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Anesthetic Depression of Spinal Motor Neurons May Contribute to Lack of Movement in Response to Noxious Stimuli

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Background: **Previous studies suggest that anesthetics produce immobility by an action on the spinal cord. We postulated that immobility results from a depression of α-motor neuron excitability *in vivo*, and that this depression would be reflected in a depression of recurrent, (F)-wave activity.**

Methods: **The lungs of 15 normocapnic, normothermic, normotensive rats were mechanically ventilated with 0.5, 0.8, 1.2, and 1.6 MAC isoflurane, in random sequence, with at least 30 min of equilibration at each step. In addition, at 1.2 MAC, inspired carbon dioxide was altered to create hypercapnia and hypocapnia. The sizes of the orthodromic (M) wave and F wave were measured in ten sequential trials as the activity in the intrinsic muscles of the ipsilateral foot evoked by stimulation of the tibial nerve.**

Results: **M-wave amplitude did not change. F-wave amplitude did not decrease between 0.5 and 0.8 MAC but decreased 50% between 0.8 and 1.2 MAC ($P < 0.001$) and 60% between 1.2 and 1.6 MAC ($P < 0.05$). Hypocapnia (17 mmHg) increased F-wave amplitude by 15%, and hypercapnia (73 mmHg) reduced it by 60% compared with normocapnia at 1.2 MAC (31 mmHg) ($P < 0.0001$).**

Conclusions: **Anesthetics may cause and moderate hypercapnia may contribute to surgical immobility by depressing excitability of α-motor neurons. Monitoring F waves may indicate the adequacy of this aspect of anesthesia and may detect states in which spontaneous or nocifensive movements might occur. (Key words: Anesthesia: mechanisms. Anesthetics, volatile: isoflurane. Carbon dioxide: hypercapnia; hypocapnia. Measurement techniques: electromyography. Potency, anesthetic: minimum alveolar concentration. Spinal cord: motor neurons.)**

SURGICAL immobility, the absence of movement after imposition of a supramaximal noxious stimulus, is one of the defining features of general anesthesia. This well-defined behavioral end point is commonly used to determine and compare the potency of anesthetic agents,[1] to serve as a guide for clinical administration, and to serve as an experimental probe in studies of anesthetic action.[2]

Recent evidence suggests that, at least in some experimental circumstances, anesthetics act to produce immobility by an effect on the spinal cord. Neither acute precollicular decerebration[3] nor high thoracic spinal cord transection[4] alters the nature of the motor responses of rats after tail-clamping (*i.e.*, the full range of complex, coordinated movements such as alternating stepping, albeit with somewhat less vigor), nor do such transections alter the concentration of isoflurane that produces immobility. In addition, extracellular recordings have demonstrated that general anesthetics, applied *in vitro* or *in vivo* depress neuronal traffic in the dorsal horn caused by noxious stimuli.[5–8]

Spinal motor neurons exposed to anesthetics also demonstrate depressed excitability.[9–13] Using intracellular recordings, Nicoll and Madison found that several inhaled and intravenous anesthetics directly hyperpolarize frog motor neurons.[14] γ-Aminobutyric acid antagonists blocked the hyperpolarization due to barbiturates and α-chloralose but not hyperpolarization due to the volatile agents diethyl ether, enflurane, halothane, and methoxyflurane. Takenoshita and Takahashi have described motor neuron hyperpolarization (5.4 ± 0.6 mV) by halothane (2%, ≈2 MAC)[15] in neonatal rats. Both studies provide evidence that volatile agents produce hyperpolarization by increasing non–voltage-sensitive transmembrane potassium current. Jones *et al.*[16] recently demonstrated in cultured rat hippocampal neurons that volatile anesthetics also enhance a hyperpolarizing chloride ion current *via* a channel associated with a γ-aminobutyric $acid_a$ receptor. There is also clinical evidence that motor-evoked potentials are exquisitely sensitive to general anesthetics.[17]

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To clarify the role and sensitivity of α-motor neurons to general anesthetics, we studied "F waves," which are the late muscle potentials (depicted on electromyograms [EMG]) that follow stimulation of a peripheral motor nerve.[18,19] F waves arise from motor neurons and are not the result of central synaptic transmission. That is, stimulation of a peripheral motor axon leads to simultaneous orthodromic and antidromic action potentials (fig. 1). The orthodromic potential quickly leads to a compound muscle action potential or EMG wave known as the "M wave." Concurrently, the antidromic action potential is conducted back to the soma of the neuron, where it induces a "backfire" or recurrent discharge[20] that is orthodromically conducted to the innervated muscle, producing a second wave of EMG activity, the F wave. Assuming supramaximal stimulation, the M-wave amplitude reflects the synchronous discharge of all motor units and is larger than the F wave, because recurrent discharge occurs only in a fraction of the α-motor neurons, and the fraction of responding neurons in turn depends on the somatodendritic membrane excitability of the stimulated pool of neurons[21-24] at that instant.

In the current study, we examined the effect of isoflurane in a range of concentrations on the F-wave responses of lumbar α-motor neurons in the intact rat.

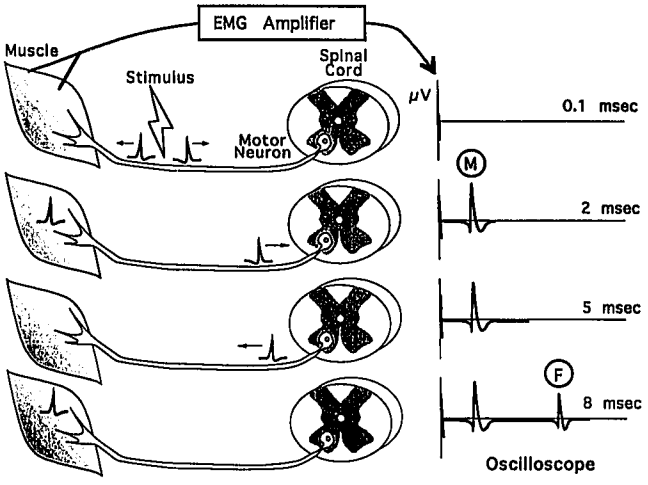

Fig. 1. The generation of F waves begins (*first frame, top*) with a stimulus applied to a peripheral motor neuron, inducing the generation of action potentials that begin to propagate both centrally and peripherally. A plot (*far right*) of the recorded EMG signal reveals a stimulus artifact. After approximately 2 ms (*second frame*), and the orthodromic action potential has reached and depolarized the muscle, creating an M wave on the electromyogram (EMG). In the same period, the antidromically conducted action potential has nearly reached the ventral horn of the spinal cord. The antidromic potential depolarizes the soma of the motor neuron (*third frame*), initiating a recurrent pulse that begins its orthodromic propagation toward the muscle, reaching and depolarizing it (*fourth frame*), creating the F wave on the EMG.

Materials and Methods

Experimental Preparation

With approval of the University of California, San Francisco Committee on Animal Research, we studied 15 young adult (≈3 months) Sprague-Dawley rats (7 female and 8 male, 264 ± 37 [SD] g). Animals were allowed food and water *ad libitum* until the day of surgery. Anesthesia was induced by inhalation of isoflurane in air, and tracheas were intubated with a 5.1-cm 16-G intravenous catheter. Anesthesia was maintained with isoflurane in oxygen and approximately 2% carbon dioxide. Mechanical ventilation (peak inspiratory airway pressures ≤20 mmHg) was adjusted to achieve normocapnia. Airway gas concentrations were continuously monitored with an infrared analyzer (CapnoMac Ultima, Datex Instrumentarium, Helsinki, Finland) using an expiratory limb dead space sampling point previously described.[3] Normothermia was thermostatically maintained using a heat lamp. Through a left femoral arterial incision, we advanced a polyethylene (PE-50, Clay-Adams, Parsippany, NJ) catheter into the distal abdominal aorta. Continuous infusion of heparinized (1 IU/ml) lactated Ringer's solution at 2 ml/h *via* the arterial catheter maintained hydration.

Anesthetic Protocol

From previous (unpublished) data in this species, we prospectively defined 1.0 MAC as 1.4% isoflurane. After intubation, but before invasive or painful procedures were performed, we applied 1.2 MAC isoflurane for at least 30 min and attained a preoperative (baseline) set of electrophysiologic (F-wave) data (see below). After recording this baseline data set, we surgically inserted the arterial catheter, and secured the rat supine, with ear bars, in a custom designed stereotactic frame. In a prospectively randomized sequence, the rat received four concentrations of isoflurane (0.5, 0.8, 1.2, and 1.6 MAC) with equilibration for at least 30 min at each step before data acquisition. The concentration given as the first step was repeated as the last step to assess the effect of increasing anesthetic duration.

After F-wave data collection from the postoperative 1.2 MAC step, the inspired carbon dioxide concentration was altered to achieve, in random order, hypo- and hypercapnia. Each alteration in carbon dioxide content was maintained 5–10 min before F-wave data collection. Arterial blood gas samples (≈400 μl/sample) were drawn for the normocapnic (control) and the hypocapnic and hypercapnic states immediately after electrophysiologic data collection.

MAC was determined in the last eight rats studied. After F-wave data collection at each concentration step, an alligator clip was applied to the proximal portion of the tail and oscillated ±45° for 60 s. Movement of the extremities was considered a positive response. MAC was determined by a single cross-over, the mean of the least concentration which caused immobility and the greatest concentration which allowed movement.

Electrophysiologic Data Acquisition

The right tibial nerve was stimulated with the cathodal electrode at the popliteal fossa using platinum sub-dermal needle electrodes (E-2, Grass Instruments, Quincy, MA) driven through a Grass SIU-5 isolator by an Grass S-88 constant voltage stimulator. The stimulus width was fixed at 500 μs, and the intensity was varied among 10, 20, 30, 40, 50, and 60 V in prospectively randomized sequence. To assess reproducibility, the voltage applied first was repeated as the last. A new voltage randomization sequence was used at each isoflurane concentration. Stimulation at each stimulus intensity was repeated at 3.0 ± 0.1–s intervals (with pseudorandom variation to avoid phase-locked artifact) to obtain ten artifact-free traces. Evoked EMG activity was recorded from E-2 needle electrodes in the intrinsic muscles of the right foot, and referenced to a ground electrode in the right heel. The EMG data were amplified approximately 1,330 times by a Grass 7P511 amplifier and bandpass-filtered (10 Hz–10 kHz), monitored on an oscilloscope, and digitized with 12-bit resolution at 10 kHz. The digitized EMG waveform data were displayed, analyzed, and stored on computer (Macintosh IIfx, Apple Computer, Cupertino, CA). Stimulator trigger timing and all aspects of data acquisition and analysis were automated and controlled by a LabView program (National Instruments, Austin, TX) written for this study by one of the authors (I.J.R.).

Data Analysis

Each animal generated at least 560 evoked EMG waveforms. After exclusion of artifact-contaminated traces, the analysis software determined the maximal peak-to-peak amplitude in the range of 0.9–3.0 ms as the M-wave amplitude, and the maximal peak-to-peak amplitude in the range of 6.0–9.0 ms as the F-wave amplitude in each trace. The ten pairs of M- and F-wave amplitudes for each experimental condition (isoflurane dose, stimulus voltage, and carbon dioxide content) were averaged to provide a single pair of M- and F-wave amplitudes for statistical analysis. Small differences among rats in the positioning of both the recording and stimulating electrodes relative to muscle and nerve resulted in a range (approximately 10:1 over all rats) of M- and F-wave amplitudes. Accordingly, we normalized the wave amplitude data for each rat to the largest M wave obtained in that rat. We also tested an alternative means of controlling for electrode positioning by determining the ratio of mean F/M amplitudes for each experimental condition.

In three additional rats, we examined the possibility of fatigue at the neuromuscular junction as a possible mechanism of F-wave amplitude depression. The experimental preparation, anesthesia, stimulation and EMG recording of these rats were identical to that of the animals in the primary study, with the following exceptions: (1) the use of paired pulses to stimulate the tibial nerve with an interpulse pair latency of 2 or 5 ms; (2) determination of the amplitude ratio of the two resulting M waves at 0.8, 1.2, and 1.6 MAC; 3) no arterial catheterization; and 4) no assessment of changing arterial carbon dioxide tension (Pa_{CO_2}). More than five stimuli pairs with each interstimulus latency were applied at each anesthetic concentration, and the resulting M-wave amplitudes were measured.

The observed wave amplitudes were compared by analysis of variance with repeated measures (Statview 4.02, Abacus Software, Berkeley, CA). *Post hoc* comparisons were performed by the Student-Newman-Keuls test with software written locally (provided by J. Feiner, M.D. and D. Fisher, M.D.). Significance was assumed where $P \leq 0.05$.

Results

Data were recorded during all experimental conditions in 13 of 15 rats. Two rats had sufficiently vigorous spontaneous movements at the lowest isoflurane concentration to cause the loss of the data from the final step (repeat of first concentration) and, in one of these rats, from an additional concentration step. In one of these rats, movement dislodged the femoral arterial

catheter leading to hypovolemic shock, and in the other, dislodgment of the electrodes made replicated measurements impossible.

The waveforms characteristics documented that the secondary waves of evoked EMG activity were F waves (recurrent motor activity) rather than sensory–motor reflex arc (H-reflex) activity (table 1). Specifically, in all rats, the secondary waves were smaller than the associated M wave, demonstrated interrepetition variability of shape (fig. 2), and had a stimulus threshold equal to or exceeding that for eliciting an M wave (fig. 3). The latency between the M and F waves was stable at approximately 6 ms, varying slightly with electrode position, but was not assessed in detail because the variability in F-wave morphologic features caused variability in detection of onset or peak times.

Effect of Stimulus Voltage

In each rat, stimuli of 40 V or greater were supramaximal and produced stable, maximal M-wave amplitudes. Therefore, only evoked waveforms that followed stimuli of 40, 50, or 60 V were included in the subsequent statistical analyses.

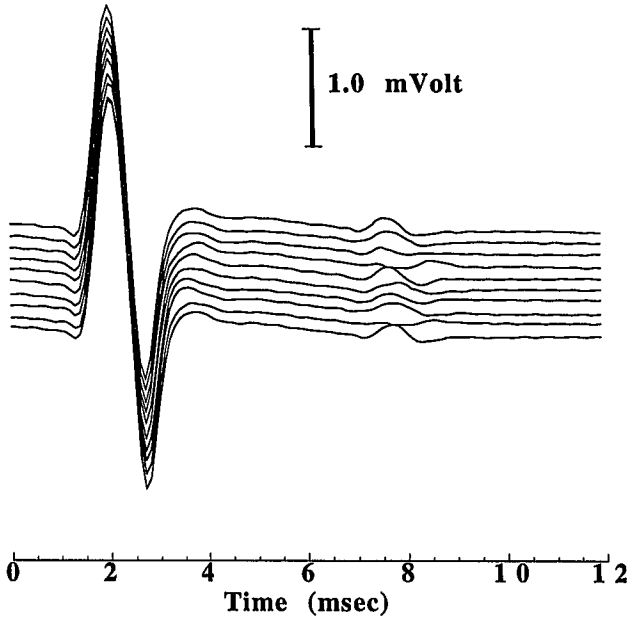

Fig. 2. This set of ten traces recorded sequentially at 3-s intervals demonstrates typically variable F-wave morphologic appearance. These data were acquired at 1.2 MAC with a stimulus intensity of 50 V.

Effect of Isoflurane

Of the eight rats tested by tail-clamping, all moved at the prospectively predicted 0.8 MAC level (1.12 vol%); all but one did not move at 1.2 MAC (1.68 vol%); and none moved at 1.6 MAC (2.2 vol%), confirming that the MAC of this population of rats was comparable to the prospectively estimated MAC of 1.4 vol%. At concentrations greater than 0.8 MAC, isoflurane caused a dose-dependent depression of spinal motor neuron excitability, demonstrated by a reduction in F-wave amplitude (fig. 4). The M-wave amplitude, an indicator of the condition of the neuromuscular junction and muscle, did not change over the range of isoflurane concentrations studied. In the range of 0.8–1.6 MAC, the sensitivity (slope) of the F-wave response was 10% amplitude change per 10% MAC change. The F/M ratio also decreased significantly ($P < 0.0001$) above 0.8 MAC (fig. 5). Although the mean arterial blood pressure decreased with increasing isoflurane concentration, it never decreased to less than 65 mmHg, and vasopressors were never used. The end-tidal carbon dioxide concentration also did not change (table 2).

Effect of Changes in Carbon Dioxide

The values for mean Pa_{CO_2} during hypocapnia, normocapnia, and hypercapnia were 18 ± 0.88, 31 ± 0.63, and 73 ± 3.7 mmHg (mean ± standard error), respectively. Carbon dioxide altered the evoked motor neuron activity (fig. 6). The peripheral effect (M-wave amplitude) was small but significant ($P < 0.0001$), with the hypercapnic and hypocapnic states causing respective 19% and 8% reductions in M-wave amplitude compared

Table 1. Criteria for Discrimination of F Wave *versus* H Reflex

Feature	F Wave	H Reflex
Stimulus threshold	≥ M-wave threshold	< M-wave threshold
Response to increasing stimulation	Increase to plateau	Decrease to plateau from an amplitude > M
Morphology	Variable	Constant

Adapted.[39]

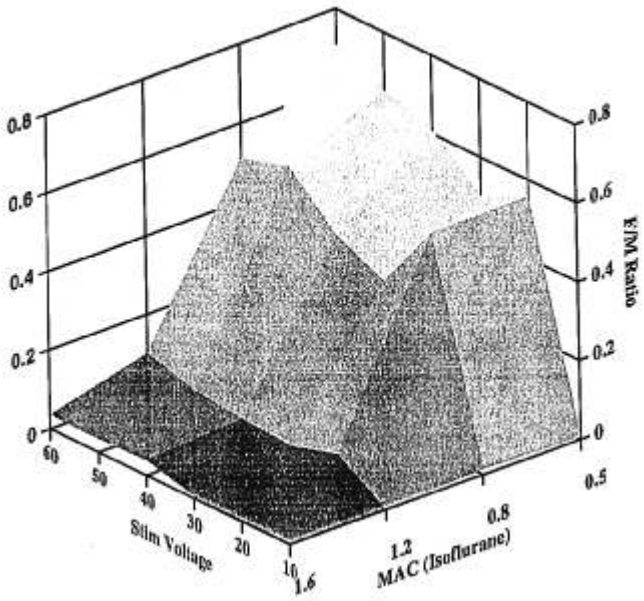

Fig. 3. This sample three-dimensional summary of postoperative F/M ratio data obtained from a single rat confirms that the observed secondary wave is an F wave and not an H-reflex response. At all isoflurane concentration steps, the expected F-wave pattern—a smaller amplitude than that of the M wave (F/M ratio < 1.0)—is present, and the F wave is absent at low stimulus voltages (*e.g.*, 10 V) and then rises to a plateau that is a significant fraction (50–70%) of the M wave. In this particular rat, the F/M ratio was depressed slightly at 30 V compared with the measurement at 20 V, but the ratio increased again at 40, 50, and 60 V. An H-reflex/M response ratio would be expected to be maximal (>1.0) at 10 V and to decline with increasing stimulus voltage. At each stimulus voltage, increasing isoflurane concentration depressed the F but not the M amplitude, thus reducing the F/M ratio.

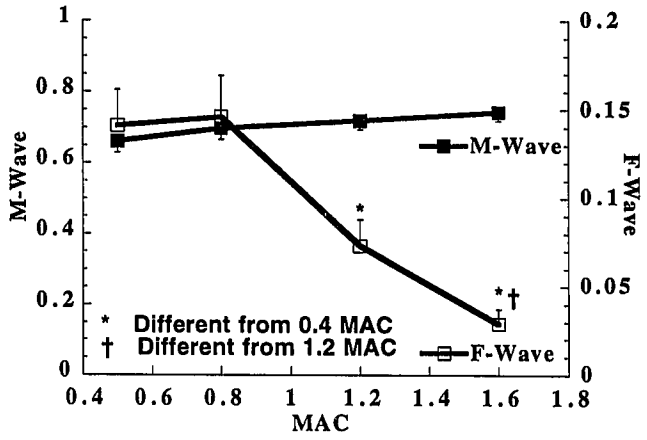

Fig. 4. Isoflurane decreases the F-wave amplitude in a dose-dependent manner and has little or no effect on the M wave. The amplitudes shown are the means ± standard errors of the normalized (to the largest observed M-wave amplitude in each rat) waves. The F-wave amplitude decreased by 50% between 0.8 and 1.2 MAC ($P < 0.001$), and at 1.6 MAC the amplitude was 60% of that at 1.2 MAC ($P < 0.05$).

with the baseline normocapnic state. Carbon dioxide produced a central monotonic depression ($P < 0.0001$), yielding respective F-wave amplitudes of 115% and 40% of the normocapnic control amplitude for hypocapnia and hypercapnia. Based on the calculated (above) sensitivity of F-wave amplitude to change in MAC exposure, a 15% increase in F-wave amplitude during mild hypocapnia might be expected to represent the equivalent of a 15% increase in the MAC of isoflurane under these conditions.

Effect of Time and Surgical Incision

Comparison of the electrophysiologic responses to the concentration of isoflurane given as the first and last step indicated a mixed response to increasing duration of anesthesia (table 3). Aggregate analysis (repeated-measures analysis of variance, by rat, independent of the concentration repeated) demonstrated a significant decrease in M-wave amplitude and a trend toward reduced F-wave amplitude with time. Analysis of these data by concentration revealed that the lowest isoflurane concentration (0.5 MAC) caused the greatest reduction in M- and F-wave amplitudes over time, whereas the highest concentration (1.6 MAC) tended to increase F-wave amplitude with increasing duration.

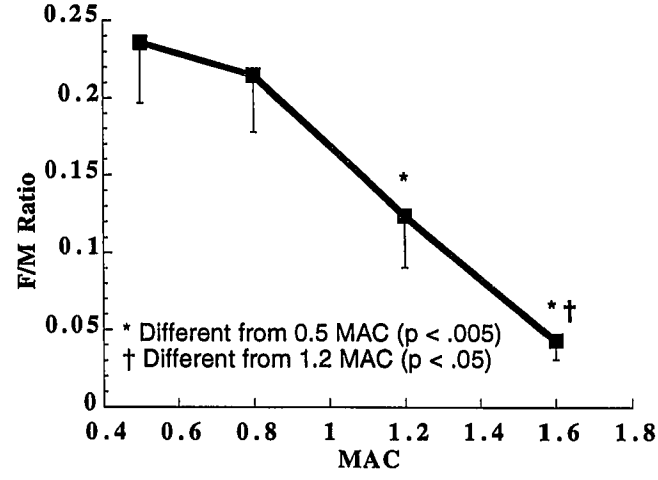

Fig. 5. F/M ratio dose–response to isoflurane. The pattern of response is similar to that of the F wave, with a 42% decrease between 0.8 and 1.2 MAC ($P < 0.01$) and an additional 38% (to 35% of the 1.2 MAC amplitude) decrease between 1.2 and 1.6 MAC ($P < 0.05$).

Table 2. Dose–Response of Blood Pressure and End-tidal (ET) Carbon Dioxide Content

Dose (MAC fraction)	MAP (mmHg)	ET CO_2 (mmHg)
Preoperative (1.2)	—	36 ± 2
0.5	142 ± 5	36 ± 1
0.8	131 ± 4	34 ± 1
1.2	114 ± 3	35 ± 1
1.6	114 ± 3	33 ± 1

Values are mean ± SE.

To assess the effect of incision on the motor neuron responses, the preoperative 1.2 MAC baseline amplitude values were compared with the postoperative 1.2 MAC values in all rats by paired, two-tailed *t* test. M-wave amplitude increased by approximately 20% after incision (0.893 ± 0.021 *vs.* 0.719 ± 0.025; $P \leq 0.0001$), whereas F-wave amplitude decreased after incision by almost 40% (0.073 ± 0.015 *vs.* 0.111 ± 0.029; $P = 0.019$).

The rats subjected to paired stimulus pulses revealed no fatigue at the neuromuscular junction at either stimulus latency in the amplitude of the second M wave.

Discussion

Isoflurane significantly depresses spinal α-motor neuron F-wave amplitude. This F-wave depression is a central (spinal) rather than a peripheral (axonal, neuromuscular junctional, or muscle) phenomenon, as indicated by the lack of effect of isoflurane on the orthodromically conducted M-wave amplitude, even when repeated at 5-ms intervals. The depression of excitability may play a major role in causing the immobility produced by general anesthetics like isoflurane.

Other mechanisms for isoflurane-induced F-wave depression were considered and tested. For example, at concentrations greater than 0.5 MAC, isoflurane causes rapid fade of tetanically induced force of contraction.[25] In the current study, an M wave–F wave couplet resembles two pulses of a 200-Hz tetanic burst arriving at the neuromuscular junction. Therefore, the observed reduction may not represent a true reduction of F-wave amplitude; rather, it may be attributable simply to tetanic fade at the neuromuscular junction. However, our double-stimulus pulse trial revealed no reduction in the second M-wave amplitude at a test latency of 5 ms, a latency shorter than the average F-wave latency of 6 ms observed in the primary study. We chose an interstimulus latency of 5 ms rather than 6 ms for trial to avoid collision of the second stimulus with the F wave returning from the first. Depression of the second M wave occurred only at the highest isoflurane concentration (1.6 MAC) and extremely brief (2 ms) interstimulus latency. Miller *et al.*[25] observed rapid tetanic fade by measuring generated force (with low temporal resolution), whereas in the current study we measured muscle-derived electrical activity, with sufficient resolution to quantify the amplitude of individual M waves.

Hypercapnia (Pa_{CO_2} 73 mmHg) in the presence of isoflurane also depressed both motor neuron and peripheral neuromuscular excitability. This finding is consistent with previous reports that hypercapnia depresses monosynaptic spinal reflexes in animals[26] and human volunteers[27] and, at 63 mmHg, depresses both evoked peripheral twitch strength and spontaneous EMG activity.[28] We speculate that this effect is caused by reductions in postsynaptic ligand-gated (nicotinic) channel conductance with alterations away from physiologically neutral *p*H.[29] In sufficiently high concentrations, carbon dioxide is a general anesthetic (MAC in dogs is 245 mmHg[30]). Thus the 60% decrease in F-wave amplitude during hypercapnia (73 mmHg) and 1.2 MAC isoflurane in our animals might be expected to correspond to a significant increase in anesthetic potency. Supporting this hypothesis is the observation that patients with Pa_{CO_2} greater than 80 mmHg often

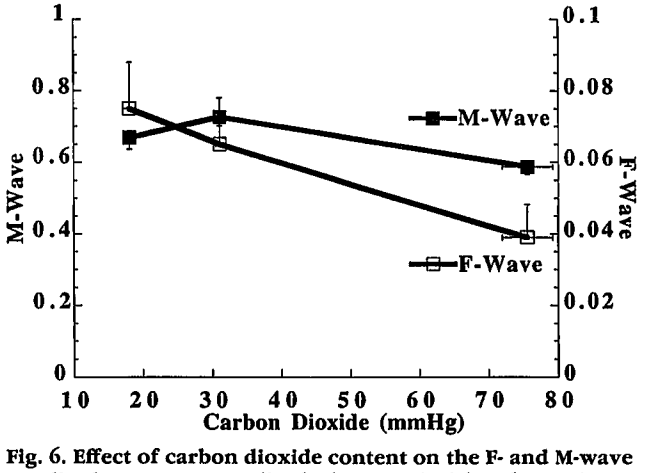

Fig. 6. Effect of carbon dioxide content on the F- and M-wave amplitudes. M-wave amplitude decreased with a change in arterial carbon dioxide tension (Pa_{CO_2}) in either direction from normocapnia. The F-wave amplitude was depressed by increasing Pa_{CO_2}. The amplitudes shown are normalized to the largest M-wave amplitude observed in each rat.

Table 3. Effect of Incision and Duration of Anesthesia on Wave Amplitudes

	Repeat MAC Dose	N	Preoperative	Exposure 1	Exposure 2	*P* Value*
M wave	0.5	2	—	0.719 ± 0.084	0.548 ± 0.051	0.256
	0.8	3	—	0.822 ± 0.051	0.528 ± 0.017	0.001†
	1.2	4	0.894 ± 0.079	0.805 ± 0.085	0.594 ± 0.060	0.002†
	1.6	4	—	0.821 ± 0.046	0.750 ± 0.040	0.178
	Combined	13	—	0.800 ± 0.031	0.632 ± 0.027	<0.0001†
F wave	0.5	2	—	0.251 ± 0.057	0.115 ± 0.044	0.015†
	0.8	3	—	0.134 ± 0.047	0.105 ± 0.039	0.156
	1.2	4	0.127 ± 0.114	0.066 ± 0.050	0.063 ± 0.036	0.515
	1.6	4	—	0.011 ± 0.003	0.030 ± 0.014	0.220
	Combined	13	—	0.092 ± 0.023	0.068 ± 0.016	0.096

Values are mean ± SE.

N = only the number of rats reexposed to the enumerated isoflurane MAC concentration. The comparison between "Preoperative" and Exposure 1 is discussed in the text.

* The listed *P* values pertain to the comparisons between Exposure 1 and Exposure 2.

have altered mentation. However, Eisele *et al.* have reported that this Pa_{CO_2} does not significantly change halothane MAC in dogs.[30] Because we did not investigate the possible change in MAC with changing Pa_{CO_2} by direct measurement of motor response, we cannot resolve this apparent contradiction between our hypothesis and Eisele *et al.*'s measurements. If the effect observed at 1.2 MAC disappeared at 1.0 MAC or lower concentrations, both the hypothesis and those measurements would be accommodated. Alternatively, the 20% step changes in halothane concentration used by Eisele *et al.* to assess MAC might not have provided sufficient resolution to detect a small decrease in MAC during moderate hypercapnia.‡

The interactions of hyperventilation and hypocapnia with anesthetic effect are controversial. Some authors report that hypocapnia appears to reduce clinical anesthetic requirements,[31–33] perhaps by actions at the neuromuscular junction.[28] However, other reports suggest that hypocapnia does not alter MAC in dogs or humans.[34,35] Our findings confirm that hypocapnia depresses the neuromuscular junction, but the observed increase in (central) motor neuron excitability suggests a slight decrease in isoflurane potency (increased MAC requirement). Kitahata *et al.* also have reported hypocapnia-induced monosynaptic and polysynaptic reflex arc facilitation within the spinal cord.[36] Possibly the peripheral, neuromuscular junction effects of hypocapnia counterbalance the central excitation. Alternatively, carbon dioxide–induced decreases in excitation at sites above the spinal cord[37] may alter, *via* descending pathways, the expected effect of changes in motor neuron depression on MAC.

Over time, mean M-wave amplitude decreased, suggesting reduction in neuromuscular transmission, displacement of the electrodes with repeated stimulation, or change in the muscle's electrical state. The mean F-wave amplitude did not change significantly in aggregate, but demonstrated an isoflurane dose dependence. The mechanism and significance of these dose-dependent changes remain to be elucidated.

After incision, the F-wave amplitude decreased slightly, but whether due to this noxious stimulation or to the 60–90–min interval between the preoperative (baseline) and the first postoperative (1.2 MAC) test is not clear. Although MAC is reportedly unchanged by the duration of anesthesia[1] in dogs, a recent report suggests that anesthetic duration or incision *per se* may decrease MAC in humans.[38]

Limitations

Two additional factors limit the interpretation of the results of this study. First, there are species differences in the characteristics of the F wave. That is, the F-wave amplitudes obtained at the 0.5 MAC concentration averaged approximately 25% of the M-wave amplitude at that concentration. This ratio is approximately twice that found in nonmedicated humans, suggesting greater motor excitability in rats. It was not possible to measure F-wave amplitude in nonmedicated rats, and the presence of low-dose isoflurane may confound this comparison. Second, the F-wave amplitude model cannot

‡ Eger EI II: Personal communication. 1994.

discriminate between presynaptic and postsynaptic sources of changes in motor neuron excitability. The changes in F-wave amplitude observed in this study may represent direct effects of isoflurane on the α-motor neuron cell membrane potential, or they may represent a change in the balance of excitatory *versus* inhibitory afferent input to that motor neuron.

Monitoring General Anesthesia

The observations obtained in this study link an essential behavioral component of general anesthesia with a quantifiable phenomenon at a specific neuronal site. Our findings may allow a more anatomically and physiologically focused approach to the investigation into mechanisms of some anesthetic actions. Monitoring of F-wave activity also may allow detection of inadequate anesthesia, that is, a state in which motor neurons can mediate spontaneous or nocifensive movement during surgery. In summary, isoflurane depresses spinal motor neuron excitability, and the dose–response characteristics of this depression suggest that this effect may play an important role in the creation of surgical immobility.

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