

Auditory cortical neuron response differences under isoflurane versus pentobarbital anesthesia

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Abstract

Response properties of the middle layers of feline primary auditory cortex neurons to simple sounds were compared for isoflurane versus pentobarbital anesthesia in a within subject study control design. Initial microelectrode recordings were made under isoflurane anesthesia. After a several hour washout period, recordings were repeated at spatially matched locations in the same animal under pentobarbital. The median spatial separation between matched recording locations was 50 microns. Excitatory frequency tuning curves ($n = 71$ pairs) to tone bursts and entrainment to click train sequences ($n = 64$ pairs) ranging from 2 to 38 Hz were measured. Characteristic frequency and BW10 and BW30 were not different under either anesthetic. The spontaneous rate was slightly decreased ($P < 0.05$) for isoflurane (median 4.2 spikes/s) compared to pentobarbital (median 5.8 spikes/s). Minimum median threshold and latency were elevated by 12 dB and 2 ms, respectively, under isoflurane. Entrainment to click sequences assumed a lowpass filter profile under both anesthetics, but was markedly impoverished under isoflurane. Responses to click sequences under isoflurane were phasic to the first click but had very poor following to subsequent elements. Compared to pentobarbital, isoflurane appears to have a profound impact on response sensitivity and temporal response properties of auditory cortical neurons. © 2001 Elsevier Science B.V. All rights reserved.

Key words: Auditory cortex; Isoflurane; Pentobarbital; Anesthesia; Frequency tuning curve; Cat

1. Introduction

Inhalation and barbiturate agents are two classes of anesthetics commonly used in cortical studies of the auditory (Schreiner et al., 1992; Nelken et al., 1994;

Rauschecker et al., 1995; Zurita et al., 1994; Nelken et al., 1999; Sutter, 2000), somatosensory (Stryker et al., 1987; Recanzone et al., 1992; Wang et al., 1995) and visual (Tigwell and Sauter, 1992; Issa et al., 1999; Lisberger and Movshon, 1999; Issa et al., 2000) systems. The effect of anesthesia on functional properties of central neurons is a longstanding concern; there is evidence that spectral, binaural, and, in particular, temporal receptive field properties in the anesthetized preparation may differ from the awake (Kuwada et al., 1989; Zurita et al., 1994; Bieser and Muller-Preuss, 1996; deCharms et al., 1998; Wang et al., 1999). It is not always feasible or necessary to conduct electrophysiological studies in awake animals, so it would be advantageous to choose an anesthetic regimen that ap-

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Abbreviations: AI, primary auditory cortex; ANOVA, analysis of variance; BW10, bandwidth at 10 dB above minimum threshold; BW30, bandwidth at 30 dB above minimum threshold; CF, characteristic frequency; IV, intravenous; PSTH, peristimulus time histogram; SPL, sound pressure level; SR, spontaneous rate

proaches the awake condition. By knowing which properties are most affected by a given anesthetic, interpretation of experimental results can be placed into a more critical perspective. Isoflurane and pentobarbital are different in their route of administration and pharmacokinetics. A direct comparison of response profiles of cortical neurons under these anesthetic regimens will help to develop a comparative framework for interpretation of data derived under these two conditions.

Isoflurane is an inhalational anesthetic that has lower blood solubility than its related isomers, halothane and enflurane, so alveolar concentrations reach inspired concentrations quickly (Eger, 1981). As a consequence, anesthetic induction with isoflurane is similar to halothane and enflurane in its rapid onset, but its elimination is even faster. In humans, eyes open less than 20 min after the termination of isoflurane anesthesia (Eger, 1981). Rapid emergence from isoflurane anesthesia enables subjects undergoing recovery procedures to regain consciousness in a short time.

Pentobarbital sodium is a barbiturate sedative–hypnotic agent that is generally delivered intravenously (IV) or intraperitoneally in auditory neurophysiology to induce and/or maintain anesthesia. The pharmacokinetics of its elimination are dependent on metabolism, excretion and redistribution from tissue stores. Compared to isoflurane, pentobarbital is substantially tissue bound (muscle and fat). After a single dose of pentobarbital, the estimated drug half-life is 15–48 h (Harvey, 1980; Piatt and Schiff, 1984). In view of pentobarbital's extended half-life, its use in acute preparations is attractive, while its use in recovery procedures obligates an undesirable prolonged convalescent period.

The goal of this study is to contrast and compare response properties of cortical neurons in feline primary auditory cortex (AI) under these two anesthetic conditions. Simple sound stimuli, tone bursts and click train sequences, are used to explore spectral and temporal aspects of receptive field properties. Tone bursts are specific in frequencies and extended in time, whereas click train sequences are specific in time and extended in frequencies. Together, they provide an elemental view of how response properties are affected by the choice of anesthesia.

2. Materials and methods

2.1. Surgical preparation

Experiments were conducted on three young adult cats, in accordance with an approved institutional protocol and congruent with applicable international, national, state and institutional welfare guidelines at the University of California, San Francisco, CA, USA.

Cats were anesthetized with an isoflurane/oxygen mixture to reach a surgical plane of anesthesia. Tracheotomy was performed and an endotracheal tube was inserted to secure the airway. IV access was established and continuous fluid (normal saline with 1.5% glucose+20 milliequivalent KCl) was delivered at 6–8 cc/kg/h to support cardiovascular function. Ceftizoxime (10–20 mg/kg IV every 12 h), an antibiotic, was given to retard infection. The animal's core temperature was monitored and maintained at $\sim 38^{\circ}\text{C}$ with a feedback-controlled heated water blanket. Electrocardiogram and respiratory rate were monitored continuously throughout the experiment. Isoflurane concentration was titrated to maintain an areflexic state. The endotracheal tube was connected to a respiratory circuit, which sampled inspiratory and expiratory airflow from the animal for isoflurane concentration determination (Ohmeda). Under isoflurane anesthesia, expiratory concentrations were in the range 1.7–2.7%.

The head was stabilized with a fixation device that permitted the external auditory meati to remain patent. A scalp incision followed by soft tissue mobilization was carried out to expose the temporoparietal cranium. Burr holes over the auditory forebrain were positioned extradurally, and a bone plate was removed. The dura was reflected to expose AI bounded by the suprasylvian, anterior ectosylvian and posterior ectosylvian fissures. The brain was kept moist under a layer of viscous silicone oil. A magnified video image of the recording zone was captured with a camera and stored in a microcomputer for labeling penetrations relative to cortical vessels. At the conclusion of cortical response mapping under isoflurane, the inhalational agent was stopped and IV pentobarbital was administered and titrated to effect. The conversion of anesthetic agent from isoflurane to pentobarbital was complete within 1 h (expired isoflurane concentration $< 0.1\%$) of stopping isoflurane. An additional 2–4 h anesthetic washout period was instituted to minimize the effect of any possible residual isoflurane. After the isoflurane washout period, cortical response mapping resumed under pentobarbital. A vigorous effort was made to place penetrations at or very close to sites mapped under isoflurane anesthesia. These corresponding locations constituted 'matched pairs'. At the termination of each study, the animal was euthanized with an overdose of IV pentobarbital, followed by bilateral thoracotomies.

2.2. Stimulus generation

All experiments were performed in a double-walled sound attenuating chamber (Industrial Acoustics Company). Auditory stimuli were delivered through a STAX-54 headphone enclosed in a small chamber that was connected via a sealed tube into the external acous-

tic meatus of the contralateral ear (Sokolich, US Patent 4251686; 1981). The sound delivery system was calibrated with a sound meter (Brüel and Kjær 2209) and waveform analyzer (General Radio 1521-B). The frequency response of the system was largely flat (within 6 dB) up to 14 kHz. Above 14 kHz, the output rolled off at a rate of 10 dB/octave.

Tone bursts (3 ms linear rise and fall, total duration 50 ms and interstimulus interval 400–1000 ms) were generated by a microprocessor (TMS32010, 16-bit digital to analog converter at 120 kHz). Frequency–level response areas were recorded by presenting 675 pseudorandomized tone bursts of different frequency and sound pressure level (SPL) combinations. The entire matrix of frequency–level pairs covered an intensity range from 2.5 to 77.5 dB SPL in 5 dB steps, and 45 frequencies in logarithmic steps that spanned a 2–4 octave range, centered on the neuron’s estimated characteristic frequency (CF). A single tone burst was presented at each frequency–level combination (Schreiner and Mendelson, 1990).

Periodic click train sequences of constant 500 ms duration were generated by the TMS32010 microprocessor board. Each click element waveform was bi-phasic, with 200 μ s per phase, and presented at constant intensity 58 dB_{peak} SPL. The number of clicks ranged from a single click to 19 clicks over 500 ms to generate stimulus rates of 2–38 Hz in 4 Hz steps. A particular click train sequence was delivered with 10–20 repetitions and in a consecutive manner. A pause of 1–2 s separated successive click train sequences.

2.3. Recording procedure

All mapping experiments were performed on the left hemisphere. Parylene-coated tungsten microelectrodes (Microprobe) with 1–2 M Ω impedance at 1 kHz were used for multiunit recordings at depths 700–950 μ m, corresponding to layers IIIb and IV in AI, along the dorsal–ventral axis. Microelectrodes were introduced perpendicular to the surface of the cortex with a hydraulic microdrive (Kopf) guided by a depth counter. On occasion, dimpling of the cortical surface was eliminated by first advancing the electrode to a greater depth, followed by retraction to the target depth. Action potentials were isolated from background noise by an on-line window discriminator (BAK DIS-1). The number of discriminated spikes and times of arrival that occurred within 50 ms of tone burst onsets and 950 ms of the first element in click trains were recorded and stored in a microcomputer for off-line analysis.

2.4. Data analysis

For each penetration site, responses to the matrix of

frequency–intensity combinations determined the frequency response area (Sutter and Schreiner, 1991, 1995; Schreiner and Sutter, 1992), including the excitatory tuning curve. Typically, a brief phasic discharge was recorded 8–30 ms following tone burst onset for a range of frequencies within the boundary of the excitatory tuning curve.

Six measures were derived from each excitatory tuning curve (Schreiner and Mendelson, 1990). These were spontaneous rate (SR), CF, bandwidths at 10 and 30 dB above minimum threshold (BW10 and BW30), minimum threshold, and minimum latency.

SR is calculated from the total number of spikes recorded at the lowest level of sound intensity stimulation (2.5 dB SPL; 45 frequencies; 22 ms time window) divided by the time window for units with minimum threshold equal to or higher than 7.5 dB. CF is the frequency of the tone that evokes a response at minimum threshold (hereafter, simply ‘threshold’). The bandwidth of the excitatory receptive field is calculated from the upper and lower frequency bounds of the excitatory tuning curve at 10 dB and 30 dB above threshold and expressed in octaves. For some high threshold units, BW30 values are occasionally not obtainable. Threshold is the SPL of the quietest tone burst that evokes a response above the spontaneous activity. Latency is a measure of the asymptotic minimum of first spike time arrivals across the full range of stimulus levels at CF. At progressively higher intensities, the timing for first spike arrival reaches or approaches a minimum plateau (Mendelson et al., 1997; Heil, 1997).

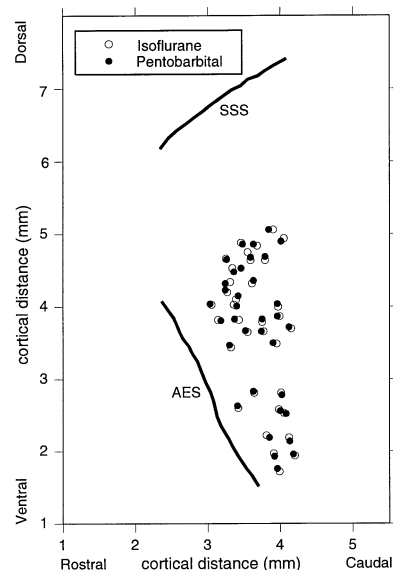


Fig. 1. The recording positions of spatially matched sites under two anesthetics in the left hemisphere of a single animal. Open and closed circles are for isoflurane and pentobarbital, respectively. SSS – suprasylvian sulcus. AES – anterior ectosylvian sulcus.

Matched Location A: CF = 3.1 kHz

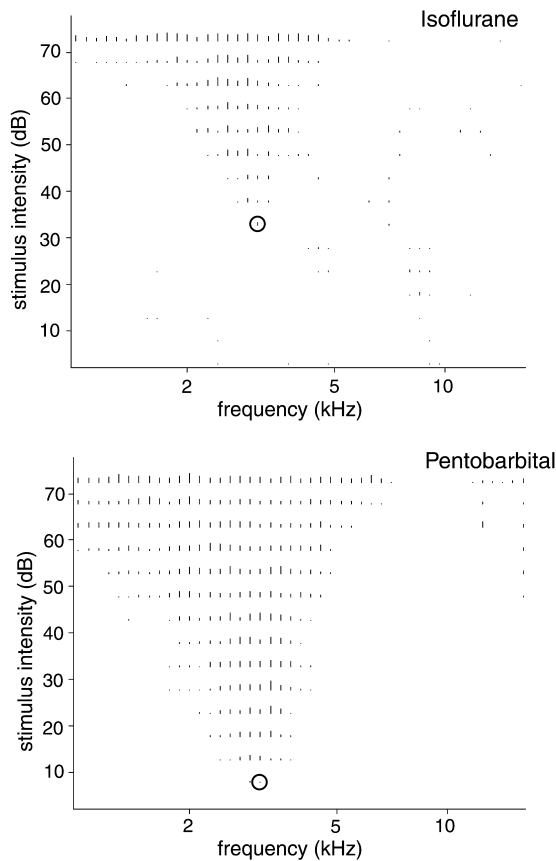


Fig. 2. Excitatory frequency response curves for matched location A. CF = 3.1 kHz under both anesthetics. Threshold is higher under isoflurane. Open circle marks CF and threshold.

Statistical treatments to evaluate for differences in response parameters under the two anesthetic conditions are accomplished using modified pairwise *t*-test and non-parametric Wilcoxon signed rank test.

Additionally, entrainment functions are derived from peristimulus time histograms (PSTHs) to click train sequences. The number of spikes per click element is calculated by computing the average number of spikes per stimulus presentation at each click train rate. A 25 ms window following the onset of each click element is used for this calculation. For click train rates equal to or greater than 6 Hz, response to the first click element is not included in the calculations. This is because response to the first click element is not rate dependent and, therefore, is a constant that can be removed. A two-way analysis of variance (ANOVA) with group (isoflurane vs. pentobarbital) and click train rate is used to evaluate for differences for both group and rate.

3. Results

3.1. Description of data

For analysis of response parameters to pure tone stimuli, 71 spatially matched pairs in AI form the complete data set. For the population analysis of entrainment to click train stimuli, the data set is reduced to 64 spatially matched pairs. The data set reduction is a result of lost units during click train sequence recording epochs. Fig. 1 shows the penetration sites in the left hemisphere under isoflurane and pentobarbital in a single animal. The recording sites are positioned along the dorsoventral axis to capture a wide range of response variations along this dimension. In this animal, the neurons have relatively high CFs (> 12 kHz), which is expected for cortical cells adjacent to the anterior ecto-

Matched Location B: CF = 22 kHz

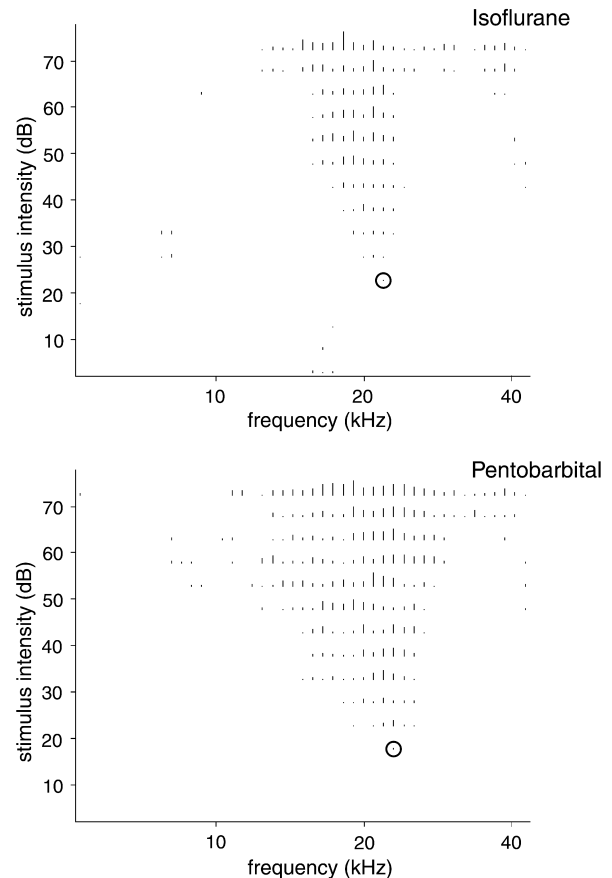


Fig. 3. Excitatory frequency response curves for matched location B. CF = 22 kHz under both anesthetics. For these higher frequency units, threshold is also higher under isoflurane. Open circle marks CF and threshold.

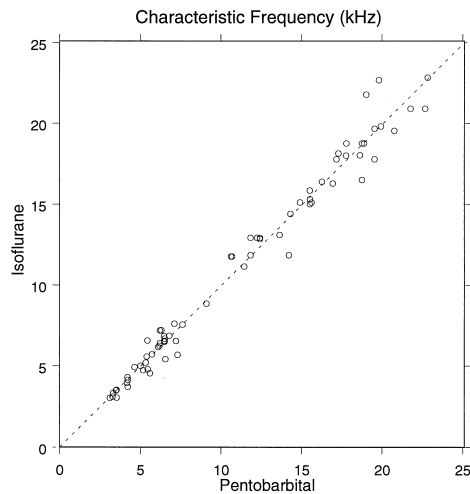


Fig. 4. Distribution of CF values under isoflurane and pentobarbital. CF is well matched for the entire range under isoflurane and pentobarbital.

sylvian fissure. The recording sites for both anesthetic conditions are spatially matched as close as possible. Based on electrode positioning relative to cortical vascular patterns, the median spatial separation is 50 microns (first quartile = 40 microns; third quartile = 70 microns) for matched pairs.

Under both anesthetic conditions, AI neurons respond to tone bursts and clicks with short latency phasic activity. SRs are comparably low under both conditions. Under isoflurane the median SR (spikes/s) is 4.2 (first quartile = 1.3, third quartile = 8.5, $n = 70$); under pentobarbital the median SR (spikes/s) is significantly higher at 5.8 (first quartile = 3.6, third quartile = 10.3, $n = 53$, Wilcoxon signed rank test, $z = -2.16$, $P = 0.031$).

Illustrations of the comparative effects of isoflurane versus pentobarbital on low and high CF neurons in two matched locations (A and B) are shown in Figs. 2 and 3. The open circles mark the CF and threshold of the neurons. In Fig. 2, excitatory frequency tuning curves for matched cells for location A are illustrated. Here, CF and bandwidth parameters are similar under the two anesthetic conditions (isoflurane CF = 3.05 kHz, pentobarbital CF = 3.11 kHz; isoflurane BW30 = 1.33 octaves, pentobarbital BW30 = 1.03 octaves). However, there are clear differences in threshold and latency. Under isoflurane, threshold is 25 dB higher and latency is 1.6 ms longer. The findings of minor differences in CF and bandwidth and major differences in threshold and latency response parameters when comparing isoflurane versus pentobarbital anesthesia are further highlighted in matched location B (Fig. 3). The response parameter values under the two anesthetics are: isoflurane CF = 20.9 kHz, pentobarbital CF = 22.7 kHz; isoflurane BW30 = 0.51 octaves, pentobarbital BW30 = 0.63 octaves; isoflurane threshold =

22.5 dB, pentobarbital threshold = 17.5 dB; isoflurane latency = 10.7 ms, pentobarbital latency = 8.9 ms. In the following sections, population data differences for the two anesthetic conditions are presented.

3.2. Spectral receptive field parameters

3.2.1. CF

CF representation is a robust response parameter that is largely invariant under isoflurane and pentobarbital anesthetic conditions. The consistency of this response parameter includes the full range of sampled neurons, from 3 to 23 kHz. Fig. 4 shows the relationship of CFs for all matched pairs under the two anesthetics. The CF of matched units is essentially identical ($r = 0.99$, $t = -0.03$, $df = 140$, $P = 0.98$). There is minor scatter at the highest CF values. This finding provides corroborative evidence that the matched pairs, while slightly offset in their penetration locations, are functionally coherent in this response dimension and likely to be members of the same local neuronal ensemble. In essence, CF topography is preserved under the two anesthetic conditions.

3.2.2. Excitatory bandwidth

The bandwidth values for BW10 and BW30 for the two anesthetic conditions have variations that are not systematic. No difference in bandwidth (BW10 $t = 0.65$, $df = 139$, $P = 0.51$; BW30 $t = 0.66$, $df = 131$, $P = 0.51$) is evident under the two anesthetics. Fig. 5 shows the relationship of BW10 and BW30 values for all matched pairs. The data scatter for both bandwidth measures is substantial and there is no orderly difference for BW10 and BW30, under the two anesthetics.

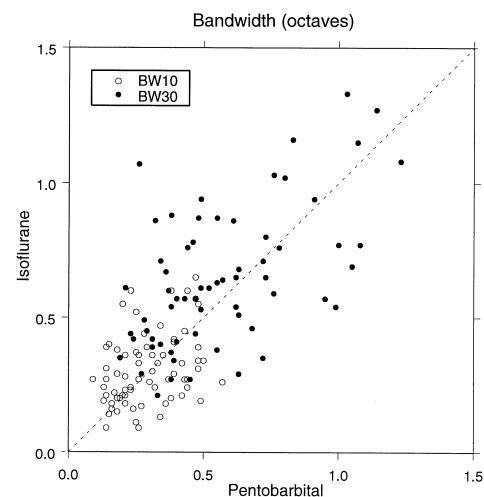


Fig. 5. Distribution of BW10 and BW30 values under isoflurane and pentobarbital. BW10 and BW30 have substantial scatter and do not appear to change in a systematic way under the two anesthetic conditions.

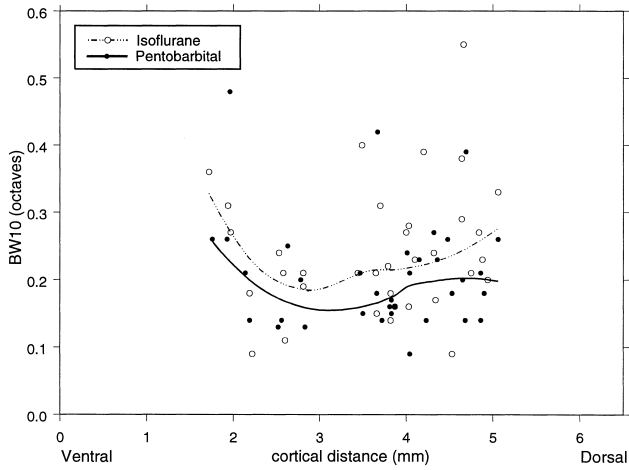


Fig. 6. Distribution of BW10 values for spatially matched neurons along the dorsoventral axis for a single animal. Locally weighted regression curves are drawn in for data under the two anesthetic regimens. The local BW10 minimum ~ 3 mm in the dorsoventral axis is conserved under both anesthetic conditions. The spatial distribution of bandwidth measurements under isoflurane and pentobarbital anesthetics is not statistically different.

While fluctuations in bandwidth measures for all matched pairs are rather unstructured, the global spatial gradient for bandwidth along the dorsoventral axis appears conserved. In the central region of cat AI, neurons have relatively narrow bandwidths (Schreiner and Mendelson, 1990); neurons dorsal and ventral to this sharply tuned region have broader excitatory tuning curves. Fig. 6 shows BW10 values for a single animal where bandwidth data under the two anesthetics are reconstructed along the dorsoventral axis. The other two cases did not have sampling density sufficient to support this type of reconstruction. Locally weighted regression curves (loess span = 0.75, SPLUS, MathSoft) of the data are drawn in to capture the global spatial gradient of bandwidth values under isoflurane (dashed line) and pentobarbital (solid line) anesthetic regimens. There is a bandwidth minimum centered at ~ 3 mm in the dorsoventral axis that is unchanged under both anesthetics. The bandwidths of sampled neurons are on average broader for cells dorsal and ventral to this sharply tuned region. For all matched units in Fig. 6, the median difference between BW10 (isoflurane minus pentobarbital) under the two anesthetics is 0.02 octaves (Table 1). There is no significant difference (paired t -test $t = 1.53$, $df = 34$, $P = 0.14$) in the spatial distribution of

Table 1
Summary statistics for matched pairwise differences

	Median	First quartile	Third quartile	Significance
BW10 (octaves)	0.02	-0.03	0.08	$P = 0.14$
Threshold (dB)	12	5	21	$P < 0.01$
Latency (ms)	2	0.6	3.1	$P < 0.01$

bandwidth measurements between isoflurane and pentobarbital anesthetics.

3.2.3. Response threshold

Response threshold is significantly higher under isoflurane. Fig. 7 is a scatter plot for thresholds under isoflurane and pentobarbital anesthetic conditions. Application of the Wilcoxon signed rank test non-parametric statistical test ($z = 6.41$, $P < 0.01$) for thresholds under the two anesthetics shows a significant difference. When matched pairs are treated in pairwise comparisons, the median difference is 12 dB (Table 1) higher under isoflurane.

In summary, the CF and bandwidth parameters of the spectral receptive field are comparable under isoflurane and pentobarbital anesthesia. However, the response sensitivity is significantly reduced under isoflurane, when compared to pentobarbital, and reflected by a median threshold increase by 12 dB. It should be noted that the threshold differences do not represent a physiological deterioration of the preparation since the lower thresholds were recorded in the second half of the experiment.

3.3. Temporal receptive field parameters

3.3.1. Response latency

Latency is significantly (paired t -test $t = 7.14$, $df = 135$, $P < 0.01$) longer under isoflurane anesthesia. Fig. 8 is a scatter plot for latencies under isoflurane and pentobarbital anesthetic conditions. When matched pairs are treated in pairwise comparisons, the median difference is 2 ms (Table 1) longer under isoflurane. The prolongation of latency under isoflurane anesthesia covaries with threshold. The relationship is evaluated by

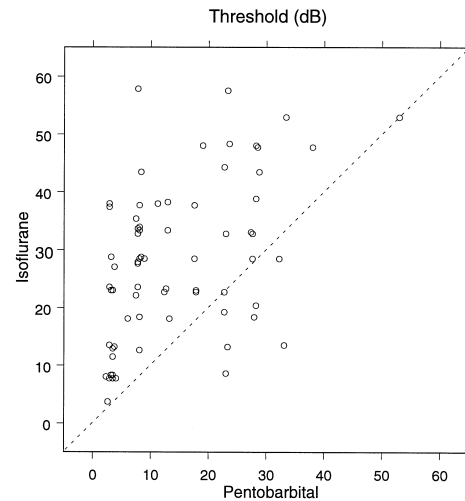


Fig. 7. Scatter plot of threshold values for all neurons under isoflurane and pentobarbital conditions. The two groups are different, with threshold values higher under isoflurane.

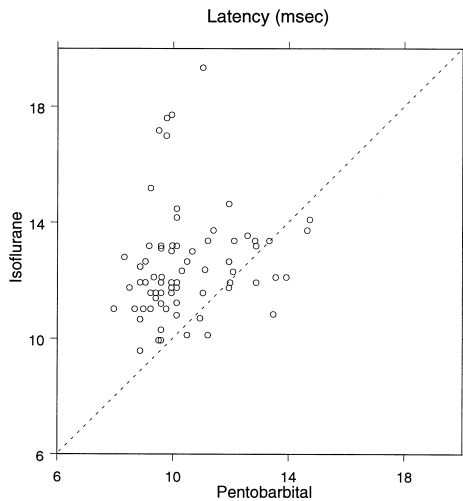


Fig. 8. Scatter plot of latency values for all neurons under isoflurane and pentobarbital conditions. The two groups are different, with latency values longer under isoflurane.

assessing differences in threshold and latency for pairwise matched locations. Fig. 9 reveals the covariation of threshold and latency differences, with a linear regression line fitted ($r^2 = 0.29$, $P < 0.001$) to the data.

3.3.2. Click train responses

Cortical neuron entrainment to temporally sharp, spectrally broad periodic click trains is significantly reduced under isoflurane anesthesia. Illustrations of the comparative effects of isoflurane versus pentobarbital for the previously featured low and high CF neuron pairs (Figs. 2 and 3) are shown in Figs. 10 and 11. The small dots at the top of individual panels mark the onsets of click elements. In both figures, responses to periodic click trains under isoflurane are limited to the first click in any sequence. By contrast, there are time-locked responses for individual click elements for repetition rates up to 34 Hz under pentobarbital. Overall, the entrainment to click trains takes on a lowpass filter profile.

Under pentobarbital, the response to the first click element is relatively constant as a function of repetition rate, although a small decline in activity is seen at and above 34 Hz. This suggests that the inter-trial interval was sufficiently long to avoid strong adaptation effects on the response. By contrast, under isoflurane, a progressive decline in responses to the first element at higher stimulation rates is seen above 14 Hz for neuron B and above 22 Hz for neuron A. This finding suggests a pronounced increase in post-stimulus adaptation or inhibition under isoflurane.

Fig. 12 shows population histograms for click train stimuli from 2 to 38 Hz, in 4 Hz steps, for all matched units under the two anesthetics. The responses for the two groups are markedly different. Under isoflurane,

there is a phasic response to the initial click that is followed by weakly driven responses to subsequent clicks and which diminishes as rate increased. In contrast, under pentobarbital, the initial phasic response to the first click is accompanied by relatively vigorous entrained responses to click train rates up to 22 Hz.

Entrainment functions derived for both populations are displayed in Fig. 13. The number of spikes evoked by each click element is plotted on a logarithmic scale. Thick and thin lines correspond to responses for isoflurane and pentobarbital, respectively. The error bars represent standard deviations. Under both anesthetics, the entrainment functions have lowpass filter profiles for responses to periodic click train stimuli. Entrainment to click trains is different for the two anesthetic conditions. A two-way ANOVA with group (isoflurane versus pentobarbital) and click train rate as factors shows highly significant differences for both group and rate, and significant interaction (all $P < 0.0001$). A post-hoc one-way ANOVA for the two anesthetic conditions with rate as factor reveals significant differences ($P < 0.01$) between the groups for stimulation rates 6, 10, 14 and 18 Hz. Large dots within lines in Fig. 13 highlight these differences.

In summary, cortical responses under isoflurane show impoverished temporal response properties, manifested as prolonged response latencies and reduced following capacity to periodic click train stimuli.

4. Discussion

4.1. Methodology

The data in this study contrast and compare the effects of isoflurane and pentobarbital, two commonly

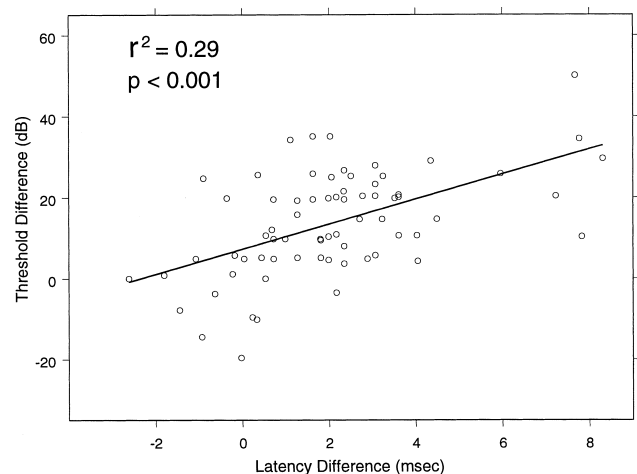


Fig. 9. Scatter plot with a linear regression line fitted to data for threshold and latency differences of pairwise matched locations under isoflurane and pentobarbital.

Matched Location A: CF = 3.1kHz

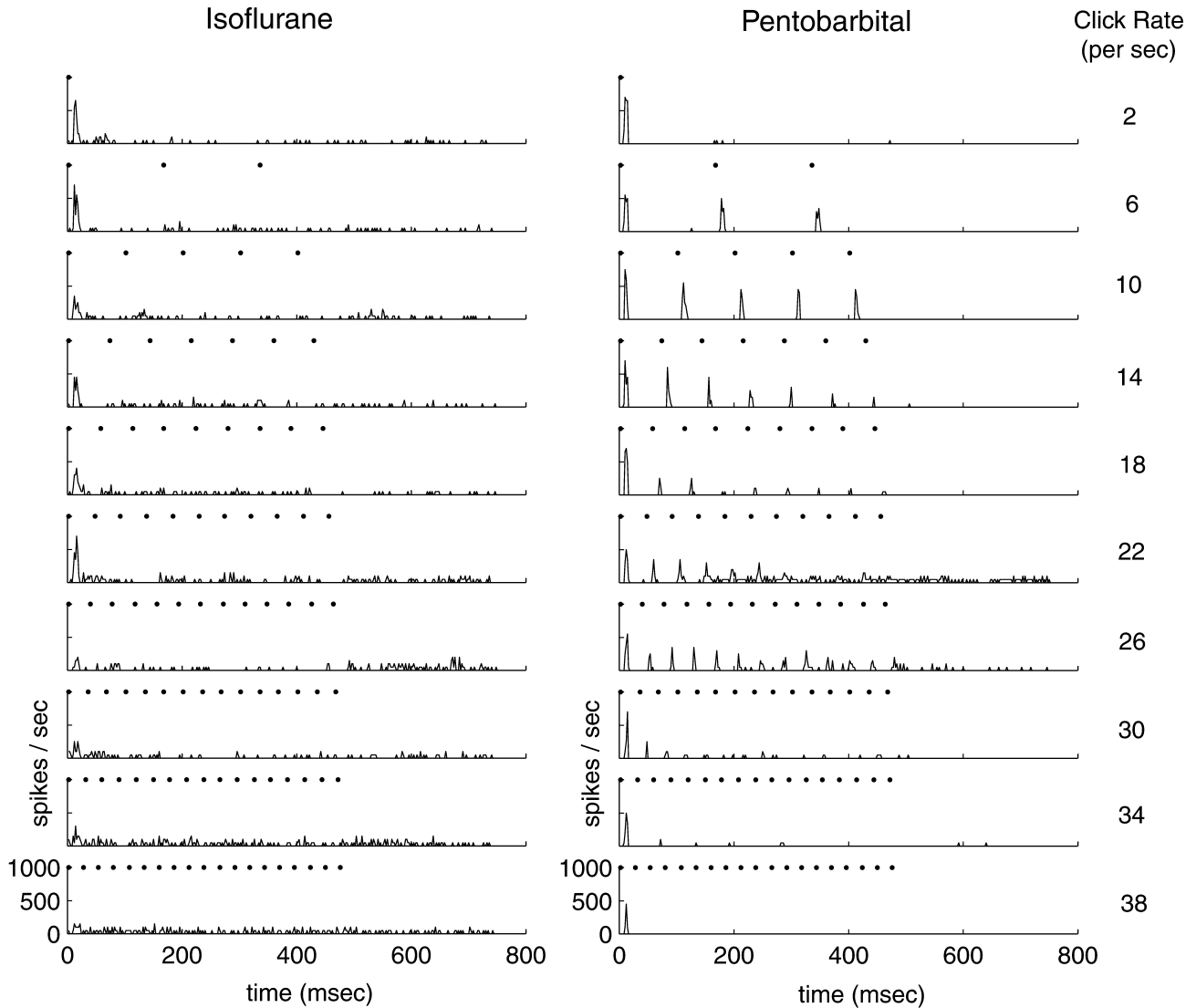


Fig. 10. PSTHs for responses to periodic click trains for matched location A (CF=3.1 kHz). In these relatively low CF units, the responses under isoflurane are limited to an initial phasic response to the first click element that is accompanied by poor entrainment to subsequent clicks.

used anesthetics for recovery and acute experiments, on measurements of receptive field properties of auditory cortex neurons to tone burst and click train stimuli. Significant differences in response profiles are evident under the two anesthetics; they are unlikely accounted for by the choice of anesthetic sequence, isoflurane followed by pentobarbital, or physiological deterioration of the preparation. Lower thresholds, shorter minimum latencies, higher SRs (Zurita et al., 1994; Kuwada et al., 1989) and greater entrainment to periodic stimuli –

all measures that indicate a more responsive cortex – are found under pentobarbital anesthesia. Any residual effect of isoflurane, which was delivered as the initial agent and permitted to washout over several hours, would have likely diminished cortical response efficacy under pentobarbital, thereby reducing estimated differences. Furthermore, physiological deterioration of the preparations would have coincided with the later pentobarbital anesthetic phase, and its impact would likely have been to decrease overall brain responsiveness,

thereby further reducing the magnitude of estimated differences. Despite these two considerations that may have diminished observed differences in response profiles under the two anesthetics, the results show clear and significant differences in thresholds, latencies and entrainment under isoflurane versus pentobarbital.

4.2. Spectral response property differences

CF organization is invariant under isoflurane and pentobarbital anesthesia. Tonotopic organization of

AI is a representation of the cochlear receptor surface and appears stable under the two anesthetic regimens. In primary somatosensory cortex of owl monkeys, area 3b, maps of hand representation were also found to be stable in the alert state and under a variety of anesthetic states that included pentobarbital, nitrous oxide, and ketamine (Stryker et al., 1987). It is evident that cochleotopic and somatotopic organization in primary sensory cortex within layers III/IV are preserved under a number of IV and inhalational anesthetic agents.

Excitatory bandwidths, measured at 10 and 30 dB

Matched Location B: CF = 22 kHz

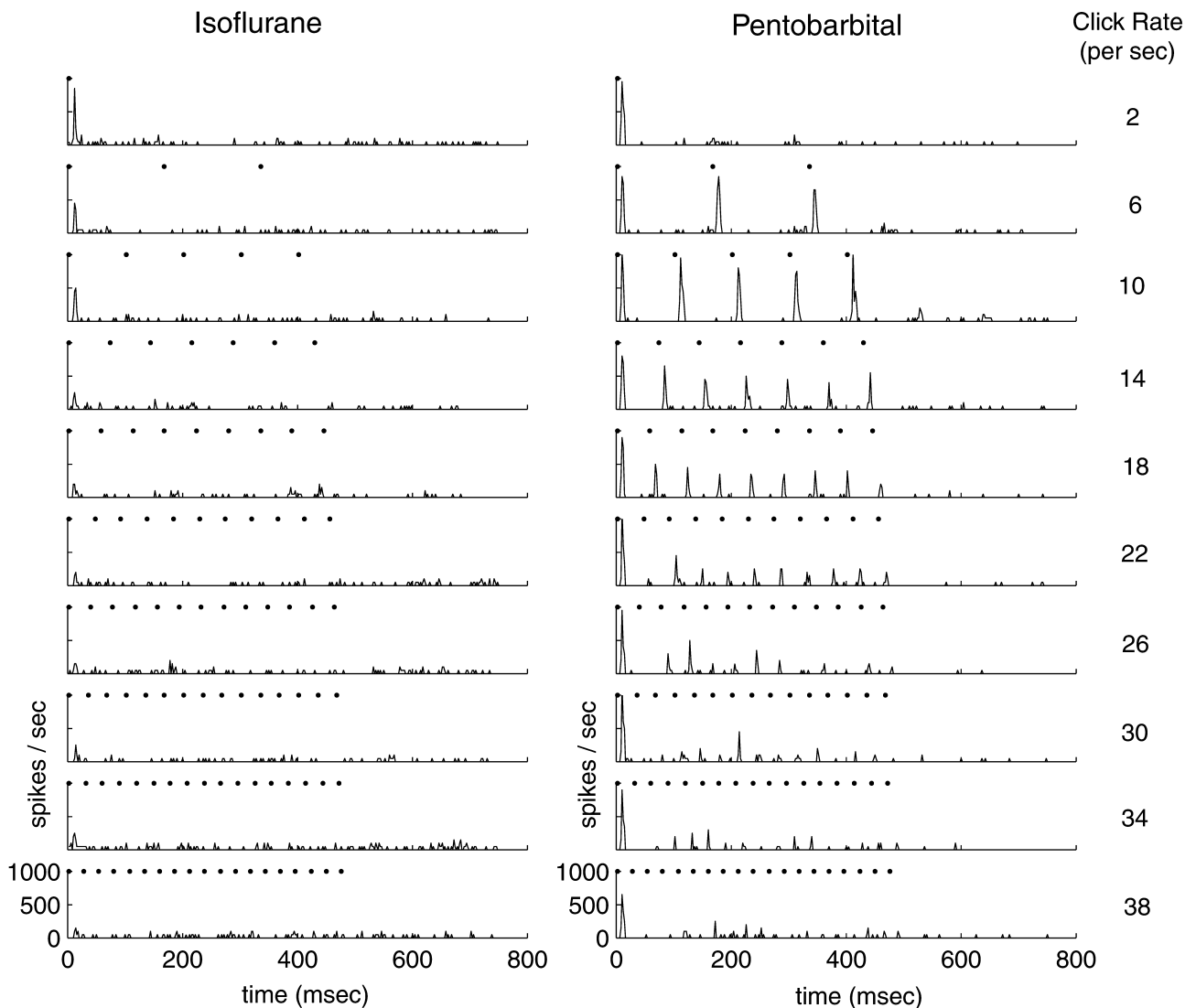


Fig. 11. PSTHs for responses to periodic click trains for matched location B (CF=22 kHz). In these relatively high CF units, the responses under isoflurane are also limited to an initial phasic response to the first click element that is accompanied by poor entrainment to subsequent clicks.

Population Histograms

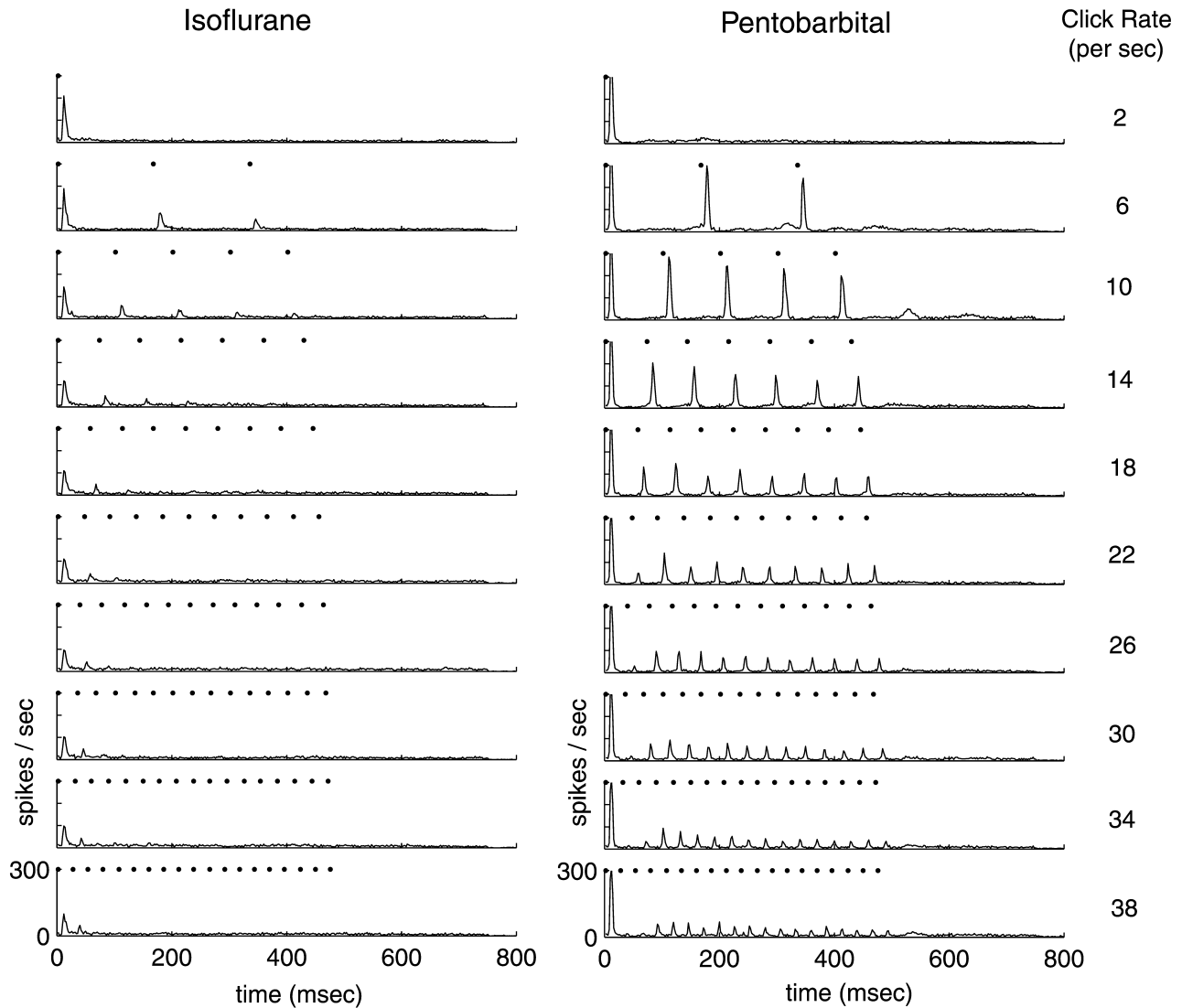


Fig. 12. Population histograms of responses to periodic click train sequences. The onset of each click element is marked by a small dot at the top of individual sequence panels. Under isoflurane, responses to periodic click trains are impoverished and limited to the first click element. There is poor entrainment to subsequent clicks.

above the minimum threshold, are statistically indistinguishable under isoflurane and pentobarbital anesthesia. Similarly, digital receptive field areas in somatosensory cortex were also not significantly different when measured under several anesthetic states (Stryker et al., 1987). The mapping strategy to cover the entire dorsoventral extent of an iso-frequency contour was adopted to ensure that a wide range of different BW and threshold conditions were sampled. The relatively large scatter in both BW10 and BW30 measures, com-

pared to CF, is not unexpected. Previous mapping studies also showed a larger local variability in BW than in CF, even within the same penetration (Schreiner and Sutter, 1992; Sutter and Schreiner, 1995). In one animal, where the spatial distribution of bandwidth (Fig. 6) is reconstructed along the dorsoventral axis, there is a central region of slightly more sharply tuned neurons flanked by broader and more variably tuned neurons dorsally and ventrally (Schreiner and Mendelson, 1990; Schreiner, 1998). Several lines of evidence sup-

port the notion of a spatial clustering of sharply and broadly tuned region in AI (Schreiner et al., 2000). This global organization of tuning bandwidth in feline AI appears conserved under both anesthetics.

Minimum response threshold averages 12 dB higher for isoflurane compared to pentobarbital anesthesia. However, the range of threshold differences spanned 50 dB with approximately 30% of the sites had threshold shifts of more than 20 dB (see Fig. 7). This suggests that threshold distributions under isoflurane may constitute a critical distortion of response sensitivity profiles obtained under pentobarbital (Heil et al., 1994; Schreiner et al., 1992; Sutter and Schreiner, 1995). Given the non-systematic differences in CF and BW, it is not likely that the threshold differences are a consequence of the test/retest mapping strategy. Neuronal sensitivity discrepancy under isoflurane versus pentobarbital anesthesia was evident in eighth nerve recordings (Dodd and Capranica, 1992) in the tokay gecko (*Gekko gecko*). Minimum eighth nerve thresholds measured under isoflurane and ketamine were 10–15 dB higher than for thresholds measured under pentobarbital and oxymorphone anesthesia. It is likely that the higher thresholds established in the periphery are also reflected in responses of cat cortical neurons.

4.3. Temporal response property differences

Minimum response latency to tone burst stimuli is 2 ms longer for isoflurane compared to pentobarbital anesthesia. Latencies of click-evoked brain stem auditory potentials in the cat were no different under pentobarbital, ketamine, choralose anesthetics (Cohen and

Britt, 1982). Also in the rat, evoked auditory potentials were no different under pentobarbital and ketamine anesthesia compared to the alert state (Bobbin et al., 1979) and pentobarbital compared to halothane (Jewett and Romano, 1972). Statistically significant, but sub-millisecond (< 0.4 ms) prolongation of later waveforms was seen in mice with the administration of pentobarbital (Church and Shucard, 1987). The effect of pentobarbital on response of latency of inferior colliculus neurons was mixed, with both prolongation and shortening observed (Kuwada et al., 1989). Covariation of threshold and minimum latency differences fitted with a linear regression model is demonstrated in Fig. 9, where the slope of the line is ~ 10 dB/3 ms. Taking this relationship into account, the several millisecond latency prolongation under isoflurane observed in association with a 12 dB increase in threshold may be primarily a consequence of cofactor dependence and not a difference in anesthetic state. This interpretation should be viewed in the context of substantial scatter in the linear regression fit.

Entrainment to click sequences is substantially impoverished under isoflurane anesthesia. While the response profiles under both anesthetics are similar with respect to assuming a lowpass character (see Fig. 13), entrainment to click train sequences at and greater than 6 Hz is decreased and largely eliminated under isoflurane compared to pentobarbital. This consequence of isoflurane anesthesia is arguably the most dramatic deviation from the awake preparation. Studies of temporal response characteristics in awake animals suggest improved temporal following capacities compared to pentobarbital or ketamine anesthesia (Bieser and Muller-Preuss, 1996; deCharms et al., 1998; Wang et al., 1999). The observed severe reduction of neuronal capacity to follow rapid click sequences under isoflurane separates this preparation further from the awake condition than either pentobarbital or ketamine anesthesia.

In thalamocortical brain slices, isoflurane decreases thalamic neuron membrane excitability by enhancing K^+ channel leak, resulting in a conductance shunt (Krnjevic, 1992; Ries and Puil, 1999a,b), and decreases the tendency for the membrane potential to oscillate (Tennigkeit et al., 1997). These oscillations have been shown to be closely related to the temporal following capacities of cortical neurons (Eggermont and Smith, 1995).

5. Conclusion

Comparison of auditory cortical neuron response properties to simple spectral and temporal stimuli under isoflurane and pentobarbital anesthesia is marked by consistency and discrepancy. CF and bandwidth show

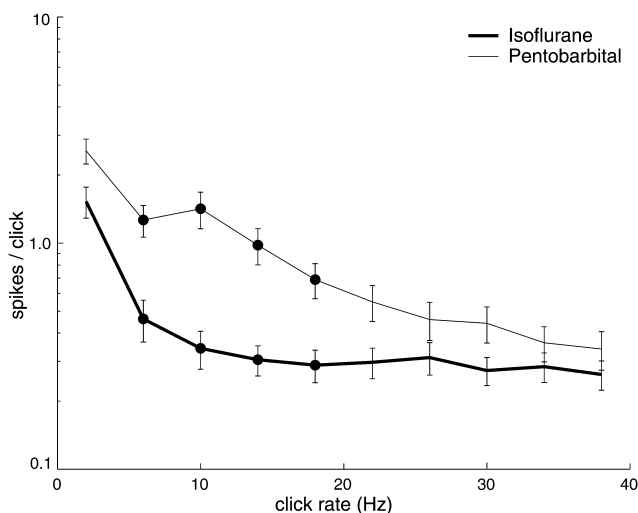


Fig. 13. MTFs for responses to periodic click trains under isoflurane and pentobarbital anesthesia. Entrainment to clicks is rather weak under isoflurane. The error bars represent standard deviations. Large dots mark the stimulation rates that are statistically different for the two groups.

no systematic differences under both anesthetics. By contrast, response threshold is higher, minimum latency is longer, spontaneous activity is lower and entrainment is considerably weaker under isoflurane at the expiratory concentration range of 1.7–2.7%.

These findings have practical implications. Compared to pentobarbital, isoflurane is minimally metabolized and eliminated quickly. For some recovery procedures, such as implantation of chronic recording devices that require intraoperative location of sensory cortex, isoflurane offers the advantages of supporting physiological recordings and rapid emergence from general anesthesia. When using isoflurane anesthesia at surgical levels, however, decreased spontaneous activity, higher thresholds and a more phasic response pattern to sequential stimuli should be expected and the ensuing consequences for estimating response sensitivity and temporal following capacity need to be considered. It should be noted that cortical responses under mixed inhalational agents, such as isoflurane with nitrous oxide, which can lower isoflurane levels to the 1–2% range, are not addressed in this study.

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