The Effect of Halothane on Thermosensitive Neurons in the Preoptic Region of the Anterior Hypothalamus in Acutely Instrumented Cats

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Normal thermoregulatory processes are significantly impaired by halothane anesthesia. However, the direct effects of halothane on thermosensitive neurons in the preoptic region of the anterior hypothalamus, a major thermoregulatory site, have not been previously investigated. Thirty-eight cats were anesthetized with α-chloralose (60 mg/kg) and urethane (600 mg/kg) and placed in stereotactic restraint. Stainless steel thermodes for highly selective local heating and cooling were stereotactically placed into the preoptic region with thermocouples used to monitor regional temperature. Using tungsten microelectrodes, 148 single neurons in the preoptic region were identified and subjected to local heating (to 42° C) and cooling (to 30°C). Eighteen percent (n = 27) in 15 different cats were classified as thermosensitive by accepted criteria (change in firing rate per degree centigrade of > 0.8 spikes·s⁻¹·° C⁻¹ or < −0.6 spikes·s⁻¹· ° C⁻¹). Thermosensitive units were then subjected to graded concentrations of halothane (0.25–1.0% end-tidal), and local heating and cooling were repeated. The spontaneous firing rate (spikes per second) at 37° C of 21 warm-sensitive neurons was significantly (P < 0.05) reduced, to 65.5 ± 8.3, 42.6 ± 10.7, 28.0 ± 9.5, and 18.1 ± 6.0% of control at 0.25, 0.50, 0.75, and 1% halothane, respectively. Spontaneous firing rate returned to 99.5 ± 19.8% of control within 30 min after discontinuation of halothane. Thermosensitivity (change, per degree centigrade, in spikes per second) was also significantly reduced, to 33.3 ± 5.6, 28.5 ± 14.6, and 13.9 ± 6.6% of control at 0.50, 0.75 and 1.0% halothane (all P < 0.05 compared to control). Thermosensitivity returned to 97.0 ± 11% of control within 30 min after halothane. In order to assess the variability of neuron

firing rates, the train of impulses produced by single neurons was subjected to statistical analysis of the time intervals between successive spikes (interspike interval analysis) to derive the autocorrelation function. The coefficient of variation (standard deviation ÷ mean of interspike intervals), a normalized index of variability of firing rate data from single neurons, was unchanged by halothane administration. Processed electroencephalographic parameters (spectral edge 50, 80, 95, total activity, and percent activity in δ, θ, α, and β bands) did not show consistent changes with hypothalamic heating and cooling before or after halothane administration. The alterations in thermosensitive unit activity and impairment of hypothalamic thermal detection abilities produced by halothane may contribute to the altered thermoregulatory function observed during general anesthesia. (Key words: Anesthetics, volatile: halothane. Brain: electroencephalography; hypothalamus. Temperature: regulation.)

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PRESENT MODELS of thermoregulation include a central integration of peripheral and central thermosensor input with the appropriate activation of heat gain or loss mechanisms in order to maintain a set-point temperature.[1–4] A primary central integration of thermal afferent neurons is believed to occur in the hypothalamus but may involve additional regions in the central nervous system (CNS).[1–4] Peripheral thermosensors are found in all skin regions (most importantly, the scrotum and face) and visceral structures.[5–6] Central thermosensors have been demonstrated in the hypothalamus, the lower brain stem, and the spinal cord.[1–3,7] These CNS areas may activate both heat gain and heat loss mechanisms, including behavioral adaptations and physiologic responses such as shivering, sweating, piloerection, and vasodilation or vasoconstriction.[8–10]

General anesthetic agents have been demonstrated to interfere with thermoregulation by abolishing appropriate heat gain or heat loss responses to thermal challenge.[11–13] Both intravenous and inhalational anesthetic agents increase muscle and cutaneous blood flow, presumably by disrupting normal vasomotor tone and the control mechanisms of thermoregulation.[13–14] Whether peripheral thermosensory affecter activity remains intact after anesthesia is unclear.[13,15]

The role of the preoptic region (POR) of the anterior hypothalamus as a central site of both thermodetection and integration is well established.[1–3,9–11,15–17] Previous

investigations have demonstrated the production of appropriate thermoregulatory responses to local heating or cooling of the POR.[3,5,10,18] The presence of specific POR neurons that alter their firing rates and patterns to local thermal stimulation is well documented.[19-23] These neurons are believed to mediate normal thermoregulatory processes. Various interventions, including thermal stimulation of skin or spinal cord,[5] hypercarbia,[21] or the administration of pyrogen,[22,23] hypothermic agents,[20] putative neurotransmitters,[24,25] barbiturates,[26] and opioid agonists[27] have been shown to alter the thermal response patterns of these POR neurons.

Although the ability of anesthetics to disrupt normal thermoregulation is well established, few studies have examined the effects of general anesthetics, including halothane, on single thermosensitive neurons. The purpose of the present investigation was to examine the effects of graded concentrations of halothane on the spontaneous firing rate (spikes per second), thermosensitivity (change, per degree centigrade, in spikes per second) and variability in firing rate of single neurons in the POR. Since alterations in the cortical electroencephalogram (EEG) have been previously correlated with hypothalamic thermosensitive unit activity,[28-31] the effect of hypothalamic heating and cooling on the processed EEG was also evaluated.

Materials and Methods

GENERAL PREPARATION

All studies were approved by the Animal Use and Care Committee of the Medical College of Wisconsin. All experimental procedures and protocols conformed to the Guiding Principles in the Care and Use of Animals of the American Physiological Society and were in accordance with National Institutes of Health guidelines.§ Thirty-eight cats (average weight 2.8 kg) were anesthetized by an intraperitoneal injection of α-chloralose (60 mg/kg) and urethane (600 mg/kg). The femoral artery and vein were cannulated; a tracheostomy tube was inserted; and the lungs were ventilated with an Ohio ventilator in a semiclosed circle system. End-tidal carbon dioxide was continuously monitored by mass spectrometry (Marquette Gas Analysis, St. Louis, MO), and ventilation was adjusted to maintain an end-tidal carbon dioxide tension of 30–35 mmHg. Arterial blood gas tensions were intermittently measured and ventilation adjusted or sodium bicarbonate administered as needed to maintain normal values. Systolic arterial blood pressure was maintained greater than

100 mmHg by a phenylephrine infusion (approximately 10–20 μg/min) as needed after halothane administration.

A thermocouple was inserted 10 cm into the rectum to monitor deep core temperature, which was maintained at 37.0 ± 0.5° C at all times by means of a thermoregulatory unit connected to a heating pad surrounding the animal and by heating lamps. Ambient temperature was 24.0 ± 1.0° C. Humidity was not controlled. The animal was positioned in hip pin and stereotaxic restraint. A lumbar laminectomy was performed at L3–L4. After exposure of the epidural space, a U-shaped thermode constructed of PE-20 tubing and a small thermocouple were threaded epidurally to approximately the level of T1–T2 in order to allow thermal monitoring and thermal stimulation of the spinal cord. A midline cranial incision was performed, extending from the nasion to the first cervical vertebra. The atlantooccipital membrane was opened and a drain placed in the cistern to minimize cerebral pulsations. Burr holes were made through the calvarium and small dural punctures performed.

A small copper-constantan thermocouple (contained within a length of 23-G stainless steel tubing) and 18-G double-walled paired thermodes were inserted from the rostrum into the POR at an 80° angle from the zero horizontal plane to target stereotaxic (Horsely-Clark) coordinates: anterior 14.5, lateral 2.5, and depth −4.0 cm according to the atlas of Jasper and Ajmone-Marsan.[32] The paired thermodes, 2.5 mm lateral to the midline, were double-walled to allow circulation of water from temperature-controlled water baths, providing for precise local thermal challenge of the POR with selected temperatures. With the use of an electronic microdrive (Burleigh Inchworm, Fishers, NY), a 10-μm tip tungsten recording microelectrode (nominal impedence 5 MΩ) was advanced vertically into the POR at the coordinates specified above (fig. 1). In selected cats (n = 4), stainless steel screws were placed extradurally through burr holes, with one indifferent ground at the nasion and two bifrontal and bioccipital electrodes to allow continuous recording of two channels of hemispheric EEG activity. A Vetter frequency-modulation tape deck and a Grass polygraph were used to record continuously and display the following parameters: arterial blood pressure, heart rate, spinal cord temperature, preoptic region brain temperature, unit spike activity, and two channels of EEG activity.

RECORDING OF SINGLE NEURON ACTIVITY

Single neuron unit activity was recorded using BAK (BAK Electronics, Germantown, MD) model MDA-3 microelectrode amplifiers referenced to 0–80 stainless steel screws inserted into the calvarium. The output of the amplifiers was continuously displayed on Tektronix oscilloscopes. Isolation of single-unit spikes from background
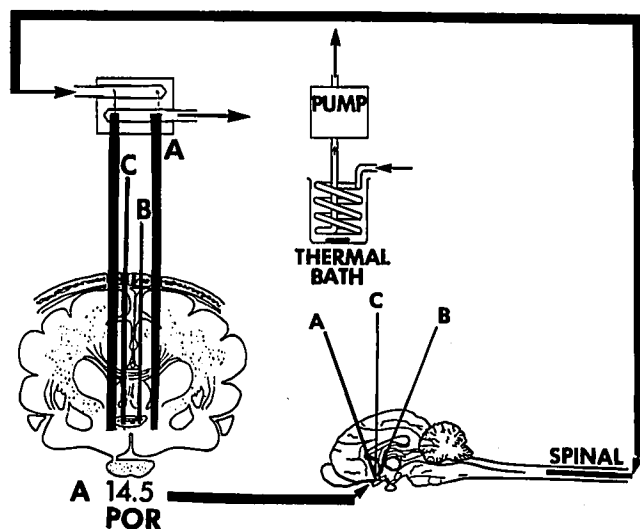
FIG. 1. The heating/cooling thermodes (A), thermocouple (B), and recording microelectrode (C) positioned at Horsely-Clark coordinates A = 14.5, L = 2.5, D = −4.0 in the preoptic region of the anterior hypothalamus.

activity was accomplished using a selective time-voltage window discriminator and a Mentor N-750 spike analyzer coupled to digital electronic counters to determine firing rate. The output from the spike analyzer also was fed to a Grass 7P10BS integrator for graphic display. Raw and processed single unit activity, EEG activity, and monitored temperatures were simultaneously recorded using a Vetter frequency-modulation tape deck. An IBM-PC AT clone computer (Novas Computrade, San Jose, CA), a Metrabyte Dash-16 12-bit analog-to-digital convertor, and specialized Asyst (Keithly Metrabyte, Taunton, MA) software was used for the analysis of thermosensitivity, firing rates, EEG parameters, the calculation of interspike intervals, and autocorrelation of neuronal discharge patterns.

Single neurons in the POR were identified during each passage of the electrode. In order to minimize CNS damage, no more than three electrode insertions were performed in any cat. After quantifying baseline discharge activity, local heating (to a maximum of 42° C) and cooling (to a minimum of 30° C) of the POR or spinal cord was then performed in random sequence by selectively cycling hot or cold water through the thermodes. During this local heating or cooling, the heating pad surrounding the animal and the heat lamps were kept off to prevent the possible confounding effects of skin surface heating on hypothalamic neuronal thermosensitivity.[5] Three to 10 min of recovery time were allowed between perfusion sequences.

Thermosensitivity was calculated by computer-assisted linear regression analysis of the plot of firing rate (spikes per second) versus local (POR or spinal cord) temperature.

The slope of the regression line was calculated over the entire range of temperature challenge (i.e., 10–12° C) in neurons that showed an essentially linear response to thermal challenge, or over the $\geq 3°$ C range at which the thermosensitivity curve was most linear in those neurons whose response to thermal challenge was nonlinear. If a subset of the entire range was used for calculation of thermosensitivity in a particular neuron, the same temperature range was used for all calculations involving that neuron. The significance of the correlation (probability of rejection of the null hypothesis and the true population correlation = 0) was determined at the $P < 0.05$ level according to the method of Fisher and Yates.[33] Neurons were defined as warm-sensitive if they exhibited an increase in firing rate of ≥ 0.8 spikes $\cdot$ s^{-1} $\cdot$ ° C^{-1} or as cold-sensitive if they exhibited a decrease in firing rate per degree centigrade of ≤ -0.6 spikes $\cdot$ s^{-1} $\cdot$ ° C^{-1}. All other neurons were considered to be thermally insensitive. These definitions of thermosensitivity conform to previously published widely accepted criteria.[1,3–5,18–26]

DETERMINATION OF INTERSPIKE INTERVAL PATTERNS OF NEURON FIRING (AUTOCORRELATION)

In an attempt to evaluate the effect of halothane anesthesia on the variability of neuron firing, time intervals between successive spikes of a neuron's spike train (interspike intervals) were calculated and an interval histogram (histogram of the distribution of time intervals between successive spikes) generated. The histogram can also be interpreted as a probability density function, i.e., as an estimate of the likelihood of a neuron firing at any given time after a previous spike.[34,35] A function with a large standard deviation would represent a more irregular firing pattern, and one with a small standard deviation, a more regular pattern. Interspike interval analysis was always performed during normothermic POR conditions. The mean interval, the interval variance, the standard deviation, the standard error, and the coefficient of variation (standard deviation ÷ mean) were calculated for the interspike-interval histogram as scalar indices of the variability of neuronal firing.[34,35]

EEG ANALYSIS

Right- and left-hemispheric EEG activity was digitized at 200 Hz with a 12-bit analog-to-digital converter, corrected for direct-current offset, digitally filtered, and subjected to a fast-Fourier transform and spectral analysis in the 0–50-Hz band width. Eight consecutive 2-s epochs were analyzed. This analysis was separately performed three times and averaged. Three separate groups of eight epochs each were analyzed rather than one continuous group of 24 epochs, in order to minimize the effect of

brief variations in EEG activity.[36] This method provided data from three different points in similar time rather than three consecutive points in absolute time. Absolute integrated EEG power, normalized frequency distributions (*i.e.*, a normalized power spectrum, corrected by subtracting the standard deviation of the array from the entire array, which is then expressed as a percent of total power) in the δ (0–4-Hz), θ (4–8-Hz), α (8–12-Hz), and β (12–20-Hz) bands, and 50, 80, and 95% spectral edges of the 0–25-Hz activity were calculated.

ADMINISTRATION OF HALOTHANE

After quantification of baseline thermosensitive response, single units were then subjected to graded (0.25, 0.5, 0.75, and 1.0% end-tidal) concentrations of halothane, delivered by an Ohio vaporizer into the circuit and continuously measured by mass spectrometry. After a 15–30-min equilibration period, thermal challenge was repeated in a similar fashion at each concentration of halothane. Halothane was discontinued after thermal challenge at 1% end-tidal concentration or at a lower concentration if spontaneous firing rate and thermosensitivity were abolished. In order to verify the transient nature of halothane on single-unit responses, thermal challenge was repeated for each unit 30–45 min after discontinuing halothane. End-tidal concentrations of halothane were always less than 0.013% (0.1 mmHg) during this thermal challenge. In selected animals, blood samples were drawn for analysis of blood halothane concentrations by gas chromatography by the method of Lowe.[37]

HISTOLOGIC DOCUMENTATION OF ELECTRODE SITES

At the completion of all experiments, the animal was killed with a lethal intravenous injection of pentobarbital and a small lesion was accomplished at the site of the recording electrode tip by passing a 5-mA direct current between the tip and an indifferent ground for 15 s. All thermocouple tubes and thermodes were also lesioned. Brains were perfused *in situ* with normal saline followed by 10% formalin in saline and subsequently stored in the 10% formalin solution containing 0.5% sodium ferrocyanide for tissue fixation and for development of Prussian blue marks at thermocouple and thermode sites. After 48 h in the fixing solution, the brains were blocked, frozen-sectioned, and electrode, thermode and thermocouple placement verified histologically using techniques previously described.[20,38]

STATISTICAL ANALYSIS

Changes in spontaneous firing rate, thermosensitivity, interspike-interval parameters, and the processed EEG were analyzed with a repeated-measures analysis of variance.[39] Pair-wise comparisons of interventions were performed with contrasts derived from the repeated-measures analysis of variance, adjusting for multiplicity by Duncan's method using the SAS software system. Changes at each concentration of halothane were compared with control and considered significant when the P value was less than 0.05. EEG data during control, at each halothane concentration, and after discontinuation of halothane were analyzed at each intervention, with comparison of heating and cooling to control.

Results

One hundred forty-eight single units were isolated and subjected to local thermal challenge. One hundred twenty-one (82%) of these units were found to be thermally insensitive. Spontaneous firing rates for these units ranged from 0.1 to 30 Hz. The remaining 27 (18%) units (in 15 cats) were defined as thermosensitive by established criteria and were further categorized as warm-sensitive or cold-sensitive. Twenty units sensitive to hypothalamic thermal challenge were studied during epidural heating and cooling, but only 1 unit was thermosensitive to spinal thermal challenge. This unit's signal was lost during halothane administration and thus could not be analyzed; therefore these results will not be discussed further.

THE EFFECT OF HALOTHANE ON SPONTANEOUS FIRING RATE AND THERMOSENSITIVITY OF WARM- AND COLD-SENSITIVE UNITS

Twenty-one of the thermosensitive units (78%) were warm-sensitive. The control spontaneous firing rate of these units was 7.8 ± 1.4 Hz (mean ± SEM). These units exhibited a significant ($P < 0.05$) and progressive decrease in spontaneous firing rate at 37° C during 0.25, 0.5, 0.75 and 1.0% halothane (fig. 2). The spontaneous firing rate of single units returned to control levels (99.5% ± 19.8) after halothane was discontinued. The control calculated thermosensitivity of the warm sensitive units was 1.9 ± 0.3 spikes·s^{-1}·°C^{-1} (mean ± SEM). The calculated thermosensitivity initially insignificantly increased to 116.9 ± 34.0% of control during 0.25% halothane. However, with increasing concentrations of halothane, calculated thermosensitivity progressively decreased to 13.9 ± 6.6% of control values at 1.0% end tidal halothane concentrations (fig. 2). After discontinuation of halothane, thermosensitivity returned to control (97.0 ± 11.1%). Figure 3 illustrates a strip-chart recording from a typical warm-sensitive unit.

Twenty-two percent (N = 6) of all thermosensitive units exhibited a cold sensitive type response to thermal challenge. Spontaneous firing rates for these six units was 3.8
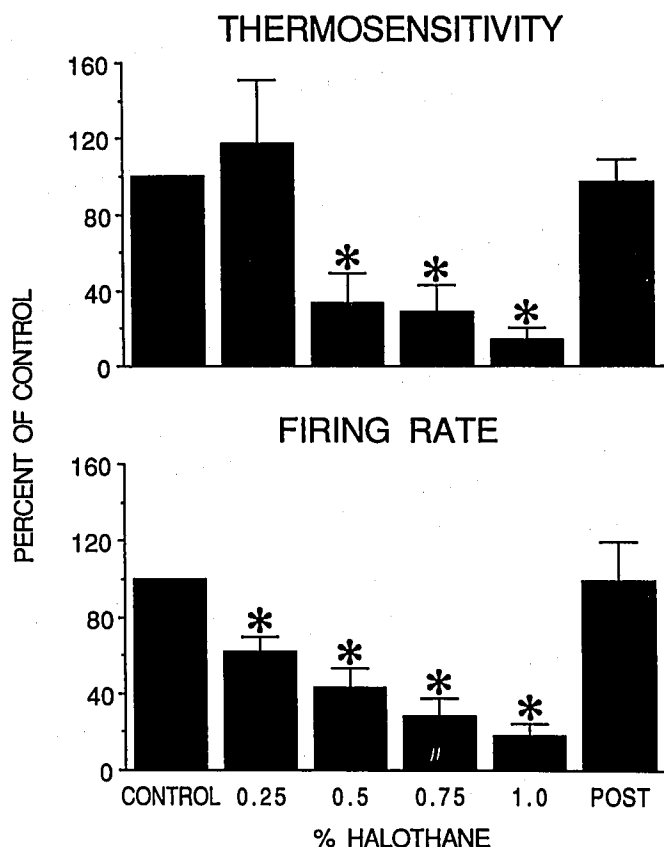
THERMOSENSITIVITY

FIG. 2. Changes in spontaneous firing rate (spikes per second) at 37° C and thermosensitivity (spikes per second per degree centigrade) produced by halothane for 21 warm-sensitive units. Data are expressed as mean ± SEM. *Significantly different from control, $P < 0.05$.

Hz ± 0.6 Hz (mean ± SEM) and calculated thermosensitivity was -6.2 ± 4.6 spikes$\cdot$s$^{-1}\cdot$°C^{-1} (mean ± standard error). However, only two of these units were examined long enough to receive halothane and only one was thermally challenged after halothane. A strip-chart recording from this cold-sensitive unit is shown in figure 4. Halothane produced a graded decrease in spontaneous firing rate and increase in thermosensitivity (i.e., thermosensitivity became less negative); thermosensitivity returned toward control after halothane was discontinued.
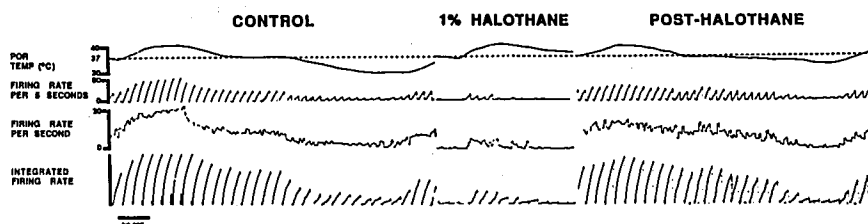
THE EFFECT OF HALOTHANE ON UNIT FIRING VARIABILITY DETERMINED BY INTERSPIKE-INTERVAL PARAMETERS (AUTOCORRELATION)

Seventeen of the warm-sensitive units were analyzed for interspike interval parameters. (Four units were not analyzed because of technical difficulties.) The mean interval between spikes (seconds per spike) of these units demonstrated a progressive increase to 301% of control values at 1% halothane ($P < 0.05$), confirming the decreases in spontaneous firing rates determined by conventional single-unit analysis (spikes per second). However, the coefficient of variation, a normalized index of the variability in firing rate of each neuron,[28,34,35] did not change significantly at any concentration of halothane, implying no specific change in the regularity of unit discharge. Figure 5 demonstrates this effect of halothane on the interspike-interval histogram of a representative warm-sensitive unit.

THE EFFECT OF PREOPTIC REGION HEATING AND COOLING ON THE EEG

Warm-sensitive units in four different cats were studied during heating and cooling and correlated with simultaneous cortical EEG recording. No significant changes in any of the processed EEG parameters (spectral edge 50, 80, and 95%; total integrated activity; and normalized frequency distribution) were observed during POR heating and cooling (fig. 6). Similarly, heating and cooling of the POR during halothane administration did not significantly alter the EEG.

ANALYSIS OF BLOOD HALOTHANE CONCENTRATIONS

Comparison of blood halothane concentrations (millimolar) with end-tidal halothane concentration (percent) revealed a highly linear correlation (R = 0.91). Blood concentrations at 0% end-tidal halothane concentration were (mean ± standard error) 0.06 mM ± 0.01; at 0.25%, 0.3 mM ± 0.01; at 0.5%, 0.5 mM ± 0.04; at 0.75%, 0.7 mM ± 0.01; at 1%, 0.91 mM ± 0.25.

FIG. 3. The typical effect of halothane on the activity of a warm-sensitive neuron. Note the decrease in spontaneous firing rate and the attenuated response to hypothalamic heating produced by halothane, and the return toward control responses posthalothane.
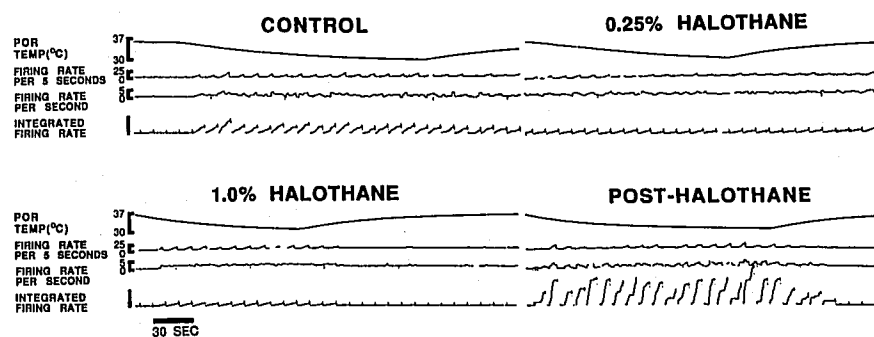
FIG. 4. The effect of halothane on the activity of a cold-sensitive neuron. Note the decrease in firing rate produced by halothane as well as the attenuated response to hypothalamic cooling, and the return toward control responses post-halothane.

HISTOLOGIC DOCUMENTATION OF ELECTRODE SITES

Post mortem histologic examination of selected brains, as described above, documented that the locations of all electrode tips were within 1.0–1.5 mm of the target coordinates in all three axes (fig. 7). This placed all electrode sites examined within generally accepted boundaries of the POR.

Discussion

The present investigation documents the ability of the volatile anesthetic halothane to alter significantly both the spontaneous firing rate and the calculated thermosensitivity of neurons in the POR, a major thermoregulatory area. However, consistent changes in the periodicity of neuronal firing were not produced by halothane. Previous investigations have demonstrated that halothane may alter normal thermoregulation by inhibiting peripheral vasoconstriction, altering behavioral thermoregulation, decreasing basal metabolic rate, and inhibiting shivering.[2,11–14,17] However, no previous studies have investigated the specific actions of halothane on the CNS neurons that mediate these responses. Halothane and other general anesthetics have been considered to produce a poikilothermic state, *i.e.,* an inhibition of thermoregulation with a tendency of the deep-core temperature to approach the prevailing ambient temperature.[11] However, there is no direct evidence for such an action, and several previous investigations have concluded that thermoregulation still occurs, but at a reduced thermoregulatory set-point.[12,13]

Previous studies of the direct effects of other anesthetic agents on thermosensitive POR neurons have been limited by the small numbers of single units analyzed and a lack of specific statistical analysis. Thiopental was demonstrated to decrease the firing rate and thermosensitivity of five neurons, whereas ether produced inconsistent effects on two thermosensitive neurons in a previous descriptive study.[26] Both *in vivo* and *in vitro* (brain slice) studies of POR units have revealed a depression of the spontaneous firing rate of warm-sensitive units and a facilitation of the firing rate of cold-sensitive units by

pyrogenic agents (lipopolysaccharide),[22] prostaglandin E_2,[40] norepinephrine,[41] and thyrotropin-releasing hormone[42]—agents that produce a generalized increase in body temperature. Pharmacologic agents that result in hypothermia, including capsaicin,[43] serotonin,[44] Δ-9-tetrahydrocannabinol,[20] angiotensin II,[40] and morphine[27] have been demonstrated to produce excitation of warm-sensitive units and inhibition of cold-sensitive units. These effects have led other investigators to conclude that warm-sensitive units mediate heat-loss responses, because such neurons are inhibited by hyperthermic agents and excited by hypothermic agents.[1,3,40] Conversely, cold-sensitive units may mediate heat gain responses because they are excited by hyperthermic agents and inhibited by hypothermic agents.[1,3,40] However, in a number of these studies, although the spontaneous firing rate of thermosensitive units was measured after pharmacologic intervention, thermosensitivity, or change per degree centigrade in spikes per second, was not quantified. Therefore, the specific change in response to thermal challenge was not assessed. Additionally, an *in vitro* study by Kelso and Boulant[45] demonstrated that warm-sensitive units retained thermosensitivity, whereas most cold-sensitive units were insensitive to thermal challenge in the presence of synaptic blockade produced by increased concentrations of magnesium and decreased concentrations of calcium. This observation is consistent with the functioning of warm-sensitive neurons as local detectors of hypothalamic temperature, and cold-sensitive units as interneurons that integrate thermal information from thermosensitive afferents in both the CNS and periphery. The observation that skin-warming decreased the thermosensitivity of warm- and cold-sensitive neurons,[5] whereas skin-cooling increased the thermosensitivity of warm- and cold-sensitive neurons,[5] provides additional evidence that cold-sensitive neurons may be synaptically driven by warm-sensitive neurons.

The inhibition of the warm-sensitive neuron firing rate produced by halothane in the present study is consistent with an impairment of hypothalamic thermal detection abilities. Since halothane decreased thermosensitivity at higher concentrations, these results suggest a global im-
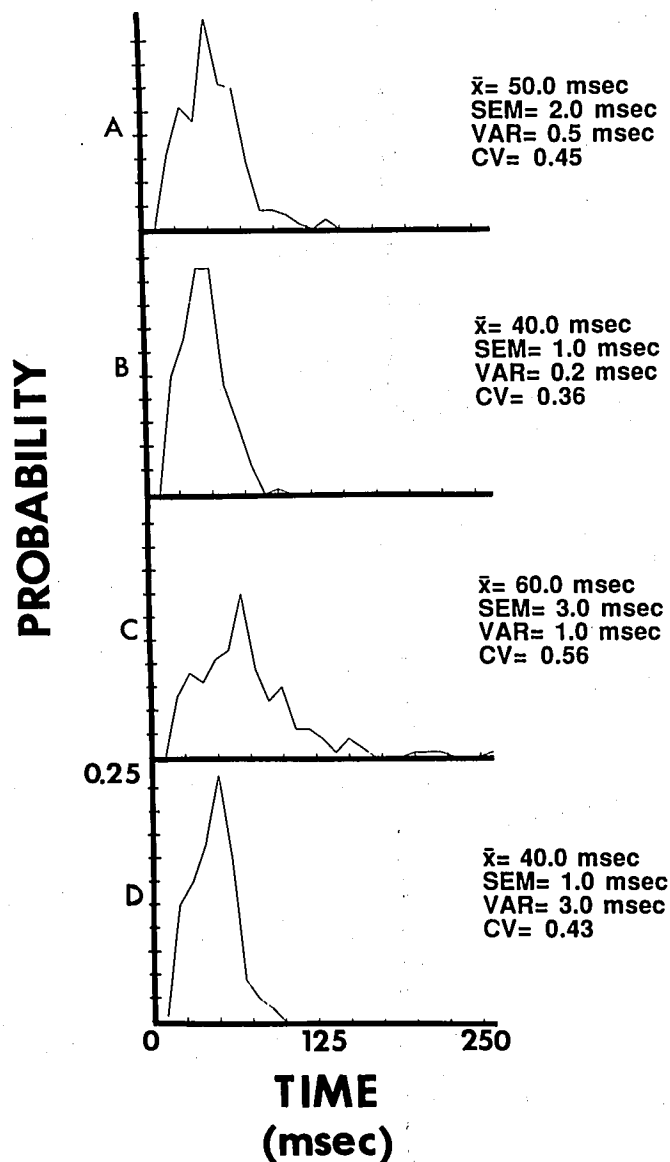
FIG. 5. The effect of halothane on the interspike-interval histogram as an estimate of the probability density function (after Perkel *et al.*[34]): the firing pattern of a representative warm-sensitive unit during control (*A*), 0.25% halothane (*B*), and 0.5% halothane (*C*) and after halothane (*D*). The administration of halothane resulted in an increase in the mean firing interval but did not change the normalized distribution of the firing intervals, indicating no specific effect on the periodicity of unit discharge. $\bar{x}$ = mean firing interval; SEM = standard error of the mean; VAR = variance; and CV = coefficient of variation for the interspike-interval sample.

pairment of all thermoregulatory abilities modulated by POR neurons and the subsequent production of a poikilothermic state, rather than a specific hypothermic action (lowering of the thermoregulatory set point), as previously demonstrated for other hypothermic agents such as morphine or Δ-9-tetrahydrocannabinol.[8,20,27] The marked depression of the spontaneous firing rate without

a significant change in response to thermal challenge produced by low concentrations (0.25%) of halothane may represent the disruption of appropriate thermal detection abilities with the preservation of some mechanism to provoke thermoregulatory responses. Such incongruity in neuronal thermal responses may contribute to the shivering observed during emergence from anesthesia with halothane. In these terms, emergence shivering may represent an appropriate response at an inappropriate temperature (normothermia).

The firing rates analyzed in this and most previous investigations were averaged over 1–2 s; however, these thermosensitive neurons often exhibited some amount of discharge variability, including periodic bursting. It has been suggested that this bursting and firing rate variability may specifically encode thermal data.[30,46,47] Kaitin examined the periodicity of discharge of POR units during various sleep and waking states and demonstrated an increase in the coefficient of variance, which implied a decrease in the synchronicity of neuronal discharge, during slow-wave or rapid-eye-movement sleep in comparison to waking states.[28] In the present investigation, no consistent change in firing rate variability as expressed by the coefficient of variance could be detected at any concentration of halothane. This may reflect a preexistent effect of the
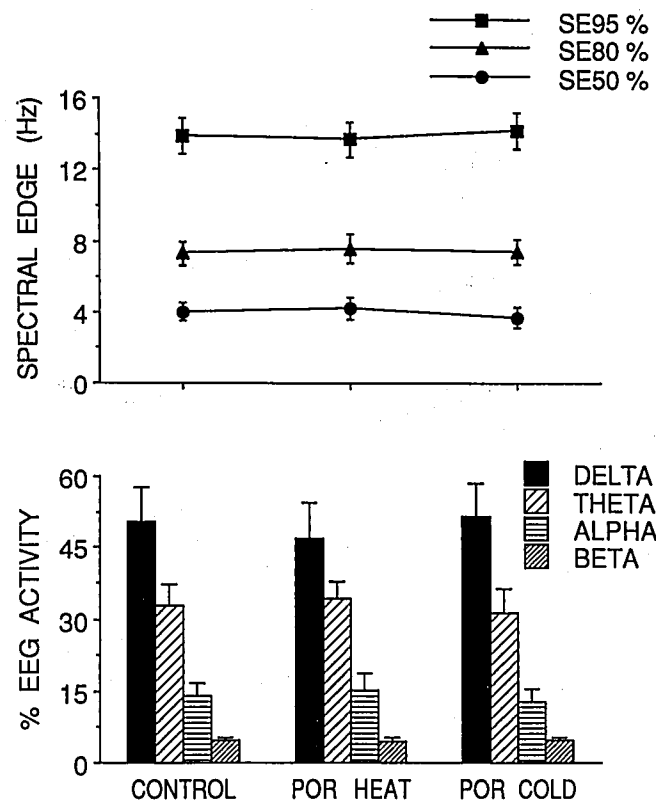

FIG. 6. The effect of preoptic-region heating and cooling on the processed EEG parameters during the control state.
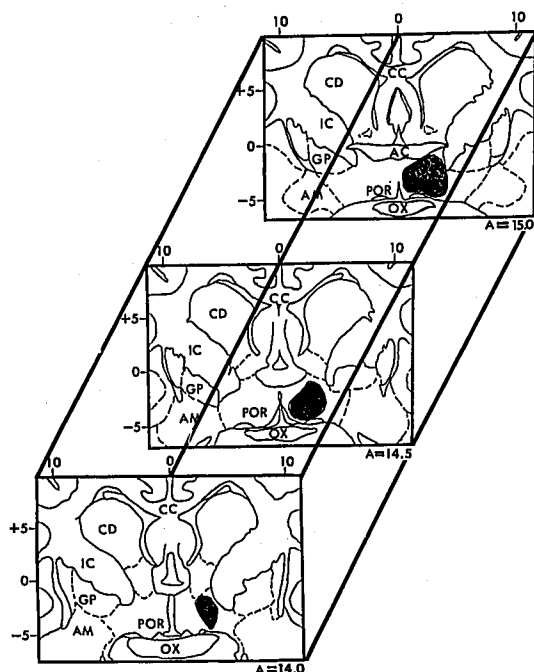
FIG. 7. The results of histologic documentation of electrode sites within the hypothalamus is illustrated by the cross-hatched areas. POR = preoptic region; AC = anterior commissure; AM = amygdala; CC = corpus callosum; CD = caudate nucleus; GP = globus pallidus; IC = internal capsule; and OX = optic chiasm.

chloralose/urethane anesthesia. Studies examining the action of halothane on neuronal discharge in the absence of a baseline anesthetic are required.

Other investigations have attempted to relate changes in neuronal activity during hypothalamic thermal challenge to changes in brain state (arousal), as determined by the cortical EEG.[28,29] Desynchronization or an increased frequency and decreased amplitude of the raw EEG in response to POR cooling has been observed.[31,48] Such changes in neuronal firing rate were suggested to result from the changes in arousal or anesthetic state produced by POR heating or cooling.[48] In the present study, no consistent quantitative changes in the processed cortical EEG were seen during thermal challenge. Clearly, in the present study, consistent changes in brain state as detected by the EEG did not appear to be related to the firing rate changes recorded. The lack of EEG changes seen may be related to the use of a baseline anesthetic.

Chloralose and urethane were used in this investigation as baseline anesthetics because these agents are generally believed to have minimal disruptive effects on neuronal activity and because they have been used in many prior investigations of thermosensitive neurons.[3,5–7,20–22,40] A previous investigation of the direct effects of chloralose and urethane on thermosensitive neurons in an encephale isole preparation did not reveal significant or consistent changes in spontaneous firing rate or thermosensitivity.[26]

In contrast, another study found a modest increase in thermosensitivity of two single neurons after administration of chloralose and urethane in decerebrate cats.[49] It has been noted that proportions of warm-, cold- and non-temperature-sensitive neurons differ between investigations conducted in chloralose- and urethane-anesthetized animals and those conducted in unanesthetized or decerebrate animals: fewer temperature-sensitive neurons are encountered in the anesthetized preparations.[1] This may represent an inhibitory effect of chloralose and urethane or a facilitating effect (*i.e.*, removal of descending inhibition) of decerebration. Whereas recording from neurons in chronically instrumented conscious animals would be an ideal control, possible electrode movement during the excitement phase of volatile anesthetic induction would be a significant problem. Thus, some type of CNS perturbation (baseline anesthetic, decerebration, or chronic instrumentation) is necessary to conduct these experiments and may represent a limitation of the current study.

The exact function of thermosensitive POR neurons in thermoregulation has been questioned. Neurons responding to local temperature change have also been identified in other CNS sites. However, the existence of temperature-sensitive neurons in a region with demonstrable thermoregulatory function and the observation that a subpopulation of these neurons responds to extra-hypothalamic thermal challenge and shows appropriate responses to the administration of pyrogens has led numerous investigators to ascribe a specific thermoregulatory role to these neurons.[1–3]

In summary, POR neurons that respond to local thermal challenge with consistent alterations in firing rate were identified in normothermic, artificially ventilated, chloralose- and urethane-anesthetized cats. The administration of halothane produced progressive decreases in the spontaneous firing rate and thermosensitivity of these neurons. No significant consistent changes in the periodicity of firing rate were produced by halothane. The suppression of thermosensitivity produced by halothane may abolish that aspect of thermoregulatory control modulated by the hypothalamus and contribute to the altered thermoregulation produced by inhalational anesthetics.

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