487–98. [PubMed: 11717383]
- Brenowitz S, Trussell LO. Minimizing synaptic depression by control of release probability. *J Neurosci*. 2001b; 21:1857–67. [PubMed: 11245670]
- Burger RM, Cramer KS, Pfeiffer JD, Rubel EW. Avian superior olivary nucleus provides divergent inhibitory input to parallel auditory pathways. *J Comp Neurol*. 2005a; 481:6–18. [PubMed: 15558730]
- Burger RM, Pfeiffer JD, Westrum LE, Bernard A, Rubel EW. Expression of GABA(b) receptor in the avian auditory brainstem: Ontogeny, afferent deprivation, and ultrastructure. *J Comp Neurol*. 2005b; 489:11–22. [PubMed: 15977167]
- Carr CE, Konishi M. A circuit for detection of interaural time differences in the brain stem of the barn owl. *J Neurosci*. 1990; 10:3227–46. [PubMed: 2213141]
- Carr CE, Boudreau RE. Central projections of auditory nerve fibers in the barn owl. *J Comp Neurol*. 1991; 314:306–18. [PubMed: 1723997]
- Carr CE. Processing of temporal information in the brain. *Annu Rev Neurosci*. 1993; 16:223–43. [PubMed: 8460892]

- Carr CE, Soares D, Parameshwaran S, Perney T. Evolution and development of time coding systems. *Curr Opin Neurobiol.* 2001; 11:727–33. [PubMed: 11741025]
- Carr CE, Soares D. Evolutionary convergence and shared computational principles in the auditory system. *Brain Behav Evol.* 2002; 59:294–311. [PubMed: 12207085]
- Celio, M.; Pauls, T.; Schwaller, B. Guidebook to the calcium-binding proteins. Oxford University Press, Inc; Oxford: 1996.
- Conlee JW, Parks TN. Origin of ascending auditory projections to the nucleus mesencephalicus lateralis pars dorsalis in the chicken. *Brain Res.* 1986; 367:96–113. [PubMed: 3697720]
- Cook DL, Schwindt PC, Grande LA, Spain WJ. Synaptic depression in the localization of sound. *Nature.* 2003; 421:66–70. [PubMed: 12511955]
- Dingledine R, Borges K, Bowie D, Traynelis SF. The glutamate receptor ion channels. *Pharmacol Rev.* 1999; 51:7–61. [PubMed: 10049997]
- Ferragamo MJ, Golding NL, Oertel D. Synaptic inputs to stellate cells in the ventral cochlear nucleus. *J Neurophysiol.* 1998; 79:51–63. [PubMed: 9425176]
- Friauf E. Distribution of calcium-binding protein calbindin-d28k in the auditory system of adult and developing rats. *J Comp Neurol.* 1994; 349:193–211. [PubMed: 7860778]
- Fujita I, Konishi M. The role of GABAergic inhibition in processing of interaural time difference in the owl's auditory system. *J Neurosci.* 1991; 11:722–39. [PubMed: 2002359]
- Fukui I, Ohmori H. Developmental changes in membrane excitability and morphology of neurons in the nucleus angularis of the chicken. *J Physiol.* 2003; 548:219–32. [PubMed: 12576492]
- Gardner SM, Trussell LO, Oertel D. Time course and permeation of synaptic AMPA receptors in cochlear nuclear neurons correlate with input. *J Neurosci.* 1999; 19:8721–9. [PubMed: 10516291]
- Gardner SM, Trussell LO, Oertel D. Correlation of AMPA receptor subunit composition with synaptic input in the mammalian cochlear nuclei. *J Neurosci.* 2001; 21:7428–37. [PubMed: 11549753]
- Geiger JR, Melcher T, Koh DS, Sakmann B, Seeburg PH, Jonas P, Monyer H. Relative abundance of subunit mRNAs determines gating and Ca²⁺ permeability of AMPA receptors in principal neurons and interneurons in rat CNS. *Neuron.* 1995; 15:193–204. [PubMed: 7619522]
- Grothe, B.; Carr, CE.; Casseday, J.; Fritzsche, B.; Köppl, C. The evolution of central pathways and their neural processing patterns. In: Manley, G.; Popper, A.; Fay, R., editors. *Evolution of the vertebrate auditory system.* Springer; New York: 2005. p. 289-359.
- Hackett JT, Jackson H, Rubel EW. Synaptic excitation of the second and third order auditory neurons in the avian brain stem. *Neuroscience.* 1982; 7:1455–69. [PubMed: 6289171]
- Hyson RL, Reyes AD, Rubel EW. A depolarizing inhibitory response to GABA in brainstem auditory neurons of the chick. *Brain Res.* 1995; 677:117–26. [PubMed: 7606455]
- Hyson RL. The analysis of interaural time differences in the chick brain stem. *Physiol Behav.* 2005; 86:297–305. [PubMed: 16202434]
- Jhaveri S, Morest DK. Neuronal architecture in nucleus magnocellularis of the chicken auditory system with observations on nucleus laminaris: A light and electron microscope study. *Neuroscience.* 1982a; 7:809–36. [PubMed: 7099420]
- Jhaveri S, Morest DK. Sequential alterations of neuronal architecture in nucleus magnocellularis of the developing chicken: A Golgi study. *Neuroscience.* 1982b; 7:837–53. [PubMed: 7099421]
- Joshi I, Shokralla S, Titis P, Wang LY. The role of AMPA receptor gating in the development of high-fidelity neurotransmission at the calyx of Held synapse. *J Neurosci.* 2004; 24:183–96. [PubMed: 14715951]
- Kawaguchi Y, Kondo S. Parvalbumin, somatostatin and cholecystokinin as chemical markers for specific GABAergic interneuron types in the rat frontal cortex. *J Neurocytol.* 2002; 31:277–87. [PubMed: 12815247]
- Keller CH, Hartung K, Takahashi TT. Head-related transfer functions of the barn owl: Measurement and neural responses. *Hear Res.* 1998; 118:13–34. [PubMed: 9606058]
- Knudsen EI, Konishi M. Monaural occlusion shifts receptive-field locations of auditory midbrain units in the owl. *J Neurophysiol.* 1980; 44:687–95. [PubMed: 7431048]

- Konishi, M.; Takahashi, T.; Wagner, H.; Sullivan, WE.; Carr, CE. Neurophysiological and anatomical substrates of sound localization in the owl. In: Edelman, GM.; Gan, WE.; Cowan, WM., editors. Auditory function: Neurobiological bases of hearing. Wiley; New York: 1988. p. 721-745.
- Konishi M. Coding of auditory space. *Annu Rev Neurosci.* 2003; 26:31–55. [PubMed: 14527266]
- Köppl C. Tonotopic projections of the auditory nerve to the cochlear nucleus angularis in the barn owl. *J Assoc Res Otolaryngol.* 2001a; 2:41–53.
- Köppl C. The tonotopic organization of nucleus angularis. *J Assoc Res Otolaryngol.* 2001b; 2:41–58.
- Köppl C, Carr CE. Computational diversity in the cochlear nucleus angularis of the barn owl. *J Neurophysiol.* 2003; 89:2313–29. [PubMed: 12612008]
- Kuba H, Koyano K, Ohmori H. Synaptic depression improves coincidence detection in the nucleus laminaris in brainstem slices of the chick embryo. *Eur J Neurosci.* 2002; 15:984–990. [PubMed: 11918658]
- Kubke MF, Carr CE. Development of AMPA-selective glutamate receptors in the auditory brainstem of the barn owl. *Microsc Res Tech.* 1998; 41:176–86. [PubMed: 9605336]
- Kubke MF, Gauger B, Basu L, Wagner H, Carr CE. Development of calretinin immunoreactivity in the brainstem auditory nuclei of the barn owl (*Tyto alba*). *J Comp Neurol.* 1999; 415:189–203. [PubMed: 10545159]
- Lachica EA, Kato BM, Lippe WR, Rubel EW. Glutamatergic and GABAergic agonists increase $[Ca^{2+}]_i$ in avian cochlear nucleus neurons. *J Neurobiol.* 1998; 37:321–37. [PubMed: 9805276]
- Levin MD, Kubke MF, Schneider M, Wenthold R, Carr CE. Localization of AMPA-selective glutamate receptors in the auditory brainstem of the barn owl. *J Comp Neurol.* 1997; 378:239–53. [PubMed: 9120063]
- Lohmann C, Friauf E. Distribution of the calcium-binding proteins parvalbumin and calretinin in the auditory brainstem of adult and developing rats. *J Comp Neurol.* 1996; 367:90–109. [PubMed: 8867285]
- Lu T, Trussell LO. Mixed excitatory and inhibitory GABA-mediated transmission in chick cochlear nucleus. *J Physiol.* 2001; 535:125–31. [PubMed: 11507163]
- MacLeod KM, Carr CE. Synaptic physiology in the cochlear nucleus angularis of the chick. *J Neurophysiol.* 2005; 93:2520–9. [PubMed: 15615833]
- MacLeod KM, Soares D, Carr CE. Interaural timing difference circuits in the auditory brainstem of the emu, *Dromaius novaehollandiae*. *The Journal of Comparative Neurology.* 2006; 495:185–201. [PubMed: 16435285]
- Manis PB, Marx SO. Outward currents in isolated ventral cochlear nucleus neurons. *J Neurosci.* 1991; 11:2865–80. [PubMed: 1880553]
- Manley GA, Köppl C, Konishi M. A neural map of interaural intensity differences in the brain stem of the barn owl. *J Neurosci.* 1988; 8:2665–76. [PubMed: 3411346]
- Markram H, Gupta A, Uziel A, Wang Y, Tsodyks M. Information processing with frequency-dependent synaptic connections. *Neurobiol Learn Mem.* 1998; 70:101–12. [PubMed: 9753590]
- May BJ. Role of the dorsal cochlear nucleus in the sound localization behavior of cats. *Hear Res.* 2000; 148:74–87. [PubMed: 10978826]
- Mogdans J, Knudsen EI. Representation of interaural level difference in the VLVp, the first site of binaural comparison in the barn owl's auditory system. *Hear Res.* 1994; 74:148–164. [PubMed: 8040085]
- Moiseff A, Konishi M. Binaural characteristics of units in the owl's brainstem auditory pathway: Precursors of restricted spatial receptive fields. *J Neurosci.* 1983; 3:2553–62. [PubMed: 6655499]
- Monsivais P, Yang L, Rubel EW. GABAergic inhibition in nucleus magnocellularis: Implications for phase locking in the avian auditory brainstem. *J Neurosci.* 2000; 20:2954–63. [PubMed: 10751448]
- Nemeth EF, Jackson H, Parks TN. Pharmacologic evidence for synaptic transmission mediated by non-n-methyl-d-aspartate receptors in the avian cochlear nucleus. *Neurosci Lett.* 1983; 40:39–44. [PubMed: 6138740]
- O'Donovan MJ, Rinzel J. Synaptic depression: A dynamic regulator of synaptic communication with varied functional roles. *Trends Neurosci.* 1997; 20:431–433. [PubMed: 9347607]

- Oertel D. Synaptic responses and electrical properties of cells in brain slices of the mouse anteroventral cochlear nucleus. *J Neurosci.* 1983; 3:2043–53. [PubMed: 6619923]
- Oertel D, Wu SH, Garb MW, Dizack C. Morphology and physiology of cells in slice preparations of the posteroventral cochlear nucleus of mice. *J Comp Neurol.* 1990; 295:136–54. [PubMed: 2341631]
- Oertel D. The role of timing in the brain stem auditory nuclei of vertebrates. *Annu Rev Physiol.* 1999; 61:497–519. [PubMed: 10099699]
- Oertel D, Bal R, Gardner SM, Smith PH, Joris PX. Detection of synchrony in the activity of auditory nerve fibers by octopus cells of the mammalian cochlear nucleus. *Proc Natl Acad Sci U S A.* 2000; 97:11773–9. [PubMed: 11050208]
- Oleskevich S, Clements J, Walmsley B. Release probability modulates short-term plasticity at a rat giant terminal. *J Physiol.* 2000; 524(Pt 2):513–23. [PubMed: 10766930]
- Otis TS, Raman IM, Trussell LO. AMPA receptors with high Ca²⁺ permeability mediate synaptic transmission in the avian auditory pathway. *J Physiol.* 1995; 482 (Pt 2):309–15. [PubMed: 7714824]
- Parks TN. Morphology of axosomatic endings in an avian cochlear nucleus: Nucleus magnocellularis of the chicken. *J Comp Neurol.* 1981; 203:425–40. [PubMed: 7320234]
- Parks TN, Code RA, Taylor DA, Solum DA, Strauss KI, Jacobowitz DM, Winsky L. Calretinin expression in the chick brainstem auditory nuclei develops and is maintained independently of cochlear nerve input. *J Comp Neurol.* 1997; 383:112–21. [PubMed: 9184990]
- Parks TN. The AMPA receptors of auditory neurons. *Hear Res.* 2000; 147:77–91. [PubMed: 10962175]
- Pena JL, Viete S, Albeck Y, Konishi M. Tolerance to sound intensity of binaural coincidence detection in the nucleus laminaris of the owl. *J Neurosci.* 1996; 16:7046–54. [PubMed: 8824340]
- Pettigrew JD, Konishi M. Neurons selective for orientation and binocular disparity in the visual Wulst of the barn owl (*Tyto alba*). *Science.* 1976; 193:675–8. [PubMed: 948741]
- Raman IM, Zhang S, Trussell LO. Pathway-specific variants of AMPA receptors and their contribution to neuronal signaling. *J Neurosci.* 1994; 14:4998–5010. [PubMed: 7913958]
- Rhode WS, Oertel D, Smith PH. Physiological response properties of cells labeled intracellularly with horseradish peroxidase in cat ventral cochlear nucleus. *J Comp Neurol.* 1983; 213:448–63. [PubMed: 6300200]
- Rhode, WS.; Greenberg, S. Physiology of the cochlear nuclei. In: Popper, AN.; Fay, R., editors. *The mammalian auditory pathway: Neurophysiology.* Springer; New York: 1992. p. 53–120.
- Rogers J. Calretinin: A gene for a novel calcium-binding protein expressed principally in neurons [published erratum appears in *J Cell Biol* 1990 may;110(5):1845]. *J Cell Biol.* 1987; 105:1343–1353. [PubMed: 3654755]
- Rouiller, E. Functional organization of auditory pathways. In: Ehret, G.; Roman, R., editors. *The central auditory system.* Oxford; Oxford: 1997.
- Rouiller EM, Ryugo DK. Intracellular marking of physiologically characterized cells in the ventral cochlear nucleus of the cat. *J Comp Neurol.* 1984; 225:167–86. [PubMed: 6327782]
- Ryugo DK, Parks TN. Primary innervation of the avian and mammalian cochlear nucleus. *Brain Res Bull.* 2003; 60:435–56. [PubMed: 12787866]
- Sachs MB, Sinnott JM. Responses to tones of single cells in nucleus magnocellularis and nucleus angularis of the redwing blackbird (*Agelaius phoeniceus*). *J Comp Physiol A.* 1978; 126:347–361.
- Salvi RJ, Saunders SS, Powers NL, Boettcher FA. Discharge patterns of cochlear ganglion neurons in the chicken. *J Comp Physiol [A].* 1992; 170:227–41.
- Saunders J, Ventetuoilo C, Plontke S, Weiss B. Coding of sound intensity in the chick cochlear nerve. *J Neurophysiol.* 2002; 88:2887–2898. [PubMed: 12466415]
- Schneggenburger R, Sakaba T, Neher E. Vesicle pools and short-term synaptic depression: Lessons from a large synapse. *Trends Neurosci.* 2002; 25:206–212. [PubMed: 11998689]
- Simon JZ, Carr CE, Shamma SA. A dendritic model of coincidence detection in the avian brainstem. *Neurocomputing.* 1999; 26–27:263–269.

- Soares D, Carr CE. The cytoarchitecture of the nucleus angularis of the barn owl (*Tyto alba*). *J Comp Neurol*. 2001; 429:192–205. [PubMed: 11116214]
- Soares D, Chitwood RA, Hyson RL, Carr CE. Intrinsic neuronal properties of the chick nucleus angularis. *J Neurophysiol*. 2002; 88:152–62. [PubMed: 12091541]
- Sugden SG, Zirpel L, Dietrich CJ, Parks TN. Development of the specialized AMPA receptors of auditory neurons. *J Neurobiol*. 2002; 52:189–202. [PubMed: 12210103]
- Sullivan WE, Konishi M. Segregation of stimulus phase and intensity coding in the cochlear nucleus of the barn owl. *J Neurosci*. 1984; 4:1787–99. [PubMed: 6737041]
- Sullivan WE. Classification of response patterns in cochlear nucleus in the barn owl: Correlation with functional response properties. *J Neurophysiol*. 1985; 53:201–216. [PubMed: 3973658]
- Takahashi T, Moiseff A, Konishi M. Time and intensity cues are processed independently in the auditory system of the owl. *J Neurosci*. 1984; 4:1781–6. [PubMed: 6737040]
- Takahashi TT, Carr CE, Brecha N, Konishi M. Calcium binding protein-like immunoreactivity labels the terminal field of nucleus laminaris of the barn owl. *J Neurosci*. 1987; 7:1843–56. [PubMed: 2439666]
- Takahashi TT, Konishi M. Projections of nucleus angularis and nucleus laminaris to the lateral lemniscal nuclear complex of the barn owl. *J Comp Neurol*. 1988; 274:212–38. [PubMed: 2463287]
- Takahashi TT, Keller CH. Commissural connections mediate inhibition for the computation of interaural level difference in the barn owl. *J Comp Physiol [A]*. 1992; 170:161–9.
- Takahashi TT, Bala AD, Spitzer MW, Euston DR, Spezio ML, Keller CH. The synthesis and use of the owl's auditory space map. *Biol Cybern*. 2003; 89:378–87. [PubMed: 14669018]
- Takahashi Y, Konishi M. Manipulation of inhibition in the owl's nucleus laminaris and its effects on optic tectum neurons. *Neuroscience*. 2002; 111:373–8. [PubMed: 11983322]
- Tang YZ, Carr CE. Development of NMDA R1 expression in chicken auditory brainstem. *Hear Res*. 2004; 191:79–89. [PubMed: 15109707]
- Taschenberger H, von Gersdorff H. Fine-tuning an auditory synapse for speed and fidelity: Developmental changes in presynaptic waveform, EPSC kinetics, and synaptic plasticity. *J Neurosci*. 2000; 20:9162–73. [PubMed: 11124994]
- Taschenberger H, Leao RM, Rowland KC, Spirou GA, von Gersdorff H. Optimizing synaptic architecture and efficiency for high-frequency transmission. *Neuron*. 2002; 36:1127–1143. [PubMed: 12495627]
- Trussell LO, Zhang S, Raman IM. Desensitization of AMPA receptors upon multiquantal neurotransmitter release. *Neuron*. 1993; 10:1185–96. [PubMed: 7686382]
- Trussell LO. Synaptic mechanisms for coding timing in auditory neurons. *Annu Rev Physiol*. 1999; 61:477–96. [PubMed: 10099698]
- Trussell LO. Modulation of transmitter release at giant synapses of the auditory system. *Curr Opin Neurobiol*. 2002; 12:400–4. [PubMed: 12139987]
- Tsodyks MV, Markram H. The neural code between neocortical pyramidal neurons depends on neurotransmitter release probability. *Proc Natl Acad Sci U S A*. 1997; 94:719–23. [PubMed: 9012851]
- Tsuchitani C. Functional organization of lateral cell groups of cat superior olivary complex. *J Neurophysiol*. 1977; 40:296–318. [PubMed: 845625]
- Viete S, Pena JL, Konishi M. Effects of interaural intensity difference on the processing of interaural time difference in the owl's nucleus laminaris. *J Neurosci*. 1997; 17:1815–24. [PubMed: 9030640]
- von Gersdorff H, Borst JG. Short-term plasticity at the calyx of held. *Nat Rev Neurosci*. 2002; 3:53–64. [PubMed: 11823805]
- Warchol ME, Dallos P. Neural coding in the chick cochlear nucleus. *J Comp Physiol [A]*. 1990; 166:721–34.
- Wong AY, Graham BP, Billups B, Forsythe ID. Distinguishing between presynaptic and postsynaptic mechanisms of short-term depression during action potential trains. *J Neurosci*. 2003; 23:4868–77. [PubMed: 12832509]

- Wu SH, Oertel D. Intracellular injection with horseradish peroxidase of physiologically characterized stellate and bushy cells in slices of mouse anteroventral cochlear nucleus. *J Neurosci.* 1984; 4:1577–88. [PubMed: 6726347]
- Yang L, Monsivais P, Rubel EW. 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.* 1999; 19:2313–25. [PubMed: 10066281]
- Young, ED. Cochlear nucleus. In: Shepherd, GM., editor. *The synaptic organization of the brain.* Oxford University Press; New York: 1998. p. 121-158.
- Zhang S, Trussell LO. Voltage clamp analysis of excitatory synaptic transmission in the avian nucleus magnocellularis. *J Physiol.* 1994a; 480:123–136. [PubMed: 7853216]
- Zhang S, Trussell LO. A characterization of excitatory postsynaptic potentials in the avian nucleus magnocellularis. *J Neurophysiol.* 1994b; 72:705–18. [PubMed: 7983529]
- Zhou N, Parks TN. Developmental changes in the effects of drugs acting at NMDA or non- NMDA receptors on synaptic transmission in the chick cochlear nucleus (nuc. Magnocellularis). *Brain Res Dev Brain Res.* 1992; 67:145–52.
- Zhou N, Taylor DA, Parks TN. Cobalt-permeable non-NMDA receptors in developing chick brainstem auditory nuclei. *Neuroreport.* 1995; 6:2273–76. [PubMed: 8747135]

Figure 1. Avian auditory brainstem pathways

A) The cochlear nuclei in birds and the ascending auditory pathways via nucleus angularis. NA and NM receive input from the auditory nerve. NA projects to SON, VLVp, LLV and IC (specifically, IC, central nucleus, lateral shell). VLVp in turn projects to IC, which sends ascending information via the thalamus to the forebrain. The ascending inputs to SON are bilateral, but are heavier to the ipsilateral SON; the ascending inputs to VLVp, LLV and IC are heavily contralateral.

B) The ILD circuit. NA projects contralaterally to the VLVp, which in turn projects to the contralateral VLVp with an inhibitory connection. Neurons in the VLVp are sensitive to ILD, with a sigmoidally shaped response curve that is most excited by contralateral stimuli. VLVp sends input to the IC, where there are neurons sensitive to ILD (contingent on ITD).

C) The ITD circuit. Nucleus laminaris receives input from both ipsilateral and contralateral NM, and projects to the IC (central nucleus, core region).

D) “Gain control” circuit of the SON. NA and NL project ipsilaterally to the SON, which makes ipsilateral inhibitory feedback projects to NM, NL and NA. SON also makes presumed inhibitory (GABAergic) connections onto the contralateral SON.

Arrows represent excitatory connections; circles represent GABAergic, presumed inhibitory connections (but see text about potential excitatory effects of GABA).

Figure 2. Auditory response properties of NA neurons in vivo

Poststimulus time histograms (columns 1 and 3) and rate intensity curves (columns 2 and 4) illustrate the different response types to pure-tone stimulation. Stimuli were 50 ms tones at CF, 20–35 dB above threshold. The dashed lines in the rate intensity curves indicate the spontaneous rate, where applicable. Adapted from Köppl and Carr (2003) and Grothe et al., (2005).

Figure 3. Short-term synaptic plasticity in the auditory brainstem

Traces: EPSC responses to trains of stimuli at avian brainstem nuclei (NM, NL, NA), and mammalian brainstem nuclei (AVCN bushy cells, MNTB). All three calyceal-type synapses (NM, bushy, MNTB) and the NL synapses show strong depression, while the NA neurons can show a mixture of facilitation and depression, sometimes including transient net facilitation.

Plot: cartoon of two types of input rate dependence of the plasticity. Stimulus train input rate is plotted on the x-axis, steady state relative amplitude of the EPSC on the y-axis. The four depressing synapses (NM, NL, AVCN bushy, and MNTB) display simple depression, in which the steady state amplitude declines progressively with input rate (solid line). Synapses in NA often show a complex relationship with frequency, in which the frequency dependence is shallow or non-monotonic (dashed line). Traces adapted from: NM, Brenowitz and Trussell, 2001; NL, Kuba et al. 2002; AVCN bushy cell, Oleskevich and Walmsley, 2002; MNTB, Wong and Forsythe, 2003; NA, MacLeod and Carr, unpublished data.