Anesthesiology
2000; 92:559-66

Isoflurane Action in the Spinal Cord Blunts Electroencephalographic and Thalamic–Reticular Formation Responses to Noxious Stimulation in Goats

Joseph F. Antognini, M.D., Xiao Wei Wang, M.D.,† E. Carstens, Ph.D.‡*

Background: **Isoflurane depresses the electroencephalographic (EEG) activity and exerts part of its anesthetic effect in the spinal cord. The authors hypothesized that isoflurane would indirectly depress the EEG and subcortical response to noxious stimulation in part by a spinal cord action.**

Methods: **Depth electrodes were inserted into the midbrain reticular formation (MRF) and thalamus of six of seven isoflurane-anesthetized goats, and needle-electrodes were placed into the skull periosteum. In five of seven goats, an MRF microelectrode recorded single-unit activity. The jugular veins and carotid arteries were isolated to permit cranial bypass and differential isoflurane delivery. A noxious mechanical stimulus (1 min) was applied to a forelimb dewclaw at each of two cranial–torso isoflurane combinations: 1.1 ± 0.3%–1.2 ± 0.3% and 1.1 ± 0.3%–0.3 ± 0.1% (mean ± SD).**

Results: **When cranial–torso isoflurane was 1.1–1.2%, the noxious stimulus did not alter the EEG. When torso isoflurane was decreased to 0.3%, the noxious stimulus activated the MRF, thalamic, and bifrontal–hemispheric regions (decreased high-amplitude, low-frequency power). For all channels combined, total (−33 ± 15%), δ (−51 ± 22%), θ (−33 ± 19%), and α (−26 ± 16%) power decreased after the noxious stimulus ($P < 0.05$); β power was unchanged. The MRF unit responses to the noxious stimulus were significantly higher when the spinal cord isoflurane concentration was 0.3% (1,286 ± 1,317 impulses/min) as compared with 1.2% (489 ± 437 impulses/min, $P < 0.05$).**

Conclusions: **Isoflurane blunted the EEG and MRF–thalamic response to noxious stimulation in part *via* an action in the spinal cord. (Key words: Anesthetic mechanisms; brain; pain.)**

THE SPINAL cord is an important site of anesthetic action. Recent evidence supports the idea that anesthetics prevent movement in response to noxious stimulation *via* an action in the spinal cord.[1,2] The other critical end points of anesthesia (amnesia, unconsciousness) are presumably the result of anesthetic action in the brain. Peripheral stimulation, and noxious stimulation in particular, causes central nervous system arousal. Anesthetics might blunt the transmission of these stimuli from the periphery to the brain *via* an action in the spinal cord. Anesthetics depress dorsal horn cells that transmit stimuli to other parts of the central nervous system,[3] and thus could have indirect cerebral effects *via* an action at the dorsal horn.

We recently reported that isoflurane blunted the electroencephalographic (EEG) and thalamic-reticular formation responses that occur after noxious stimulation.[4] The abolition of this response occurred at the same isoflurane concentration necessary to prevent the movement response. We hypothesized that part of this effect was caused by isoflurane action in the spinal cord. In the current study, we directly tested the hypothesis that isoflurane, acting within the spinal cord to depress nociceptive transmission, reduces EEG and thalamic-reticular formation responses to noxious stimulation. This was accomplished using a cranial bypass preparation in goats that permits differential delivery of isoflurane to the torso, while maintaining the cranial isoflurane constant,[1] coupled with recordings of the EEG and subcortical electrical activity in response to noxious stimulation.

Methods

The local institutional animal care committee approved this study. Seven goats (55.0 ± 12.4 kg, mean ±

* Associate Professor, Department of Anesthesiology and Pain Medicine.

† Visiting Research Scientist, Department of Anesthesiology and Pain Medicine.

‡ Professor, Section of Neurobiology, Physiology, and Behavior.

Received from the Department of Anesthesiology and Pain Medicine and Section of Neurobiology, Physiology, and Behavior, University of California, Davis, Davis, California. Submitted for publication July 2, 1999. Accepted for publication October 8, 1999. Supported in part by National Institutes of Health grant R01 GM57970, Bethesda, Maryland, and the Foundation for Anesthesia Education and Research, Rochester, Minnesota, with a grant from Abbott Laboratories, Chicago, Illinois. Presented in part at the annual meetings of the Association of University Anesthesiologists, Pittsburgh, Pennsylvania, May 13–16, 1999, and the American Society of Anesthesiologists, Dallas, Texas, October 9–13, 1999.

Address reprint requests to Dr. Antognini: TB-170, University of California, Davis, Davis, California 95616. Address electronic mail to: jfantognini@ucdavis.edu

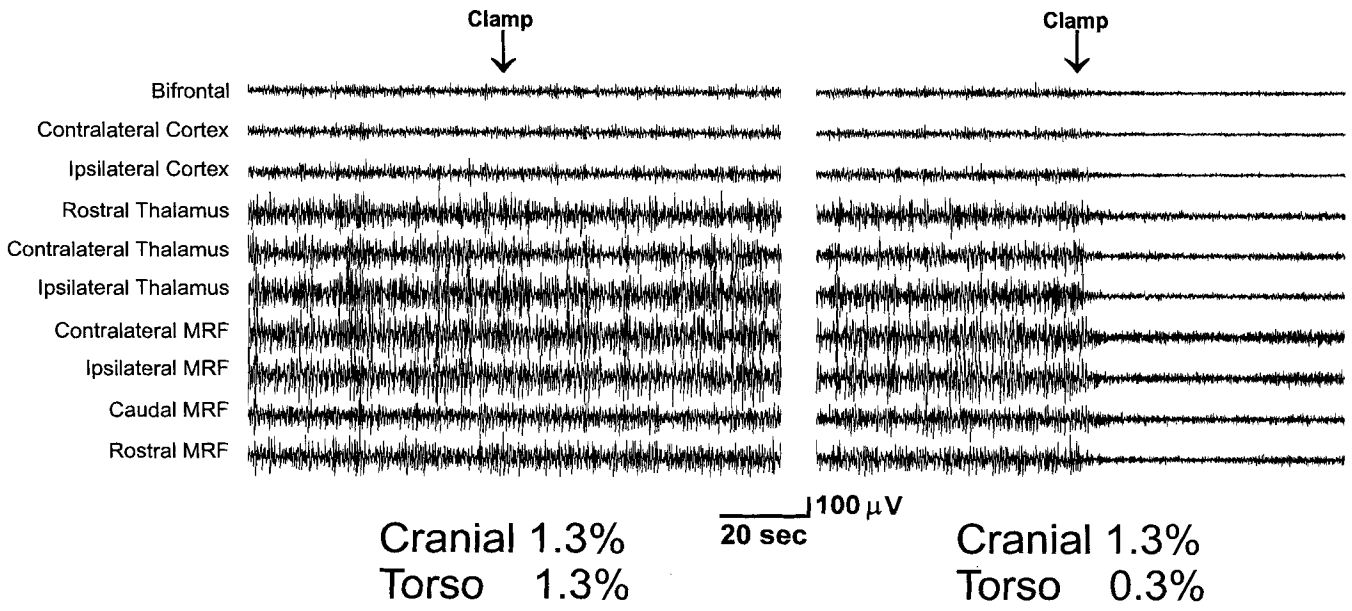

Fig. 1. This example of the raw electroencephalographic (EEG) and electrical activity of the thalamus and midbrain reticular formation shows the loss of low-frequency, high-amplitude (δ, θ, α) activity when the noxious stimulus was applied when torso isoflurane was 0.3% while the cranial isoflurane was 1.3%. When torso isoflurane was 1.3%, the noxious stimulus did not alter the EEG activity.

SD) were anesthetized by mask with isoflurane and their tracheas were intubated. End-tidal isoflurane was determined using a calibrated agent analyzer. A tube was passed through the esophagus to drain rumen contents. A peripheral intravenous catheter was placed for administration of lactated Ringer's solution. Bilateral neck dissections were performed to isolate the jugular veins and carotid arteries on both sides.[1,5] A craniotomy was performed to access the brain. Intravenous heparin (3 or 4 mg/kg initially, 1 or 2 mg/kg every 2 or 3 h) was administered. Y cannulae were placed into each jugular vein, and a cannula directed toward the head was placed into a carotid artery. A small catheter placed in the same carotid artery was directed toward the heart, thereby permitting measurement of systemic blood pressure and withdrawal of blood for analysis of glucose, hematocrit, and blood gases.

Anesthesia was maintained with isoflurane and, after administration of pancuronium (0.1–0.15 mg/kg and 0.1 mg/kg every 1 or 2 h), the head was placed in a stereotaxic frame and secured with ear bars and a mouth piece. In each of six goats, six stainless steel electrodes (28-gauge, covered with polyurethane except for the distal 2 mm) were passed into the midbrain region, with three on either side of midline.[4] The targets were the caudal midbrain reticular formation (MRF; 5 mm lateral to midline, 5 mm superior to the horizontal interaural line, and 3 mm rostral to the vertical interaural line), the rostral MRF–caudal thalamus interface (5 mm lateral, 5 mm superior, 10 mm rostral), and the rostral thalamus (5 mm lateral, 5 mm superior, 22 mm rostral).[6] No specific thalamic–MRF nuclei were targeted. For EEG recordings, four platinum needle electrodes (E-2; Grass Instruments, West Warwick, RI) were placed into the periosteum overlying the skull in the occipital and frontal areas bilaterally, with a ground electrode placed in the scalp. Impedances of the bifrontal–hemispheric scalp electrodes were less than 2 kOhm. The depth electrodes had slightly higher impedances, and were generally less than 5 kOhm. Ten channels were recorded: ipsilateral and contralateral cerebral cortex, bifrontal cortex, ipsilateral and contralateral MRF, ipsilateral and contralateral thalamus, bilateral caudal–rostral MRF and thalamus. The electrodes were connected to a Grass Model 8-10E EEG machine (Grass Instruments, Braintree, MA), and the signals were amplified and entered into a personal computer where they were digitized (12-bit resolution at 250 Hz) using a commercial program (PolyViewPro; Grass Instruments, Braintree, MA). The amplifiers filtered the signals (low: 1 Hz, high: 70 Hz; the data were further filtered off-line at 35 Hz; see Statistical Analysis section).

In each of five animals, a tungsten microelectrode (Frederick Haer, Inc., Brunswick, ME) was passed into the caudal MRF to measure single-unit activity. The coordinates were 5–7 mm lateral to midline and 3–4 mm rostral and 5 mm superior to the interaural line.[6] The

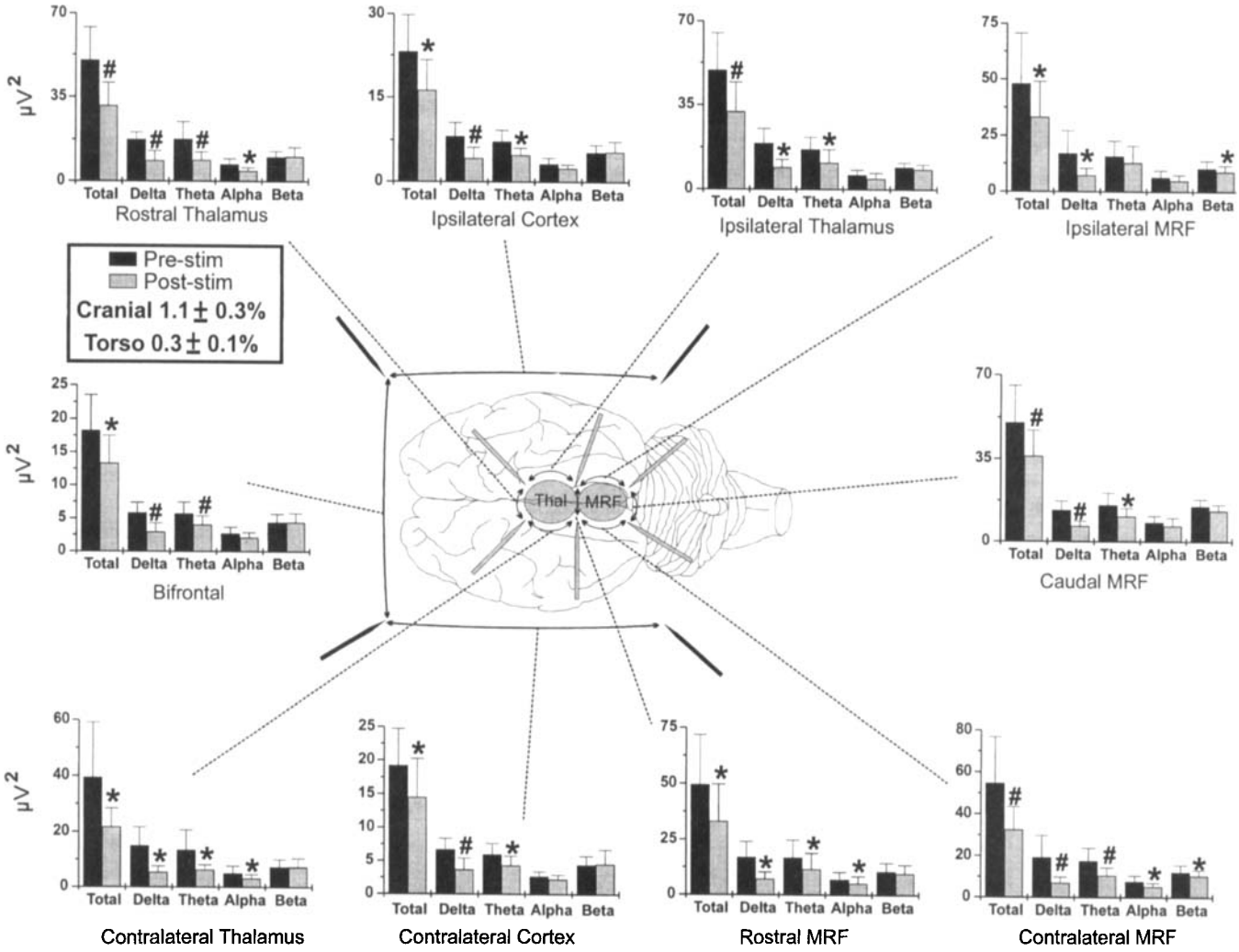

Fig. 2. Population data for all recording sites when cranial isoflurane was 1.1 ± 0.3% and torso isoflurane was 0.3 ± 0.1%. There was a significant decrease in one or more of total, δ, θ, and α power in all sites. #$P < 0.01$ prestimulus value compared with poststimulus value. *$P < 0.05$ prestimulus value compared with poststimulus value. Electroencephalographic (EEG) power is expressed as μV^2. Note that the Y scales (EEG power) differ among the various graphs. MRF = midbrain reticular formation.

microelectrode had a tip diameter of approximately 25 μ and an impedance of approximately 10 MΩ. A hydraulic microdrive (David Kopf Instruments, Tujunga, CA) was used to adjust electrode depth. The signal was amplified, filtered (0.3–3 kHz), and entered into a personal computer where the signal was digitized and stored for later analysis and construction of peristimulus-time histograms.[7] The signal-to-noise ratio usually exceeded 10:1. Single units were discriminated based on amplitude and waveform using a custom computer program (SPIKE, University of Erlangen, Erlangen, Germany).[7] Units were sought that increased activity in response to the noxious stimulus applied to the forelimb.

Blood (500 ml) was drained from the animal and used to prime a bubble oxygenator (Bentley B-10Plus; Baxter, Irvine, CA). Gas flow to the oxygenator was 95% O_2–5% CO_2. An isoflurane vaporizer was placed in line with the gas flow. Isoflurane concentration in the arterial blood of the bypass unit was estimated from the isoflurane concentration in the exhaust of the oxygenator, which was measured using a calibrated agent analyzer.[1,5] Cranial bypass was initiated by draining cranial venous blood into the oxygenator and infusing it into the cranial circulation *via* a roller pump (cranial flows 200–500 ml/min). The remaining carotid artery that transmitted systemic blood to the cranial circulation was temporarily ligated to establish complete bypass, thereby separating the cranial and systemic circulations at the level of the

upper cervical spinal cord and caudal medulla.[5] The vertebral arteries do not contribute to the goat cerebral circulation.[5] Mean cranial blood pressure was 61 ± 14 mmHg and mean systemic blood pressure was 122 ± 22 mmHg. Glucose (10–20 mg/min) was infused into the oxygenator. Torso temperature was measured from the rectum and maintained at 38.6 ± 0.8°C (mean ± SD) using a heating lamp. During bypass, nasopharyngeal temperature was maintained at 38.2 ± 0.7°C using the heat exchanger of the bypass unit.

The cranial isoflurane concentration was kept at 1.1 ± 0.3% (1.2 ± 0.2% in the five goats for which recording of both the EEG and the MRF single-unit activity was recorded). Although the cranial isoflurane was slightly different among the goats, in each individual goat the cranial isoflurane was always maintained at the same concentration. The torso (end-tidal) isoflurane concentration was alternated between 1.2 ± 0.3% and 0.3 ± 0.1%, with at least 15 min elapsing at a new concentration, to permit equilibration before data collection. We did not seek lesser torso isoflurane concentrations because of the additional time necessary to remove residual isoflurane. The order of the torso isoflurane concentrations was alternated experiment to experiment. At each of the two torso isoflurane concentrations, the MRF single-unit and EEG and thalamic–reticular formation responses were recorded 1 min before and during a 1-min application of a noxious mechanical clamp (10-in hemostat) to the dewclaw of a forelimb. In several animals, the MRF responses were recorded 2 or 3 times using an interstimulus interval of at least 5 min.

At the conclusion of the experiment, electrolytic lesions were made (6–8 V DC for 30–40 s). The animals were killed with potassium chloride and the brains were removed and fixed in 10% formalin and 1% potassium ferricyanide. The brains were frozen and sectioned with a microtome (50 μm) and the recording sites were determined using a light microscope.

Statistical Analysis

The data are presented as mean ± SD. The raw EEG and depth macroelectrode signals were visually inspected and artifacts were deleted before analysis (< 1% of data). The electrical activity data for each channel were analyzed using the PolyViewPro software (Grass Instruments, Braintree, MA). The raw data were filtered at 1–35Hz. Total power and power in the δ (1–3 Hz), θ (3–8 Hz), α (8–13 Hz), and β (13–35 Hz) ranges were determined. The EEG data were analyzed for 1 min before and 1 min during the application of the noxious stimulus, using 4-s consecutive epochs of time. The power in these epochs was averaged over each 1-min period. Because the data appeared to be normally distributed, the means of the prestimulus and poststimulus data (for cranial and torso isoflurane concentration combinations) were compared using repeated-measures analysis of variance to detect overall differences, and a Student-Newman-Keuls test was used to determine differences between the pre- and poststimulus data at each cranial or torso anesthetic combination. The percent change in power after the noxious stimulus application for each frequency range (all channels combined) was analyzed using analysis of variance. The single-unit activity was analyzed by counting the total number of action potentials in 1-min intervals before and after application of the noxious stimulus. The single-unit activity was not normally distributed and was first subjected to log transformation,[8] followed by repeated-measures analysis of variance and the Student-Newman-Keuls test; a $P < 0.05$ was considered significant.

Results

When the torso isoflurane concentration was 1.2 ± 0.3%, the noxious stimulus had no effect on the EEG or subcortical electrical activity, which exhibited a predominantly low-frequency, high-amplitude pattern. When the torso isoflurane was decreased to 0.3%, the noxious stimulus caused the EEG and subcortical electrical activity pattern to shift from a slow-frequency, large-amplitude pattern to a fast-frequency, low-amplitude pattern. An individual example is shown in figure 1. Virtually all sites showed this pattern, with decreased total, δ, θ, or α power; β power was unchanged (figs. 2 and 3). The data for all channels combined showed that, when torso isoflurane was 0.3 ± 0.1%, there was decreased total, δ, θ, and α power after the noxious stimulus was applied (range, 26 ± 16% to −51 ± 22%; $P < 0.05$).

The MRF single-unit activity paralleled the EEG data. The MRF cells characteristically had large receptive fields that included two or more extremities and sometimes the face. Figure 4 provides an averaged peristimulus-time histogram of all MRF units (N = 5) during the two anesthetic conditions and shows the significant increase in evoked activity when the torso isoflurane was low. At the 1.2%–1.2% combination the spontaneous and noxious-evoked activity were not significantly different (370 ± 381 to 489 ± 437 impulses/min). When the torso isoflurane was decreased to 0.3%, the spontaneous and

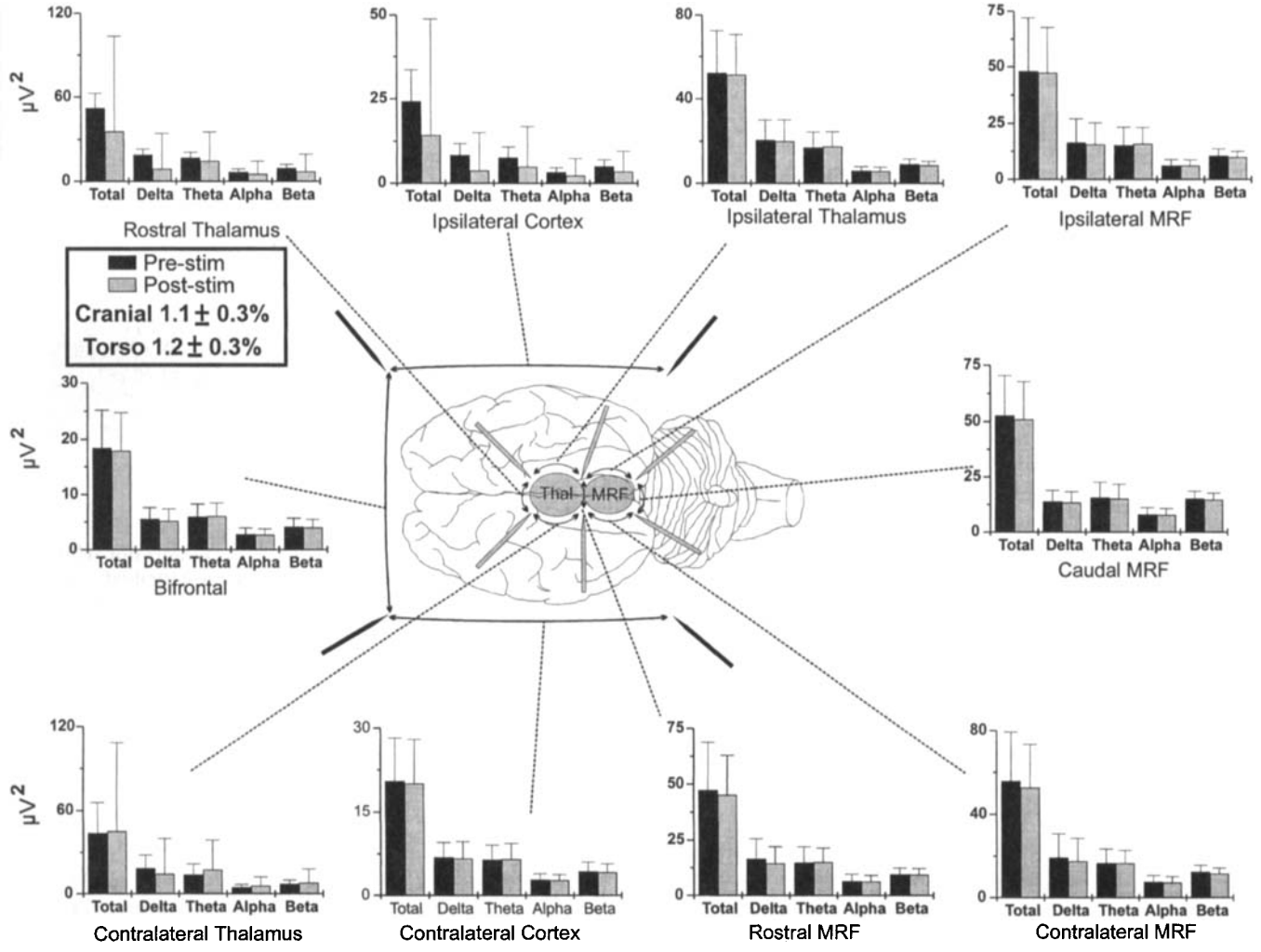

Fig. 3. Population data for all recording sites when cranial isoflurane was 1.1 ± 0.3% and torso isoflurane was 1.2 ± 0.3%. There were no significant changes after application of the noxious stimulus. Electroencephalographic (EEG) power is expressed as μV^2. Note that the Y scales (EEG power) differ among the various graphs. MRF = midbrain reticular formation.

noxious-evoked activity were significantly different from each other (712 ± 892 to 1,286 ± 1,317 impulses/min; $P < 0.05$).

Histologic analysis confirmed that the depth electrodes were located in the region of the caudal MRF, the MRF–thalamic interface and the rostral thalamus (fig. 5); the microelectrodes were located in the caudal MRF. Blood gases, glucose, and hematocrit were normal, with the exception of a mild acidosis in the oxygenator blood (table 1).

Discussion

The results of the current study are consistent with the hypothesis that isoflurane exerts an indirect effect on the brain *via* an action within the spinal cord. The desynchronization pattern evoked by the noxious stimulus when the torso isoflurane concentration was low is consistent with a transition toward arousal. This pattern was observed at cortical sites and in deeper structures (thalamus and reticular formation). The MRF single-unit activity paralleled the EEG data. The MRF and thalamus are considered to be critical to consciousness, and activity in these areas is assumed to correlate with consciousness.[9] In general, anesthetics depress MRF cells.[10,11] Angel[12,13] documented the importance of the thalamus as a site at which anesthetics blunt the centripetal transmission of ascending neural information. The current study underscores the importance of the spinal cord as well. Anesthetic action in what parts of the spinal cord might account for our current findings?

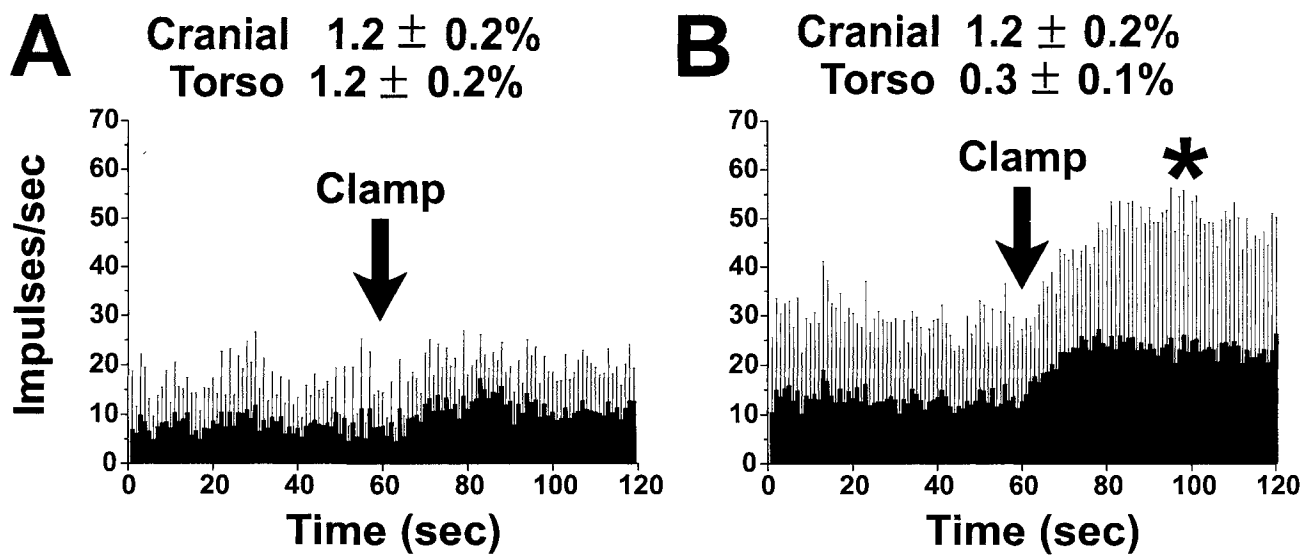

Fig. 4. Combined data for midbrain reticular formation (MRF) single-unit activity (peristimulus-time histogram, bin width 1 s; mean ± SD). (*A*) When torso isoflurane was 1.2 ± 0.2% (cranial isoflurane = 1.2 ± 0.2%), noxious stimulation evoked a minimal response. (*B*) When torso isoflurane was 0.3 ± 0.1%, the noxious stimulus evoked a marked response. *$P < 0.05$ compared with spontaneous activity when torso isoflurane was 0.3% and spontaneous and evoked activity when torso isoflurane was 1.2%.

The dorsal horn is the first relay in the transmission of peripheral stimuli to the brain. Numerous studies over several decades documented the depressant effect of various anesthetics on dorsal horn cellular responses to noxious and non-noxious stimuli.[3,14-16] To our knowledge, none of these studies determined whether the recorded dorsal horn cells had any ascending projections, in particular to the MRF, thalamus, and midbrain. Spinal cells can project to supraspinal structures *via* the spinomesencephalic, spinoreticular, spinothalamic, postsynaptic dorsal columns, and spinocervicalthalamic tracts.[17] Thus, it is possible that isoflurane could act at any or all of these different types of ascending spinal cells to depress sensory transmission to the brain. Additional work is necessary to determine whether these different classes of spinal cells have differing sensitivities to anesthetics. It is possible that some depressant effects might be the result of anesthetic action on conduction along the axon, as opposed to the synapse. In clinical concentrations, however, anesthetics appear to have minimal depressant effects on nerve conduction[18]; therefore, this is unlikely to be the cause of our findings. Last, we cannot rule out a peripheral anesthetic effect as a factor in the data. However, peripheral anesthetic actions of isoflurane and halothane appear to be minimal or paradoxically may sensitize peripheral nociceptors.[19,20] We previously determined that a peripheral anesthetic action of isoflurane, if any, does not affect minimum alveolar concentration (MAC).[21] Therefore, we do not believe that peripheral actions can explain our findings.

Clinical cases that involve spinal cord injury also are consistent with our findings. Patients with cervical spinal cord injuries have decreased global cerebral metabolism compared with volunteers without spinal cord disease.[22] These data suggest that the diminished peripheral sensory input results in decreased cerebral activation. Also, patients with high spinal cord injury have altered sleep and EEG patterns.[23]

Our technique of recording from subcortical structures (thalamus and MRF) is limited because the macroelectrodes located in these sites probably also measured electrical activity from structures farther away, such as the cerebral cortex.[4] Nonetheless, we believe that the activity recorded at each site represents activity primarily from local, and not distant, structures.[4]

We did not thoroughly investigate the spinal cord isoflurane concentration (*e.g.*, dose-response) that would have prevented the desynchronization response. However, in our previous study, we noted that isoflurane blunted the desynchronization response at concentrations between 0.9 and 1.1 MAC.[4] We expected that isoflurane would have blunted the response at lower concentrations inasmuch as the brain is more sensitive to anesthetics, compared with the spinal cord, at least when considering two anesthetic end points (amnesia

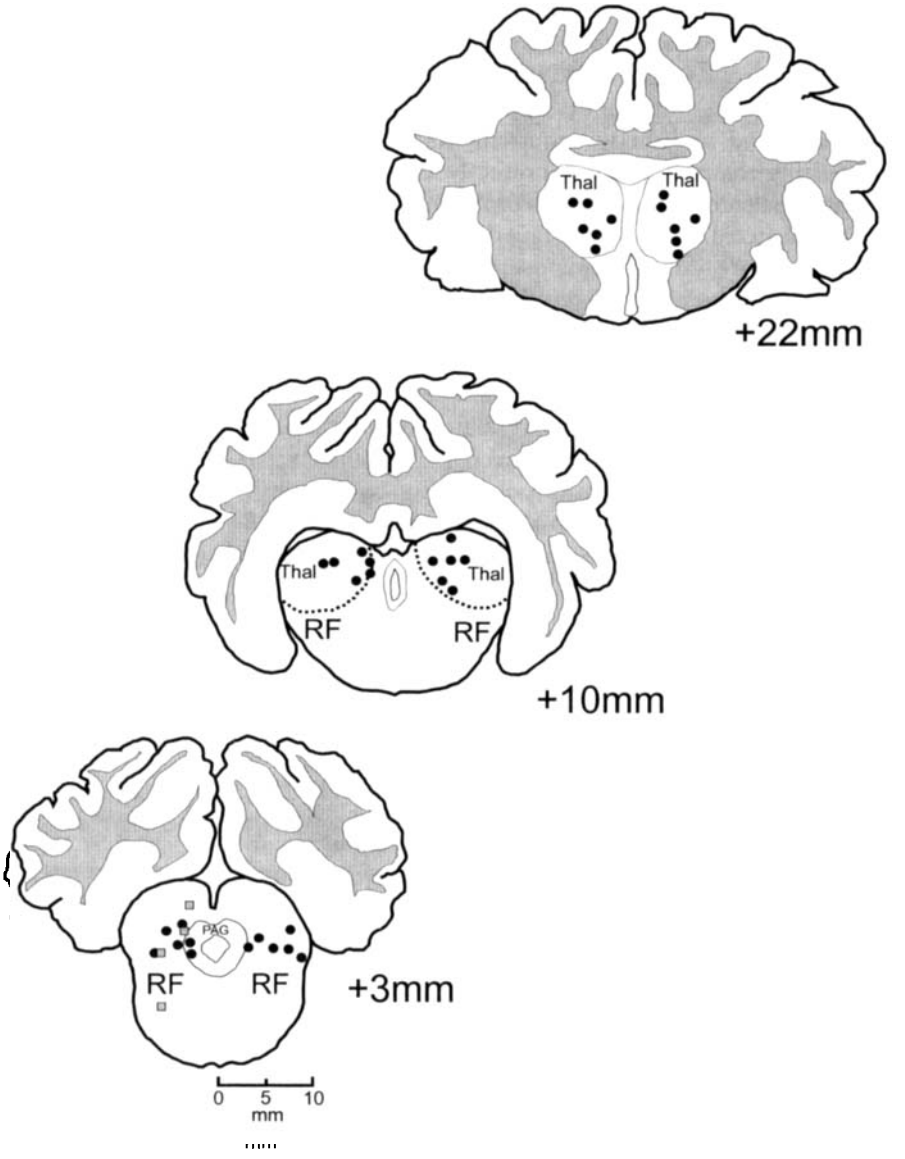

Fig. 5. Recording sites. The depth macroelectrodes (dark circles) were located in the caudal midbrain reticular formation (RF), the rostral midbrain RF–caudal thalamic interface and the rostral thalamus (thal). The microelectrodes (gray squares) were located in the caudal midbrain RF. A few of the macroelectrode sites were estimated from the location of other sites, and one of the microelectrode sites was not recovered. The *top*, *middle*, and *bottom* sections are at 22 mm, 10 mm, and 3 mm rostral to the interaural line, respectively. PAG = periaqueductal gray.

and unconsciousness).[24] There is at least a theoretical, if not physiologic, link between these end points and the EEG activity. The EEG activity can be used to investigate memory and consciousness.[25] Furthermore, analysis of processed EEG data (such as bispectral analysis) permits close monitoring of anesthetic effects vis-à-vis memory and consciousness.[26,27] Iselin-Chaves *et al.* found that a trapezius squeeze, which is noxious but not supramaximal, increased the bispectral index number, consistent with cerebral activation.[26] Studies that evaluated anesthetic requirements for amnesia and unconsciousness usually have been performed in volunteers who were not subjected to noxious stimulation.[24] We believe that, in the presence of noxious stimulation, additional anesthesia would be necessary to achieve amnesia and unconsciousness. However, clinical experience alone would suggest that amnesia and unconsciousness occur at anesthetic concentrations less than 1 MAC. Several studies that evaluated the effect of central neural block-

Table 1. Hematocrit, Glucose, and Blood Gas Values

	Torso-Arterial	Cranial-Arterial	Cranial-Venous
pH	7.39 ± 0.04	7.34 ± 0.02	7.30 ± 0.03
P_{CO_2} (mmHg)	36 ± 5	41 ± 4	45 ± 4
P_{O_2} (mmHg)	541 ± 35	468 ± 54	104 ± 59
Base-excess (mEq/l)	−2 ± 1	−3 ± 2	−3 ± 2
Glucose (mg/dl)	118 ± 40	127 ± 42	121 ± 41
Hematocrit (%)	32 ± 4	32 ± 4	32 ± 4

ade on anesthetic and hypnotic requirements are consistent with the current results. In humans, subarachnoid local anesthetics appear to lower hypnotic requirements.[28] In rats, intrathecal bupivacaine decreases the hypnotic and anesthetic requirements for thiopental, suggesting that the brain is indirectly affected by anesthetic blockade in the spinal cord.[29] Cole *et al.* found that intrathecal tetracaine in rats decreased the cerebral metabolic rate during somatosensory stimulation, suggesting that ascending afferent information activated the brain, and that local anesthetic block diminished this effect.[30]

The spinal cord has assumed an important role as a site of anesthetic action. Our work[1] and that of Rampil[2] strongly suggest that immobility is produced by anesthetics *via* action in the spinal cord. As pointed out by Kendig,[31] however, anesthetic action in the spinal cord could indirectly affect consciousness and memory by blunting the orderly transmission of stimuli to the brain, and our current results are certainly consistent with this possibility.

The authors thank Marla Piercy and Mirela Iodi Carstens for assistance.

References

1. Antognini JF, Schwartz K: Exaggerated anesthetic requirements in the preferentially anesthetized brain. ANESTHESIOLOGY 1993; 79:1244-9

2. Rampil IJ: Anesthetic potency is not altered after hypothermic spinal cord transection in rats. ANESTHESIOLOGY 1994; 80:606-10

3. de Jong RH, Wagman IH: Block of afferent impulses in the dorsal horn of monkey. A possible mechanism of anesthesia. Exp Neurol 1968; 20:352-8

4. Antognini JF, Carstens E: Isoflurane blunts electroencephalographic and thalamic-reticular formation responses to noxious stimulation in goats. ANESTHESIOLOGY 1999; 91:1770-9

5. Antognini JF, Kien ND: A method for preferential delivery of volatile anesthetics to the *in situ* goat brain. ANESTHESIOLOGY 1994; 80:1148-54

6. Tindal JS, Knaggs GS, Turvey A: The forebrain of the goat in stereotaxic coordinates. J Anatomy 1968; 103:457-69

7. Forster C, Handwerker HO: Automatic classification and analysis of microneurographic spike data using a PC/AT. J Neurosci Methods 1990; 31:109-18

8. Zar JH: Data transformations, Biostatistical Analysis, 4th edition. Prentice-Hall, Upper Saddle River, NJ, pp 273-81

9. Steriade M: Arousal: Revisiting the reticular activating system. Science 1996; 272:225-6

10. Shimoji K, Fujioka H, Fukazawa T, Hashiba M, Maruyama Y: Anesthetics and excitatory/inhibitory responses of midbrain reticular neurons. ANESTHESIOLOGY 1984; 61:151-5

11. Shimoji K, Bickford RG: Differential effects of anesthetics on mesencephalic reticular neurons: I. Spontaneous firing patterns. ANESTHESIOLOGY 1971; 35:68-75

12. Angel A: Central neuronal pathways and the process of anaesthesia. Br J Anaesthesia 1993; 71:148-63

13. Angel A: The G. L. Brown lecture. Adventures in anaesthesia. Exp Physiol 1991; 76:1-38

14. Namiki A, Collins JG, Kitahata LM, Kikuchi H, Homma E, Thalhammer JG: Effects of halothane on spinal neuronal responses to graded noxious heat stimulation in the cat. ANESTHESIOLOGY 1980; 53:475-80

15. Kitahata LM, Ghazi-Saidi K, Yamashita M, Kosaka Y, Bonikos C, Taub A: The depressant effect of halothane and sodium thiopental on the spontaneous and evoked activity of dorsal horn cells: Lamina specificity, time course and dose dependence. J Pharmacol Exp Ther 1975; 195:515-21

16. Yanagidani T, Ota K, Collins JG: Complex effects of general anesthesia on sensory processing in the spinal dorsal horn. Brain Res 1998; 812:301-4

17. Willis WD, Westlund KN: Neuroanatomy of the pain system and of the pathways that modulate pain. J Clinical Neurophysiol 1997; 14:2-31

18. de Jong RH, Nace RA: Nerve impulse conduction and cutaneous receptor responses during general anesthesia. ANESTHESIOLOGY 1967; 28:851-5

19. MacIver MB, Tanelian DL: Volatile anesthetics excite mammalian nociceptor afferents recorded in vitro. ANESTHESIOLOGY 1990; 72:1022-30

20. Campbell JN, Raja SN, Meyer RA: Halothane sensitizes cutaneous nociceptors in monkeys. J Neurophysiol 1984; 52:762-70

21. Antognini JF, Kien ND: Potency (minimum alveolar anesthetic concentration) of isoflurane is independent of peripheral anesthetic effects. Anesth Analg 1995 81; 69-72

22. Roelcke U, Curt A, Otte A, Missimer J, Maguire RP, Dietz V, Leenders KL: Influence of spinal cord injury on cerebral sensorimotor systems: A PET study. J Neurol Neurosurg Psychiatry 1997; 62:61-5

23. Adey WR, Bors E, Porter RW: EEG sleep patterns after high cervical lesions in man. Arch Neurol 19; 377-83

24. Dwyer R, Bennett HL, Eger EI, Heilbron D: Effects of isoflurane and nitrous oxide in subanesthetic concentrations on memory and responsiveness in volunteers. ANESTHESIOLOGY 1992; 77:888-98

25. Klimesch W: EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. Brain Res Rev 1999; 29:169-95

26. Iselin-Chaves IA, Flaishon R, Sebel PS, Howell S, Gan TJ, Sigl J, Ginsberg B, Glass PSA: The effect of the interaction of propofol and alfentanil on recall, loss of consciousness, and the bispectral index. Anesth Analg 1998; 87:949-55

27. Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. ANESTHESIOLOGY 1997; 86:836-47

28. Ben-David B, Vaida S, Gaitini L: The influence of high spinal anesthesia on sensitivity to midazolam sedation. Anesth Analg 1995; 81:525-8

29. Eappen S, Kissin I: Effect of subarachnoid bupivacaine block on anesthetic requirements for thiopental in rats. ANESTHESIOLOGY 1998; 88:1036-42

30. Cole DJ, Lin DM, Drummond JC, Shapiro HM: Spinal tetracaine decreases central nervous system metabolism during somatosensory stimulation in the rat. Can J Anaesth 1990; 37:231-7

31. Kendig JJ: Spinal cord as a site of anesthetic action. ANESTHESIOLOGY 1993; 79:1161-2