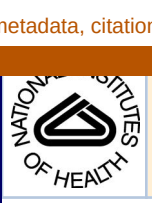

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Inhibitory projections from the ventral nucleus of the lateral lemniscus and superior paraolivary nucleus create directional selectivity of frequency modulations in the inferior colliculus: A comparison of bats with other mammals

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Abstract

This review considers four auditory brainstem nuclear groups and shows how studies of both bats and other mammals have provided insights into their response properties and the impact of their convergence in the inferior colliculus (IC). The four groups are octopus cells in the cochlear nucleus, their connections with the ventral nucleus of the lateral lemniscus (VNLL) and the superior paraolivary nucleus (SPON), and the connections of the VNLL and SPON with the IC. The theme is that the response properties of neurons in the SPON and VNLL map closely onto the synaptic response features of a unique subpopulation of cells in the IC of bats whose inputs are dominated by inhibition. We propose that the convergence of VNLL and SPON inputs generates the tuning of these IC cells, their unique temporal responses to tones, and their directional selectivities for frequency modulated (FM) sweeps. Other IC neurons form directional properties in other ways, showing that selective response properties are formed in multiple ways. In the final section we discuss why multiple formations of common response properties could amplify differences in population activity patterns evoked by signals that have similar spectrotemporal features.

1. Introduction

Over the past three decades much has been learned about the processing that occurs in brainstem auditory nuclei and how their intrinsic properties coupled with the complement of projections they receive operate together to produce each of their unique discharge properties. Investigators have used a variety of different animals to evaluate auditory processing in lower centers. Several laboratories, including this one, use bats as model systems. Here we review the features of four auditory brainstem nuclear groups and show how studies of both bats and other mammals have provided insights into their response

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properties and the impact of their convergence in the inferior colliculus (IC). The four nuclear groups are octopus cells in the cochlear nucleus, their connections with spherical cells in the ventral nucleus of the lateral lemniscus (VNLL) and the superior paraolivary nucleus (SPON), and the connections of the VNLL and SPON with the IC. The theme is that the response properties of neurons in the SPON and VNLL map closely onto the synaptic response features of a unique subpopulation of cells in the IC of bats whose inputs are dominated by inhibition. Based on these properties, we propose a hypothesis to explain how the convergence of VNLL and SPON inputs could generate both the tuning of these IC cells, their unique temporal responses to tones, and their response selectivities for both natural communication calls and the direction of frequency modulated (FM) sweeps. We also compare the proposed mechanism for creating FM directionality in these cells with mechanisms that create directional selectivity in other IC cells, and suggest that common response properties are formed in multiple ways in the IC. In the final section we discuss why multiple formations of a common response property could enhance response selectivity for complex signals and thereby amplify differences in population activity patterns evoked by signals that have similar spectrotemporal features.

1.1. The circuits connecting octopus cells to the VNLL and to the IC

Octopus cells in the posteroventral cochlear nucleus (PVCN) are among the most extraordinary neurons in the auditory system with specializations that endow them with the ability to respond to temporal features of acoustic stimuli with precisely timed discharges (Golding et al., 1995, 1999; Oertel, 1999; Trussell, 1999). The basis for the precise timing is a large complement of low voltage activated potassium (LVK) channels and hyperpolarization activated cation (HCN) channels that impart exceptionally low input resistances and fast membrane time constants. Their pronounced intrinsic properties make these cells very leaky, and thus they have high spike thresholds and require a strong, synchronized synaptic drive from many auditory nerve inputs to evoke a discharge. The dendrites of octopus cells are elongate and extend across isofrequency fibers of the auditory nerve as they run through the cochlear nucleus (Cant, 1992; Oertel et al., 2000; Osen, 1969). This anatomical arrangement allows the cells to sample the synchronized activity across many auditory nerve fibers tuned to different frequencies and creates exceptionally broad tuning curves (Rhode et al., 1983), a feature seen in all mammals, including bats (Feng and Vater, 1985). Thus, periodic broadband signals evoke a train of precisely timed spikes tightly locked to the signal waveform. Tones can also evoke discharges but only at high intensities. Low frequency tones of high intensity generate trains of phase-locked discharges whereas intense, high frequency tones evoke only a single onset spike, regardless of the tone duration (Oertel et al., 2000).

Of particular significance is that the responses of octopus cells to FM sweeps have been reported to be directional, in that they respond to FM sweeps in one direction (preferred direction) but not the other (null direction) (Rhode and Greenberg, 1992). Presumably, their FM directionality is due to dendritic filtering in a manner first proposed by Rall (Rall, 1969) and subsequently by Golding and his colleagues (Golding et al., 1995). The key feature of the hypothesis is the relative coincidence in the arrival of the inputs on different portions of their dendritic trees, where FMs that sweep in one direction would first activate the more

proximal dendrites and subsequently more distal dendrites. The filtering in the more distal dendrites creates a latency gradient along the dendritic tree that underlies directionality. In this scenario, frequencies that first activate the proximal dendrites would sum poorly with the inputs from the more distal dendrites whose arrival at the soma would be delayed. In contrast, if distal dendrites were activated first their delayed arrival at the soma would temporally sum with the later arriving inputs on the proximal dendrites and generate a powerful synaptic input. Thus, compared to the null, the excitatory inputs evoked by the preferred FM would have a greater temporal coincidence. The point is that octopus cells are endowed with features that could impart FM directionality.

Octopus cells project to spherical cells in the VNLL (Fig. 1.) (Adams, 1997).VNLL spherical cells are found in all mammals, including humans, but are especially well organized in bats where they form distinct columns along the ascending fibers of the lateral lemniscus (Covey and Casseday,1991; Winer et al., 1995). Covey and her colleagues called this cell group the columnar division of the ventral nucleus of the lateral lemniscus (VNLLc) (Covey and Casseday, 1991). VNLLc cells are innervated by large, end-bulbs of Held, similar to the end-bulbs on bushy cells in the cochlear nucleus (Fig. 1), a feature first seen by Stotler in cats (Stotler, 1953) and more recently shown by Covey and Casseday in big brown bats (Covey and Casseday, 1986), by Vater and her colleagues in horseshoe bats (Vater and Feng, 1990; Vater et al., 1985; Vater et al., 1997) and by Adams (1997) in cats and humans. Although the earlier studies could not identify the cells in the cochlear nucleus that provide the end-bulbs, Adams (1997) showed that end-bulbs derive from the axons of octopus cells in the PVCN.

VNLLc cells also have a large complement of LVK channels and thus have low input resistances and fast time constants, features well suited for temporal processing (Oertel, 1991, 1999). Given the secure excitatory innervation they receive from octopus cells, it follows that the VNLLc cells should inherit their sound evoked response properties from octopus cells. That VNLLc cells do in fact have response properties comparable to octopus cells was first shown by Covey and Casseday in studies conducted on big brown bats (Covey and Casseday, 1991) and subsequently by Adams in cats (1997). Covey and her colleagues showed that VNLLc cells respond to tones with a single onset action potential with a remarkably constant latency (Fig. 1), have high thresholds, very broad tuning curves (Covey and Casseday, 1991; Haplea et al., 1994), and importantly, are directionally selective for FM sweeps (Huffman et al., 1998), the same features that characterize the sound evoked responses of octopus cells.

VNLLc cells are purely glycinergic and provide a major source of inhibitory innervation to the ipsilateral IC (Fig. 1) (Vater et al., 1997; Winer et al., 1995). Based on their projections and response properties, Covey and Casseday (1991) suggested that the VNLLc provides precisely timed, short latency inhibitory inputs to the IC and must therefore shape a variety of IC response properties. This hypothesis was subsequently followed up by Nayagam and his colleagues (Nayagam et al., 2005). They recorded intracellularly with sharp electrodes from both the VNLLc and IC in rats, and showed that in many IC cells, sounds evoked a short latency IPSP that preceded a discharge train. They attributed the short latency IPSP to

the VNLLc projection and suggested that the inhibition from the VNLLc acts to lengthen spike latency.

2. The superior paraolivary nucleus

Some neurons in the superior paraolivary nucleus (SPON), like those in the VNLLc, have response properties well suited to convey the temporal information in acoustic stimuli. SPON cells in mice have low input resistances, fast time constants and a complement of intrinsic channels that are consistent with temporally precise electrical signaling (Magnusson et al., 2010; Scheinpflug et al., 2010). In rodents, the SPON is largely a GABAergic nucleus (Kulesza and Berrebi, 2000a; Roberts and Ribak, 1987) and is one of the major cell groups that comprise the periolivary nuclei of the superior olivary complex (Fig. 2) (Behrend et al., 2002; Dehmel et al., 2002; Grothe et al., 1994; Kulesza and Berrebi, 2000a; Schofield, 1991). The SPON is especially well developed in rodents and bats and is probably homologous to the dorsomedial perioli-vary group in other mammals. The SPON receives its principal excitatory innervation from bushy, multipolar and octopus cells in the cochlear nucleus, and inhibitory innervation from the medial nucleus of the trapezoid body (MNTB) (Fig. 2) (Friauf and Ostwald, 1988; Kuwabara and Zook, 1999, 1992; Schofield, 1995; Thompson and Schofield, 2000). Its major projections are to the ipsilateral IC (Saldana and Berrebi, 2000; Saldana et al., 2009; Schofield, 1991) and, like the VNLLc, is a major source of inhibitory innervation to the ipsilateral IC.

The SPON has been studied extensively in gerbils, a low frequency specialist, and rats whose hearing dominated by high frequencies. There are substantial differences between the SPON of gerbils and rats, and thus the nucleus appears to be species-specific. The SPON in gerbils has several cell types that express a wide variety of discharge patterns to tone bursts, where most cells fire with sustained discharges to tones and a minority fire only to the offset of tone bursts (Behrend et al., 2002; Dehmel et al., 2002). SPON cells also differ in their responses to rates of SAM stimuli, where some lock to the envelope of SAM rates as high as 900 Hz, others to only to a lower range of rates and yet others only to low rates. In addition, many SPON cells in gerbils are binaurally inner-vated, although none are sensitive to interaural intensity or time disparities.

The SPON in rats, in contrast, is far more homogeneous, composed mainly of one cell type that is GABAergic (Kulesza and Berrebi, 2000; Kulesza et al., 2003; Saldana and Berrebi, 2000). The discharge properties of rat SPON neurons are also homogeneous in that they are all monaural, driven by sound at the contralateral ear, and the majority of cells fire only to the offset of tone bursts with one or a few spikes (Kulesza et al., 2003, 2007). Tones of increasing durations evoke discharges of progressively increasing latency that follow the tone duration, as shown in Fig. 2. SPON cells in rats phase-lock precisely to the modulating waveform of sinusoidal amplitude modulations (Kulesza et al., 2003). They are also sensitive to even the briefest gaps in a train of short tone bursts, and thus have been implicated in gap detection, a classic feature of temporal processing (Kadner and Berrebi, 2008). SPON neurons also respond to FM sweeps and are non-directional in that they respond equally well to upward and downward sweeps so long as the FM sweeps completely through the cell's excitatory tuning curve (Berrebi, personal communication).

The rat SPON is dominated by cells that discharges at the offset of tone bursts, features similar, but not identical, to a minority of cells in the gerbil SPON. The main difference between off discharging cells in the two species is that in gerbils the off discharges fire repetitively as a chopping offset pattern in some cells or with a prolonged periodic discharge that can last 60 or more ms in others (Behrend et al., 2002; Dehmel et al., 2002). Similar offset types are also seen in a minority of neurons in the rat SPON, but the most common type in rats is an offset transient response in which only one or two discharges are evoked at tone offset (Kulesza et al., 2003).

Kulesza and his colleagues (2007) have proposed an explanation for the transient off response in the rat. SPON cells receive a sustained excitation, presumably from stellate cells in the cochlear nucleus, and a sustained glycinergic inhibition from the MNTB. SPON cells also receive GABAergic innervation from collaterals of axons of other SPON cells that feed back onto the somata (Saldana and Berrebi, 2000; Saldana et al., 2009). The idea is that tone bursts evoke a sustained excitation from the cochlear nucleus and a sustained inhibition from the MNTB. Their proposal is that glycinergic inhibition from MNTB completely or nearly completely suppresses the excitation, shutting down discharges throughout the duration of the tone. Upon termination of the tone, the release from inhibition, perhaps coupled with some residual excitation, evokes a rebound discharge that is the off response. Those offset discharges are conveyed to both the IC and back to the soma of the SPON neuron via collaterals. The GABAergic feedback from collaterals then inhibits the SPON cell, thereby limiting the off response to one or a few spikes.

Little is known about the neuronal architecture of the SPON in bats but the few studies that have been reported suggest that SPON connections and projections are the same as in rodents (Grothe and Park, 2000; Kuwabara and Zook, 1992). There is no information about the physiology of SPN cells in any bat species, and thus it is unclear whether the physiology of SPON cells in bats express the wide variety of tonal discharge patterns seen in gerbils or the far more homogeneous discharge patterns seen in rats. Since rats and bats rely predominately on high frequencies, whereas gerbils rely on low frequencies, we assume that the bat's SPON resembles the SPON of rats more than it does the gerbil SPON, and that at least some cells in the bat SPON express a transient offset feature similar to that reported for rats. The SPON, like the VNLL, is a nucleus in the ascending auditory pathway that provides a strong and temporally precise inhibitory innervation to the ipsilateral IC.

3. The inferior colliculus

The central nucleus of the inferior colliculus (IC) is the site of the convergence of both excitatory and inhibitory projections from the majority of lower auditory nuclei and thus is the nexus of the ascending auditory system (Casseday et al., 2002; Oliver and Huerta, 1992; Pollak and Casseday, 1986). The structure of the IC is simple and is dominated by one type of principal cell, disc-shaped, fusiform cells. The dendrites of disc-shaped cells are aligned with the plexus of afferent axons to create sheets of cells with a laminar configuration. The laminae correspond anatomically to the isofrequency contours observed in physiological experiments, and their dorsoventral stacking produces the tonotopic organization that characterizes almost all auditory nuclei. A second type of principal cell, large multipolar

cells, is far less numerous and have dendrites that extend across frequency laminae created by the dendritic alignment of disc-shaped cells (Malmierca et al., 1995a; Oliver and Morest, 1984; Rockel and Jones, 1973a,b). Axons of principal cells project upstream to the medial geniculate body, downstream to lower centers, to the opposite IC via its commissure and also send collaterals that make synaptic contacts with other IC cells (Casseday et al., 2002; Coomes and Schofield, 2004; Malmierca et al., 1995b; Miller et al., 2005; Saldana and Merchan, 1992). Finally, a large proportion of principal cells are GABAergic (Merchan et al., 2005; Oliver et al., 1994; Winer et al., 1995) and thus provide inhibitory innervation to their targets. These features have been seen in a variety of species of bats (Casseday et al., 2002; Miller et al., 2005; Pollak and Casseday, 1986; Winer et al., 1995; Zook et al., 1985), cats (Morest and Oliver, 1984; Oliver and Morest, 1984; Oliver et al., 1994; Rockel and Jones, 1973a,b; Winer et al., 1996), mice (Meininger et al., 1986), primates (FitzPatrick, 1975) including humans(Geniec and Morest, 1971).

The major structural feature that varies among species is frequency representation, where contours representing the frequencies of greatest importance for survival are more or less over-represented. Such frequency representation differences are especially prominent in bats, since various species occupy a wide range of ecological niches and tailor the spectral contents of their echolocation calls to meet the demands of the niche they occupy (Neuweiler, 1990; Pollak and Casseday, 1986). Bats that emit predominately brief FM sweeps for echolocation, such as the big brown and Mexican free tailed bats, have prototypical ICs with isofrequency contours that represent the full spectral range of their echolocation and communication calls, but with an over-representation of dominant frequencies in their echolocation calls. In contrast, bats that emit a long constant frequency component terminated by a brief FM sweep express more prominent over-representations of the constant frequency components of their calls. The most dramatic illustration of frequency over-representation is in the IC of mustache bats (Pollak and Bodenhamer, 1981; Pollak and Casseday, 1986), one of the most behaviorally specialized bats. About 1/3 of the volume of the mustache bat's IC is devoted to a single frequency, 60 kHz, the dominant frequency of their echo-location calls and the frequency through which they “see” much of their world. Yet that contour contains the same cell types and with the same structural arrangements as occur in other isofrequency contours but in highly magnified form (Zook et al., 1985). Not only does the structural arrangement conform to the basic mammalian groundplan, but the 60 kHz contour receives the same complement of projections from lower centers that innervated the contours of higher and lower frequencies (Ross and Pollak, 1989; Ross et al., 1988). The point is that the IC is quintessentially mammalian and that the structural differences that occur among mammals are quantitative, differences in size or emphasis, rather than qualitative differences (Pollak and Casseday, 1986; Pollak et al., 1995; Winer et al., 1995).

3.1. Response properties of IC neurons are diverse

Although the neuronal architecture of the IC is relatively simple, the massive convergence of inputs from lower centers confers upon its neuronal population response properties that are complex and highly diverse. IC neurons express a wide variety of both monaural and binaural response properties, due in large part to the particular complement of inputs that

innervate each neuron. Inhibitory inputs are particularly important and exert numerous and profound influences on IC cells. The impacts of inhibition are manifest in the changes in tuning curves (LeBeau et al., 2001; Yang et al., 1992), response magnitudes (LeBeau et al., 2001; Pollak and Park, 1993; Ramachandran et al., 1999), temporal discharge patterns (Park and Pollak, 1993b; Pollak and Park, 1993), binaural properties (Faingold et al., 1991, 1993; Li and Kelly, 1992; Pollak et al., 2002), and selectivity for complex signals, such as FM sweeps (Felix and Portfors, 2007; Fuzessery and Hall, 1996; Klug et al., 2002; Xie et al., 2005), that commonly occur in IC neurons when inhibition is blocked. Such effects of inhibition are seen in the IC in the various species of bats that have been studied as well as in the conventional mammals used in neurophyiological studies of the auditory system in rats, mice and guinea pigs. Below we present a hypothesis that could in large part explain how the inhibitory projections from the VNLLc and SPON create the response profiles, the tuning and shape the FM directional selectivity in a subpopulation of IC neurons in Mexican free tailed bats.

3.2. On-off cells in the inferior colliculus

The subpopulation of IC cells we consider were recorded from bats with patch electrodes and are called on-off cells because their signature feature is a tone-evoked IPSP at the onset of the tone followed by an IPSP at the tone offset (Fig. 3) (Xie et al., 2007, 2008).The interval between the onset and offset IPSPs increased with tone duration showing that the terminal IPSP is evoked by tone offset (Fig. 4). The onset-offset IPSP configuration is evoked only at intensities above 25–30 dB SPL. Lower intensities evoke strong EPSPs that are often suprathreshold with no evidence of an IPSP. At intensities above 30 dB, inhibition dominates completely and these cells never fire even a single spike to any tone. Positive current injected into on-off cells evoke one or a few spikes at the onset of the current step with a cession of firing during the subsequent depolarizing period, indicative of LVK channels. Injected negative current evokes an initial hyperpolarization followed by a sag in membrane potential, the signature feature of HCN channels (Xie et al., 2008). Thus, on-off neurons appear to have a complement of LVK and HCN channels that impart low input resistances and fast time constants.

The nearly total dominance of inhibition at higher intensities is illustrated by the on-off neurons in Fig. 3. The tones in Fig. 3 were 50 dB SPL and evoked synaptic responses in both cells that were broadly tuned and were evoked over a frequency range of at least 1.5 octaves. The true frequency range is probably even broader since IPSPs were still evoked by the lowest and highest frequencies that were presented. There are two other noteworthy features of the tuned regions. The first is that while onset IPSPs were evoked by every frequency, there was a small range of frequencies in the middle of the cell's tuned region that did not evoke offset IPSPs. We refer to small gap in frequencies that evoked no offset IPSPs as the midrange, which were 23–25 kHz for the neuron in Figs. 3A and 20–21 kHz for the neuron in Fig. 3B. The second feature is that the midrange frequencies evoked response configurations different from the on-off configuration evoked by higher or lower frequencies. Those midrange frequencies evoked an onset IPSP followed by a prominent depolarization and, as mentioned above, there were no offset IPSPs at the termination of the tone bursts. Changes in response configuration with frequency were seen in all on-off

neurons, which suggest that these cells receive innervation from several lower auditory nuclei (Xie et al., 2007), an issue that we consider in more detail below.

Although on-off cells fail to discharge to any tone burst at intensities above 20 dB SPL, they respond to FM sweeps and are selective for downward FM sweeps. As shown in Fig. 5, discharges were reliably evoked by downward FM sweeps but not by upward FM sweeps at 50 dB SPL, the same intensity at which tones failed to evoke even a single discharge in that or any on-off cell. Importantly, the FM sweeps that evoked discharges had a spectral composition similar to the range of tonal frequencies that evoked predominantly IPSPs but never evoked discharges.

On-off cells also respond to the natural communication calls emitted by these bats in a manner consistent with their responses to tones and FM sweeps. As shown in Fig. 6, the downward sweeping FM notes in their courtship songs evoke discharges whereas the response to the tone-like dominance call is simply an IPSP at the onset of the call and an IPSP at the end of the call, a configuration strikingly similar to the on-off IPSPs evoked by electronically generated tone bursts (Fig. 3).

3.3. Response features of VNLLc and SPON neurons map closely onto the response features of on-off cells

Below we argue that inhibitory inputs from the VNLLc and from transient off SPON cells are consistent with the tone-evoked responses of on-off cells. We then explain how those inputs, combined with an excitatory input, could account for the on-off response profiles, the broad tuning and FM directional selectivity (Fig. 7).

We begin by suggesting that the source of the onset IPSPs is the projection from the VNLLc, while the source of the offset IPSPs is the projection from the SPON. We suggest separate sources for the onset and offset IPSPs because the VNLLc and SPON have tone evoked response properties that closely match the features of onset and offset IPSPs. VNLLc neurons are glycinergic and respond with 1–2 spikes to the onset of tone bursts over a very broad range of frequencies (Covey and Casseday, 1991; Oertel and Wickesberg, 2002), features well suited to generate the onset IPSPs. Moreover, VNLLc cells have high spike thresholds. The high threshold could explain why onset inhibition is not apparent at low intensities. We also suggest transient off SPON cells as the source of offset IPSPs because the SPON is a GABAergic nucleus and transient off cells respond only to the offset of tone bursts with one or two discharges (Kulesza and Berrebi, 2000a; Kulesza et al., 2003), features well suited for generating the offset IPSP. Both the VNLLc and SPON send inhibitory projections to the IC and both express unique response properties appropriate for generating either onset or offset IPSPs in these IC cells.

The configurations of onset and offset IPSPs observed among onoff cells would, in this scenario, be generated by mixing and matching projections from VNLLc and projections from differentially tuned SPON cells. In almost all on-off cells, the onset IPSP is evoked over a broad frequency range that encompasses all, or almost all, of their tuned regions, a feature consistent with the broad tuning of VNLLc cells. The tuning of offset IPSPs is more variable. It seems significant in this regard that, unlike VNLLc neurons whose tuning is

exceptionally broad (Covey and Casseday, 1991), transient off SPON neurons have narrower, V shaped tuning curves (Kulesza et al., 2003). Thus some on-off cells express offset IPSPs throughout most of their tuned regions but with an offset gap at midrange frequencies e.g., the cells in Fig. 3A, B. Presumably these cells receive projections from two populations of SPON cells, where one population is tuned to lower and the other tuned to higher frequencies. Such projections from the VNLLc and SPON would account for cells expressing onset IPSPs over the entire frequency range of the tuned region and the gaps in the frequencies that evoke offset responses.

A third set of inputs is required to account for the depolarizations evoked by midrange frequencies. Those inputs must be excitatory, and have low threshold tuning curves that are narrowly tuned to the frequencies in the midrange of the neuron's synaptic tuned region. At intensities above 20 dB, the excitation from this input is normally reduced by the onset inhibition, and thus fails to evoke discharges. The sources of the midrange excitatory inputs are unknown.

3.4. Differential inputs can explain tuning but not FM directional selectivity

The projections described above can account for the synaptic tuning of on-off cells but they do not explain why these cells respond to FM sweeps nor how directional selectivity for FM sweeps is generated. Directional selectivity for FM is classically explained by an asymmetry in the spectrotemporal features of both the excitatory and inhibitory regions (Andoni et al., 2007; Fuzessery et al., 2006; Gordon and O'Neill, 1998; Suga, 1965). Spectrotemporal asymmetry posits that selectivity for downward sweeping FM is a consequence of inhibition that flanks the low frequency edge of the excitatory region and has latencies slightly longer than the latencies of excitatory frequencies. Thus, as the signal sweeps downward, it first evokes a short latency excitation that is unop-posed by a longer latency inhibition, whereas signals that sweep upward, first evoke an inhibition that prevents discharges. Given the width of their tuned synaptic regions that are dominated by IPSPs, with only a hint of any excitation, coupled with the initial IPSPs that are evoked by every frequency, it is difficult to visualize how any excitation could be evoked prior to inhibition in on-off cells. Stated differently, the linear summation of the synaptic events evoked by each frequency cannot explain why these cells respond to FM sweeps nor can a linear summation explain why on-off cells fire to downward but not to upward FM sweeps.

3.5. Non-linear features of VNLLc neurons can explain FM directional selectivity

The key feature that could account for the directional features of on-off cells is the directional selectivity of VNLLc neurons (Huffman et al., 1998), where they fire to FMs that sweep in one direction, the preferred direction, but do not fire or fire much more weakly, when the FM sweeps in the other direction, the null direction. In this scenario, FM signals sweeping in the preferred direction of the onoff cell will fail to evoke an onset inhibition, because VNLLc neurons fail to fire or fire weakly to those FMs. Although the offset inhibition is still evoked, the offset inhibition occurs either simultaneously with or slightly after the excitation, but by itself is not sufficiently strong to suppress the synchronous excitation evoked by the sweeping signal. The net result is suprathreshold excitation and a discharge. When the FM sweeps in the null direction, the onset inhibition from the VNLLc

is evoked and together with the inhibition from the SPON, suppresses excitation to subthreshold levels. In contrast to the predictions of a linear summation of tone evoked responses, this scenario includes a nonlinear response of VNLLc cells that predicts a predominantly excitatory response to FM sweeps in the preferred direction and an initial inhibition followed by a subthreshold excitation in the null direction, predictions consistent with the PSPs evoked by upward and downward FM sweeps in the on-off neuron in Fig. 5.

3.6. FM directionality is formed in multiple ways in the IC

The hypothesis to account for the tuning and directional features of on-off cells is the first that proposes specific functional outcomes for the inhibitory projections of both the VNLLc and SPON on their targets in the IC. Assuming the hypothesis is correct, it would show that FM directional selectivity is formed in several ways in the IC, where each cell group forms directionality in a particular way. For on-off cells, we propose that directional selectivity is a consequence of the inhibitory projections from the VNLLc, whereas previous studies proposed that in other IC cells, directionality is shaped by the timing asymmetries of excitation and inhibition, as described previously. In a recent study, we showed yet a third way for constructing directional selectivity in the IC (Gittelman et al., 2009). The IC cells in that study had high input resistances and long time constants. Consistent with those features, the relative timing of excitation and inhibition played a minor role in shaping their directional selectivities. Rather it was the relative strengths of the excitatory and inhibitory inputs that were the features of primary importance.

3.7. IC cells receive different complements of inputs from lower auditory nuclei

The multiple formations of FM directional selectivity requires that each cell group that forms directionality in a particular way receive a complement of inputs that differs from the complement of inputs that innervate other groups in which directionally is formed differently. The proposition that the various FM directional cells receive a different complement of inputs is consistent with the afferent innervation of the IC. Projections to the IC originate from a large number of lower nuclei, where the axonal projections from each nucleus form bands that innervate restricted regions of each frequency contour in the IC (Casseday et al., 2002; Oliver et al., 1995, 1997; Ross and Pollak, 1989). Consequently, excitatory and inhibitory inputs to any given IC cell arise only from a subset of lower nuclei. The inputs to a cell located a short distance away, but having the same best frequency, would arise from a somewhat different set of nuclei, and so on across the contour. By mixing and matching inputs, a large number of innervation combinations is created within each frequency contour. The impacts of the diverse inner-vation patterns are further enhanced by the various complements of intrinsic ion channels among IC neurons (Gittelman, 2009; Rosenberger et al., 2003; Sivaramakrishnan and Oliver, 2001; Tan et al., 2007; Xie et al., 2008), which generate the wide range of input resistances and time constants that occur among the IC population (Xie et al., 2008; Gittelman et al., 2009).

3.8. Input differences suggest differences in response features to complex stimuli

The various cell groups that express FM directionality most likely respond differently to more complex stimulus arrangements, such as trains of FMs that occur in many communication calls, or the complex spectrotemporal features of notes in the calls (Bohn et

al., 2008, 2009; Klug et al., 2002), or to other acoustic features such as tones or noise (Fuzessery et al., 2006; Xie et al., 2007, 2008). Two examples clearly illustrate how different circuits can create the same basic response feature but where each circuit also creates differential responses evoked by more complex stimuli. One example is the cells in the cat IC that have “O” type frequency response maps that are almost identical to the response maps of cells in the dorsal cochlear nucleus (DCN). By blocking the pathway from DCN to the IC, Davis (2002) showed that some IC cells inherit their O type response maps from the DCN, whereas in other IC cells, the same O type response map is created by circuitry in the IC. Although the two types of IC cells respond to tones with O type response maps, they respond differently to more complex stimuli, such as notched noise (Davis et al., 2003). Another example is binaural neurons in the IC whose discharges are evoked by stimuli to one ear but are suppressed by stimuli presented to the other ear, the so called excitatory-inhibitory (EI) neurons. All of those IC neurons express the same binaural property. However, some neurons inherit their EI property from excitatory projections from the LSO, whereas in others, the EI property is created *de novo* in the IC. The de novo creation is through an excitatory projection from a monaural nucleus that is driven by the contralateral ear, and inhibitory projections from the dorsal nucleus of the lateral lemniscus (DNLL) that is activated by stimuli presented to the ipsilateral ear. Inherited and *de novo* features of EI cells have been seen in the IC of bats (Burger and Pollak, 2001; Pollak et al., 2003a), gerbils (Pecka et al., 2007) and rats (Faingold et al., 1993; Li and Kelly, 1992). Both types of cells are indistinguishable in terms of their responses to an individual binaural signal, but the EI cells formed *de novo* in the IC respond to multiple, binaural sound sources very differently than do neurons that inherit their EI property from the LSO (Burger and Pollak, 2001; Pecka et al., 2007).

3.9. A variety of response properties may be differentially formed in IC cells

It is not known exactly how or even whether FM directional selectivity, EI properties and selectivity for notched noise are jointly expressed in various cell groups in the IC. However, there are several similar features and relationships that strongly suggest that some or all of those features may be contained in individual IC cells. One feature is that the discharge tuning curves (frequency response maps) of on-off cells correspond closely to the O type response maps described by Davis and his colleagues (Davis, 2002). Unlike some of the O cells in the cat that inherit their response maps entirely from DCN excitatory projections, the dominant inputs to on-off cells are inhibitory, and thus on-off cells could not inherit their response maps from the DCN. Rather the maps of on-off cells may correspond to the other O type in the cat IC whose response maps are created in the IC. It also seems more than likely that many IC cells express both FM directional and EI properties. Although the directional selectivities of EI cells were not evaluated in previous studies, the majority of cells in the IC of bats are EI (Barber et al., 2003; Burger and Pollak, 2001; Grothe et al., 1996; Klug et al., 1995; Park and Pollak, 1993a; Pollak et al., 2003a; Wenstrup et al., 1988) and are also directionally selective for FM (Andoni et al., 2007; Fuzessery et al., 2006; Gittelman et al., 2009; Yue et al., 2007), suggesting that many EI cells are also FM directionally selective. If so, then some EI cells whose binaural properties are created *de novo* in the IC may derive their directional selectivity through spectrotemporal asymmetries (Andoni et al., 2007; Fuzessery et al., 2006; Poon et al., 1991). Other EI cells, in contrast,

may derive their directional selectivities through magnitude asymmetries of the sort reported by Gittelman et al. (2009), whereas others from VNLLc projections, as described above for onoff cells. Similar arguments can be made for EI cells that inherit their binaural property from the LSO.

3.10. Transformations in the IC are more complex than in lower nuclei

What all this suggests is that differential formations of common response properties are a general feature of the mammalian IC and that the differential formations are not confined to one or even two properties, but may well apply to multiple properties. Differential formation of common response properties also suggests that both the processing and complexity of responses is fundamentally different in the IC than in lower nuclei. The neuronal populations in the majority of lower nuclei are comprised of one, or at most a few, cell types, where each type receives a similar complement of inputs and responds even to complex signals, such as a suite of communication calls, in virtually the same way (Bauer et al., 2002; Xie et al., 2005). As described above, the innervation of the IC is markedly different and far more complex than the patterns of innervation in lower nuclei. Thus, one of the principal transformations that occur in the IC is a change from processing that emphasizes similarity among principal cells in lower nuclei to one that emphasizes diversity and selectivity among cells in the IC.

Selectivity in the IC is expressed in preferences for various acoustic features, as was shown above for directional preferences for FM direction or for particular interaural intensity disparities in EI cells. Another, even more dramatic expression of selectivity is seen in the responses of IC cells in bats when presented with a suite of communication calls. Selectivity refers to isofrequency neurons that, when presented with a suite of communication calls, only respond to a few of those calls and fail to respond to others even though all of the calls have suprathreshold energy that encroaches on their excitatory tuning curves (Andoni et al., 2007; Klug et al., 2002; Xie et al., 2005). The selectivity is largely a consequence of inhibition since the selectivity can be largely, or in some cases entirely, eliminated by blocking inhibition by the iontophoretic application of bicuculline and strychnine (Klug et al., 2002; Xie et al., 2005). Due to their selective properties, a particular communication signal presented to a population of IC cells results in discharges from only a subset of the IC population, where some cells respond to the call whereas others do not. Presenting a different call that has a similar spectrotemporal structure evokes a different pattern, in that some cells that fired to the first call drop out whereas others that failed to fire to the first call are recruited.

Presumably the various selectivities expressed by IC neurons for communication calls in bats are a consequence of the multiple ways in which their selectivities for features of acoustic signals, such as the direction and rate of FM sweeps, are created. The advantage conferred by the multiple formations of response properties in the IC is to amplify differential response selectivities for complex signals. The amplification is expressed by different and unique patterns of activity among the neuronal population in the IC that are evoked even by signals with only subtle differences in their spectrotemporal features (Klug et al., 2002; Pollak et al., 2003b; Xie et al., 2005).

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Abbreviations

EPSP	excitatory postsynaptic potential
FM	frequency modulation
HCN	hyperpolarization activated cation channel
IC	inferior colliculus
IPSP	inhibitory postsynaptic potential
LVK	low voltage activated potassium channels
MNTB	medial nucleus of the trapezoid body
PVCN	posteroventral cochlear nucleus
SPON	superior paraolivary nucleus
VNLL	ventral nucleus of the lateral lemniscus
VNLLc	columnar division of the ventral nucleus of the lateral lemniscus

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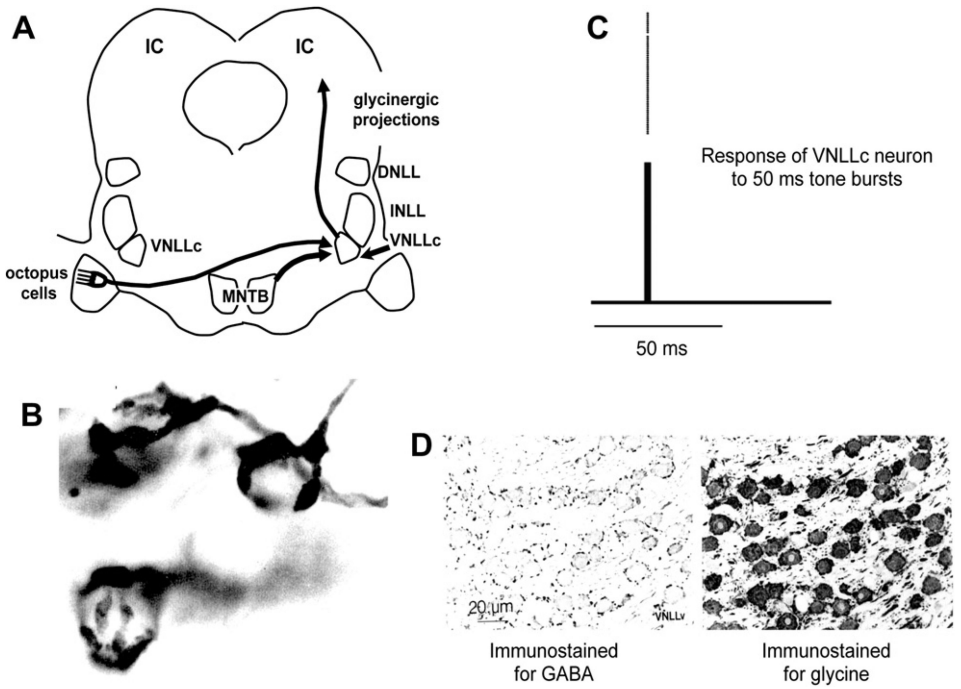

Fig. 1.

Circuitry and features of VNLLc cells. A: circuit showing projections to VNLLc from octopus cells in the cochlear nucleus and from MNTB cells. Redrawn from Vater, M., Covey, E., and Casseday, J.H. (1997). The columnar region of the ventral nucleus of the lateral lemniscus in the big brown bat (*Eptesicus fuscus*): synaptic arrangements and structural correlates of feed-forward inhibitory function. Cell Tissue Res 289:223–233. By permission of Springer-Verlag. B: End-bulbs of Held from octopus cells terminate on spherical cells in VNLLc. Adapted from Vater, M. and Feng, A.S. (1990) Functional organization of ascending and descending connections of the cochlear nucleus of horseshoe bats. J Comp Neurol 292:373–395. By permission of John Wiley & Sons. C: Responses of VNLLc cell to tone bursts. Top is raster display of responses evoked by tones while lower record shows same responses displayed as a PST histogram. D: Immunostained sections of the VNLLc from mustache bats showing that all neurons stain intensely for glycine but not GABA. Adapted from Winer, J.A., Larue, D.T. and Pollak, G.D. (1995) GABA and glycine in the central auditory system of the mustache bat: structural substrates for inhibitory neuronal organization. J Comp Neurol 355:317–353. By permission of John Wiley & Sons.

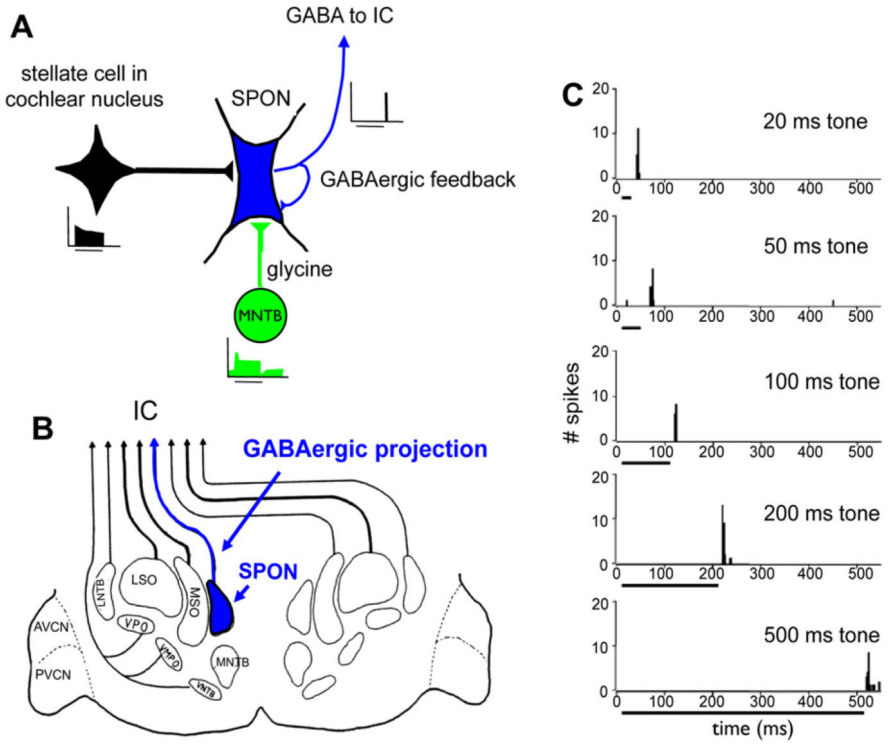

Fig. 2.

Connections and tone evoked responses in SPON cells. A: Connectional basis for tone evoked off responses. SPON cells receive tonic excitation from stellate cells and a tonic inhibition from MNTB that suppresses discharges for the duration of the tone burst. Rebound from inhibition then generates the off response at the termination of the tone. SPON cells then send GABAergic inhibition to the ipsilateral inferior colliculus (IC) and autaptic feedback that acts to limit the duration of the off discharge. Adapted from Kulesza R.J., Jr., Kadner, A., Berrebi, A.S. (2007) Distinct roles for glycine and GABA in shaping the response properties of neurons in the superior paraolivary nucleus of the rat. J Neurophysiol 97:1610–1620. By permission of American Physiological Society. B: Projections from auditory brainstem nuclei in Mexican free tailed bats to IC. C: Off responses recorded from SPON of rats to tones IC in Mexican free tailed bats. Adapted from Grothe, B. Schweizer, H., Pollak, G.D., Schuller, G. and Rosemann, C. (1994) Anatomy and projection patterns of the superior olivary complex in the Mexican free-tailed bat, *Tadarida brasiliensis mexicana*. J Comp Neurol 343:630–646. By permission of John Wiley & Sons.

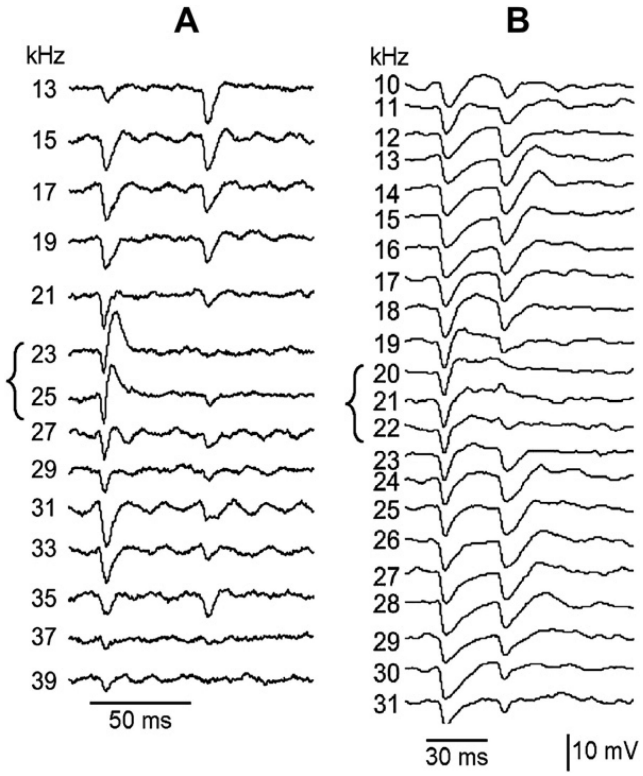

Fig. 3.

Two on-off cells recorded from the inferior colliculus of Mexican free-tailed bats with patch electrodes. Tone bursts were 50 dB SPL in both cells and in each cell the tones evoked an onset and offset IPSP over a wide range of frequencies. Tone burst durations are shown by the time bars. Brackets indicate the small range of mid-frequencies that evoked an onset IPSP but no offset IPSP. The midrange frequencies also evoked a depolarization that is most prominent in panel A. Data adapted from Xie, R., Gittelman, J.X. and Pollak, G.D. (2007).

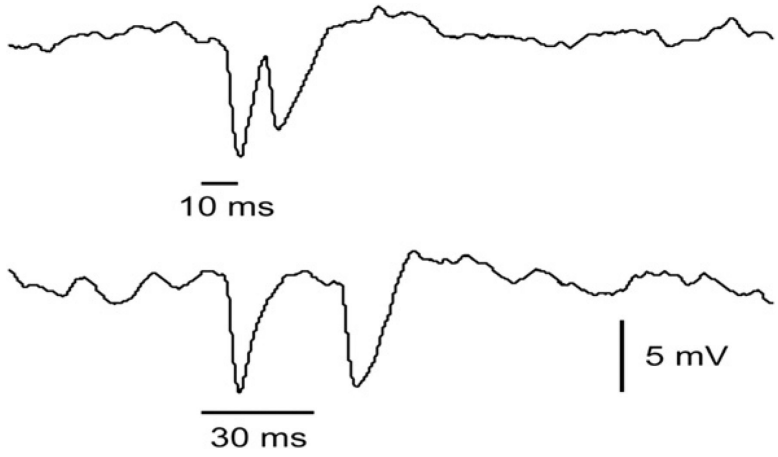

Fig. 4.

Responses evoked in an on-off neuron with two different tone burst durations, showing that the neuron responded with IPSPs to the onset and offset of the tone bursts. Tone bursts were 25 kHz at 50 dB SPL. Adapted from Xie, R., Gittelman, J.X. and Pollak, G.D. (2007) Rethinking tuning: in vivo whole-cell recordings of the inferior colliculus in awake bats. J Neurosci 27:9469–9481. By permission of Society for Neuroscience.

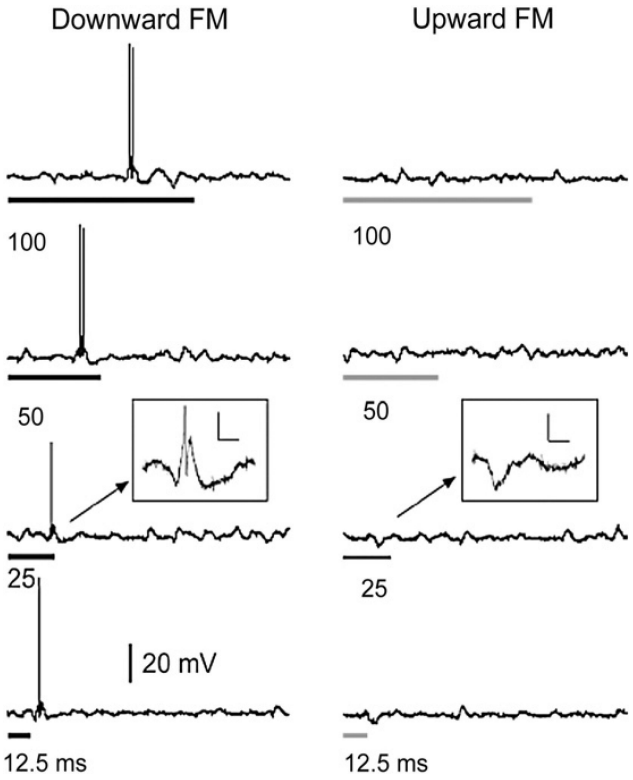

Fig. 5.

Responses evoked in an on-off cell by frequency modulated (FM) signals having different durations and sweep directions. Discharges were evoked by all downward sweeping FMs regardless of duration (sweep rate) but no discharges were evoked by any upward sweeping FM. All FMs were 50 dB SPL. Adapted from Xie, R., Gittelman, J.X. and Pollak, G.D. (2007) Rethinking tuning: in vivo whole-cell recordings of the inferior colliculus in awake bats. J Neurosci 27:9469–9481. By permission of Society for Neuroscience.

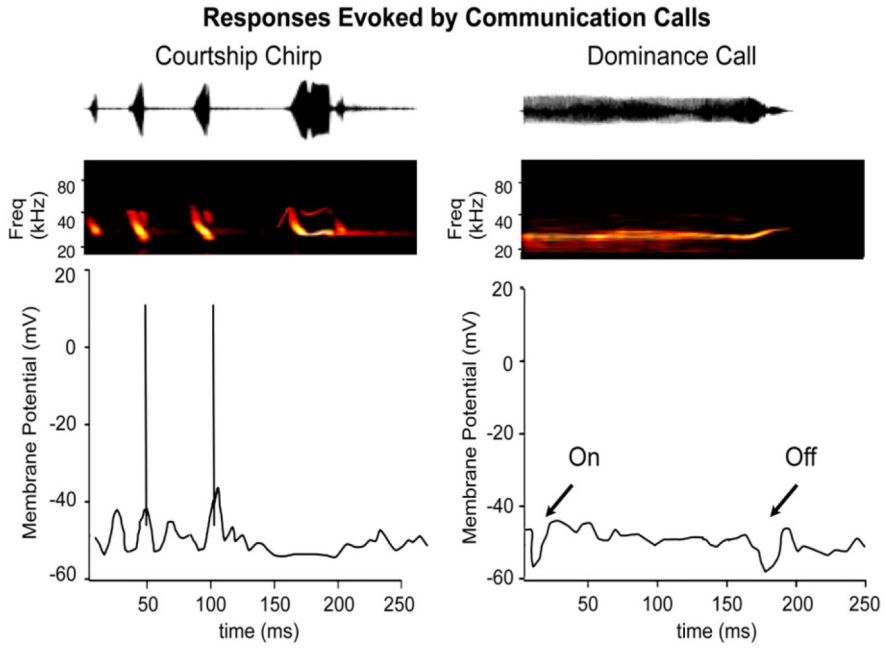

Fig. 6.

Intracellular responses recorded in an on-off cell from the IC of an awake bat with a patch electrode. Responses were evoked by two communication calls, a courtship chirp that had several notes that swept downward in frequency, and a dominance call composed largely of a constant frequency component. The cell discharged to the FM sweeps in the courtship call but responded to the tone-like dominance call with IPSPs at the onset and offset of the call, in a manner similar to the way on-off cells respond to tones. Both signals were 50 dB SPL (Xie and Pollak, unpublished data).

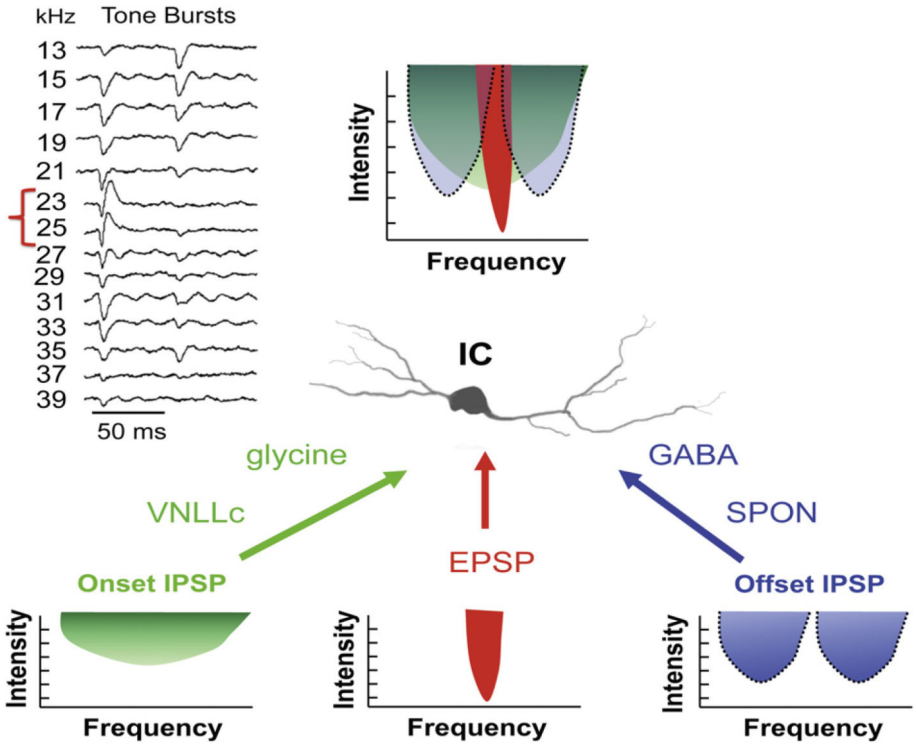

Fig. 7.

Circuitry that could account for the tuning features of on-off cells in the inferior colliculus. The responses of an on-off cell evoked by 50 dB SPL tones are shown in upper left panel (same cell shown Fig. 3A). The hypothesis proposes that the onset IPSPs are evoked by glycinergic projections from the VNLLc. The broad tuning of VNLLc cells is shown in lower left (green tuning curve) and accounts for the broadly tuned onset IPSPs of on-off cells. Projections from two differently tuned SPON cells could account for the IPSPs evoked at the offset of tone bursts (blue tuning curves in lower right panel). Two differently tuned SPON cells are suggested because off IPSPs are not evoked by midrange frequencies of 23–25 kHz, but are prominent at lower frequencies, from about 13 to 21 kHz, and at higher frequencies, from about 27 to 35 kHz. A more sharply tuned excitatory input from an unknown source with a best frequency in a midrange frequency is shown in red in the lower middle panel. That excitatory input accounts for the prominent depolarizations evoked by 23–25 kHz tone bursts in the tuned region, shown with brackets in the upper left panel. The top panel shows the superposition of the proposed inputs. Note that at 50 dB SPL, the midrange frequencies should evoke an onset IPSP, due to activation of the broadly tuned VNLLc, but not offset IPSPs since those frequencies fail to excite either of the two SPON inputs. The midrange frequencies should also activate the proposed excitatory input and thus evoke depolarizations.