Hearing Research, 63 (1992) 7–11
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HEARES 01807

Modulation of cochlear nerve spike rate by cardiac activity in the gerbil

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(Received 19 February 1992; Revision received 1 June 1992; Accepted 3 June 1992)

Among primary auditory axons with characteristic frequencies (CFs) below 2500 Hz, a substantial subpopulation was found in which spike activity was driven by cardiac events. The presence of cardiac-driven activity was inferred from cycle histograms triggered on the peak of the electrocardiogram (ECG). This driven activity was either like a simple onset response (often followed by a reduction of spike activity to below background level), or as a longer lasting series of peaks and troughs. In two axons with high CFs (7 kHz and 12.5 kHz), cardiac-driven suppression was observed. Recordings made by a probe microphone revealed the presence of heart-related sound in the external ear canal. The onset of that sound coincided with the onset of cardiac-driven spike activity (and suppression).

Cochlear nerve; One-tone suppression; Cardiac; Gerbil

Introduction

One-tone rate suppression of background spike activity in cochlear primary afferent axons has been described by several authors (Schmiedt and Zwislocki, 1980; Rupert et al., 1963). In a companion paper, we demonstrated that suppression can occur when the background spike activity is not dependent on extraneous sounds leaking through the acoustic barrier of the experimental setup, or on spurious signals or noise from the audio amplifier driving the stimulus earphone (Henry and Lewis, 1992). Our study did not eliminate the possibility that the background spike activity was driven by sounds from acoustic sources within the animal (e.g., gastro-intestinal sounds, respiratory sounds, cardiovascular sounds) rather than by highly localized sources at the cellular level (e.g., synaptic activity, ion-channel activity). Activity driven by localized cellular sources seems to fit the conventional notion of spontaneous activity. It is generally agreed that background spike activity can be phase-locked to low-frequency sinusoidal stimuli with amplitudes that are too low to cause an increase in mean spike rate (i.e., the spike rate averaged over a complete stimulus cycle, over many cycles). This phase locking is seen as a sinusoidal modulation of the probability of spike production, with enhanced spike production during half of the modulation cycle and suppressed spike production during the other half (Rose et al., 1967). Nevertheless, there is a widely held opinion (not often published) that spontaneous activity in primary auditory afferents in the mammal cannot be suppressed (e.g., Manley, 1978; Hill, 1989; Patuzzi, 1989; Dolan et al., 1990), but that activity driven by external acoustic sources can be suppressed. In that regard, gastro-intestinal sounds, respiratory sounds and cardiovascular sounds presumably are equivalent to external sounds.

If such internally-generated sounds are able to generate spike activity in cochlear afferent axons, then the arguments about whether or not a particular suppressible activity was spontaneous or not should be accompanied by discussions about how the possible effects of such sounds were taken into account (e.g., turning the respirator off temporarily–Fay, 1990; cutting the columella or inserting earplugs in birds–Temchin, 1988). In this paper, we describe the results of experiments in which background spike activity of some low- and mid-frequency cochlear afferent axons was found to be strongly correlated with the cardiac cycle–implying that this activity is driven or modulated by cardiovascular events. We present evidence that cardiac-generated sounds in the external ear canal could be the physical basis of this synchronization.

Materials and Methods

The gerbil preparation, experimental apparatus, and acoustic isolation system were the same as those described in the companion paper (Henry and Lewis,

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1992). The closed-field (ER-2) acoustic driver system included an ER-10 microphone, which was used to monitor the applied acoustic stimulus at the level of the external ear canal. Single axons were penetrated with glass micropipette electrodes, and were identified as being primary afferent fibers by their position in the nerve (within 500 μm of the surface), their response latencies (legs than 1.5 ms), and their primary-like responses to tone-bursts at frequencies near CF. The stimuli used during the search for auditory axons were noise bursts of 10 ms duration and 290 ms interburst interval. The noise was band-limited by a filter with a 10 kHz cutoff frequency and rolloff of 30 dB per octave. In each animal, an ECG signal was detected by means of two stainless-steel needle electrodes attached to the skin close to the heart, one on the ventral surface of the animal and one on the dorsal surface. The ECG signal was amplified and filtered (300–5000 Hz pass band, 6 dB/oct band-edge slopes) and recorded on one channel (used also intermittently for voice notes) of a four-channel tape recorder (TASCAM model 234), while the stimulus, stimulus trigger and spike response were recorded on the other channels. In one set of experiments, the positive peak of the filtered (QRS complex of the) ECG signal was used to trigger (with variable delay) the stimulus tone burst. In this way, the beginning of the tone burst could be fixed at a particular phase of the cardiac cycle. Spike responses were analyzed with cycle histograms synchronized to the positive peak of the filtered ECG or with peristimulus time histograms synchronized to the trigger for the applied stimulus. After finding positive results in the early subjects, in order to detect possible heart-related sounds in the external ear canal, we made extended recordings of the output of the ER-10 ear-canal microphone in the absence of stimuli applied to the driver. This was done in closed-field configuration with the (open-bulla, pinna removed) gerbil preparation from which afferent spike activity was recorded, as well as in open- and closed-field configuration with intact gerbils (bulla closed, pinna present).

Results

From 8 gerbils, 57 cochlear nerve axons were recorded and analyzed for synchrony between spike activity and heart beat. Among those axons, 23 (from 6 gerbils) showed clear synchronous activity. In the remaining 34 axons (from 7 gerbils), the cycle histograms showed no evidence of synchrony between spike activity and the heart beat. The CFs of 7 of these nonresponsive axons fell between 1.5 kHz and 2.4 kHz; the CFs of the remaining 17 fell between 2.5 kHz and 12 kHz. The estimated thresholds of the 34 axons ranged from 15 to 40 dB SPL.

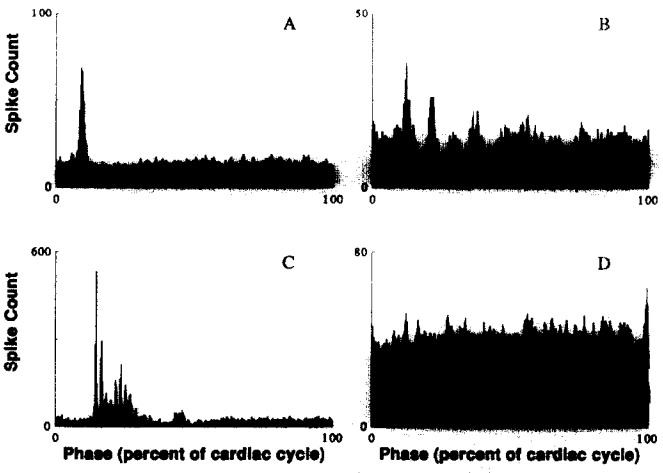

Fig. 1. Cycle histograms of spike activity in four afferent axons from the gerbil cochlear nerve: the vertical axis is number of spikes; the horizontal axis is phase (percent) of the cardiac cycle, with 0 and 100 both corresponding to the leading edge of the peak of the filtered ECG (see Fig. 3). In each case, the average duration of the cardiac cycle was approximately 160 ms; the number of bins was 300. (a) CF ≈ 1.5 kHz; (b) CF ≈ 1.5 kHz; (c) CF ≈ 600 Hz; (d) CF ≈ 12.5 KHz. Histograms (b) and (c) are for axons from the same subject; (a) and (d) are from different subjects. The peaks in (b) are separated by approximately 13.7 ms; those in (c) are separated by approximately 2.8 ms.

For 14 axons (from 4 gerbils), the cycle histograms showed a transient increase of spike activity that began 10 to 15 ms after the trigger, lasted approximately 5 ms (Figs. 1A, 2A, 2B) and often was followed by transient decrease (to levels below the mean spontaneous rate) of similar duration (see Figs. 1B, 2D). The CFs of these axons ranged from 500 Hz to 2.4 kHz; and their estimated thresholds ranged from 15 to 30 dB SPL.

For 7 axons (from 3 gerbils), the cycle histograms showed an initial transient increase of spike activity essentially identical to that described in the previous paragraph (beginning 10 to 15 ms after the trigger, lasting approximately 5 ms, and followed by transient decrease of spike activity), but this activity often was followed by several more cycles of increased spike activity alternating with decreased spike activity. This complex response pattern lasted from 20 to 100 percent of the approximately 160-ms cardiac period (see Fig. 1B). The CFs of these axons ranged from 600 Hz to 1.8 kHz; and their estimated thresholds ranged from 15 to 25 dB SPL.

For 13 of the 21 axons of the previous two paragraphs, the trigger was sufficiently stable and the numbers of spikes in the cycle histograms were sufficiently large to allow examination of the spike activity at higher temporal resolution (e.g., of the order of 0.1 to 0.2 ms per bin). For 12 of these 13 axons, higher resolution showed that the initial transient increase consisted of multiple peaks and troughs (Fig. 2A and 2B). Five of these 13 axons exhibited prolonged cycles

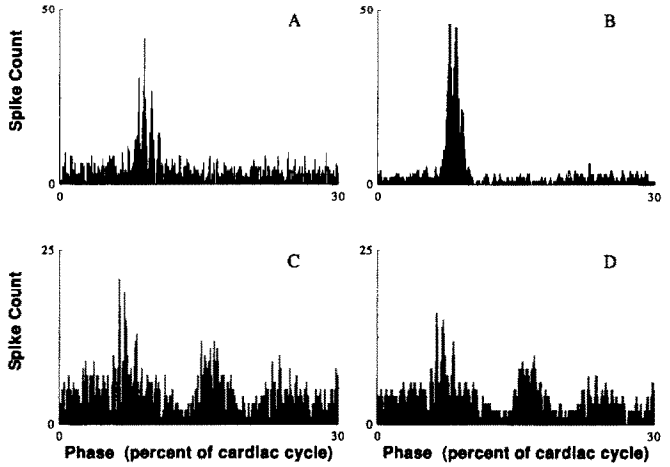

Fig. 2. Cycle histograms under higher resolution. The cycle histograms of Figs. 1(a) and (b) are shown with greater phase resolution in 2(a) and 2(c), respectively. Fig. 2(b) shows the histogram of 2(c) smoothed by convolution with a three-bin filter (0.25, 0.5, 0.25).

of activity correlated with the ECG; and for 4 of these 5, the higher resolution showed that each of those cycles comprised multiple peaks and troughs (Fig. 2C and 2D).

Finally, for 2 axons (from 1 gerbil), the cycle histograms exhibited a decrease of activity (to below the spontaneous level), bordered by small, brief increases (see Fig. 1D). The CFs of these two axons were 7 kHz and 12.5 kHz. Their estimated thresholds were 25 dB SPL and 10 dB SPL, respectively.

In summary to this point, 23 of the 57 axons examined showed clear response to some aspect of cardiac activity. Of these 23, all but 2 had CFs below 2.5 kHz; and those two (previous paragraph) exhibited responses that were distinctly different from those of the other 21. Seven of the 34 axons showing no response also had CFs below 2.5 kHz. Among 29 axons with CFs above 2.5 kHz, only 2 were responsive to the cardiac cycle; and their responses consisted primarily of a transient decrease of spike activity.

The filtered ECG complex lasted between 15 and 20 ms and ended approximately 10 ms after the peak used for triggering (Fig. 3). We assume that the fast, large-amplitude component of the ECG complex itself corresponded approximately to the peak of the filtered ECG and therefore occurred approximately 10 ms before the time of the transient increase in spike rate in those axons that responded to the heart beat.

In five gerbils prepared for auditory-nerve recording, attempts were made to record sound correlated

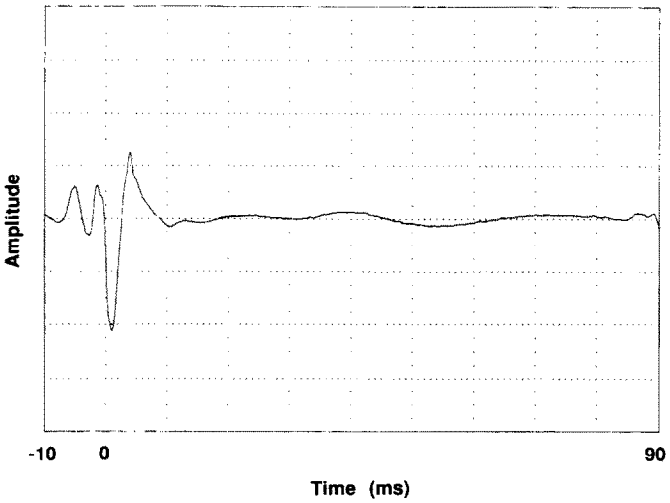

Fig. 3. Filtered ECG for the subject of Figs. 1(b), 1(c) and 2(b), averaged over 100 cardiac cycles. Vertical axis is voltage; horizontal axis is time (100 ms total), with 0 being the time of the trigger used for the cycle histograms of the corresponding cycle histograms of Figs. 1 and 2.

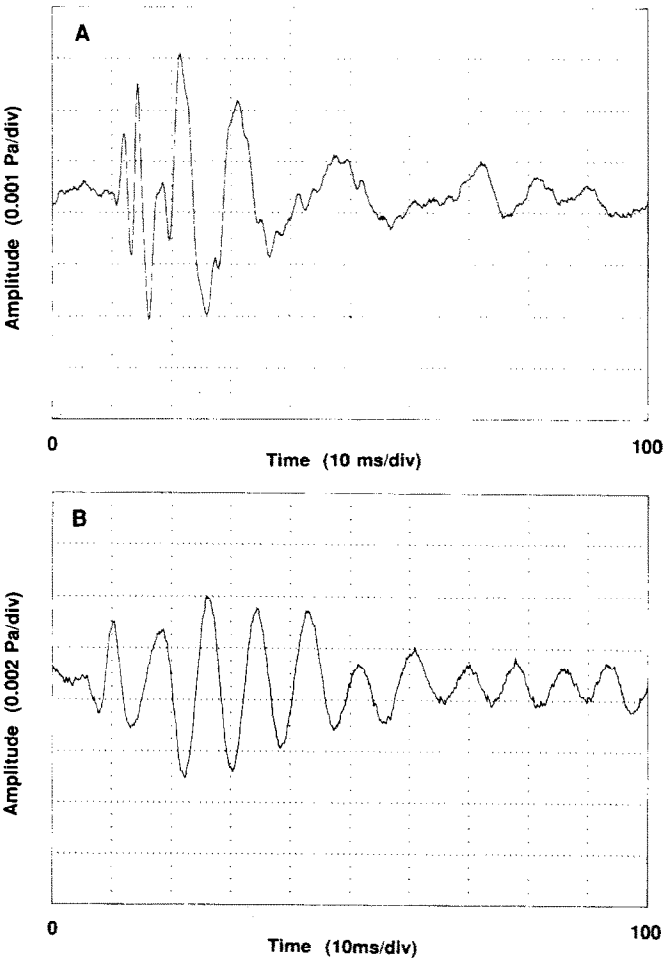

Fig. 4. Sounds recorded from the external ear canals of two gerbils prepared for electrophysiological recording (open bulla), in the absence of externally applied stimuli. Each waveform was averaged over 100 cardiac cycles. Vertical axis is sound pressure; horizontal axis is time, with 0 being the time of the trigger from the ECG. The peak amplitudes of the waveforms were approximately 40 dB SPL (4a) and 45 dB SPL (4b). Fig. 4(a) was taken from the subject of Figs. 1(b), 1(c), 2(b) and 3 (0 on the horizontal axes of all five figures corresponds to the same trigger event). The heartbeat sounds recorded from the ear canals of the three intact gerbils (closed bulla) had waveforms very similar to that of 4(a).

with the heartbeat in the external ear canal with the ER-10 microphone in closed-field configuration. The recorded ER-10 outputs were averaged over sets of 100 samples, making the noise floor for the measurements (with averaging) −3 dB SPL. In four of the five animals the sounds correlated with the heartbeat were well above the noise floor (e.g., Fig. 4). The largest of the recorded sounds had a peak amplitude of 44 dB SPL (in closed-field configuration). In three intact gerbils, closed-field recording with the ER-10 gave similar results. In these same three animals, open-field recording (with a 2 mm gap between the microphone coupler and the opening of the external ear canal) yielded heartbeat sounds with peak amplitudes approximately

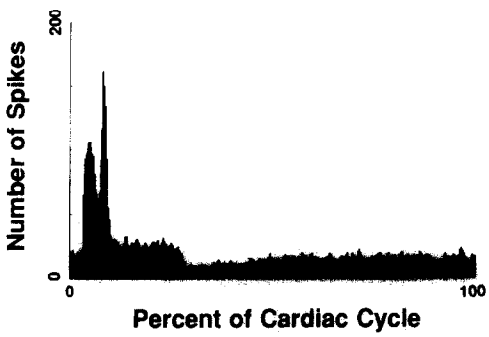

Fig. 6. Cycle histogram over the entire cardiac cycle (approximately 160 ms total period, 0.53 ms per bin) for the unit of Fig. 5 over the same 84-second stimulus run (with 1.2 kHz, 40-ms tone bursts synchronized to the cardiac cycle).

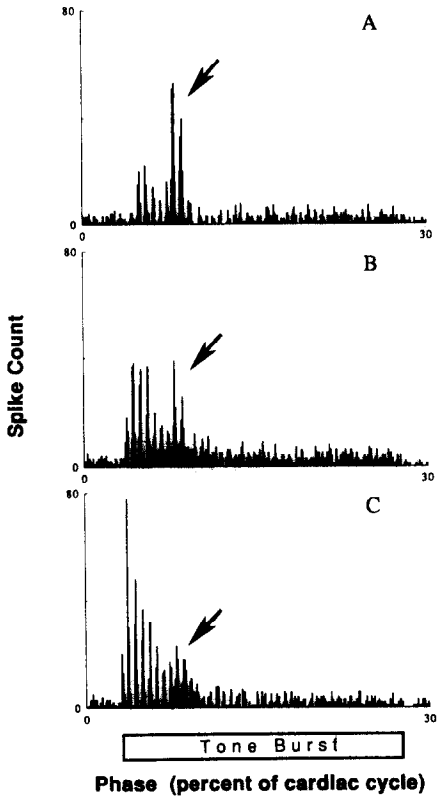

Fig. 5. Cycle histograms (over the 30% of the cardiac cycle, approximately 0.16 ms per bin), taken in the presence of a 1.2 kHz, 40-ms tone burst synchronized to the cardiac cycle. The CF of the axon was between 500 and 1000 Hz; threshold at 1 kHz was approximately 15 dB SPL. Data were taken over 84 s, during which the amplitude was increased in 5-dB steps. (a) Data pooled from first 28 s of the run, during which the following stimulus amplitudes were presented: 20, 25, 30 and 35 dB SPL. (b) Data pooled from second 28 s of the run, during which the stimulus amplitudes were 35, 40, 45, 50 and 55 dB SPL. (c) Data pooled from last 28 s of the run; stimulus amplitudes were 55, 60, 65 and 70 dB SPL. Fig. 2d shows the spike activity component synchronized to the cardiac cycle for this same axon, without the superimposed tone burst. The arrow in each panel of Fig. 5 shows the position of this component in the midst of the tone-burst response. The time scale and origin (time of synchronizing pulse) are the same in Figs. 2d and 5. The box shows the approximate position of the tone burst, which had 1-ms rise and fall times. The response latency to the tone burst at 70 dB SPL was 2.6 ms.

6 dB less than they were in closed field. In all seven animals in which it was measurable, the sound started abruptly, approximately 10 ms after the ECG peak used for triggering.

As one might expect, spike activity synchronized to the cardiac cycle, such as that in Figs. 1 and 2, was affected by the presence of experimentally introduced sounds. For example, presentation of broad-band noise reduced the amplitudes of all histogram components synchronized to the heartbeat, and this reduction became greater as the amplitude of the noise was increased. Additionally, when short tone bursts were triggered with fixed delays from the ECG peak, each corresponding cycle histogram showed a component correlated with the tone burst as well as the transient increase correlated with the heartbeat. As long as those two components did not coincide, we saw no obvious relationship between the phase of the tone burst (relative to the cardiac cycle) and the amplitude of either component. When the two components did coincide, however, interaction was observed. Fig. 5, for example, shows decrease in the spike activity synchronized to the cardiac cycle as the intensity of the tone bursts was increased.

Discussion

The results of this work clearly show that the activity of gerbil primary auditory axons having CFs below approximately 2.5 kHz is capable of being modulated or driven by events associated with the heartbeat. In some axons (e.g., Figs. 1B and 1D), the effects of excitation appear to be primarily a modulation of background spike activity that is not correlated to the heartbeat. In other axons (e.g., Fig. 1A), the excitation clearly generates a large fraction of the total activity (in the absence of external sound sources). In conventional auditory experiments, all of this activity, whether corre-

lated with heartbeat or not, would be identified as spontaneous.

The near-coincidence of the onset of the cardiac-driven spike activity and the onset of cardiac sound in the external ear canal suggests that this sound is the immediate cause of the activity. The observations that the peak of the filtered ECG voltage occurs 10 to 15 ms before the onset of the driven spike activity and that the filtered ECG voltage is nearly zero by that time suggest that the electrical activity associated with the ECG is not the immediate cause.

Regardless of the nature of the stimulation, the ability of the cochlear nerve to respond to the gerbil's heartbeat suggests that this internal stimulus might play a role in the development of the auditory brain in gerbils in their natural habitat (in subterranean burrows in Mongolia, where sound levels are extremely low; K. Wynn-Edwards, pers. comm.). The feasibility of such a role is supported by several development studies. For example, early acoustic deprivation has been shown to alter the anatomy of the cochlear nucleus (Webster and Webster, 1977; McGinn and Faddis, 1987) and auditory cortex (McGinn and Henry, 1985). Neonatal removal of the inner ear was found to have more pronounced effects on the developing auditory brain than did interruption of sound transmission through the outer- or middle-ear paths. It was suggested that this difference could have been a result of internally-generated sounds (Rubel et al., 1984).

Birren et al. (1963) and Wynn (1980) observed that the reaction time to auditory stimuli varied systematically with the phase of the cardiac cycle at which the stimulus was presented. Lacey and Lacey (1978) suggested that the increased blood pressure following cardiac contraction produces a brief change of CNS activity, resulting in altered sensory processing. Some, but not all behavioral and electrophysiological studies designed to test this hypothesis have provided support for it (e.g., Callaway and Buchbaum, 1965; Delfini and Campos, 1972; Walker and Sandman, 1979). The interactions that we observed between cardiac-driven responses and responses to externally-applied tone bursts suggest that the explanation for the auditory reaction-time observations could be, at least in part, more peripheral.

Returning to the topic of the companion paper (Henry and Lewis, 1992), we note that the two axons in which the cardiac-driven responses were principally suppression of background spike activity (see Fig. 1D) both had CFs in the range associated with one-tone suppression (Schmiedt and Zwislocki, 1980). In this case, the cardiac activity evidently is doing the suppressing, not generating the suppressed background. The range of CFs of axons we found to be excited by cardiac activity is well below that (> 4 kHz) reported for one-tone suppressible axons (Schmiedt and Zwislocki, 1980; Henry and Lewis, 1992). Therefore, we conclude that it was not cardiac-driven activity that was suppressed in one-tone suppressible axons of the gerbil.

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