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Inhibition in the balance: binaurally coupled inhibitory feedback in sound localization circuitry

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Burger RM, Fukui I, Ohmori H, Rubel EW. Inhibition in the balance: binaurally coupled inhibitory feedback in sound localization circuitry. *J Neurophysiol* 106: 4–14, 2011. First published April 27, 2011; doi:10.1152/jn.00205.2011.—Interaural time differences (ITDs) are the primary cue animals, including humans, use to localize low-frequency sounds. In vertebrate auditory systems, dedicated ITD processing neural circuitry performs an exacting task, the discrimination of microsecond differences in stimulus arrival time at the two ears by coincidence-detecting neurons. These neurons modulate responses over their entire dynamic range to sounds differing in ITD by mere hundreds of microseconds. The well-understood function of this circuitry in birds has provided a fruitful system to investigate how inhibition contributes to neural computation at the synaptic, cellular, and systems level. Our recent studies in the chicken have made significant progress in bringing together many of these findings to provide a cohesive picture of inhibitory function.

coincidence detection; interaural time disparity; efferent; phase locking; γ-aminobutyric acid

BINAURAL HEARING provides important perceptual information for localizing acoustic information in space and for enhancing signal detection in noisy environments. Localization of low-frequency sounds depends on the accurate computation of interaural time differences (ITDs), an acoustic cue that varies systematically with sound source position in space (Rayleigh 1907; Blauert 1983; Konishi 2003; Grothe et al. 2010). Specialized neural circuitry in both mammals and birds is devoted to processing ITDs, and these circuits share many fundamental properties (see Fig. 1 for an ITD cue primer). These include anatomic and physiological specializations in excitatory pathways that ultimately lead to binaural "coincidence-detecting" neurons that compute ITDs in the analogous medial superior olive (MSO) of mammals and the nucleus laminaris (NL) of birds (Goldberg and Brown 1969; Yin and Chan 1990; Carr and Konishi 1990; Overholt et al. 1992). Such specializations include fast channel kinetics, secure synapses, and neuron morphologies that function to enhance the processing of temporal information (Oertel 1997; Reyes et al. 1994, 1996; Trussell 1997; Burger and Rubel 2008). In addition, both systems feature inhibitory feedback to monaural and binaural centers from neurons located in the superior olivary complex in mammals or the superior olivary nucleus (SON) in birds (Thompson and Schofield 2000; Grothe 2003; Yang et al. 1999; Burger and Rubel 2008). However, these systems differ in important ways, both with respect to the arrangement of excitatory inputs and their complement and function of inhibitory inputs (for comparative reviews, see Grothe 2003, 2010; Schnupp and Carr 2009).

Over the past decade, this circuitry in the avian brain stem has been intensively studied by several laboratories (Lu and Trussell 2000; Monsivais and Rubel 2001; Kuba et al. 2005; Köppl and Carr 2008). Understanding of the biological function of this circuitry combined with detailed knowledge of the anatomy of excitatory pathways in birds has provided a fruitful substrate for investigation of the anatomy and cellular physiology of inhibitory processes in the avian brain stem. These studies, in turn, have led to specific testable hypotheses regarding exactly how inhibition transforms and enhances auditory computation in vivo. For example, models from our laboratories and others have predicted how processing acoustic stimuli from one ear influences the processing of input to the other ear at multiple levels of the circuitry. Our recent work testing these models has revealed several modes of influence that inhibition exerts on binaural computation in the auditory brainstem of birds.

In this review, we highlight some of the significant progress in understanding this circuitry in the last 10–15 yr and focus on recent work shedding new light on the nature of inhibitory function in binaural processes. The major findings of our recent studies broadly demonstrate that this inhibitory input serves several simultaneous functions in the pathway leading to and including the NL. First, it is involved in conditioning the input for coincidence-detecting neurons from the nucleus magnocel-

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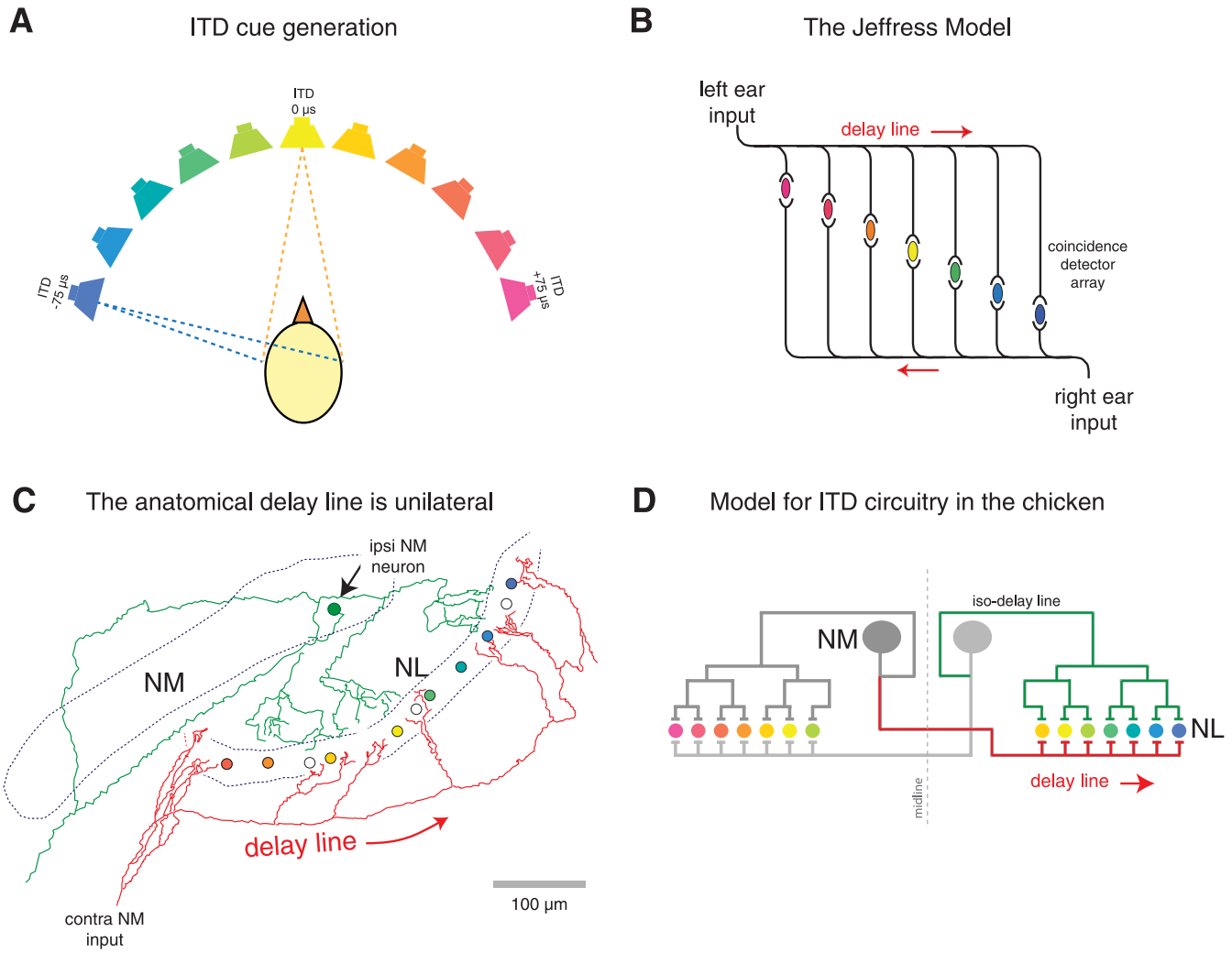

Fig. 1. The interaural time difference (ITD) cue: generation and computation. The difference in the arrival time of sound to the two ears varies systematically with the position of a sound source along the azimuth (*A*). A particular ITD value depends on *1*) the acoustic distance between the ears, *2*) the speed of sound, and *3*) the angle of incidence of the sound to the listener. For example, a sound source emanating from a position in space on the midline with respect to the listener (yellow speaker) arrives at both ears simultaneously, yielding an ITD of 0 μs. This value will systematically increase as the sound is shifted laterally such that a sound source at roughly 90° to the midline will lead in the ipsilateral ear by the maximal ITD, a value that is generally determined by the distance between the two ears. For humans, the maximal ITD is ~700 μs, whereas for small animals, such as the chicken, it is in the range of ~100 μs. *B*: model circuit for computing ITDs adapted from Jeffress (1948). The model includes an array of coincidence-detecting neurons, each of which fires optimally when action potentials arrive simultaneously from the two ears. These neurons are innervated by axons of systematically varying length or "delay lines." The opposing axon length gradients generate systematically increasing conduction delays that offset the binaural acoustic delays. This arrangement imparts differential spatial selectivity on the coincidence-detecting neurons. In *A–D*, neuron color corresponds to selectivity for speaker positions in *A*. In birds, anatomic delay lines arise in the nucleus magnocellularis (NM) projection to the nucleus laminaris (NL) and are not bilaterally symmetrical. Rather, the delay is a function of axon length gradient seen in the contralateral axon from the NM to NL. *C*: axonal arrangement observed in the chicken. The red axon arises from the contralateral NM, forming a delay line that imparts spatial selectivity on NL neurons (colored circles) (adapted from Young and Rubel 1983). The green axon originates ipsilaterally and projects with roughly equal segment lengths to the ipsilateral NL, giving rise to an "isodelay" input. Conduction speed is further "tuned" by the asymmetry in axon diameter and internodal distances among the inputs to NL neurons (not shown). *D*: schematic representation of the bilateral delay line arrangement in the chick (*A* and *D* were adapted from Seidl et al. 2010).

lularis (NM) by *1*) extending the dynamic range of NM responses to sound by preventing spike rate saturation, *2*) enhancing temporal coding by restricting the temporal window available for monaural temporal integration in the NM, and *3*) balancing the binaural excitatory drive such that interaural intensity differences (IIDs) are negated between the bilateral inputs to the NL. Second, it acts directly upon binaural coincidence-detecting neurons to maintain a full dynamic modulation range in responses to ITD stimuli, and it sharpens the coincidence window in NL neurons. In the sections below, we first describe the circuit's functional connectivity. We then describe recent findings that provide new insights into inhibitory function in sound localization.

Anatomy of the Avian Brain Stem ITD Processing Circuitry

The avian auditory brain stem circuitry devoted to processing ITDs is composed of just four major nuclei (Fig. 2). Primary afferents (nVIII) branch upon entering the brain stem to innervate two cochlear nuclei: the nucleus angularis (NA) and NM. The nVIIIth synapse in the NM, the end bulb of Held, is the first major specialization of the pathway devoted to processing ITDs (Konishi 2003; Burger and Rubel 2008). The

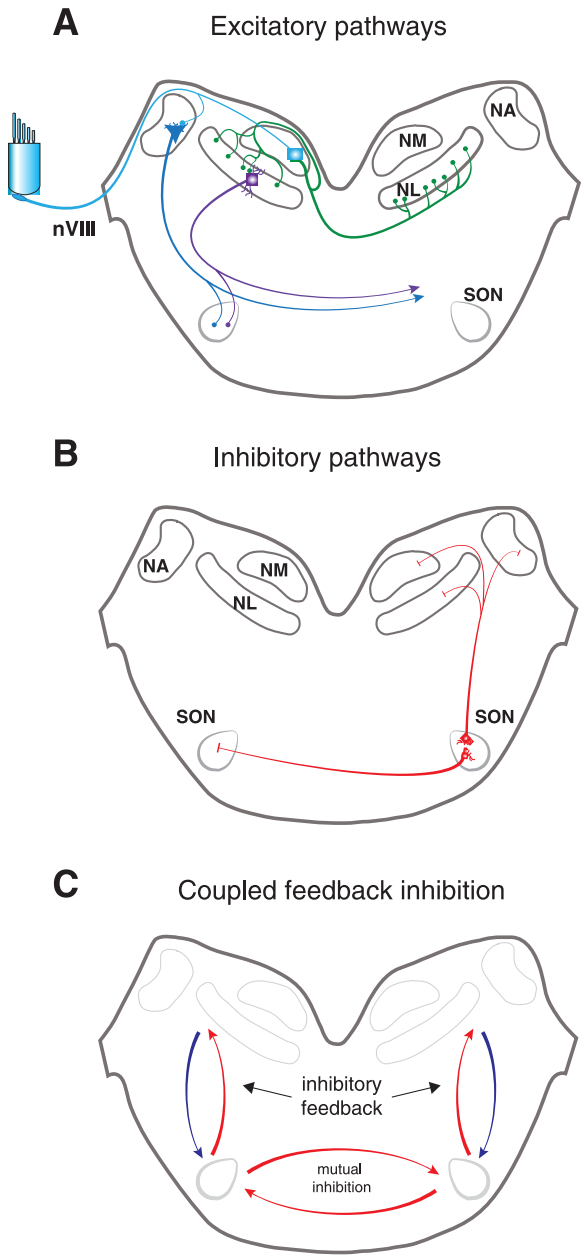

Fig. 2. Anatomic arrangement of excitatory and inhibitory pathways in the avian brain stem auditory system. *A*: sound is transduced by hair cells, which synapse on primary afferents (nVIII). nVIII axons branch upon entering the brain to innervate two cochlear nuclei: the nucleus angularis (NA) and NM. In the NM, nVIII axons form large end bulb synapses. Each NM neuron projects bilaterally and forms the sole excitatory input to coincidence-detecting neurons in the NL. NM axons form delay lines in the contralateral projection. Both the NA and NL project to higher-order targets, including the superior olivary nucleus (SON), a major source of GABAergic inhibition in the circuit. *B*: the SON has two output pathways within the brain stem, a descending (feedback) pathway to the ipsilateral NA, NM, and NL and an ascending pathway that innervates the contralateral SON, forming a mutually inhibitory interaction. *C*: simple schematic model of this circuitry composed of two inhibitory feedback loops, which are negatively coupled to each other via the SON-SON connectivity. This arrangement suggests that elevated activity in one unilateral feedback loop will tend to disinhibit targets on the opposing side, bilaterally balancing overall activity.

end bulb is an electrically secure synapse, ensuring reliable transmission of nVIII information. The NM is composed of a rather homogeneous population of large, round neurons arranged tonotopically with low frequencies represented caudolaterally and high frequencies represented rostromedially (Rubel and Parks 1975). NA neurons have a diverse array of cell types and response properties and appear to be involved in processing many features of acoustic stimuli (Soares and Carr 2002; Fukui and Ohmori 2003; Köppl and Carr 2003). Axons emanating from NM neurons bifurcate to innervate the nucleus laminaris (NL) bilaterally, as shown in Fig. 1*C* (Parks and Rubel 1975; Jhavari and Morest 1982; Young and Rubel 1983). In chickens, the ipsilateral branch ramifies to innervate a roughly medial-to-lateral ribbon of NL neurons running orthogonal to its tonotopic organization such that the length of each axon segment is approximately equal. In contrast, the contralateral projection, which is roughly twice the length of the ipsilateral branch (Seidl et al. 2010), innervates a medial-to-lateral ribbon of NL neurons with systematically short to long axon segments. Young and Rubel (1983) proposed that this systematic arrangement of axons gives rise to the "delay lines" that could underlie the coincidence detection mechanism of ITD computation (see Fig. 1*C*). Recent anatomic and modeling analysis of this arrangement found that, in addition to variations in the length of different axon segments, the action potential propagation through the delay lines is substantially tuned by differential myelin internodal lengths and axon diameters in the ipsilateral and contralateral branches (Carr and Konishi 1990, Seidl et al. 2010). Numerous physiological studies have confirmed that this arrangement (or a similar pattern of delay lines in owls) is the primary mechanism for ITD computation in birds (Sullivan and Konishi 1986; Carr and Konishi 1988, 1990; Overholt et al. 1992; Joseph and Hyson 1993; Köppl and Carr 2008).

Pathways originating in both the NA and NL project to higher-order auditory nuclei in the pons and midbrain. However, NA and NL axon collaterals also innervate a fourth brain stem nucleus, the ipsilateral SON. SON neurons are densely immunostained by antisera directed against the inhibitory neurotransmitter GABA or its synthesizing enzyme glutamic acid decarboxylase (Carr et al. 1989; Code et al. 1989; Lachica et al. 1994; von Bartheld et al. 1989), and we have recently shown that many SON neurons also appear to contain glycine (Coleman et al. 2011). The SON has two major output pathways, arising from separate populations of neurons (shown in Fig. 2*B*) and constituting the dominant source of inhibition in the circuit (Burger et al. 2005a). The first is a descending pathway containing axons that ramify to innervate the NA, NM, and NL ipsilaterally. The second pathway innervates the contralateral SON and higher-order targets (Conlee and Parks 1986; Monsivais et al. 2000; Burger et al. 2005a). Immunohistochemical evidence has suggested that GABA and glycine appear to be coreleased at all SON targets. However, physiological responses to the glycinergic component have only been shown in the NA and SON (Kuo et al. 2009; Coleman et al. 2011). The inhibitory nature of the contralateral projecting pathway is predicted based on the prominence of GABA/glycine immunoreactivity in the SON (Code et al. 1989; Lachica et al. 1994; Coleman et al. 2011), and, while this has not been directly demonstrated, our recent studies have suggested that this is indeed the case for the SON-SON projection (Nishino et al. 2008; Fukui et al. 2010).

When viewed as an integrated system, as shown schematically in Fig. 1*C*, the auditory brain stem is composed of two inhibitory feedback loops, one on each side of the brain stem.

The output of the NA and NL drives activity in the SON, which, in turn, provides inhibitory feedback to all three lower nuclei: the NA, NM, and NL. Furthermore, the crossed reciprocal pathway between the SONs negatively couples these feedback loops to one another. Thus, the inhibitory input from the SON is well situated to influence processing in both second-order monaural neurons (the NM and NA) and in third-order binaural neurons (the NL), the site of ITD computation. Next, we review the influence of inhibition on the computational function of the NM and then move on to discuss the binaural interactions of the SON circuitry.

SON Inhibition in the Cochlear Nucleus Influences Spike Rate, Spike Timing, and Frequency Tuning

The NM provides the sole excitatory input to the NL, and information processing in the NM can be considered in one of two ways. First, with its large and secure synapses, the NM may be thought of as a relay, ideally transmitting one output discharge for each phase-locked, presynaptic, nVIII input spike. Alternatively, the NM may be viewed as integrative, computing its outputs from several inputs that may differ slightly in tuning or phase selectivity. There is compelling evidence that both scenarios apply in the NM and that the bias toward one mode of transmission or the other depends on stimulus frequency and intensity as well as the recruitment of inhibition in the circuit (Brenowitz and Trussell 2001; Fukui et al. 2006, 2010; Howard and Rubel 2010, Kuba and Ohmori 2009).

A key feature of NM neuron responses is that their discharges phase lock to the fine structure of the acoustic stimulus (Fig. 3). Phase-locking behavior provides the temporally precise information to the NL required for ITD computation. In the chicken NM, robust phase locking is maintained up to ~2 kHz (Warchol and Dallos 1990; Fukui et al. 2006), whereas in the owl it persists to much higher frequencies (~8–9 kHz) (Köppl 1997). This exquisite precision is achieved via contributions from a number of factors, including those that influence synaptic transmission at NM neurons. First, mature NM neurons receive only a few nVIII inputs (Parks and Rubel 1978; Hackett et al. 1982; Jackson et al. 1982). However, each synapse is anatomically large, kinetically fast, and electrically secure (Reyes et al. 1994; Zhang and Trussell 1994; Fukui and Ohmori 2004). Second, each NM neuron receives many small terminals that stain positively for GABA (Code and Rubel 1989; Carr et al. 1989; Kuo et al. 2009). This GABAergic input is unusual in that it is depolarizing with a reversal potential near −35 mV even into maturity (Hyson et al. 1995; Lu and Trussell 2000, 2001; Monsivais and Rubel 2001; Howard et al. 2007). In contrast to the fast excitatory input, the kinetics of the GABAergic response are remarkably slow and give rise to plateau potentials (Hackett et al. 1982; Lu and Trussell 2000). The strength and speed of the depolarizing input is tempered by $GABA_B$ receptors on presynaptic GABAergic terminals limit-

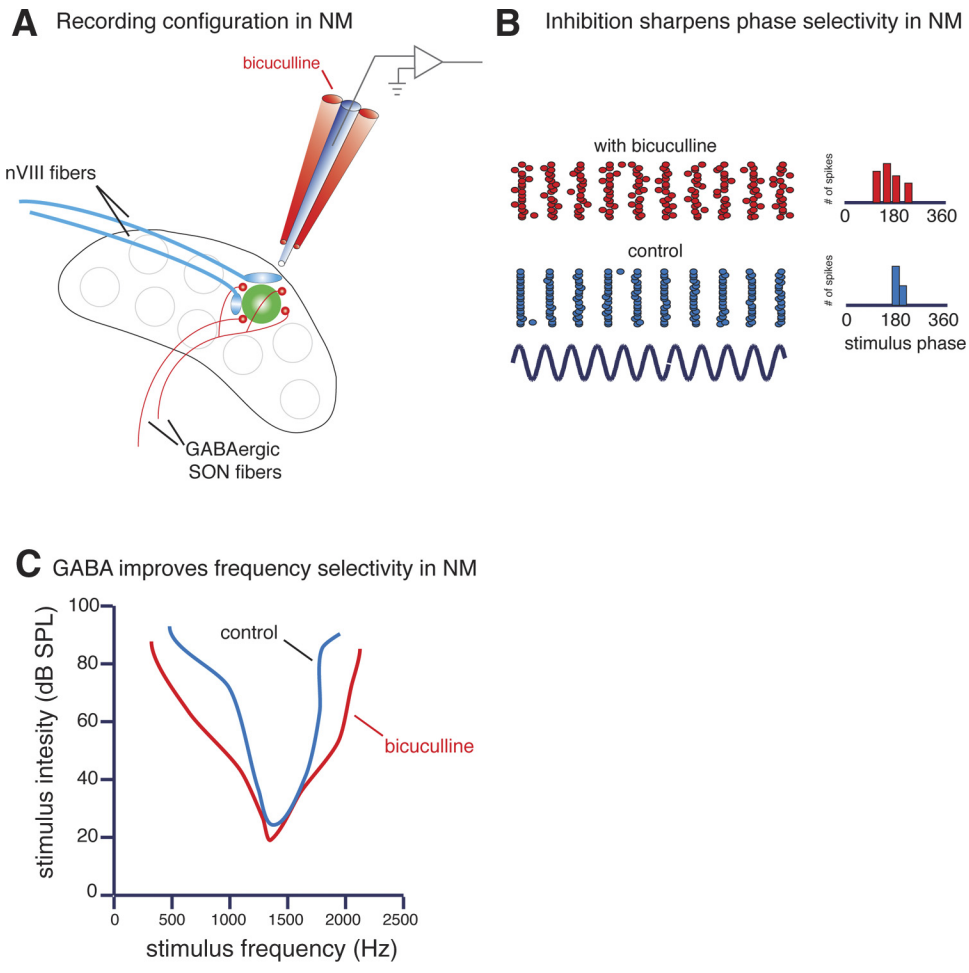

Fig. 3. GABAergic inhibition in the NM influences both phase locking and frequency tuning. *A*: NM neurons receive excitatory input from a few end bulb nVIII synapses and inhibitory input predominantly from small GABAergic SON terminals. Recordings were made from NM neurons in vivo using multibarrel piggyback electrodes composed of one recording barrel (blue) and drug barrels (red) containing bicuculline, a GABA antagonist. This arrangement allowed for the independent manipulation of inhibition during acoustic stimulation experiments. *B*: NM neuron responses phase lock to the fine structure of tone stimuli, and this phase locking is GABA dependent. Iontophoretic application of bicuculline caused a degradation of phase selectivity that is observable in the raster display of the response and the accompanying phase histograms. *C*: NM neuron frequency selectivity is also inhibition dependent. Blockade of GABAergic signaling broadens NM tuning functions, particularly at high intensities.

ing GABA release (Burger et al. 2005b; Lu et al. 2005). Despite the depolarizing nature of this input, it is strongly inhibitory and sufficient to suppress discharges in response to excitatory input (Monsivais and Rubel 2001; Fukui et al. 2010).

The potency of this inhibition derives from two physiological mechanisms coupled to the slow, mild depolarization. First, membrane resistance is reduced both by the activation of $GABA_A$ Cl^- channels and by the simultaneous activation of low-voltage-gated K^+ channels. Reduced membrane resistance shortens the membrane time constant, speeding voltage changes evoked by excitatory postsynaptic conductances and narrowing the window for coincidence detection (Fig. 4). Second, a significant fraction of voltage-gated Na^+ channels inactivate at the depolarized potential and become unavailable for spike generation (Monsivais and Rubel 2001; Howard et al. 2007; Howard and Rubel 2010). The net inhibitory effect of this depolarizing input is so powerful that it can render the membrane refractory, even in response to a subthreshold excitatory postsynaptic conductance (Howard and Rubel 2010). Howard and Rubel (2010) showed that the coincidence window for an inhibited NM cell is as brief as 0.5 ms. This property has important implications for how phase-locked responses are generated in the NM from the summation of presynaptic inputs. Poorly timed or noncoincident input fails to evoke postsynaptic responses because the temporal constraints imposed by GABAergic depolarization are so restrictive.

The requirement for the summation of multiple inputs to evoke discharges in the NM serves several functions. It can extend the dynamic range of intensities encoded by these neurons. In addition, and potentially of greater significance, it can improve phase locking and facilitate the rejection of poorly timed inputs or jitter. There is evidence that all of this does occur in the NM and that each depends on auditory stimulus characteristics and on inhibition. Two studies by Fukui and colleagues have shown in vivo that phase locking in the NM is indeed improved relative to nVIII fibers over the low frequency range (<800 Hz) and that this process depends partially on inhibition (Fukui and Ohmori 2006; Fukui et al. 2010). Application of bicuculline, a GABA antagonist, to NM neurons in vivo results in a reduction in temporal precision, especially in response to intense stimuli, demonstrating that inhibition contributes to phase locking (Fukui et al. 2010). In contrast, high-characteristic frequency (CF) neurons have fewer inputs (~2–3), but these inputs are roughly an order of magnitude larger than in low-CF NM neurons (low CF: 1.0 ± 0.25 nA and high CF: 12.84 ± 1.80 nA) (Fukui and Ohmori 2004). The benefit of this arrangement is that low-CF NM neurons improve phase locking by generating output responses from the summation of multiple jittery inputs. The cost of integrating multiple small inputs is a tendency for these inputs to reduce membrane excitability by activating low-voltage-gated K^+ channels and inactivating Na^+ channels, especially when input synchrony is low. Kuba and Ohmori (2009) showed that these low-CF neurons overcome this problem with a larger complement of voltage-gated Na^+ channels in the initial axon segment sufficient to compensate for Na^+ channel inactivation caused by their smaller, temporally dispersed excitatory input.

Across the population of high-CF NM neurons, phase-locking precision does not significantly exceed that of their nVIII inputs (Fukui et al. 2006). Nevertheless, recordings in high-CF neurons, in which inhibition was blocked, showed that inhibition does sharpen phase locking in these cells (Fukui et al. 2010) (Fig. 3*B*). The smaller number of inputs observed in high-frequency NM neurons is likely due to temporal con-

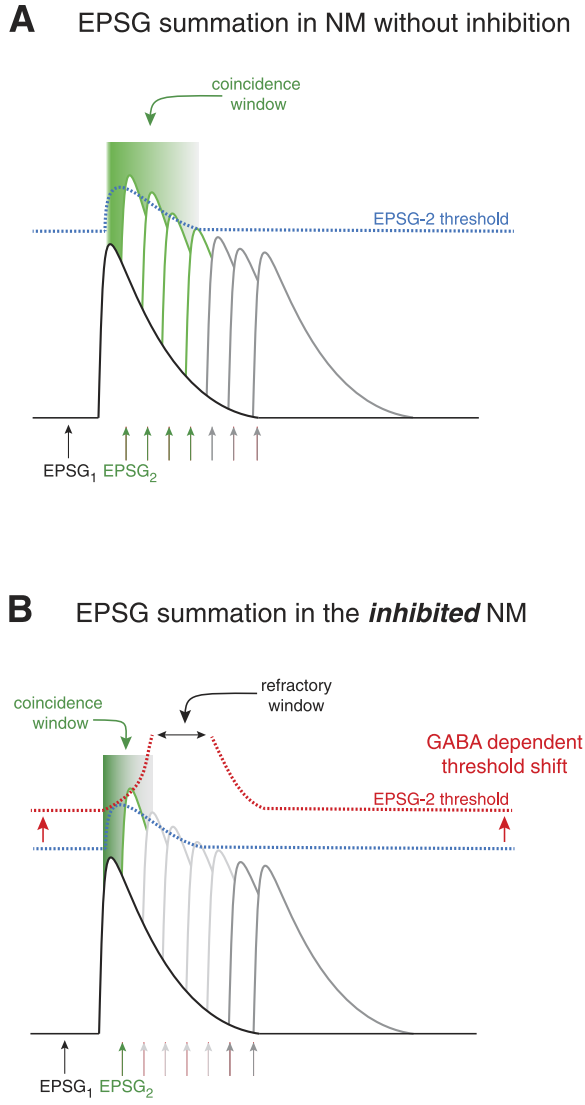

Fig. 4. Depolarizing inhibition reduces excitability and coincidence window in NM neurons. NM neurons were presented with pairs of subthreshold excitatory postsynaptic conductances (EPSGs) without stimulation of the GABAergic input (*A*) and with stimulation of the GABAergic input (*B*). The black trace shows the first synaptic input, $EPSG_1$, followed by a second, $EPSG_2$, at systematically increasing intervals. In *A*, EPSGs sum to suprathreshold values over a relatively broad range of delays (green traces, arrows), giving rise to a relatively wide interval over which inputs can sum to produce an output spike indicated by the "coincidence window." Receipt of $EPSG_1$ mildly and transiently raises the $EPSG_2$ threshold, illustrated as a "hump" in the blue dotted line. However, at longer delays, the summed value falls below threshold (gray traces). In *B*, the NM neuron is inhibited, raising the overall threshold for EPSG summation (red dotted line) from the control level (blue dotted line). In addition, the GABAergic depolarization coupled with $EPSG_1$ causes rapid inactivation of Na^+ channels and activation of low-voltage-gated K^+ current, rendering the membrane refractory after this initial subthreshold excitatory input. No increase in EPSG magnitude is sufficient to evoke a response, and the threshold for $EPSG_2$ is functionally infinite indicated by refractory window and light gray EPSGs. The combination of increased $GABA_A$ and low-voltage-gated K^+ conductance with Na^+ channel inactivation compresses the coincidence window green gradient to as little as ~0.5 ms. Functionally, the net effect of inhibition is to improve temporal precision in NM neurons by restricting the time window over which synaptic input will sum to evoke a spike.

straints on the cells that process these frequencies. As stimulus frequency increases, the duration of the stimulus cycle declines, approaching the temporal limits of membrane responses (Howard and Rubel 2010). Finally, a study by Fukui et al. (2010) demonstrated that GABAergic input also influenced NM frequency tuning. Application of bicuculline broadened the frequency selectivity of NM neurons, especially at high intensities (Fig. 3*C*). Sharper frequency tuning in NM neurons should result in improved temporal signaling as phase locking in individual NM neurons would be constrained to narrower bandwidth signals. GABAergic input to the NM in conjunction with the tonotopic variation in afferent and postsynaptic features of the NM may underlie the observation that phase locking is more robust at the level of the cochlear nucleus than the nVIII (Köppl 1997; Fukui et al. 2006).

As we have shown, GABAergic input to the NM improves frequency tuning and phase locking, both of which are advantageous for ITD processing. Additionally, inhibition derived from the SON influences the firing rate in NM neurons, but does so in an interesting and elegant way when one considers the role of the NM in sound localization. To fully convey the impact of this rate modulation, we discuss it below in the context of the ITD circuit in its entirety.

Functional Implications of the SON Circuitry for Binaural Processing

SON-dependent inhibition influences processing at the level of the NL in two ways. First, as we have shown, the SON indirectly impacts the NL through its interactions with NM inputs, modulating frequency selectivity and phase locking. In this section, we discuss how the SON also bilaterally couples activity in the two NMs to reduce or eliminate firing rate differences between them. Second, the SON also acts directly on the NL through its synaptic connectivity with ipsilateral NL neurons.

The binaural influences of the SON are mediated through a key feature of its circuitry, the robust reciprocal projections between the SONs. We and others have proposed that this coupling is essential for ITD processing in the NL (Monsivais et al. 2000; Burger et al. 2005a; Dasika et al. 2005). Our recent work, in which this pathway was disrupted by pharmacological or electrolytic lesion, supports these hypotheses (Nishino et al. 2008; Fukui et al. 2010).

A fundamental challenge to the auditory system is to maintain ITD selectivity and computational stability over a large dynamic range of input levels. For NL neurons, which are likely to receive input from multiple NM cells, the task is particularly exacting for several reasons. First, single NM neurons may change their firing rate severalfold over a 30- to 50-dB range of intensities (Sachs and Sinnott 1978; Warchol and Dallos 1990; Fukui et al. 2010). Second, while binaural coincidence results in maximal firing rates in the NL, these neurons respond quite well to monaural stimuli in a level-dependent manner in both barn owls and chickens (Rubel and Parks 1975; Overholt et al. 1992; Joseph and Hyson 1993; Pena et al. 1996). Third, an air-filled canal acoustically couples the middle ears in birds, effectively expanding the range of ITDs beyond that which is predicted by the distance between the two ears (Rosowski and Saunders 1980; Calford and Piddington 1988; Hyson et al. 1994). However, another consequence of this coupling is that lateralized sounds induce de facto IIDs at the level of the tympanic membranes (Hyson et al. 1994), and these IIDs may generate large differences in firing rates between the two NMs according to their steep and generally monotonic rate level functions. This bilateral asymmetry in firing rates generates a computational challenge for the NL. Put simply, a given NL neuron must have mechanisms to distinguish between a more intense monaural input and an ideally timed binaural input. Imbalanced input could cause the firing rate and phase selectivity of coincidence-detecting neurons to be dominated by the stimulus at the louder ear, causing systematic errors in sound localization. Interestingly, earlier models of binaural interaction developed by Durlach and colleagues in the 1970s included the necessity to normalize and bilaterally equalize input magnitude for ITD computations (Colburn and Durlach 1978) but did not identify neural mechanisms to serve this function. The SONs are well positioned to eliminate bilateral imbalances in NM activity through their putatively mutually inhibitory interactions. Our recent data have demonstrated that a single SON inhibits the ipsilateral NM while simultaneously disinhibiting the contralateral NM (Fukui et al. 2010).

Figure 5 shows the experimental method used by Fukui et al. (2010) for revealing the bilateral SON function by manipulating signaling from a single SON with pharmacological lesions. For efficiency, we will consider the left ear ipsilateral to the stimulus and the manipulated SON and the right ear contralateral to each. Figure 5*A* shows a recording electrode placed in the left NM, and the speaker is in the left hemifield generating tone signals. As stimulus intensity increases, more excitation from nVIII inputs drives NM neurons to very high firing rates, but it also recruits feedback inhibition from the ipsilateral SON that is driven by a parallel pathway through the NA. The resulting input-output functions of NM neurons are generally monotonic but with a mild depression for high-intensity stimuli. After elimination of the ipsilateral SON input by iontophoresis of TTX into the SON, NM firing rates increased, suggesting that the ipsilateral SON was indeed contributing to spike suppression during intense stimulation. This type of feedback inhibition is rather straightforward and commonly observed in sensory processing. However, the left SON also has interesting effects on the response properties of the right (contralateral) NM.

Figure 5*B* shows the same stimulus and SON manipulation arranged as in Fig. 5*A*; however, the recording electrode has been moved to the right NM, contralateral to the speaker, where the stimulus at the ear is less intense. The right NM receives two primary inputs. The first input is the excitatory input from ipsilateral nVIII fibers, and the second input is from the right (ipsilateral) SON. However, the right SON is itself inhibited by activity in the left SON. The stimulus intensity bias to the left ear preferentially drives the left SON, which disinhibits the right NM. When the left SON was inactivated with TTX, thereby removing its disinhibitory influence on the right SON feedback circuit, the activity in the right NM was suppressed compared with controls.

The picture that has emerged from these experiments confirms that the SONs function in a dynamic equilibrium opposing each other. When stimuli favor one ear, the balance of inhibition is shifted toward that ear by greater activation of the ipsilateral inhibitory feedback and simultaneous disinhibition of the contralateral SON-NM projection. This process

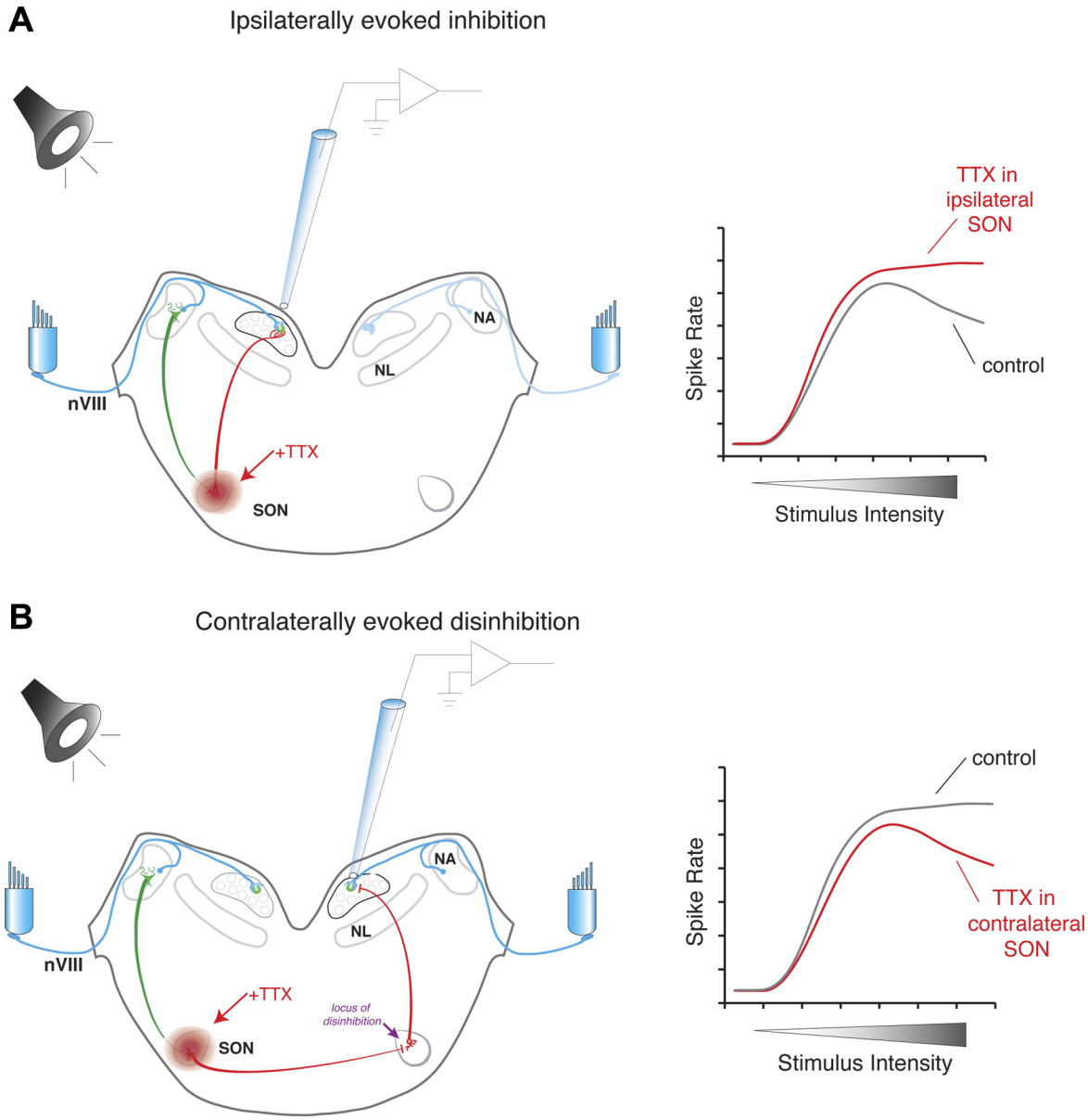

Fig. 5. The SON influences the NM bilaterally through its inhibitory connection with the contralateral SON. *A*: lateralized sound source that generates an ITD but also an intensity disparity favoring the left ear. Activity in the ipsilateral NA drives the recruitment of ipsilateral SON-derived inhibition to the NM and suppresses firing in the NM. Inactivation of the ipsilateral SON by iontophoresis of TTX relieves this inhibition and raises firing rates in the NM ipsilateral to the sound source. *B*: effect of the SON on the contralateral NM. Sound lateralized to the contralateral (left) ear evokes activity in the left SON. This activity inhibits the ipsilateral (right) SON, thereby disinhibiting the right NM. In this case, inactivation of the left SON by TTX causes a reduction in firing rates in the right NM, contralateral to the sound source.

equalizes the bilateral input magnitudes for coincidence detectors in the NL. Thus, the SON influences the NL indirectly. This mutual inhibition within the SON feedback system factors out the disruptive influence of relative NM input magnitude, leaving only relative timing information for ITD computation.

Direct Modulation of NL Neuron Activity by GABAergic SON Inputs

Studies in both the chicken and barn owl have shown clear evidence for remarkable stability in ITD selectivity (Peña et al. 1996; Nishino et al. 2008) by NL neurons. Several interrelated mechanisms may contribute to this property in addition to those we have discussed so far. First, synaptic depression at the NM to NL synapse may reduce inputs to the NL under high-intensity stimulus conditions (Kuba et al. 2002; Cook et al. 2003). Second, nonlinear summation of inputs in dendrites may limit the impact of an overall increase in input strength (Agmon-Snir et al. 1998). Third, the high expression levels of low threshold K^+ conductances in the NL reduces the temporal window for summation, effectively increasing the threshold for coincidence of inputs (Reyes et al. 1996; Kuba et al. 2005). Finally, inhibition, especially inhibition that is scaled to sound input level, dynamically influences ITD processing directly in the NL by shifting the action potential threshold, speeding kinetics of excitatory postsynaptic potentials, and reducing the duration of the coincidence window.

GABAergic signaling in the NL operates through both $GABA_A$ and $GABA_B$ receptors. $GABA_A$ signaling in the NL,

like in the NM, is depolarizing (Hyson et al. 1995). Additionally, NL neurons are enriched with low-voltage-gated K^+ channels (Kuba et al. 2003, 2005). Thus, GABAergic input to the NL is likely to evoke both Cl^- and K^+ conductances that may impact coincidence detection in a manner similar to the NM. To investigate the effect of GABAergic input to the NL functionally, Funabiki et al. (1998) used a slice preparation where ITDs were simulated in vitro by pairing intracellular depolarizing current with unilateral afferent stimulation where the timing between the two inputs was systematically varied. When exogenous GABA was applied to these preparations, the halfwidth of the ITD response was decreased by >50%, enhancing computational precision. In this way, the net inhibitory effect of GABA signaling in the NL enhances ITD encoding by reducing the temporal window over which convergent excitatory inputs from each NM can sum to evoke a response and potently inhibits spike generation when excitatory postsynaptic potentials arrive just outside that window (Howard and Rubel 2010).

The role of SON input for ITD coding has also been investigated in vivo. Nishino et al. (2008) recorded from NL neurons before and after electrolytic lesion of the ipsilateral SON. The results are shown in Fig. 6. In control conditions, chicken NL neurons showed stable ITD selectivity with increasing stimulus intensity and strong modulation of the firing rate as ITD varied, especially for low-CF neurons. These results were similar to those observed in the barn owl by Pena and colleagues (1996). When the SON was eliminated from the circuit, there were two major outcomes. First, the dynamic range of the ITD rate modulation became compressed. The peak firing rates were similar to those in the control condition, but the response rate minima did not extend below spontaneous rates, as they did in control recordings (Fig. 6*C*). This was particularly the case for high-intensity stimuli, as predicted from several previous models (Peña et al. 1996; Burger et al. 2005a; Dasika et al. 2005). Second, elimination of SON input strongly influenced the phase selectivity of NL neurons. In the control condition, NL neuron phase selectivity was stable and narrow, reflecting the summation of coincident phase delays between bilateral NM input spikes. However, after SON lesion, the NL neurons' best phase shifted with ITD and appeared to shift in concordance with the stimulus phase at the ipsilateral ear (Fig. 6*D*). The latter result suggests that lesion of the ipsilateral SON caused an imbalance in the input magnitude, allowing the ipsilateral NM to dominate. This "imbalanced input" feature of NL processing is complementary to the findings of Fukui et al. (2010), which showed that the SON circuitry binaurally equalizes activity between NMs.

Inhibitory Feedback in Mammalian ITD Circuitry

What does the investigation of inhibitory circuitry in birds offer to inform us about mammalian hearing? The role of inhibition in ITD processing in mammals has been the subject of rather intense research effort over many years by several laboratories. Recently, much of this attention has been directed toward revealing the contributions of a prominent feedforward

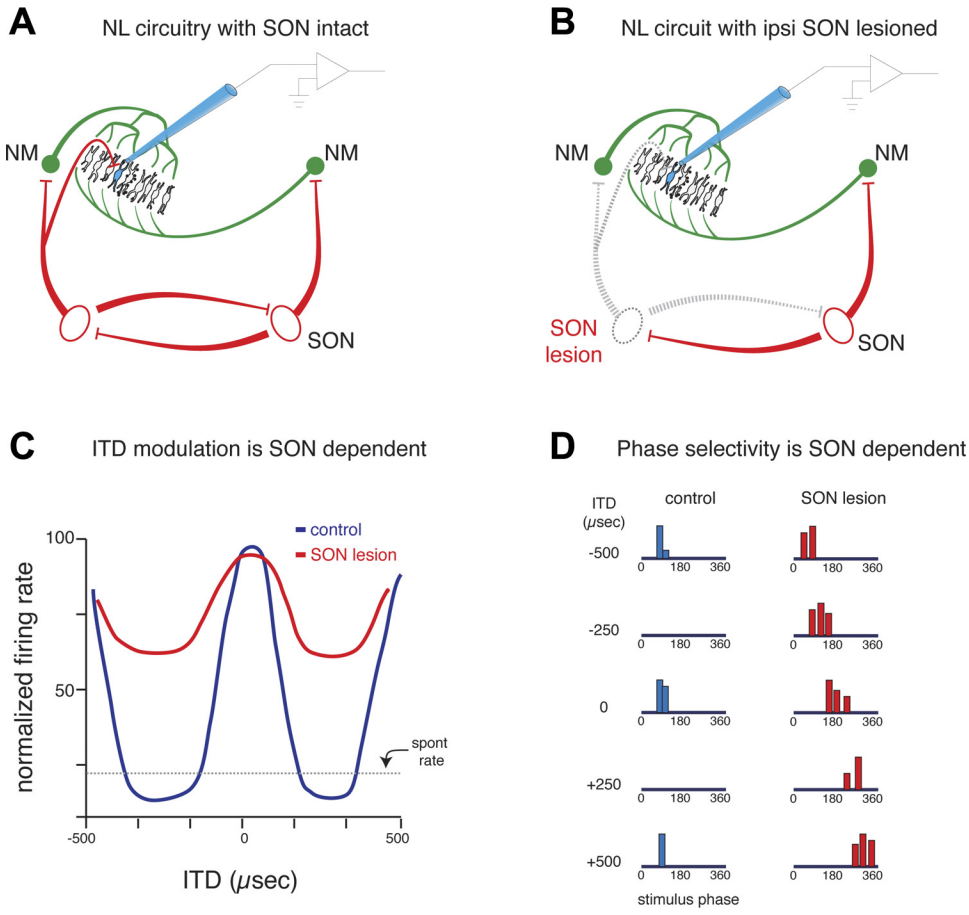

Fig. 6. ITD and phase selectivity in the NL depend on feedback from the SON. *A* and *B*: schematic arrangement for NL recording and circuitry during in the intact (*A*) and lesioned (*B*) SON. *C*: illustration of typical ITD functions for low-characteristic frequency neurons before (blue trace) and after (red trace) a SON lesion. Lesion of the SON compresses rate modulation with ITD primarily by elevating the response minima above the spontaneous rate (indicated by the gray dashed line). The corresponding effect of lesion on phase selectivity is shown in *C*, where lesion of the ipsilateral SON causes shifting phase selectivity in the NL with ITD. The shift corresponds to the phase change of the ipsilateral input, suggesting that the ipsilateral NM becomes the dominant input in the absence of the balancing influence of the SON.

glycinergic inhibition to the MSO from the medial nucleus of the trapezoid body (MNTB), an input that does not appear to have an analog in birds (for reviews, see McAlpine and Grothe 2003; Joris and Yin 2007; Grothe et al. 2010). The glycinergic input has been shown to actively shift the ITD selectivity of MSO neurons to preferentially respond to stimuli that lead in the contralateral ear (Brand et al. 2002; Pecka et al. 2008). Glycinergic inhibition via the MNTB in mammals is hypothesized to create the internal delay to compensate for ITD by a phase-locked inhibition rather than by the delay line mechanism that is present in birds. The internal delay determines the characteristic delay, and the nature of phase-locked inputs determines the characteristic phase. Both have been well studied in low-frequency binaural mammalian neurons in the inferior colliculus and MSO (Rose et al, 1966; Goldberg and Brown 1969; Stillmann 1971; Yin and Kuwada 1983; Yin and Chan 1990); however, little is understood in birds (but see Wagner et al. 2005; Köppl and Carr 2008). This feedforward glycinergic pathway clearly differentiates mammalian and avian binaural circuitry. However, mammals also possess many hallmarks of inhibitory feedback circuitry that may be functionally akin to those observed in birds.

Anatomic and physiological evidence for this feedback inhibition in the mammalian cochlear nucleus is abundant and arises from studies of several species. All subdivisions of the mammalian cochlear nucleus receive glycinergic and GABAergic input from periolivary regions, in particular, the contralateral ventral nucleus of the trapezoid body, the ipsilateral MNTB, and the lateral nucleus of the trapezoid body (Adams 1983; Spangler et al. 1987; Schofield 1994; Warr and Beck 1996; Ostapoff et al. 1997). Physiological studies have demonstrated inhibitory modulation of responses in several classes of mammalian cochlear nucleus neurons. These studies used pharmacological manipulations to assess the acute impact of inhibition at the postsynaptic neuron and have shown that spike rate and frequency tuning depend on this inhibitory feedback (Caspary et al. 1994; Ebert and Ostwald 1995a, 1995b; Kopp-Scheinpflug et al. 2002).

A major function of the SON in birds appears to be the equalization of bilateral input magnitude for coincidence-detecting neurons. The binaural balance function that we revealed in the NM when inactivating the contralateral SON has not been observed in mammals. However, a functionally similar mechanism appears to operate at the level of the cochlea. An excellent study by Darrow et al. (2006) showed that lesion to the lateral olivochoclear bundle, which provides feedback to the outer hair cells of the ear, caused imbalances in nVIII activity reminiscent of those we observed at the level of the cochlear nucleus (NM) with SON inactivation. This study strongly suggests that bilateral inhibitory coupling is a feature of the olivocochlear system. Thus, candidate feedback mechanisms exist in mammals that may serve similar functions in binaural hearing to those that depend on the SON in birds, although at multiple levels of processing.

Summary

The results of recent studies in birds highlight the essential role of brain stem inhibitory circuitry in shaping the binaural processes required for sound localization and signal detection. The SON inhibits the cochlear nucleus to improve phase selectivity and narrow frequency tuning. Both effects result in improved temporal information for binaural coincidence detection, a process that takes place in the NL. In the NM and NL, temporal acuity is gained via depolarizing GABAergic input that influences an extensive group of membrane properties. This input shortens integration time, speeding electrical signaling such that in the NM, where the input threshold is extremely plastic, neurons can become refractory after a strong but subthreshold input. The inhibition, of course, also suppresses the firing rate in the NM, but in an interesting and elegant way. The negatively coupled SONs interact and generate inhibitory feedback bilaterally that offsets imbalances in acoustic intensity at the two ears. This offset reduces the firing rate in the NM ipsilateral to loud sounds and elevates the firing rate at the contralateral NM via a disinhibitory process. These effects are also observable at the level of the NL, where neurons become preferentially phase selective to ipsilateral NM inputs after SON lesion. Finally, we showed that modulation of the firing rate across ITDs in the NL is highly dependent on SON input, especially for low-CF neurons.

The studies highlighted in this review from our laboratories and others have generated a rather thorough understanding of inhibitory function in the brain stem auditory system in birds. However, a complete picture of this circuit awaits further work on the role of glycinergic input and on the nature of the SON itself, where many important questions remain. Only recently have we and others demonstrated that the SON provides GABAergic and glycinergic output to its targets by the corelease of both transmitters (Kuo et al. 2009; Coleman et al. 2011). Coleman et al. (2011) showed that many SON neurons phase lock to acoustic stimuli and that phase-locking precision in the SON is tuned by both GABA and glycinergic inputs. It is not yet understood how corelease of GABA and glycine imparts functionally distinct modulation to neurons in the NA, NM, or NL, with the notable exception that rapid glycinergic inhibitory postsynaptic currents have been observed in the NA (Kuo et al. 2009). It is also unknown how the neurons in the feedforward and feedback circuits relate to each other anatomically and physiologically within the nucleus. How are the SON's inputs from the NA and NL integrated or segregated? More broadly, how does this pattern of circuit organization and function relate to mammalian hearing?

The computational challenges shared by avian and mammalian auditory systems and the simplicity of this circuit in birds support the notion that the avian system remains a very useful experimental preparation for studying the cellular and systems level impact of efferent feedback in vertebrate auditory function. Ongoing work in our laboratories aims to address these issues in an effort to achieve a holistic and mechanistic understanding of binaural computation in auditory neuroscience.

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