Published in final edited form as:
Adv Exp Med Biol. 2013 ; 787: 353–361. doi:10.1007/978-1-4614-1590-9_39.

Better Temporal Neural Coding with Cochlear Implants in Awake Animals

Yoojin Chung[1,2], **Kenneth E. Hancock**[1,2], **Sung-Il Nam**[2,3], and **Bertrand Delgutte**[1,2,4]

[1]Eaton-Peabody Laboratories, Massachusetts Eye & Ear Infirmary, Boston MA 02114, USA

[2]Department of Otology and Laryngology, Harvard Medical School, Boston MA 02115, USA

[3]Department of Otolaryngology, School of Medicine, Keimyung University, Daegu, South Korea

[4]Research Laboratory of Electronics, Massachusetts Institute of Technology, Cambridge MA 02139, USA

Abstract

Both the performance of cochlear implant (CI) listeners and the responses of auditory neurons show limits in temporal processing at high frequencies. However, the upper limit of temporal coding of pulse train stimuli in the inferior colliculus (IC) of anesthetized animals appears to be lower than that observed in corresponding perceptual tasks. We hypothesize that the neural rate limits have been underestimated due to the effect of anesthesia. To test this hypothesis, we developed a chronic, awake rabbit preparation for recording responses of single IC neurons to CI stimulation without the confound of anesthesia, and compared these data with earlier recordings from the IC of anesthetized cats. Stimuli were periodic trains of biphasic pulses with rates varying from 20 to 1280 pulses per second (pps). We found that the maximum pulse rates that elicited sustained firing and phase-locked responses were 2–3 times higher in the IC of awake rabbits than in anesthetized cats. Moreover, about 25% of IC neurons in awake rabbit showed sustained responses to periodic pulse trains at much higher pulse rates (> 1000 pps) than observed in anesthetized animals. Similar differences were observed in single units whose responses to pulse trains were monitored while the animal was given an injection of an ultra short-acting anesthetic. In general, the physiological rate limits of IC neurons in awake rabbit are more consistent with the psychophysical limits in human CI subjects compared to the data from anesthetized animals.

Keywords

cochlear implants; temporal coding; inferior colliculus; anesthesia

1. Introduction

Previous studies of neural responses to cochlear implant (CI) stimulation in anesthetized animals show upper frequency limits to temporal processing. Neurons in the inferior colliculus (IC) show sustained and pulse-locked responses to periodic pulse trains only up to a few hundred pulses per second (pps). A similar pulse rate limit is observed for neural sensitivity to interaural time differences (ITD). Although human CI listeners also show limits in the ability to discriminate the pitch or ITD of periodic pulse trains at high pulse rates, these limits are higher than those observed from IC neurons in anesthetized animals (Table 1).

Correspondence to: Yoojin Chung, Eaton-Peabody Laboratories, Massachusetts Eye & Ear Infirmary, Boston, MA 02114, USA, Phone: +1-617-573-5592, Fax: +1-617-720-4408, yoojin.chung@gmail.com.

We hypothesize that neural pulse-locking, ITD sensitivity and sustained firing to CI stimulation at high pulse rates may be underestimated due to the effect of anesthesia. We developed an awake animal model of CIs for single-unit recording from the IC to avoid this confound. Results show higher pulse-rate limits for sustained firing and temporal pulse-locking compared to anesthetized preparations. We further demonstrate that these differences are due to the effect of anesthesia by monitoring the responses of single units in the rabbit before and after injection of an ultra short-acting barbiturate.

2. Methods

We measured responses of IC neurons to electric pulse trains presented through 8-contact intracochlear electrode arrays (Cochlear Corp.) in both anesthetized cats and awake rabbits. Experiments on awake rabbits were performed on 2 female Dutch-belted rabbits that received unilateral cochlear implantations. The implanted ear was deafened during surgery with an injection of distilled water into the cochlea (Ebert et al., 2004). Although no attempt was made to deafen the unimplanted ear, auditory brainstem response thresholds were nevertheless elevated by 40–50 dB relative to normal in that ear. Rabbits were implanted with head bars and trained to sit still in the recording apparatus for 2–3 hours per day. Recordings from the IC contralateral to the implanted ear were performed from 29 to 431 days post implantation.

For comparison with the awake rabbit data, we reanalyzed data from anesthetized cats that were partially described in earlier reports (Hancock et al., 2012; Hancock et al., 2010). These experiments were performed on 8 cats deafened with ototoxic drugs either 1-week (n=3) or 6 months (n=3) before the experiment, and which received bilateral cochlear implants at the time of experiment. For the experiments, cats were anesthetized with a combination of urethane (300 mg/kg urethane, i.p.) and either diallyl barbituric acid (75 mg/kg i.p.) or sodium pentobarbital (37 mg/kg, i.p.). Data from both short-term (1 week) and long-term (6 months) deafened cats are combined herein because the differences in response patterns between the two groups were minimal.

In both preparations, stimuli were 300-ms trains of biphasic pulses (50 μs/phase) presented every 600 ms using a wide bipolar configuration. The current was 2 dB above the single-pulse threshold and the stimuli were presented diotically in anesthetized cats and monaurally in awake rabbits. Pulse rate was varied in random order from 20 to 1280 pps in half-octave steps. The single-unit recording methods were as described previously (Devore and Delgutte, 2010; Hancock et al., 2010).

In one rabbit, a catheter was surgically implanted into the right jugular vein to allow the administration of an ultra short-acting barbiturate (sodium methohexital, 5 mg/kg) while recording from single units (Kuwada et al., 1989). All procedures were approved by the animal care committees at the Massachusetts Eye and Ear Infirmary and the Massachusetts Institute of Technology.

3. Results

3.1 Pulse-rate Limits are Higher in Awake Rabbits Compared to Anesthetized Cats

Responses to electric pulse trains were measured as a function of pulse rate in 104 units in anesthetized cats and 80 units in awake rabbits. We observed clearly different response patterns in the two preparations. Results from two example units are presented in Fig 1. In the neuron from anesthetized cat, there is a strong pulse-locked response at low pulse rates indicated by the periodic pattern in the dot raster. The unit fires one spike per pulse at 20 and 40 pps, but the firing rate begins to decrease at higher pulse rates until the response is

limited to the onset for pulse rates > 80 pps. There is no spontaneous activity either during the off-period or between pulses at low pulse rates. In contrast, the neuron from an awake rabbit fires several spikes per pulse at low pulse rates (i.e. the firing rate is greater than the pulse rate) and the responses are pulse-locked up to higher pulse rates than in the neuron from anesthetized cat. Sustained responses are maintained up to the highest pulse rate tested (1280 pps). In addition, spontaneous activity is observed both during the off-period and between pulse-locked responses at low pulse rates.

Neural spike trains were cross-correlated with stimulus pulse trains to characterize the degree of temporal pulse-locking. The cross-correlograms in Fig. 2 are consistent with the temporal patterns shown for the same neurons in Fig. 1. Robust pulse-locking is evoked by low-rate pulse trains in both neurons, as shown by a prominent peak in the cross-correlogram. In the neuron from anesthetized cat, pulse-locked responses vanish above 80 pps, consistent with the limit of sustained firing. In the neuron from awake rabbit, tight pulse-locking is observed up to 224 pps. The correlogram shows multiple peaks for rates between 80 and 224 pps, reflecting the periodicity of the stimulus. Above 224 pps the responses become unsynchronized, as indicated by the absence of cross-correlogram peaks exceeding the 99% confidence bound for a random spike train.

Two metrics were used to characterize the upper pulse rate limit for sustained firing and pulse-locked responses, respectively. A neural detectability index d' was calculated for each pulse rate by comparing the firing rate during the stimulus (>30 ms after the stimulus onset) to the rate during the inter-stimulus silent interval (>100 ms after stimulus offset to discard rebound activity) in units of standard deviations. The cutoff for sustained firing was defined as the interpolated pulse rate where $d' = 1$. This can occur either when an excitatory response becomes too low or when a suppressive response becomes too high to be statistically distinguishable from spontaneous activity. Fig. 3A compares the distribution of cutoff pulse rates for sustained responses between anesthetized cat and awake rabbit. About 25% of IC neurons in awake rabbit show sustained firing to the highest pulse rate tested (1280 pps), a much higher proportion than in anesthetized cats. The median cutoff rate is about twice as large in awake rabbits (122 pps) as in anesthetized cats (65 pps). The difference is significant (Wilcoxon rank sum test, $p = 0.003$).

The temporal (pulse-locking) cutoff rate was defined as the lowest pulse rate where the area of the cross-correlogram peak above the 99% confidence bound falls below 0.02 spikes per pulse. The distribution of temporal cutoff rates in awake rabbit is biased towards higher rates compared to the anesthetized cat distribution, and ~29 % of units in awake rabbit pulse-lock at rates ≥320 pps compared to ~7% in anesthetized cats (Fig. 3B). The median temporal cutoff pulse rate is about 2.5 times higher in awake rabbits (206 pps) than in anesthetized cats (87 pps) among the units that show pulse-locking at any rate. The difference is highly significant (Wilcoxon rank sum test $p < 0.001$).

3.2 Anesthesia Administration Reduces Single-Unit Pulse Rate Limits

To ascertain whether the different effects of pulse rate on neural responses in the two preparations are due to anesthesia rather than species differences, we monitored changes in the responses of 13 single units and 3 multiunit clusters following intravenous injection of an ultra short-acting barbiturate in one rabbit.

An example is presented in Fig. 4A–E for one single unit. Before injection (Fig. 4A), the neuron showed spontaneous activity, pulse-locked spikes up to 160 pps, and unsynchronized sustained firing at higher pulse rates, much like the example in Fig. 1. One minute after injection (Fig. 4B), pulse-locked responses were observed only up to 56 pps, whereas the response was limited to the onset at higher pulse rates. The spontaneous activity also largely

disappeared. Ten minutes after injection (Fig. 4C), the response mostly recovered back to the pre-injection pattern. The firing rate was not simply attenuated across all pulse rates following injection (Fig. 4D) but rather the upper rate cutoff also shifted to lower pulse rates. This change in cutoff rate is even more apparent in the normalized firing rate-vs-pulse rate curves for each time period (Fig. 4E).

We defined the 50% cutoff rate as the point where the firing rate falls to 50% of its maximum value. Fig. 4F compares the pre-injection and post-injection 50% cutoff rates and temporal cutoff rates (defined as described earlier) across our sample. In all 16 units studied, both the 50% cutoff rate and the temporal cutoff rate decreased after injection. In some units, pulse-locking was completely eliminated. Overall, the effects of anesthesia on pulse-rate limits of single units in rabbit IC are consistent with the differences observed between anesthetized cats and awake rabbits, suggesting anesthesia is primarily responsible for these differences.

4. Summary and Discussion

Different response patterns are observed in IC units for electric pulse train stimuli in awake rabbits compared to anesthetized cats. Cutoff pulse rates for both sustained firing and pulse-locked responses are 2–3 times higher in awake rabbits than in anesthetized cats. Effects of anesthesia in single units from the rabbit are consistent with the differences between the awake rabbit and anesthetized cat preparations, suggesting that these differences are mainly due to the effects of anesthesia.

The tendency for both spontaneous and evoked firing rates to be reduced under anesthesia has also been observed in the IC of normal hearing rabbits (Kuwada et al., 1989) and in the auditory cortex of marmosets and guinea pigs wearing CIs (Johnson et al., 2011; Kirby and Middlebrooks, 2012). On the other hand, Ter-Mikaelian et al. (2007) found minimal differences between awake and anesthetized conditions in the temporal response properties of IC neurons to amplitude-modulated tones in normal-hearing gerbils, so the effects of anesthesia we observed on pulse-locking limits may be specific to deaf animals. The reduction of firing rates by anesthesia is consistent with an enhancement of inhibition mediated by GABA receptors as suggested by Kuwada et al. (1989). However, the urethane anesthesia used in our cat preparation does not act solely through GABA receptors, but rather through a wide spectrum of neurotransmitter-gated ion channels (Hara and Harris, 2002).

In earlier reports (Colburn et al., 2009; Hancock et al., 2012), we suggested that the rate limits of pulse-locked responses to electric pulse trains may be mediated by the low voltage activated potassium currents ($I_{K,LVA}$) present in many brainstem auditory neurons. The neurons expressing $I_{K,LVA}$ show a cumulative increase in membrane conductance after each stimulus pulse that increases the spiking threshold (Manis and Marx, 1991). Barbiturates decrease presynaptic neurotransmitter release by reducing voltage-dependent calcium conductance (Werz and Macdonald, 1985). The resulting reduction of excitatory drive may further limit the ability of neurons to reach threshold at high pulse rates under anesthesia.

The pulse rate following limits of IC neurons in awake animals better agree with human performance in temporal processing tasks such as rate pitch discrimination than the cutoffs observed in anesthetized cats. Specifically, more than 25% of the neurons in awake rabbit have temporal pulse-locking limits >300 pps, which is a typical temporal pitch limit in CI users. Whether the enhanced pulse-locking at high rates in awake animals also results in improved ITD sensitivity in bilaterally implanted animals will be of interest in future studies.

Acknowledgments

Supported by NIH grants R01DC005775 and P30DC005209, Curing Kids Fund from Massachusetts Eye and Ear and a Hearing Health Foundation grant to Y. Chung.

References

Colburn HS, Chung Y, Zhou Y, Brughera A. Models of brainstem responses to bilateral electrical stimulation. J Assoc Res Otolaryngol. 2009; 10:91–110. [PubMed: 18941838]

Devore S, Delgutte B. Effects of reverberation on the directional sensitivity of auditory neurons across the tonotopic axis: influences of interaural time and level differences. J Neurosci. 2010; 30:7826–7837. [PubMed: 20534831]

Ebert CS, Fitzpatrick DC, Cullen RD, Finley CC, Bassim MK, Zdanski CJ, Coffey CS, Crocker W, Skaggs J, Marshall AF, Falk SE. Responses of binaural neurons to combined auditory and electrical stimulation Abstr. Assoc Res Otolaryngol. 2004; 27:485.

Hancock KE, Chung Y, Delgutte B. Neural ITD coding with bilateral cochlear implants: effect of binaurally coherent jitter. J Neurophysiol. 2012; 108:714–728. [PubMed: 22592306]

Hancock KE, Noel V, Ryugo DK, Delgutte B. Neural coding of interaural time differences with bilateral cochlear implants: effects of congenital deafness. J Neurosci. 2010; 30:14068–14079. [PubMed: 20962228]

Hara K, Harris RA. The anesthetic mechanism of urethane: the effects on neurotransmitter-gated ion channels. Anesth Analg. 2002; 94:313–318. [PubMed: 11812690]

Johnson L, Santina CD, Wang X. Neural responses to cochlear implant stimulation in auditory cortex of awake marmeset. Abstr Assoc Res Otolaryngol. 2011; 34:943.

Kirby AE, Middlebrooks JC. Unanesthetized auditory cortex exhibits multiple codes for gaps in cochlear implant pulse trains. J Assoc Res Otolaryngol. 2012; 13:67–80. [PubMed: 21969022]

Kuwada S, Batra R, Stanford TR. Monaural and binaural response properties of neurons in the inferior colliculus of the rabbit: effects of sodium pentobarbital. J Neurophysiol. 1989; 61:269–282. [PubMed: 2918355]

Manis PB, Marx SO. Outward currents in isolated ventral cochlear nucleus neurons. J Neurosci. 1991; 11:2865–2880. [PubMed: 1880553]

Smith ZM, Delgutte B. Sensitivity to interaural time differences in the inferior colliculus with bilateral cochlear implants. J Neurosci. 2007; 27:6740–6750. [PubMed: 17581961]

Snyder R, Leake P, Rebscher S, Beitel R. Temporal resolution of neurons in cat inferior colliculus to intracochlear electrical stimulation: effects of neonatal deafening and chronic stimulation. J Neurophysiol. 1995; 73:449–467. [PubMed: 7760111]

Ter–Mikaelian M, Sanes DH, Semple MN. Transformation of temporal properties between auditory midbrain and cortex in the awake Mongolian gerbil. J Neurosci. 2007; 27:6091–6102. [PubMed: 17553982]

Tong YC, Clark GM. Absolute identification of electric pulse rates and electrode positions by cochlear implant patients. J Acoust Soc Am. 1985; 77(5):1881–1888. [PubMed: 3839004]

Townshend B, Cotter N, Compernolle D, White RL. Pitch perception by cochlear implant subjects. J Acoust Soc Am. 1987; 82:106–115. [PubMed: 3624633]

van Hoesel RJ. Sensitivity to binaural timing in bilateral cochlear implant users. J Acoust Soc Am. 2007; 121:2192–2206. [PubMed: 17471733]

Werz MA, Macdonald RL. Barbiturates decrease voltage-dependent calcium conductance of mouse neurons in dissociated cell culture. Mol Pharmacol. 1985; 28:269–277. [PubMed: 2412101]

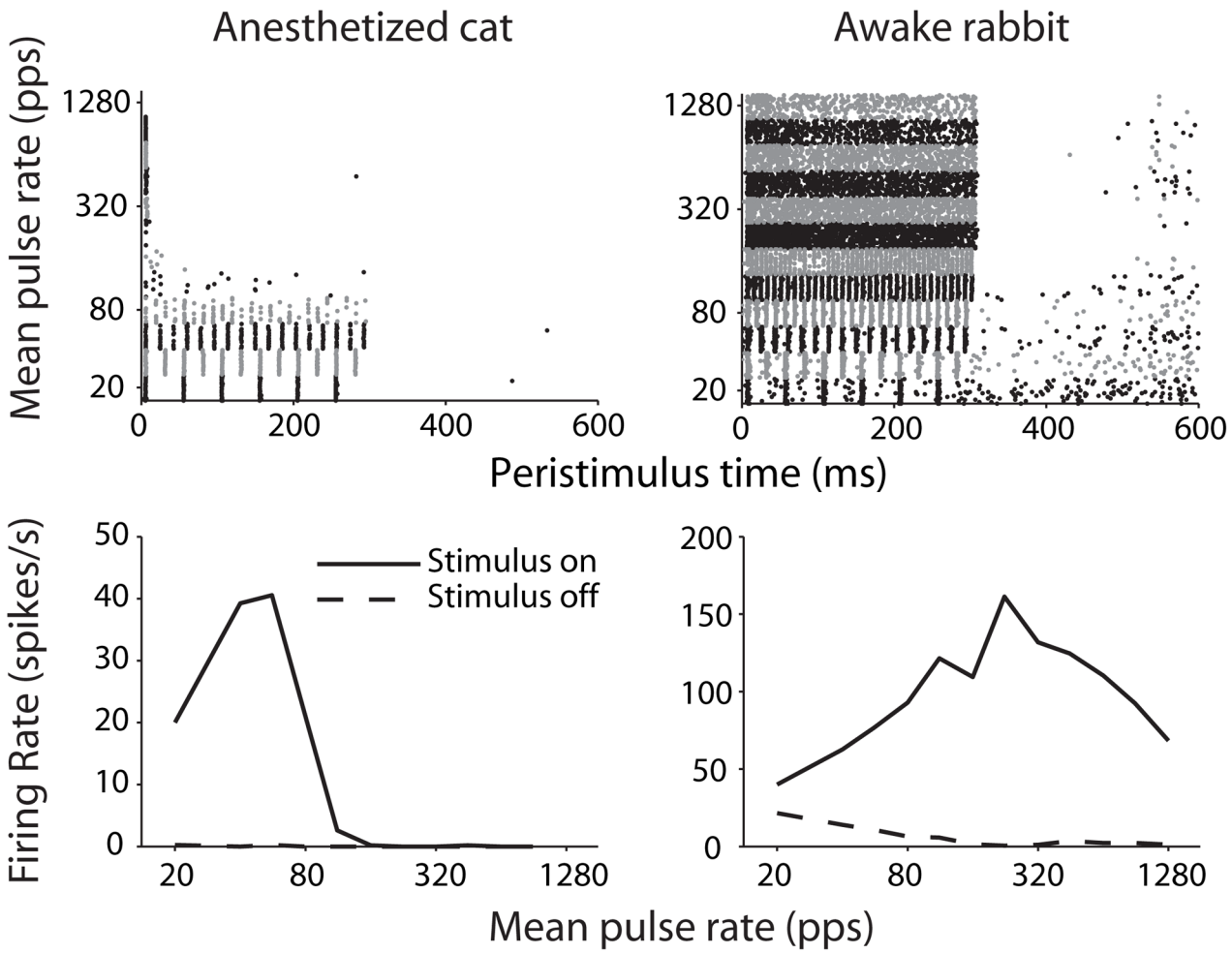

Figure 1.
Temporal response pattern (top) and average firing rates (bottom) as a function of pulse rate for two example neurons in anesthetized cat (left) and awake rabbit (right). Top panels show dot-rasters, where each dot represents a spike and alternating shades of grey distinguish blocks of stimulus trials at different pulse rates. Bottom panels represent mean sustained firing rate (excluding the first ~30 ms after stimulus onset) vs. pulse rate.

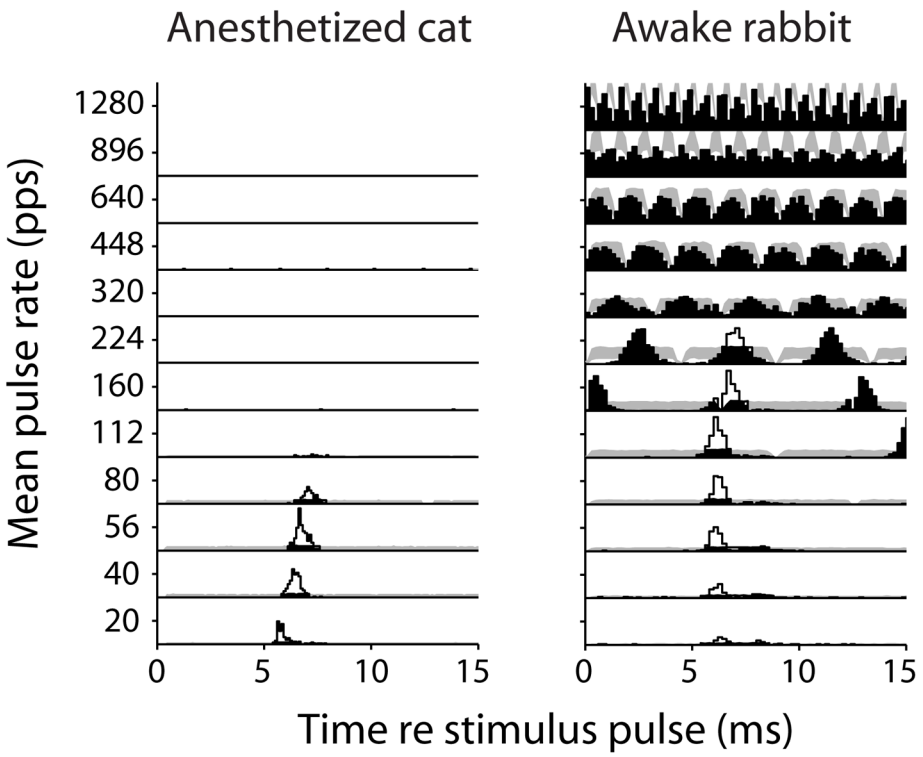

Figure 2.
Cross-correlograms between neural spike trains and stimulus pulse trains for the same two example neurons as in Fig. 1. Gray shading indicates 99% confidence bounds; correlation peaks exceeding the confidence bounds are filled in white.

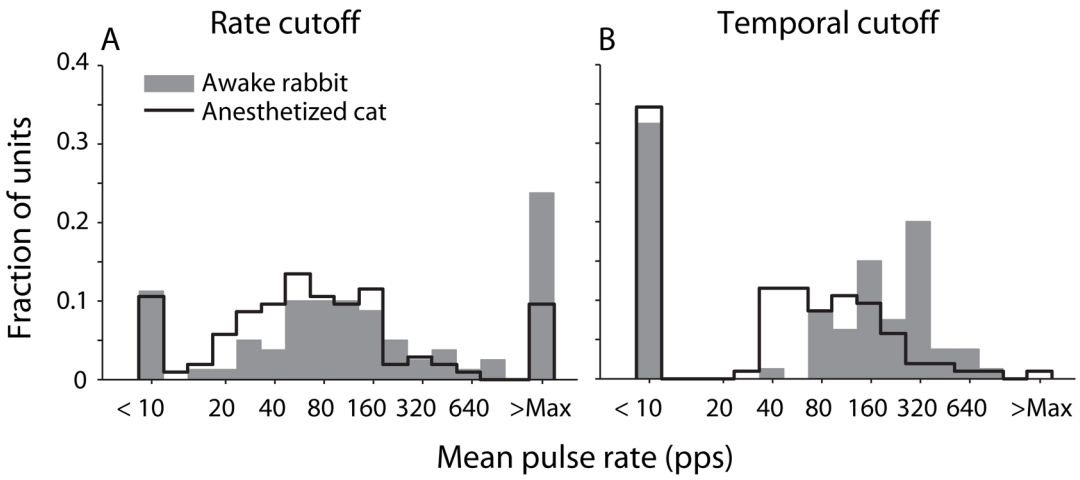

Figure 3.
Distributions of rate-based (a) and temporal cutoffs (b) across the IC neuron population in anesthetized cat (grey bars) and awake rabbit (black lines).

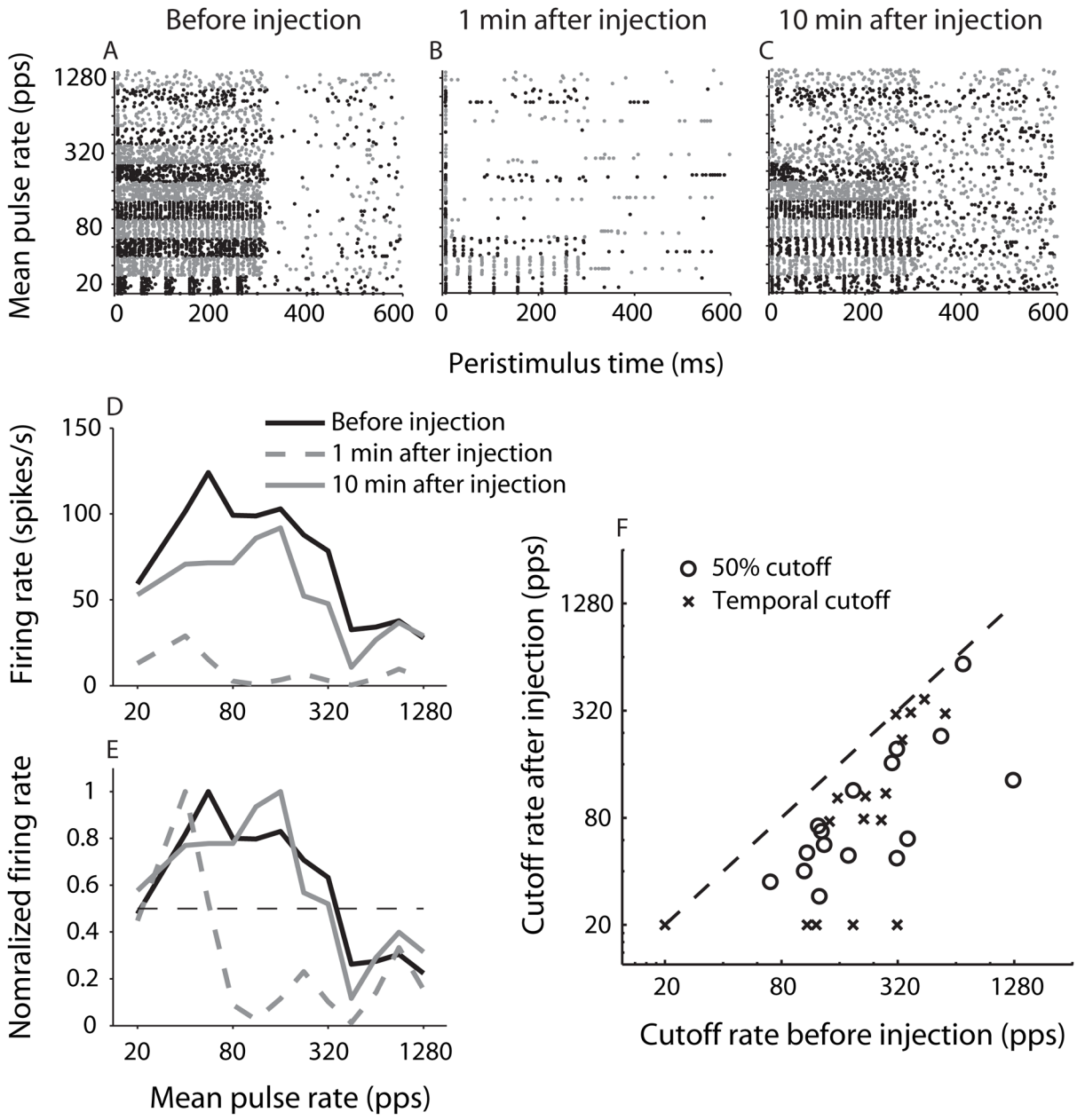

Figure 4.

Effect of barbiturate anesthesia in single units in rabbit. A–C: Effect of anesthesia in an example unit from the rabbit IC. D: Firing rate vs. mean pulse rate. E: Normalized firing rate vs. mean pulse rate. F. Comparison of rate-based cutoff and temporal cutoff before and 1–2 minutes after the injection.

Table 1

Comparison of perceptual rate limits in human CI users and neural rate limits in the IC of anesthetized animals.

Psychophysical: Human CI subjects		**Neural: IC neurons in anesthetized cats**	
Percept lasts throughout stimulus	> 2000 pps	30–300 pps[1]	Sustained responses
Rate pitch discrimination	200–1000 pps[2]	40–200 pps[1]	Temporal coding
ITD sensitivity	250–600 pps[3]	10–200 pps[4]	ITD sensitivity

[1] Snyder et al., 1995

[2] Tong and Clark, 1985, Townshend et al., 1987

[3] van Hoesel, 2007

[4] Smith and Delgutte, 2007; Hancock et al. 2010