Differential Response Properties to Amplitude Modulated Signals in the Dorsal Nucleus of the Lateral Lemniscus of the Mustache Bat and the Roles of GABAergic Inhibition

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We studied the phase-locking of 89 neurons in the dorsal nucleus of the lateral lemniscus (DNLL) of the mustache bat to sinusoidally amplitude modulated (SAM) signals and the influence that GABAergic inhibition had on their response properties. Response properties were determined with tone bursts at each neuron’s best frequency and then with a series of SAM signals that had modulation frequencies ranging from 50–100 Hz to 800 Hz in 100-Hz steps. DNLL neurons were divided into two principal types: sustained neurons (55%), which responded throughout the duration of the tone burst, and onset neurons (45%), which responded only at the beginning of the tone burst. Sustained and onset neurons responded differently to SAM signals. Sustained neurons responded with phase-locked discharges to modulation frequencies ≤400 Hz. In contrast, 70% of the onset neurons phase-locked only to low modulation frequencies of 100–300 Hz, whereas 30% of the onset neurons did not phase-lock to any modulation frequency. Signal intensity differentially affected the phase-locking of sustained and onset neurons. Sustained neurons exhibited tight phase-locking only at low intensities, 10–30 dB above threshold. Onset neurons, in contrast, maintained strong phase-locking even at relatively high intensities. Blocking GABAergic inhibition with bicuculline had different effects on the phase-locking of sustained and onset neurons. In sustained neurons, there was an overall decline in phase-locking at all modulation frequencies. In contrast, 70% of the onset neurons phase-locked to much higher modulation frequencies than they did when inhibition was intact. The other 30% of onset neurons phase-locked to SAM signals, although they fired only with an onset response to the same signals before inhibition was blocked. In both cases, blocking GABAergic inhibition transformed their responses to SAM signals into patterns that were more like those of sustained neurons. We also propose mechanisms that could explain the differential effects of GABAergic inhibition on onset neurons that locked to low modulation frequencies and on onset neurons that did not lock to any SAM signals before inhibition was blocked. The key features of the proposed mechanisms are the absolute latencies and temporal synchrony of the excitatory and inhibitory inputs.

INTRODUCTION

The dorsal nucleus of the lateral lemniscus (DNLL) occupies a strategic position in the ascending auditory pathway. Located immediately below the inferior colliculus, the DNLL receives innervation from a complement of lower nuclei that have excitatory as well as glycinergic and GABAergic inhibitory components (Fubara et al. 1996; Glendenning and Baker 1988; Glendenning et al. 1981; Huffman and Covey 1995; Hutson et al., 1991; Shneiderman et al. 1988; Vater et al. 1995; Winer et al. 1995; Yang et al. 1996; Zook and Casseday 1982b, 1987). The large convergence of excitatory and inhibitory inputs is consistent with single-unit and pharmacological studies, which have shown that DNLL neurons sample and integrate diverse sources of information which they express in their temporal discharge patterns (Covey 1993; Markovitz and Pollak 1993; Yang and Pollak 1994b).

DNLL neurons are distinguished by three features: they are largely binaural, and those neurons tuned to high frequencies are driven by stimulation of the contralateral ear and inhibited by stimulation of the ipsilateral ear (Bruggene et al. 1970; Buckthought et al. 1993; Covey 1993; Markovitz and Pollak 1994; Yang and Pollak 1994a); they are strongly immunoreactive for antibodies against conjugated GABA or glutamic acid decarboxylase (GAD), the rate limiting enzyme for the synthesis of γ-aminobutyric acid (GABA) (Adams and Mugnaini 1984; Covey 1993; Glendenning and Baker 1988; Moore and Moore 1987; Roberts and Ribak 1987; Thompson et al. 1985; Vater 1995; Vater et al. 1992a; Winer et al. 1995); and their axons terminate in the central nucleus of the inferior colliculus (ICc) (Bajo et al. 1993; Brunso-Bechtold et al. 1981; Hutson et al. 1991; Kudo 1981; Merchán et al. 1994; Ross and Pollak 1989; Ross et al. 1988; Shneiderman et al. 1988; Zook and Casseday 1982b, 1987). These features suggest that the DNLL is a major source of inhibitory inputs to the inferior colliculus, a point underscored by Shneiderman and Oliver (1989), who reported that approximately one-third of all inhibitory synapses in the cat inferior colliculus are from DNLL projections.

The putative inhibitory impact of the DNLL on its targets in the ICc, suggested by its connections and neurochemistry, has been confirmed by neurophysiological studies. In several studies, binaural properties of high-frequency ICc neurons were changed dramatically either when GABAergic inhibition was blocked by the iontophoretic application of bicuculline or when the DNLL was reversibly inactivated with pharmacological agents (Faingold et al. 1989, 1993; Klug et al. 1995; Li and Kelly 1992; Park and Pollak 1993, 1994; Vater et al. 1992b).

Although the inhibitory influences of the DNLL play a substantial role in forming the binaural properties of many ICc neurons, DNLL neurons receive inputs from lower cen-
FIG. 1. Poststimulus time (PST) histograms showing phase-locking to sinusoidal amplitude modulated (SAM) signals in 3 sustained neurons. Responses to tone bursts at best frequency are shown (top) as are responses to SAM signals of varying modulation frequencies (bottom). Coefficient of synchronization (CS) is shown to right of each PST histogram. Signal intensity was 30 dB SPL for all 3 units. Best frequencies were 77 kHz for unit 97 (A), 85 kHz for unit 66 (B), and 40 kHz for unit 104 (C). Responses to 700-Hz modulation frequency were obtained for units 97 (A) and 104 (C) but were not obtained for unit 66 (B). CSs at 700 Hz for units 97 and 104 are shown in Fig. 4.

FIG. 2. Expanded portions of PST histograms showing phase-locking to higher modulation frequencies for 3 sustained units shown in Fig. 1. Top: histograms generated by 70 ms SAM signals at 500 Hz. Dashed line indicates 15-ms periods in middle of responses that are expanded in histograms below. CS is shown above each histogram.

In the horseshoe bat DNLL, the question of how DNLL neurons respond to modulated signals has received little attention. Here we report on the response properties of DNLL neurons evoked by sinusoidally amplitude modulated signals in neurons whose discharges are phase-locked to the patterns of amplitude and frequency fluctuations contained in auditory signals that animals normally receive. Except for a study of the horseshoe bat DNLL by Metzner and Radtke-Schuller (1987), the question of how DNLL neurons respond to modulated signals has received little attention.
that the bat not only distinguishes its prey from background objects but also identifies its prey (Goldman and Henson 1977). Because mustache bats, like other echolocating bats, “see” much of their world through their sense of hearing, the nuclei of their brain stem auditory systems are relatively larger than in nonecholocating mammals.

Although their auditory systems are hypertrophied, the auditory nuclei in the mustache bat are structurally, connectionally and functionally similar in most respects to those of other, less specialized mammals (Markovitz and Pollak 1993, 1994; Park and Pollak 1993, 1994; Pollak and Casseday 1989; Ross et al. 1988; Wenstrup et al. 1988; Winer et al. 1995; Yang et al. 1996; Zook and Casseday 1982a,b, 1985, 1987). One nucleus that is especially prominent and clearly demarcated from surrounding structures in mustache bats is the DNLL (Markovitz and Pollak 1993; Winer et al. 1995; Yang et al. 1996). In a previous study, we used this feature of the DNLL to map the response properties of DNLL neurons to both tone bursts and sinusoidally amplitude modulated (SAM) signals and to evaluate the afferent inputs to the DNLL (Yang et al. 1996). We found that the mustache bat DNLL is divided functionally into two parts. The neurons in each division are distinguished by their temporal discharge patterns evoked both by tone bursts and SAM signals. Neurons in the anterior one-third of the DNLL respond to tone bursts with an onset discharge pattern and only phase-lock to SAM signals with low modulation frequencies (<300 Hz). Neurons in the posterior two-thirds of the DNLL respond to tone bursts with a sustained discharge pattern and phase-lock to SAM signals that have much higher modulation frequencies.

Here we describe the phase-locking of sustained and onset DNLL neurons to SAM signals with different modulation frequencies in greater detail and show how phase-locking is affected by signal intensity. In addition, we show that blocking GABAergic inhibition has different effects on the phase-locking of sustained and onset neurons, and propose mechanisms that could explain the differential influences of GABAergic inhibition.

**METHODS**

**Surgical procedures**

Ten mustache bats, *Pteronotus pammeli pammeli*, were used in this study. Before surgery, each animal was anesthetized with methoxyflurane inhalation (Metofane, Pitman-Moore) and 0.02 mg/gm neuroleptic, Innovar-Vet (Pitman-Moore), injected intraperitoneally. The hair on the head was removed with a depilatory, and the head was secured in a head holder with a bite bar. The muscles and skin overlying the skull were reflected and lidocaine (Elkins-Sinn) was applied topically to all open wounds. The surface of the skull was cleared of tissue, and a foundation layer of cyanoacrylate and small glass beads was placed on the surface. A small hole then was drilled around the center portion of the inferior colliculus using the landmarks visible through the skull for orientation.

The bat was transferred to a heated recording chamber, where it was placed in a restraining cushion constructed of foam molded to the animal’s body. The restraining cushion
was attached to a platform mounted on a custom made stereotaxic instrument (Schuller et al. 1986). A small metal rod was cemented to the foundation layer on the skull and then attached to a bar mounted on the stereotaxic instrument to ensure a uniform positioning of the head. A ground electrode was placed between the reflected muscle and the skin. Recordings were begun after the bats recovered from the anesthetic. The bats typically lay quietly in the restraining cushion and showed no signs of pain or discomfort. Supplementary doses of the neuroleptic were given if the bat struggled or otherwise appeared in discomfort.

After the animal was fixed in the stereotaxic instrument, the portion of the instrument in which the bat was held was rotated and adjusted to maximize the extent of the DNLL that would be encountered by the electrode penetration. Using visual landmarks viewed with an operating microscope, the electrode was advanced from outside of the experimental chamber with a piezoelectric microdrive (Burleigh 712IW). The tonotopic organizations of the inferior colliculus and DNLL were used to determine when the electrode had left the inferior colliculus and entered the DNLL. As the electrode was advanced through the inferior colliculus, there was an abrupt change in the best frequency (the frequency to which the cluster or single unit was most sensitive) of the background activity at a depth of ~2,200–2,400 μm. Subsequently, the electrode was advanced from outside of the experimental chamber with a piezoelectric microdrive (Burleigh 712IW).

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Electrodes

In some experiments, single units were recorded with single barrel micropipettes whose tips were blunted slightly to diameters of ~1.0 μm. The micropipettes were filled with buffered 1 M NaCl and 2% Fast Green (pH 7.4). In other experiments “piggy back” multibarrel micropipettes were used for recordings and iontophoresis of drugs (Havey and Caspary 1980). Single-barrel micropipettes were pulled to a tip diameter <1 μm and blunted under microscope observation so that the tip diameter was between 1 and 2 μm. A multibarrel electrode was pulled from a five-barrel blank (H-configuration, Omega dot, Glass Company of America) and the tip blunted so that the tip diameter of the multibarrel array was 15–20 μm. The single-barrel pipette was attached to the five-barrel pipette under microscopic observation and glued with cyanocrylate so that the tip of the single-barrel pipette protruded ~10–15 μm from the broken tip of the five-barrel pipette. The single-barrel micropipette was used for recording and filled with buffered 1 M NaCl and 2% Fast Green (pH 7.4). Electrode impedances ranged from 5 to 15 MΩ. Fast Green was used to enhance the visibility of the electrode for placement in the small hole made in the skull. One barrel of the five-barrel pipette was the balancing (sum channel) barrel, which also was filled with buffered 1 M NaCl and 2% Fast Green (pH 7.4). Two of the remaining four ejection barrels were filled with GABA (500 mM, pH 3.5–4.0, Sigma) and two others with bicuculline methiodide (10 mM, pH 3.0, Sigma).

The drug and balancing barrels were connected via silver-silver chloride wires to a six-channel microiontophoresis constant current generator (Medical Systems Neurophore BH-2) that was used to generate and monitor ejection and retention currents. The sum channel that connected to the
A Macintosh 7100 computer to a real time clock (Restek model 86) and a two-channel digital attenuator (Wilsonics, model PATT). The output of each independently controlled channel of the attenuator was sent to two 1/4-in Brüel & Kjaer (B&K) microphones biased with 200 V DC and driven as speakers. At the start of each experiment, speakers, with wind screens attached, were inserted into the funnels formed by the bat’s pinnae, and positioned adjacent to the external auditory meatus. The pinnae were folded onto the housing of the microphones and wrapped with Scotch tape. The acoustic isolation with this arrangement was ≈40 dB.

Only well-isolated spikes with a high signal-to-noise ratio of ≈8:1 were studied. Spikes were fed to a window discriminator and the output of the discriminator was fed to the real-time clock. Upon encountering a DNLL neuron, its best frequency and its threshold at the best frequency were determined by audio-visual inspection. The frequency of the tone burst then was set at the neuron’s best frequency. The binaural property then was assessed by driving the cell with a tone burst presented to the contralateral ear at 20 dB above the threshold of the best frequency. With the intensity fixed at the contralateral ear, the same frequency then was presented simultaneously to the ipsilateral ear and the intensity of the ipsilateral signal was increased from 10 to 20 dB below the intensity at the contralateral ear to 40 dB above that intensity in 10-dB steps. After determining the neuron’s binaural property, the ipsilateral signal was turned off and SAM signals of 70 ms duration were presented to the contralateral ear. The carrier frequencies of the SAM signals were set at the neuron’s best frequency. A set of SAM signals, each with a different modulation frequency, was presented to each unit. For most units, we presented modulation frequencies ranging from 100 to 800 Hz but omitted 700 Hz. Spikes evoked by both tone bursts and SAM signals were fed to a window discriminator and then to a Macintosh 7100 computer for generating poststimulus time (PST) histograms and raster displays. PST histograms or raster displays were generated from the spikes evoked by 20 presentations of each stimulus, and the computer calculated the total spike-counts. For SAM signals, the computer also calculated spikes per cycle and the coefficient of synchronization (CS), as described by Goldberg and Brown (1969). The coefficient of synchronization provides a quantitative value of phase-locking or how well discharges are synchronized to the phase of the SAM waveform. A CS of 1.0 is generated when the unit fires at exactly the same phase of each cycle of the modulation waveform whereas a CS of 0.0 is generated when the spikes are uncorrelated with the waveform. To exclude the effect of the onset response, the spikes generated during the initial 6–10 ms of the response were not included in the calculation of the CS.

The effects of blocking GABAergic inhibition with bicuculline were evaluated in 29 units. In these neurons, responses were recorded before, during, and after drug application. When a drug was not being applied, a retention current of 15 nA (electrode negative) was applied to balancing barrel was employed to balance current in the drug barrels and reduce current effects. The recording barrel was connected by a silver-silver chloride wire to a Dagan AC amplifier (model 2400) for analysis of single unit activity.

**Acoustic stimuli and data acquisition**

Sine waves from a Wavetek function generator (model 136) were shaped into tone bursts with a custom made analog switch. Two tone bursts could be generated independently by the switch, and the relative timing of the two signals was controlled by a custom made pulse delay system with digital interface. SAM signals were created digitally on a Macintosh 7100 computer. The tone bursts and SAM signals were 70 ms in duration and had 0.5 ms rise-fall times. Stimuli were presented at a rate of four per second. Tone burst frequency was monitored by a frequency counter. A 24-bit digital interface NuBus card (Metabyte MAC PIO-24) and a digital distributor (Restek model 99) connected...
each drug barrel to prevent leakage of drugs. Drugs were applied iontophoretically by turning off the negative retaining current and switching to a positive ejection current. For each neuron, GABA first was applied iontophoretically and the ejection current was increased progressively until the neuron was inhibited completely. The negative retaining current then was reapplied to the GABA barrel and a positive current was applied to the bicuculline barrel. Low (10 nA, electrode positive) ejection currents of bicuculline were used initially. The rate-intensity functions were taken repeatedly until the shape and maximum spike-count stabilized. The ejection current then was increased and the procedure repeated until the maximum spike count no longer increased. The currents finally employed ranged from 10 to 30 nA with bicuculline.

RESULTS

Here we report on 89 single units recorded from the DNLL of the mustache bat. The best frequencies (BFs) ranged from 22 to 92 kHz, although almost half of the units (45/89) had best frequencies ~60 kHz, the dominant component of the animal’s orientation calls. All units were excited by stimulation of the contralateral ear and were inhibited by stimulation of the ipsilateral ear. In the present study, we focused on the discharge patterns evoked by monaural stimulation of the contralateral ear. Two major types of units were identified on the basis of their temporal discharge patterns evoked by tone bursts at the unit’s BF. The first type of unit discharged throughout the duration of the tone burst and thus had a sustained discharge pattern. Fifty-five percent (49/89) of the units exhibited a sustained discharge pattern. The other 45% (40/89) were onset and discharged only at the beginning of the tone burst, regardless of the signal duration. These percentages do not accurately reflect the actual proportion of onset and sustained units in the DNLL because we often targeted the anterior region of the DNLL, the region dominated by onset neurons. We did this because onset neurons are of particular interest and the anterior region of the DNLL is considerably smaller than the posterior region and thus is less likely to be encountered unless specifically targeted. In the following sections, we first describe the responses evoked by SAM signals in sustained neurons and compare them with the responses evoked in onset units. We then present the results from iontophoretic experiments showing that GABAergic inhibition has different influences on the discharge patterns of the neurons.

FIG. 6. Raster displays showing influence of signal intensity on discharges evoked by 100 Hz SAM signals for 2 sustained neurons. CS and S/C are shown next to each raster. Best frequencies were 83 kHz (A) and 60.8 kHz (B). Graph (C) shows decline in CS with intensity for 100 Hz SAM signals in 13 sustained neurons.
bicuculline. To make the data comparable among units, the average 3.1 spikes/cycle and discharged 427 spikes to 20 charges tightly phase-locked to modulation frequencies with modulation frequency (Yang and Pollak 1994b). The distinguishing feature of sustained neurons was that they typically responded with discharges tightly phase-locked to modulation frequencies ≤400–600 Hz, and some exhibited tight phase-locking even at 800 Hz. We quantified phase-locking by calculating coefficient of synchronization (CS). A CS value of 1 indicates that the each discharge occurred at exactly the same phase of the modulation waveform and a CS value of 0 indicates that the discharges were not synchronized to the modulation waveform.

The phase-locking abilities of sustained neurons are illustrated by three units in Fig. 1. Neuron 97 (Fig. 1A) was one of the best in our sample in terms of its tight phase-locking to modulation frequencies as high as 800 Hz, the highest frequency that we tested. The CSs, shown to the right of each PST histogram, ranged from 0.92 at 400 Hz to 0.71 at 800 Hz. The two other neurons in Fig. 1 are more representative. For neuron 66 in Fig. 1B, phase-locking at lower modulation frequencies, from 100 to 500 Hz, was high and was comparable to neuron 97 in Fig. 1A, although the CSs were slightly lower, ranging from 0.78 at 100 Hz to 0.71 at 500 Hz. Neuron 66 continued to phase-lock well at 600 Hz and 800 Hz but the CSs dropped to 0.63 at 600 Hz and to 0.50 at 800 Hz. The phase-locking of neuron 104 in Fig. 1C was not as precise as it was in the two previous neurons. The highest CS was 0.62 at 100 Hz and became progressively smaller as modulation frequency increased. At 600 and 800 Hz, the neuron continued to discharge throughout the signal, but with discharges that were either poorly synchronized (600 Hz) or unsynchronized (800 Hz) to the modulation waveform. The differences in phase-locking among the three units at modulation frequencies from 500 to 800 Hz can be seen in the magnified PST histograms in Fig. 2.

The overall trend for sustained cells was that the average CSs were highest at modulation frequencies of 100–200 Hz and then declined as modulation frequency increased (Fig. 3A). However, there was substantial variation among units. In some units, the phase-locking precision, indicated by CSs, deteriorated progressively with increasing modulation frequency (e.g., Fig. 1C). In others, the CSs were more or less constant as modulation frequency increased to 400–500 Hz, and then declined (e.g., Fig. 1B), whereas in others, the precision of phase-locking increased with modulation frequency to 400–500 Hz and then declined (e.g., Fig. 1A).

The response to SAM was evaluated by presenting modulation frequencies that varied from 100 Hz, or in a few cells from 50 Hz, to 800 Hz. In the early stages of the study, we included 50 Hz in the program of SAM frequencies that we presented to each neuron. However, because we could find no DNLL neuron that did not phase-lock well to 50 Hz, we omitted 50 Hz from the later program simply to shorten the time for obtaining this data so that we could maximize our chances of holding the units long enough to test them with bicuculline. To make the data comparable among units, the SAM signals were always fixed at 20 dB above the unit’s threshold and the carrier frequency was set at the unit’s BF. We used this intensity because it evoked vigorous discharges from each neuron and it was on the linear portion of each unit’s rate-intensity function (Markovitz and Pollak 1993; Yang and Pollak 1994b). The distinguishing feature of sustained neurons was that they typically responded with discharges tightly phase-locked to modulation frequencies ≤400–600 Hz, and some exhibited tight phase-locking even at 800 Hz. We quantified phase-locking by calculating coefficient of synchronization (CS). A CS value of 1 indicates on the ways in which sustained and onset neurons respond to SAM signals.

**Coding of SAM frequencies by sustained neurons**

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of 600–800 Hz, the sustained discharges of neuron 104 as well as the majority of other sustained neurons, were no longer locked tightly to each modulation cycle, but the total spike-counts were still similar to those evoked by lower frequencies, at which the phase-locking was tight. It follows, therefore, that the modulation frequencies cannot be coded by the overall spike-count but rather seem to be coded by the temporal synchrony of the discharges, at least at intensities 10–30 dB above threshold.

In contrast to neuron 104 described above, those with the highest CSs had spike-counts that changed substantially with modulation frequency. For example, neuron 97 in Fig. 4B, which is the same neuron shown in Figs. 1A and 2A, responded to 100 Hz SAM signals with a CS of 0.80 (top right). The CS was high because the neuron fired only one to two spikes to each cycle with an average of 1.3 spikes/cycle. Consequently, the overall spike-count was relatively low (190 spikes to 20 stimulus presentations). As modulation frequency increased, the spikes/cycle declined exponentially but the change was much smaller than it was in neurons with lower CSs as described above, e.g., for neuron 104 in Fig. 4A. The total spike-counts increased with modulation frequency because the relatively small decline in spikes/cycle was more than offset by the increase in the number of modulation cycles. Thus the spike-count more than doubled from 190 spikes at 100 Hz to 389 spikes at 600 Hz and then fell slightly at 700–800 Hz.

**Effect of intensity on phase-locking in sustained neurons**

We also evaluated how phase-locking changed with intensity for 100 Hz SAM signals in 17 sustained neurons. In almost all of these neurons, the largest CSs, and thus the most precise phase-locking, was evoked only at intensities 10–30 dB above threshold. At higher intensities, smaller CS values were obtained as illustrated by the two neurons in Fig. 6. At lower intensities, discharges were evoked at the peak or only during a relatively small portion of each modulation cycle. Thus there were only a few phase-locked discharges to each cycle, and consequently there were relatively high SCs. At higher intensities, 40–60 dB above threshold, discharges were evoked during a longer portion of each cycle thereby smearing the temporal synchrony. The decline in CSs with intensity for 13 sustained neurons is shown in Fig. 6C.
Responses of onset neurons to SAM

The response patterns of onset units to SAM frequencies differed markedly from patterns of sustained neurons. The majority of onset cells (70%, 28/40) phase-locked to SAM signals but only at low-modulation frequencies, from 100 to 300 Hz. In some onset neurons, the highest frequency that evoked phase-locking was 100 Hz (Fig. 7B), whereas in others, it was 200 Hz (Fig. 7A) or, in a few cases, 300 Hz. At these low-modulation frequencies, most onset neurons responded with one or occasionally two to three discharges to each cycle of the modulation waveform, whereas others responded to some but not to every cycle. At modulation frequencies of ≥300 Hz, they either phase-locked to the initial two to three cycles of the SAM signal and then failed to respond to any later cycles or responded with a few scattered discharges. Some onset neurons responded only to the onset of the signals when the modulation frequencies were at or above 300 Hz.

Because onset neurons responded to low modulation frequencies with one or occasionally two to three discharges per cycle, the CSs were generally higher than the CSs of sustained neurons, which typically responded with a burst of discharges to each cycle at these low modulation frequencies. The two onset neurons in Fig. 7 illustrate this feature. Neuron 49 in Fig. 7A responded strongly to modulation frequencies of 100 and 200 Hz, with CSs of 0.92 and 0.93. At 300 and 400 Hz, the neuron fired mainly to the initial three cycles with phase-locked discharges and then fired only infrequently to any of the subsequent cycles. Although the spikes/cycle were low at 300 and 400 Hz, the CSs were 0.79 and 0.73, respectively. Interestingly, the onset responses of unit 49 were greatly reduced at higher modulation frequencies. The reason for the onset response attenuation is unclear. Neuron 110 in Fig. 7B locked only to 100 Hz with a CS of 0.86. At modulation rates of ≥200 Hz, it fired almost exclusively to the onset of the signal and not to any of the following cycles.

The average CSs of the 28 onset neurons that locked to low modulation frequencies are shown in Fig. 3B. This figure also shows that the average CSs evoked by modulation frequencies from 100 to 300 Hz were higher in onset than in sustained neurons.

In contrast to sustained neurons, the spike-counts of onset neurons that phase-locked changed markedly with modulation frequency. The general pattern was that there was a moderate to large increase in spike count as modulation frequency increased from 50–100 Hz to 200–300 Hz followed by a steep decline at higher frequencies. The characteristically peaked modulation functions of 15 representative examples are shown in Fig. 5B. The initial increase in spike count was a consequence of the neurons responding with one to two spikes to a larger number of cycles as modulation frequency increased from 50 or 100 Hz to 300 Hz. The spike-counts then declined markedly because almost all of these neurons responded largely,
if not exclusively, with an onset response to the higher modulation frequencies.

**Effect of intensity on phase-locking in onset neurons**

Although the large increase in discharge rate with intensity caused CSs to deteriorate substantially in sustained neurons, onset neurons maintained high CSs even at relatively high intensities (Fig. 8). The number of discharges evoked by each cycle increased with intensity in onset units, but the increase was from less than one spike per cycle to ~1.4 spikes per cycle over a 30–50 dB intensity range (Fig. 8). Because the increase in discharge rate with intensity was far more limited in onset than sustained neurons, the large CSs at low intensities were reduced only slightly at higher intensities in onset neurons.

**Onset neurons that did not phase-lock to SAM**

The most striking and heterogeneous onset cells were the 12 cells (30% of onset neurons) that did not phase-lock to any modulation frequency (Fig. 9). In response to SAM frequencies, these cells either failed to respond even to the onset of the signal (Fig. 9A) or responded only to the onset of the SAM signal. In some neurons that responded to the onset of the modulated signal, the onset response was weak at low modulation frequencies and became more vigorous at higher frequencies (Fig. 9B). Others behaved in the opposite fashion, where the onset response was stronger to low modulation frequencies and became weaker at higher frequencies (Fig. 9C). Finally, others appeared indifferent to SAM and responded to a tone burst and to all frequencies with about the same spike-counts (Fig. 9D). No type was dominant and each appeared with equal frequency in our sample.

**Effects of blocking GABAergic inhibition on SAM coding in sustained neurons**

The responses evoked by SAM signals were evaluated in 14 sustained and 15 onset units before and during bicuculline application. In four sustained neurons, bicuculline had no effect or only a small effect on both response magnitude and the precision of phase-locking. In 10 sustained neurons, however, bicuculline increased response magnitude. This was manifest as an increase in the spike-counts evoked by tone bursts and in the number of discharges evoked by each cycle of the SAM signals, and thus a reduction in CS across modulation frequencies. An example is shown in Fig. 10. The bicuculline-induced increase in spikes/cycle is apparent in the raster displays and from the graph in Fig. 10A, and the increases in total spike-counts is shown by the graph in Fig. 10B. Because the number of spikes per cycle was enhanced by bicuculline, the phase-locking was smeared and thus there was a substantial reduction in the CS at all modulation frequencies. These effects of blocking GABAergic inhibition are similar to those caused by increases in signal intensity described previously. The effects of bicuculline on CSs of the 10 units are shown in Fig. 11.

**Effects of blocking GABAergic inhibition on SAM coding in onset neurons**

In phase-locking onset units, bicuculline also caused an overall increase in response magnitude. With tone bursts, the blockage of inhibition allowed the neurons to discharge throughout the duration of the signal. In some units, the sustained portion of the discharge was prominent whereas in others it was less prominent (e.g., the unit in Fig. 12). The increase in response magnitude, however, did not smear the phase-locking as it did in sustained neurons but rather caused onset neurons to respond much more vigorously to later cycles of the modulated signal than they did before GABAergic inhibition was blocked. An example is shown in Fig. 12. In the predrug condition, this neuron fired weakly to modulation frequencies from 200 to 300 Hz, although the discharges were locked tightly to the modulating waveform. At higher modulation frequencies, the discharges to the initial two to four cycles were phase-locked but the discharges to subsequent cycles were even less frequent than with lower modulation frequencies. The effect of bicuculline was substantial in that after blocking GABAergic inhibition the neuron responded briskly with phase-locked discharges throughout the duration of signals ~500 Hz. It continued to phase-lock for the duration of the 600- and 800-Hz signals, although the number of spikes/cycle was reduced during the later portions of the signal.

DISCUSSION

There are four main findings of this study. First, DNLL neurons can be divided into two principal types, those that respond to tone bursts with onset patterns and those that respond with sustained patterns. Second, sustained neurons respond to SAM signals with discharges tightly phase-locked to modulation frequencies ~400–600 Hz, and some exhibited tight phase-locking even at 800 Hz. In contrast, most onset neurons phase-lock only to low modulation frequen-
cies of $\leq 100-300$ Hz, and others do not phase-lock to any modulation frequency. These findings are consistent with those reported previously (Yang et al. 1996). Third, intensity differentially affected the phase-locking of sustained and onset neurons. The phase-locking of sustained neurons is smeared markedly at higher intensities, whereas in onset neurons, the phase-locking is only marginally reduced and remains strong at higher intensities. The fourth finding is that GABAergic inhibition has different effects on the phase-locking of sustained and onset neurons. In sustained neurons, blocking GABAergic inhibition increased response magnitude and caused an overall decline in phase-locking at all modulation frequencies. In onset neurons, blocking GABAergic inhibition either allowed the neurons to phase-lock to higher modulation frequencies than they did when the inhibition was intact or it allowed them to phase-lock to SAM signals although they fired only with an onset response to the same signals before inhibition was blocked. In both cases, blocking GABAergic inhibition transformed their responses to SAM signals into patterns that were more like those of sustained DNLL cells.

**Temporal coding of signal amplitude fluctuations by onset and sustained DNLL neurons**

The properties exhibited by sustained and onset neurons suggest that the two types are not equally suited for conveying information about signal amplitude fluctuations to their higher order targets. It would appear that sustained neurons could provide such temporal information, but only at relatively low intensities where phase-locking is high and not at higher intensities where their phase-locking is much less precise. In contrast, the onset neurons that we recorded fired in tight registration with modulating waveforms at both high and low intensities. These cells appear to have properties more appropriate for conveying temporal information then do sustained neurons. The trade-off is that onset cells can convey information only for relatively low-modulation frequencies and become virtually ineffective at higher modulation frequencies.

**GABAergic inhibition plays different roles in sustained and onset neurons**

The disparities in response properties between sustained and onset neurons is to a large extent due to the differential...
inhibition is blocked. The relatively weak effects of GA-

frequencies below

tively weak and temporally coincident with the excitation in like many onset DNLL neurons, respond to SAM signals

the effects of GABAergic inhibition appear to be both rela-
tional ear ( Covey et al. 1991; Grothe et al. 1992 ) . In an

durred throughout the duration of the signal.

The second effect of GABAergic inhibition is in onset
cells that phase-locked to SAM signals. In these cells,
blocking GABAergic inhibition allowed the cells to respond
not only throughout the duration of modulated signals but
also to respond with phase-locked discharges to frequencies
several hundred Hertz higher than those to which they phase-
locked when the inhibition was intact. The features that re-
quire explanation are how the principal effects of the inhibi-
tion could be exerted only at higher modulation frequencies
and how that inhibition could have had only minor effects
on the phase-locked responses evoked by low modulation
frequencies.

**Inhibitory delays may shape the low-pass characteristics
of onset neurons**

Insights into the mechanisms that could generate the low-
pass characteristics of onset neurons in the DNLL are pro-
duced greatly in the mustache bat, and because of this fea-

common with other mammals, the MSO of the mustache bat receives excitatory
innervation from the contralateral cochlear nucleus and gly-
cineric, inhibitory innervation from the medial nucleus of the trapezoid body ( MNTB ) ( Covey et al. 1991 ). However,

the innervation from the ipsilateral cochlear nucleus is re-
duced greatly in the mustache bat, and because of this fea-
ture, most MSO cells receive innervation only from the con-
tralateral ear ( Covey et al. 1991; Grothe et al. 1992 ). In an
elegant study, Grothe ( 1994 ) showed that MSO neurons,
like many onset DNLL neurons, respond to SAM signals
with phase-locked discharges, but only to low-modulation
frequencies below ~300 Hz. He then showed that tone bursts
evoke an excitation followed by a delayed inhibition and
that after blocking glycineric inhibition with strychnine,
MSO cells phase-lock to modulation frequencies of ~800
Hz. To account for these features, he proposed that both
the excitatory inputs from the cochlear nucleus and the inhibi-

FIG. 11. Changes in CSs in 10 sustained neurons due to blocking GA-
Bergic inhibition with bicuculline. Each symbol shows coefficients of
synchronization for an individual neuron. Coefficients of synchronization
were obtained for modulation frequencies ranging from 100 to 800 Hz for
each neuron. Symbols falling on solid line indicate no change in phase-
locking due to bicuculline whereas symbols below solid line indicate that
phase-locking was poorer when GABAergic inhibition was blocked by
bicuculline.

impact of GABAergic inhibition on the two cell types. In
some sustained cells, the effects of GABAergic inhibition are
difficult to discern because the response magnitude, temporal
discharge pattern to tone bursts and the phase-locking to
SAM signals are all unchanged when GABAergic inhibition
is blocked by bicuculline. In others, response magnitude
increases and, as a consequence, they fire more spikes per
cycle, causing the phase-locking to deteriorate. In these cells,
the effects of GABAergic inhibition appear to be both rela-
tively weak and temporally coincident with the excitation in
that the entire response is uniformly enhanced when the
inhibition is blocked. The relatively weak effects of GA-
Bergic inhibition on responses evoked by contralateral
stimulation is consistent with our previous study where we
evaluated the influence of inhibition on responses evoked
by tone bursts ( Yang and Pollak 1994b ).

GABAergic inhibition has much stronger and more pro-
found effects on onset cells, a feature also noted in our
previous study ( Yang and Pollak 1994b ). Not only does it
increase response magnitude in all of these cells, but it also
strongly suppresses an underlying phase-locked excitation.
There are two different effects of GABAergic inhibition that
can be distinguished from the temporal features of the inhibi-
tion. One effect is exemplified by onset cells that did not
phase-lock to any modulated signal. The GABAergic inhibi-
tion on these cells is not only strong but with SAM signals
it inhibits all discharges except for the onset discharge. The
simplest explanation for these effects is that the inhibition
to these cells is delayed slightly relative to the excitation
and that the inhibition is uniformly strong throughout the
duration of the SAM signal. One way that this could be
achieved is if these cells receive inhibition from several
sustained cells or cells like them ( Fig. 15 ). The inhibitory
discharges from each input are phase-locked but each input
has a slightly different delay and thus a different relative
phase. Under these conditions, the DNLL cell would receive
repetitive excitatory inputs phase-locked to the signal enve-
lope and a delayed inhibition that is continuous and uninterr-
upted throughout the duration of the signal.

The general idea is that due to the delayed inhibition,
repetitive excitatory inputs phase-lock to even high-modulation
frequencies. The general idea is that due to the delayed inhibition,
at low-modulation frequencies the excitation of the initial
cycles evoke discharges in the MSO cell whereas the subse-
quent cycles evoke both excitation and inhibition that are
out of phase ( Fig. 16 ). Because the two inputs are out of
phase at low-modulation frequencies, the inhibition and exci-
tation are not coincident at the target cell and thus discharges
are evoked during the periods of excitation that are inter-
leaved between the periods of inhibition. The key events
occur at higher modulation frequencies. Here the initial exci-
tation still evokes phase-locked discharges, but for subse-
quent cycles, the delayed inhibition falls into phase with the
FIG. 12. PST histograms showing enhanced phase-locking evoked by SAM signals in an onset unit due to blocking GABAergic inhibition with bicuculline. CS is shown next to each histogram. Signal intensity was 40 dB SPL and best frequency was 57 kHz. Ejection current used to apply bicuculline was 30 nA.

excitation thereby bringing the two inputs into coincidence and suppressing discharges. Even higher modulation frequencies create a phase shift between the two inputs, but now the cycles are so short and the repetition so high that the period between inhibition and the following excitation is too short to allow the inhibition to decay before the next excitation arrives. Thus the effect of blocking the inhibition is to unmask an underlying phase-locked excitation.

Because both the discharge properties to SAM and the effects of blocking inhibition in MSO cells are so similar to onset DNLL cells, the delay mechanism outlined above for the MSO also can explain our results from onset DNLL cells. Furthermore, this mechanism is consistent with the observation that at low-modulation frequencies onset cells have lower spikes/cycle and higher synchronization coefficients than sustained neurons and with the observation that intensity reduces phase-locking to a much lesser degree in onset than in sustained neurons. These features follow if the inhibition is, in fact, interleaved between periods of excitation at low modulation frequencies. Under these conditions, the inhibition would suppress a few of the initial or trailing spikes evoked by each excitatory cycle, thereby enhancing the precision of phase-locking, and this should occur regardless of intensity.

As mentioned previously, blocking GABAergic inhibition

FIG. 13. Normalized spike-counts evoked by different modulation frequencies before and during application of bicuculline for the onset neuron in Fig. 12. Blocking GABAergic inhibition with bicuculline did not change shape of spike-count functions in onset cells. Spike-counts were normalized to highest count evoked in that unit by SAM signals before and during application of bicuculline.
transformed the SAM-evoked responses of onset neurons into patterns that were more like those of sustained DNLL cells. This finding suggests that both the inherent properties and excitatory innervation of onset cells are similar to those of sustained cells. It further suggests that one of the principal features that distinguish the two cell types is that onset cells receive a delayed, temporally patterned GABAergic inhibition whereas sustained cells receive a much weaker GABAergic inhibition that is temporally diffuse. It should be noted, however, that although a temporally patterned GABAergic inhibition can account for many of the differences between onset and sustained neurons, it cannot account for all of the observed differences. For example, although the phase-locking was changed to a more sustained-like pattern after GABAergic inhibition was blocked, the total-spike count function was not changed into a form that characterized sustained neurons. Whether this was due to only a partial blockage of GABAergic inhibition, or to other, perhaps glycinegic inhibitory inputs that were not blocked is unclear.

**Functional implications**

In a previous report, we showed that onset and sustained neurons occupy separate regions in the mustache bat DNLL:
Arrangement of excitatory and inhibitory inputs that could account for features of onset neurons that phase-locked to low modulation frequencies. This is same arrangement that was proposed by Grothe (1994) for mustache bat medial superior olive (MSO). The target MSO or dorsal nucleus of lateral lemniscus neuron receives excitatory inputs that are phase-locked to the modulated signal. Inhibitory inputs are also phase-locked and have a constant delay relative to excitatory inputs. For low-modulation frequencies, i.e., 100 Hz, inhibition is interleaved between excitatory inputs and the target cell responds with phase-locked discharges. For the same delay, higher modulation frequencies, in this case 200 Hz, result in an overlap of excitatory and inhibitory inputs for all but the 1st cycle. Thus neuron responds to onset of signal but not to any later cycles. With higher modulation frequencies, i.e., 500 Hz, increase in frequency allows the 1st few cycles of excitation to reach the target cell before inhibition. For later cycles, inhibition and excitation only partially overlap. Cycles are so rapid that inhibition cannot decay before next excitation arrives, thereby suppressing all but initial excitatory inputs.

Sustained neurons dominate the posterior two-thirds of the DNLL while onset neurons dominate the anterior one-third of the DNLL (Yang et al. 1996). A similar dichotomy has been reported in the DNLL of the big brown bat (Covey 1993). Additionally, injections of retrograde tracers in the inferior colliculus label cells in both the anterior and posterior DNLL bilaterally (unpublished observations), suggesting that the anterior and posterior regions of the DNLL are each influencing their targets in both the ipsilateral and contralateral inferior colliculi. Due to the pronounced difference in the response properties of onset compared to sustained neurons, it follows that the influence exerted by the DNLL region in which onset neurons predominate is substantially different from the influence exerted by the DNLL region in which sustained neurons predominate.

Studies from a number of laboratories have shown that the inhibitory influences of the DNLL play a substantial role in forming the binaural properties of many inferior colliculus neurons (Faingold et al. 1989, 1993; Klug et al. 1995; Li and Kelly 1992; Park and Pollak 1993, 1994; Vater et al. 1992b). Recent studies also have shown that DNLL neurons respond in unusual ways to multiple binaural stimuli (Yang and Pollak 1994a, c). An initial stimulus that is more intense at the inhibitory ear than at the excitatory ear evokes a long-lasting inhibition in DNLL cells. The long duration of the inhibition prevents DNLL cells from discharging to subsequent stimuli that normally would be excitatory to them. Thus whether or not a binaural signal can drive DNLL cells depends on the cell’s immediate history (whether or not an initial signal received before the second signal evoked an inhibitory response). These response properties, and the way in which they would impact their targets in the inferior colliculus, may well have a profound influence on the way the auditory system processes the reception of multiple signals that emanate from various regions of space.

We propose that the effects of the DNLL described above are produced largely by sustained cells. We propose this for two major reasons. The first is that tone bursts were used in all of experiments mentioned above, and a sustained inhibition evoked by the ipsilateral ear seemingly would be more effective than a brief onset inhibition for affecting the excitatory drive at the inferior colliculus evoked by the contralateral ear. The second reason is that sustained neurons must have the most prominent effects on the inferior colliculus because they are far more numerous than onset neurons (Yang et al. 1996). If this correct, it raises the question of what are the influences of the onset neurons in the anterior DNLL on the inferior colliculus? As discussed above, onset
neurons have response features well suited to convey precise temporal information about the amplitude fluctuations in signals with low-modulation frequencies to their higher order targets. This suggests that onset neurons may be involved in shaping the temporal coding of collicular neurons in response to more complex, amplitude modulated binaural signals.

Whether or not the two regions differentially influence the inferior colliculus in the ways proposed above and whether collicular neurons are innervated by only one type of DNLL cell or whether individual inferior colliculus neurons are innervated by both DNLL cell types are issues about which there is no current information, and remain for future studies to resolve. However, the results of the present study suggest that DNLL plays an even more complex role in the processing of acoustic information than we had previously thought.

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