

Neural Representation of Sound Duration in the Inferior Colliculus of the Mouse

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In this study we examined the neuronal responses of single units to different sound durations in the inferior colliculus (IC) of the mouse. One hundred and one recorded units were classified into onset (58%), sustained (9%), on-sustained (22%), pauser (9%) and chopper (2%) response patterns. Thirty-four percent of the recorded units showing stronger responses to long stimulus durations were defined as long-duration-selective neurons. Twenty-five percent of the units preferred a narrow range of sound durations and were classified as band-pass neurons. Ten percent of the units responded preferentially to short stimulus durations and thus displayed short-duration selectivity. Twelve percent of the units that responded with nearly constant spike counts to stimuli of varying duration were classified as all-pass neurons. In contrast to the result of no short-duration-selective neurons found in chinchilla IC, we observed that some of the onset units in the IC of the mouse displayed a short duration preference. The best duration range of the duration-selective neurons in the present study corresponds to the duration range of mouse calls. We suggest that an inhibitory mechanism contributes to the duration selectivity observed in the present study. *Key words:* auditory midbrain, duration coding, inhibition, temporal response pattern.

INTRODUCTION

One of the most primary tasks of hearing is to distinguish biologically important sounds from environmental background noise. Duration is one of the most important temporal attributes of sound and plays an essential role in the perception of sound information. Duration tuning was first reported in the midbrain of frogs (1, 2). Later, investigators reported duration tuning in the inferior colliculus (IC) of bats (3-6) and chinchilla (7) as well as in the auditory cortex (AC) of bats (8) and cats (9). It has also been reported that duration tuning is initially generated in the IC (5, 6). Early reports concerning duration tuning in mammalian ICs frequently focused on various species of bat (3-6). Duration selectivity in other mammalian ICs has only been reported to date in chinchilla (7). Unlike the bat, which uses some special short-duration sounds for hunting and navigating, most animals employ signals that display a low degree of input sound specificity, i.e. a wide range of external stimuli. Thus, animals process much non-specific environmental sound information (10).

The mouse serves as a good animal model for studying the auditory function of the IC (11). Behavioral studies have revealed that the duration of mouse calls is widely ranged from about 4 to 270 ms. Of course, a long duration call can be included as a distress signal for survival (12, 13). The aim of the present study is to investigate how sound duration information is represented in the albino mouse IC

and how the neurons provide information for further analysis at higher levels. Furthermore, the electrophysiological data obtained in the IC neurons could contribute to a better understanding of the implications for psychophysical performance of the complex temporal response property (14).

MATERIALS AND METHODS

Surgical procedures

15 albino mice (*Mus musculus*, Km) of either sex were used in this study and were obtained from the Experimental Animal Center of the Institute of Genetics, Chinese Academy of Sciences. The mouse was initially anesthetized with sodium pentobarbital (60 mg/kg body weight i.p.) and the anesthesia was maintained by supplemental doses (10 mg/kg i.p.) as necessary during the experiments. Atropine (0.25 mg/kg, subcutaneously) was injected to reduce mucous secretion in the respiratory tract. After a longitudinal midline incision was made in the scalp, a small hole was made in the skull overlying the IC. A screw was then glued upside down to the skull using dental cement. During the experiments, the mouse was placed on an experimental table inside a sound-attenuating chamber. The animal's head was immobilized by bolting the screw to a stereotactic frame. Care was taken to make the animal as comfortable as possible. The body temperature of the animal was maintained at 37-38°C with a direct current heating pad. All animal procedures were approved by the Institutional

Animal Care and Use Committee of the Institute of Biophysics.

Acoustic stimuli and recording

Tone bursts used as acoustic stimuli were generated by a stimulator programmer (Hi-Med HG-100) and sent through an attenuator (Tektronix B170-A) and a power amplifier to a loudspeaker (EAS-10TH800B; frequency range 3–100 kHz). The loudspeaker was

placed at 30° contralaterally to the recording site and the distance between the loudspeaker and the animal's head was 50 cm. Stimulus duration was varied from 3 ms to 300 ms and the stimulus presentation rate was 1 per second. The stimuli had a rise-fall time of 5 ms for all stimulus durations except for stimuli with a duration < 10 ms, for which it was set to 1 ms. Prior to the experiments, the output of the loudspeaker was measured with a $\frac{1}{4}$ in. microphone (B&K 4135) at the position of the animal's head and a measuring amplifier (B&K 2610) so that the sound levels used during the experiments could be converted from attenuator settings to sound pressure levels (SPL; 0 dB re 20 μ Pa).

Glass micropipettes filled with 3 M KCl solution (impedance 5–15 M Ω) were used to record the responses of the neurons. The recording electrodes were first placed on the dorsal surface of the IC and were then advanced into the IC vertically to the dorsal surface using a remotely controlled stepping motor microdrive (Narishige SM-21). The action potentials of a single unit were amplified, filtered and fed into a Histogrammer for generation of post-stimulus time histograms (PSTHs) and a computer (DATA 6000 Waveform Analyzer) for further analysis. After a single unit was isolated, the characteristic frequency (CF) and the response threshold at the CF of the unit were determined audiovisually using a 220-ms tone burst. The following procedure was designed to test the unit's responses to tone bursts of different sound durations for its CF at a given stimulus intensity above the threshold. Stimuli of each duration were presented 20–40 times and response data were collected in order to construct PSTHs (1-ms bin width). Most neurons in the IC responded against a background of low spontaneous activity. We subtracted the obtained spontaneous firing rate from the spike number of the neuron. The mean discharge rates were calculated for each trial.

RESULTS

Temporal response patterns

101 single units were recorded in the IC of 15 mice. The CFs of the units ranged from 3 kHz to 45 kHz. The units were classified into five categories based on their response pattern: onset; sustained; on-sustained; pauser; and chopper. Temporal response patterns in the IC are similar across a range of mammals. The classification agreed well with previously reported results in the mouse (11), guinea pig (15) and rat (16). The PSTHs of units representative of the major response types are illustrated in Fig. 1. Over one-half of the recorded units (59/101, 58%) in our study were of the onset type, which responded transiently only at

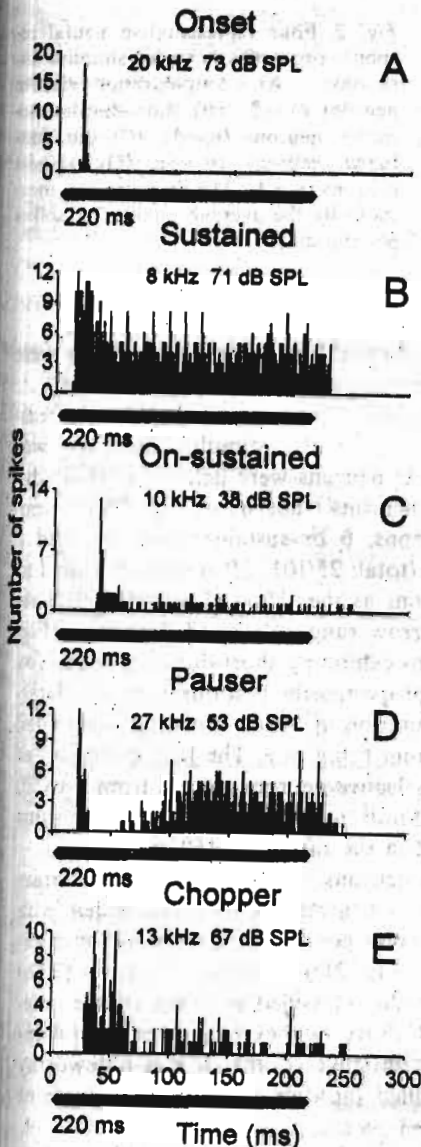


Fig. 1. PSTHs illustrating the temporal response patterns of the neurons in the IC of the mouse: (A) onset unit; (B) sustained unit; (C) on-sustained unit; (D) pauser unit; (E) chopper unit. Horizontal bars at the foot of the graphs denote stimulus duration. The values at the top of each graph indicate the stimulus frequency (CF) and intensity.

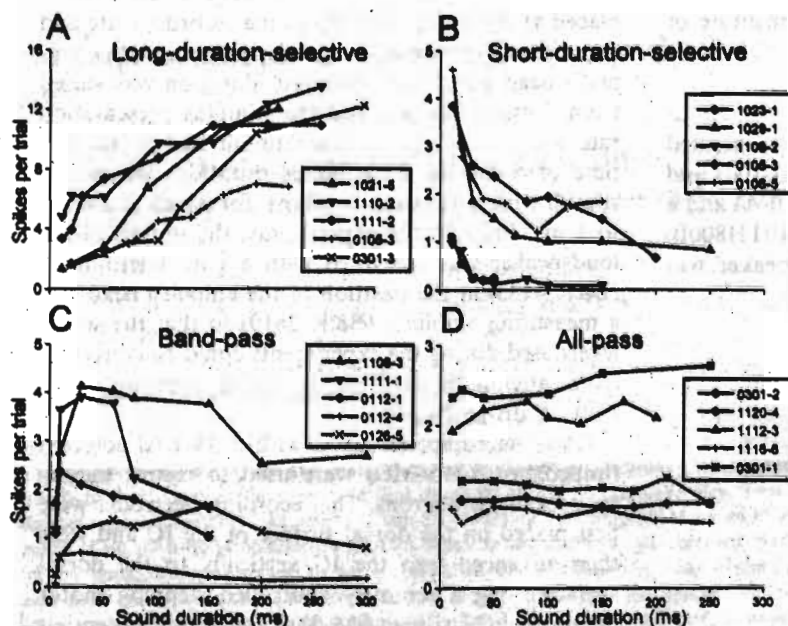


Fig. 2. Four representative neural response properties to varied stimulus durations: (A) long-duration-selective neurons ($n = 5$); (B) short-duration-selective neurons ($n = 5$); (C) duration-tuned neurons ($n = 5$); (D) all-pass neurons ($n = 5$). The response was measured by the average number of spikes per stimulus.

the start of the stimulus presentation (Fig. 1A). Sustained units (9/101, 9%) were defined as such as they displayed continuous firing throughout the duration of the stimulus with less distinct initial onset firing (Fig. 1B). On-sustained units (22/101, 22%) produced a clear onset peak followed by a low level of sustained response over the remainder of the sound stimulus (Fig. 1C). Pauser units (9/101, 9%) exhibited an initial onset response followed by a completely silent period. The unit then fired again and the response usually continued until signal duration offset (Fig. 1D). The pauser unit will be described in detail later. Only two units were defined as the chopper type, which exhibited regular firing with over three clear peaks near the stimulus onset (Fig. 1E).

Duration response functions and relation to temporal response pattern

The neural response in the IC of the mouse varied as a function of stimulus duration in terms of firing rates. Fig. 2 presents four typical response functions of the recorded units to varying stimulus duration. Thirty-four of 101 (34%) of the neurons responded with increasing spike counts to longer stimulus duration (Fig. 2A) and were defined as long-duration-selective (long-pass) neurons. Sustained and on-sustained neurons have similar responses to signal duration and their firing duration was consistent with the signal duration. Therefore, neural response to different sound durations could be predicted. All sustained neurons (9/9) and most on-sustained neurons (16/22) showed long-duration selectivity. The

other units that showed long-duration selectivity were seven pauser neurons and two chopper neurons.

10 onset units (10/101%) responded with a decreasing discharge rate as the stimulus duration was lengthened. These neurons were defined as short-duration-selective neurons (short-pass, Fig. 2B). Seventeen onset neurons, 6 on-sustained neurons and 2 pauser neurons (total: 25/101, 25%) were classified as band-pass neurons as they showed a preferential response to a narrow range of sound durations (Fig. 2C). For neurons exhibiting short-duration selectivity and band-pass properties the best duration was determined as the duration at which a neuron responded with the maximum firing rate. The best durations of short-duration-selective neurons ranged from 3 to 20 ms. The best durations for the band-pass neurons were distributed in the range 20–160 ms.

Twelve onset neurons (12/101, 12%) were characterized as all-pass neurons as they responded with nearly constant spike counts when the stimulus duration was varied (Fig. 2D). However, 20 units (20%) could not be readily classified into any of the categories described above as they responded with complicated changes in spike counts. It was noteworthy that all unclassified duration-selective units were of the onset type.

Pauser neurons displayed a response with involvement of suppression during the stimulus. They had two response components separated by the cessation: onset and offset. Two different duration response functions were found in terms of the length of the cessation period (Fig. 3). Two of the pauser neurons

displayed a constant cessation period to different sound durations. The other seven neurons showed an erratic silent period length that could not be related to the stimulus duration.

Unit 0126-4 showed onset-only discharge to stimuli durations < 30 ms. When the stimulus duration was increased to > 40 ms, the discharge pattern of the unit displayed distinct pauser characteristics (Fig. 3A). It was notable that the break usually began at 30 ms and ended at 50 ms when the sound duration ranged from 40 ms to 230 ms. Consequently, the cessation duration was always 20 ms regardless of the stimulus duration. Unit 0301-3 responded with an onset-only response to the 30-ms tone burst. When the stimulus duration was ≥ 40 ms its response, which featured a break, could clearly be classified as pauser type (Fig. 3B). The pause period of the neural response displayed complex changes with varying sound durations. The silent period increased from 24

ms to 76 ms as the sound duration varied from 40 ms to 160 ms. However, the silent period decreased to 27 ms when the stimulus duration was increased to 230 ms.

DISCUSSION

Neural response to sound duration

This study examined the influence of varying sound duration on the neural response in the mouse IC and demonstrated that sound duration information was well represented. The present data further confirm previous studies showing the presence of duration tuning in the IC of mammals. Short- and band-pass neurons have been reported in the IC of bats (5, 6). The best durations for most neurons in those studies ranged from less < 1 ms to 75 ms. In the present study, the best durations for the short-duration-selective- and band-pass neurons, together with the preferred duration of long-duration-selective neurons, were distributed over the range 3 ms to ≈ 300 ms. The best durations in the IC of the mouse were more widely distributed compared with those in the bat.

The temporal firing patterns of neurons are important in the transmission of information in sensory pathways. Sustained neurons represented the signal duration by means of ongoing firing over the sound stimulus duration (Fig. 1B). The relative temporal onset and offset times of sounds play important roles in determining perceptual information. The onset and offset of the sound were transmitted in the temporal response patterns of the neurons by means of discharges at the start and end of the sound, respectively (see Figs. 1A and 3). Studies of the mouse IC slice also suggested that the intrinsic electrophysiological properties of onset neurons enable them to encode the onset of a sound burst with a high degree of precision compared with the sustained neurons (17, 18). In contrast to the finding that the onset neurons showed an all-pass property in the chinchilla IC (7), we observed that 10 of 59 onset neurons displayed short-duration selectivity in our study. It seems reasonable that these onset units integrate features of acoustic signals with emphasis on temporal acuity and could serve as good candidates for sound duration representation.

The mechanism of duration selectivity

Some mechanisms have been put forward to explain the duration tuning of the auditory neuron. Casseday et al. (5) developed a coincidence mechanism to explain the duration tuning of offset neurons in the bat IC based on a whole-cell patch-clamp study. In their model, the coincidence of the rebound excitation after the initial inhibition (elicited by the stimulus

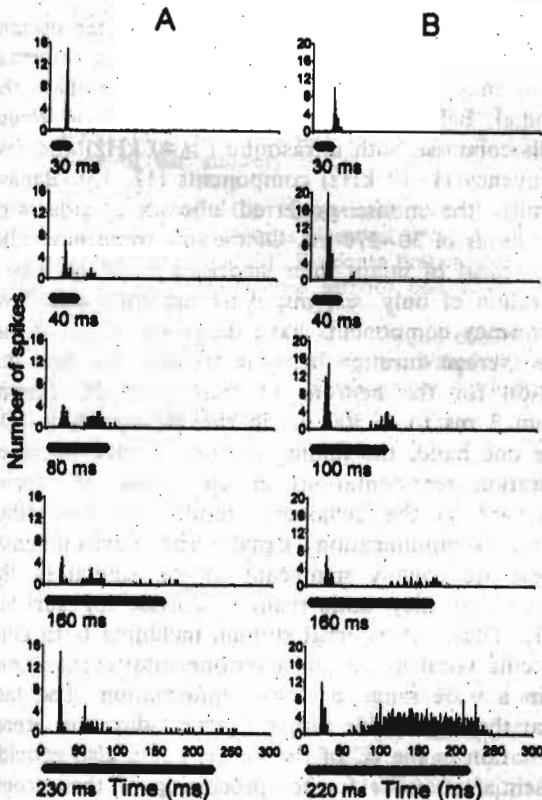


Fig. 3. Two examples of pauser neurons showing different responses to varied stimulus durations: (A) unit 0126-4, responses of pauser with constant cessation period irrespective of stimulus duration. Stimulus frequency was 7 kHz (71 dB SPL); (B) unit 0301-3, responses of pauser neuron with complex cessation period. Stimulus frequency was 27 kHz (53 dB SPL). The bars at the foot of each histogram indicate the duration of the tone burst.

onset) and a delayed weak excitation correlated with the stimulus offset creates duration selectivity in the bat IC. However, for the onset neuron showing short-duration selectivity and band-pass property in the mouse IC, the coincidence mechanism may be not applicable because the onset neurons derive their name from their tendency to discharge at the onset of the stimulus (19).

More recently, Fuzessery and Hall (3) proposed an anti-coincidence mechanism to explain the short-duration selectivity of the onset neurons in the pallid bat IC. In their model, a neuron receives both excitatory and inhibitory inputs at the sound onset. The neuron responds maximally only when the inhibitory and excitatory events do not coincide. We assumed that the mechanism for the short duration preference of the onset neurons in the present study might be similar to that described in the pallid bat IC. This suggestion is supported by the finding that some onset responses became either chopper or onset-chopper with the administration of bicuculline (15). It seemed reasonable to assume that the onset neuron receives a stronger inhibitory input that breaks the tendency to chop at onset. As for the onset neuron in the present study that showed short duration preference at the best duration, the inhibition elicited by the short duration was terminated before the arrival of the excitation and the neuron showed maximal response. In contrast the stimulus with duration longer than the best duration could elicit longer and stronger inhibition, which suppressed the concurrent excitatory event and therefore the response decreased. Ehret (20), in a mouse behavioral study, reported that the response threshold for detecting a brief sound increased as the sound duration decreased. This behavioral result could explain the weak response to durations shorter than the best duration. In order for a band-pass onset neuron to detect shorter sound durations the neuron requires a higher response threshold. Consequently, the neuron responded at a low level to shorter duration sounds, thus using less energy.

The inhibitory modification may also play a significant role in the generation of the temporal response break observed in the pause-type response. It has been suggested on the basis of a neurotransmitter study (15, 16) that differences in the timing and relative forces of excitatory and inhibitory inputs could generate a pause. If a delayed inhibition after the onset excitation was initially stronger than the sustained excitation, and then gradually decayed, a pause response during the stimulus duration might be detected. The start and end of the

inhibition might correlate with the stimulus duration. A pause response could not be observed with a stimulus duration < 30 ms. A constant silent period in the responses of some pauser neurons is due to the fixed-time occurrence of and the end of the inhibitory input (Fig. 3A). However, the significance of such a precise inhibition remains to be clarified further. The erratic changes during the silent period in some pauser neurons, as illustrated in Fig. 3B, indicate that the interplay between the excitatory and inhibitory inputs must be complex. It has been suggested that the essential features of pauser units mean that they play a crucial role in improving the signal-to-noise ratio and in processing of complex signals (19). The above results and assumptions indicate that excitatory and inhibitory components differing in their temporal discharge patterns and timing in the IC might interact in order to process sound duration information.

Biological considerations

Our finding of a large range of duration representations in the mouse IC revealed that such information may have biological significance for the animal. Behavioral studies have shown that mouse calls comprise both ultrasound (≥ 40 kHz) and low frequency (1–10 kHz) components (12, 13). Behaviorally, the mouse preferred ultrasonic calls with durations of 30–270 ms. Of the low frequency calls, the sound of infant mice smacking their lips has a duration of only ≈ 4 ms. All other calls with low-frequency components have durations of > 30 ms, the average duration being ≈ 100 ms. The best duration for the neurons of the mouse IC ranged from 3 ms to > 300 ms in the present study. On the one hand, the finding of such a wide range of duration representations in the mouse IC corresponded to the behavioral results. On the other hand, communication signals and environmental noise are equally significant to the animal in the sense that they both require analysis for survival (21). Thus, the external stimuli, including both conspecific vocalization and environmental events, contain a wide range of sound information. The fact that there is a wide range of sound duration representation in the IC of the mouse could also provide essential cues for further processing of these comprehensive sounds.

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