Sevoflurane Depresses Glutamatergic Neurotransmission to Brainstem Inspiratory Premotor Neurons but Not Postsynaptic Receptor Function in a Decerebrate Dog Model

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Background: Inspiratory bulbospinal neurons in the caudal ventral medulla are premotor neurons that drive motoneurons, which innervate pump muscles such as the diaphragm and external intercostals. Excitatory drive to these neurons is mediated by *N*-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptors and is modulated by an inhibitory γ-aminobutyric acid type A (GABA$_A$)ergic input. The authors investigated the effect of sevoflurane on these synaptic mechanisms in decerebrate dogs.

Methods: Studies were performed in decerebrate, vagotomized, paralyzed, and mechanically ventilated dogs during hypercapnic hyperoxia. The effect of 1 minimum alveolar concentration sevoflurane on extracellularly recorded activity of single neurons was measured during localized picoejection of the GABA$_A$ receptor blocker bicuculline and the glutamate agonists AMPA and NMDA. Complete blockade of the GABA$_A$ergic mechanism by bicuculline allowed differentiation between the effects of sevoflurane on overall GABA$_A$ergic inhibition and on overall glutamatergic excitation. The neuronal responses to exogenous AMPA and NMDA were used to estimate the anesthetic effect on postsynaptic glutamatergic neurotransmission.

Results: One minimum alveolar concentration sevoflurane depressed the spontaneous activity of 23 inspiratory premotor neurons by (mean ± SD) 30.0 ± 21.0% (*P* < 0.001). Overall glutamatergic excitation was depressed 19.2 ± 18.5% (*P* < 0.001), whereas overall GABA$_A$ergic inhibition was enhanced by 11.9 ± 25.1% (*P* < 0.05). The postsynaptic responses to exogenous AMPA and NMDA did not change.

Conclusion: One minimum alveolar concentration depressed the activity of inspiratory premotor neurons by a reduction of glutamatergic excitation and an increase in overall inhibition. The postsynaptic AMPA and NMDA receptor response was unchanged. These findings contrast with studies in inspiratory premotor neurons where halothane did not change overall inhibition but significantly reduced the postsynaptic glutamate receptor response.

VOLATILE anesthetics depress respiratory drive at concentrations used for general anesthesia.[1] Respiratory drive that determines tidal volume is relayed by the medullary premotor neurons to phrenic motoneurons that innervate the diaphragm. One minimum alveolar concentration (MAC) halothane depresses the activity of inspiratory premotor neurons that are located in the caudal ventral respiratory group by 20%.[2,3] It is possible to determine the specific effects of anesthetics on neurotransmission in this neuronal model *in vivo* because the discharge pattern of these neurons has been found to depend only on glutamatergic and γ-aminobutyric acid (GABA)ergic neurotransmission under physiologic conditions.[4–7]

The depression of inspiratory premotor neuronal activity by 1 MAC halothane results from a reduction of overall excitatory drive to the neurons and is, at least in part, due to a depression of postsynaptic α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) and *N*-methyl-D-aspartate (NMDA) receptor function.[2] This contrasts with findings in *expiratory* premotor neurons, where sevoflurane and halothane cause an increase in overall inhibition, a decrease in overall excitation, and no effect on postsynaptic glutamate receptor function.[4–6] We speculate that the glutamate receptors on inspiratory neurons may belong to a different subgroup with increased sensitivity to volatile anesthetics.[2]

The current study was performed to test the hypothesis that sevoflurane reduces inspiratory neuronal discharge activity by a combination of depression of overall glutamatergic excitation and enhancement of overall GABAergic inhibition. Second, we hypothesize that glutamatergic excitation is partly reduced secondary to depression of postsynaptic AMPA and NMDA receptor function as we have shown for halothane previously.

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Materials and Methods

Animal Preparation and General Methodology

This research was approved by the Medical College of Wisconsin Animal Care Committee (Milwaukee, Wisconsin) and conformed with standards set forth in the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*.[8] Anesthesia was induced in the dogs by mask with isoflurane, and the dogs were intubated with a cuffed endotracheal tube and from then on mechanically ventilated with oxygen. Isoflurane (1.3–1.8 MAC) was applied throughout the surgical procedures

and only discontinued after completion of the decerebration (1 MAC isoflurane in dogs = 1.4%[7]). The animals were positioned in a stereotactic device (model 1530; David Kopf Instruments, Tujunga, CA) with the head ventrally flexed (30°). Bilateral neck dissections were performed. The C5 phrenic nerve rootlet was desheathed for recording, and bilateral vagotomy was performed to achieve peripheral deafferentation. This avoids interference of the artificial ventilation with the underlying central respiratory rhythm. A bilateral pneumothorax was performed to minimize brainstem movement and phasic inputs from chest wall mechanoreceptors. The animals were decerebrated at the midcollicular level[9] and only then paralyzed (0.1 mg/kg pancuronium, followed by $0.1 \, mg \cdot kg^{-1} \cdot h^{-1}$). An occipital craniotomy was performed to expose the dorsal surface of the medulla oblongata for single neuron recording. Esophageal temperature was maintained at $38.5° \pm 1°C$. Mean arterial pressure was kept above 100 mmHg and did not differ more than 20% between 0 and 1 MAC. Blood pressure was supported as needed with infusions of phenylephrine ($0.5-5 \, \mu g \cdot kg^{-1} \cdot min^{-1}$). Protocols were only performed during steady state conditions for blood pressure.

Neuron Recording Technique, Data Collection, and Experimental Conditions

Multibarrel compound glass micropipettes consisting of a recording barrel containing a 7-μm carbon filament and three drug barrels were used to simultaneously record extracellular neuronal action potential activity before and during pressure ejection of the glutamate agonists and γ-aminobutyric acid type A (GABA$_A$) receptor antagonist onto inspiratory neurons of the caudal ventral respiratory group. We used the selective glutamate receptor agonists AMPA (7.5 μM; Research Biochemicals, Natick, MA) and NMDA (200 μM; Research Biochemicals) and the GABA$_A$ antagonist bicuculline methochloride (200 μM; Research Biochemicals), which were dissolved in an artificial cerebrospinal fluid.[4] Meniscus changes in the drug barrels were measured to determine the ejected dose rates (resolution 2 nl). The neurons were located approximately 1.5–3 mm caudal from the obex and 2.5–4.5 mm lateral from the midline. A previous study had shown that approximately 90% of these neurons were bulbospinal,[10] *i.e.*, their soma was located in the brainstem and their axons projected to motoneurons in the spinal cord as confirmed with antidromic stimulation techniques.[10] Single-cell inspiratory neuronal activity, phrenic nerve activity, picoejection marker pulses, airway carbon dioxide and volatile anesthetic concentrations, systemic blood pressure, and airway pressure were recorded on a digital tape system (model 3000A; A.R. Vetter Co., Rebersburg, PA). These variables or their time averages were also continuously displayed on a computerized chart recorder (Powerlab/

16SP; ADInstruments, Castle Hill, Australia). A time–amplitude window discriminator was used to produce rate-meter recordings (F$_n$: average discharge frequency per 100-ms period) of the neuronal activity. Timing pulses at the beginning and end of neural inspiration were derived from the phrenic neurogram and were used to determine the respiratory phases. The tape-recorded data were digitized and analyzed off-line. Cycle-triggered histograms (average F$_n$ per 50-ms bin), triggered at the onset of phrenic activity, were used to quantify the neuronal discharge frequency data.

The protocols were performed under hyperoxic (fraction of inspired oxygen > 0.8) and steady state hypercapnic conditions (arterial carbon dioxide tension [Pa$_{CO_2}$] 55–65 mmHg). The optimal level of Pa$_{CO_2}$ was adjusted from animal to animal, so that adequate phasic respiratory activity during the anesthetic state (1 MAC) was ensured. Great care was taken to keep the Pa$_{CO_2}$ tightly controlled within each neuron protocol. One complete neuron protocol consisted of two sets of three separate picoejection runs (run 1: AMPA; run 2: NMDA; and run 3: bicuculline). One set was performed in this sequence at 0, and the other set was performed at 1 MAC sevoflurane (= 2.4%[7]). To maximize the yield of complete neuron protocols, we performed the current protocols with the order of the sets (0 and 1 MAC) randomized, which eliminated the need for end controls.[5,6] Control ejections with the vehicle artificial cerebrospinal fluid, in which the neurotransmitters were dissolved, were performed for each experimental setup to confirm lack of vehicle effect.

Run 1: Effects of Sevoflurane on Postsynaptic AMPA Receptors

For the control period (F$_{con}$) and at each dose rate, cycle-triggered histograms (5–10 cycles) from each neuron were used to obtain values of the average peak neuronal discharge frequency (F$_n$) for each condition. The glutamate agonist AMPA was applied in increasing dose rates until an increase in peak F$_n$ of at least 25 Hz was achieved. Typically, picoejection durations of 6–8 min with two to three dose rates were needed.

Statistical Analysis, Run 1

The effect of 1 MAC sevoflurane on the postsynaptic AMPA receptor response was quantified by linear regression of F$_n$ on dose rate, because previous studies have shown the dose–response data for glutamate to be linear.[4,5] This was confirmed for inspiratory neurons. In this regression analysis, the y-intercept was constrained to pass through the F$_{con}$ value at the zero dose rate. Therefore, any change in the slope of the regression line reflected the anesthetic-induced change in the dose–response relation. To compare the dose–responses at 0 and 1 MAC, the slope values were then normalized to the slope at 0 MAC (slope$_0$), and the normalized difference was determined for each neuron, *i.e.*, Δ slope =

(slope$_1$ − slope$_0$)/slope$_0$. A Wilcoxon signed rank test was performed to test whether the slope was significantly different from no change (StatView; SAS Institute, Inc., Cary, NC).

Run 2: Effects of Sevoflurane on Postsynaptic NMDA Receptors

After recovery from AMPA, the same picoejection run was repeated with NMDA. The analysis of the NMDA data was performed using the same procedure as described for AMPA.

Run 3: Effects of Sevoflurane on Overall Synaptic Neurotransmission

After recovery from NMDA, the GABA$_A$ receptor antagonist bicuculline was picoejected until complete block of GABA$_A$ergic inhibition occurred, *i.e.*, when an increase in picoejection dose rate did not result in any further increase in F$_n$. Typically, picoejection durations of 5–10 min with several increasing dose rates were required. After the bicuculline run, complete postejection recovery was awaited, which required 30–45 min. Then, the randomized state of anesthesia was switched, and after a minimum equilibration time of 15 min, the three runs of the protocol were repeated in the same fashion. State of anesthesia refers to either 1 MAC anesthesia or absence of anesthesia (0 MAC).

Statistical Analysis, Run 3

During complete GABA$_A$ergic block with bicuculline, F$_n$ equals the overall excitatory drive to the neuron (F$_e$). Under control conditions, the prevailing GABA$_A$ergic inhibition reduces F$_e$ to F$_{con}$ by the inhibitory factor α, where $\alpha = (F_e − F_{con})/F_e$. To calculate the change in overall excitatory drive, the data were normalized to F$_e$ at 0 MAC, which was assigned a value of 100%. A two-way repeated-measures analysis of variance was used with main factors of anesthetic state (0 or 1 MAC) and neurotransmitter status (preejection control *vs.* maximal bicuculline block) (SuperANOVA; Abacus Concepts, Inc., Berkeley, CA). The values for F$_e$ and F$_{con}$ were obtained for the 0 MAC level (F$_{con0}$, F$_{e0}$) and the 1 MAC level (F$_{con1}$, F$_{e1}$) from the experimental runs. They were then used in the calculation of the anesthetic effect on overall excitation ΔF_e (where $\Delta F_e = [F_{e1} − F_{e0}]/F_{e0}$) and overall inhibition $\Delta\alpha$ (where $\Delta\alpha = [\alpha_1 − \alpha_0]/\alpha_0$). All results are given as mean ± SD, and $P < 0.05$ was used to indicate significant differences unless stated otherwise.

Results

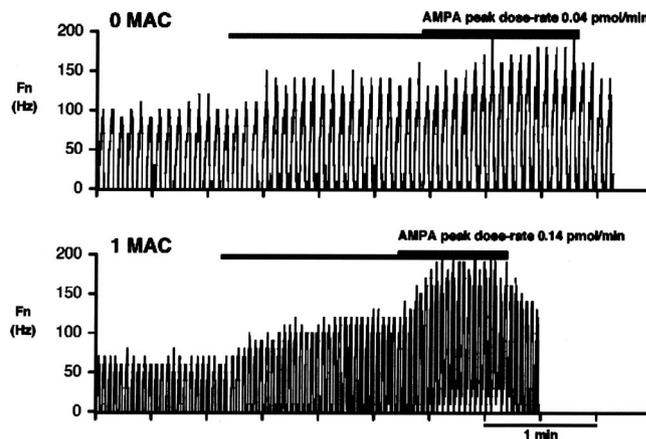Experiments were performed on 27 dogs and yielded 23 complete neuron protocols.

Fig. 1. Response of an inspiratory neuron to increasing doses of α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) at 0 and 1 minimum alveolar concentration (MAC) sevoflurane. Rate-meter recordings of the neuronal discharge frequency F$_n$ (in hertz) are shown. The *horizontal bars* indicate the picoejection duration. Only maximal dose rates are indicated (see text for details).

Effects of Sevoflurane on Postsynaptic AMPA Receptors

Figure 1 shows a representative example of an inspiratory neuronal response to increasing doses of AMPA at 0 and 1 MAC sevoflurane, respectively. The maximal picoejected dose rate was 0.04 pmol/min at 0 MAC and 0.14 pmol/min at 1 MAC. One MAC sevoflurane decreased the slope of the linear regression line fitted through the dose–response plots from 945.1 Hz $\cdot$ pM^{-1} $\cdot$ min^{-1} to 830.1 Hz $\cdot$ pM^{-1} $\cdot$ min^{-1}, *i.e.*, the AMPA receptor response was decreased by 12%.

For the calculation of the pooled AMPA, normalized data the AMPA response data of one neuron was removed from the analysis because a scatter plot of the slope data showed that the value was more than 2 SDs different from the other data points. The pooled data from 22 neurons show a decrease in AMPA receptor function of 13.0 ± 52.1%, which was not statistically significant ($P = 0.09$).

Effects of Sevoflurane on Postsynaptic NMDA Receptors

Figure 2 shows the response of the same neuron as in figure 1 to NMDA at 0 and 1 MAC sevoflurane. Sevoflurane decreased the slope from 28.6 Hz $\cdot$ pM^{-1} $\cdot$ min^{-1} to 26.1 Hz $\cdot$ pM^{-1} $\cdot$ min^{-1}, *i.e.*, by 9% (fig. 3).

The pooled normalized data from 23 neurons show an increase in NMDA receptor function by 4.5 ± 59.2%, which was not significant ($P = 0.76$).

Effects of Sevoflurane on Overall Synaptic Neurotransmission

Overall excitation and inhibition were determined for the same neuron as in figures 1 and 2 (fig. 4). Complete block of GABA$_A$ergic input increased neuronal discharge

Fig. 2. Response of the same neuron as in figure 1 to increasing doses of *N*-methyl-D-aspartate (NMDA) at 0 and 1 minimum alveolar concentration (MAC) sevoflurane (*A*). The *horizontal bars* indicate the picoejection duration. Maximal dose rates are given. (*Bottom insets*) Time-expanded views of the neuronal rate-meter recording (100 ms/bin) for 1 MAC sevoflurane before picoejection (*B*) and during picoejection of NMDA (*C, arrows*). The simultaneously recorded time-averaged phrenic neurogram (PNG, in arbitrary units [a.u.], *top*) identifies the neuron as inspiratory. The neuronal raw activity (N.A., *middle trace*) is originally recorded as a train of action potential spikes. A time–amplitude window is used to discriminate the larger amplitude inspiratory activity from the lower amplitude expiratory phase activity for the rate-meter recordings (*bottom trace*) and cycle-triggered histogram analysis (not shown).
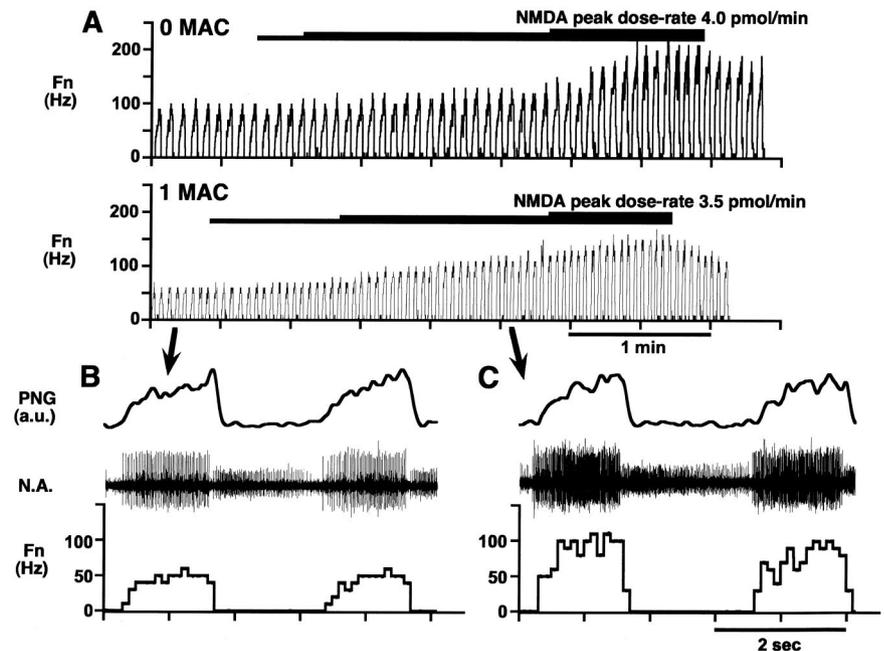
frequency at 0 MAC sevoflurane from F_{con} = 100 Hz to F_e = 285 Hz, yielding an overall inhibitory factor of α = 0.65 (fig. 5). One MAC sevoflurane decreased F_{con} to 62 Hz, *i.e.*, by 38%. F_e was decreased to 282 Hz, *i.e.*, by 1%. This yielded an α of 0.78, *i.e.*, sevoflurane increased overall inhibition by 20%.

The pooled data for 23 neurons show that 1 MAC sevoflurane decreased F_{con} by 30.0 ± 21.0% (P < 0.001) and overall excitation by 19.2 ± 18.5% (P < 0.001) (fig. 6). Overall inhibition α was increased by 11.9 ± 25.1% (P < 0.05).

Discussion

The current study is the first to show the *in vivo* effects of sevoflurane on synaptic neurotransmission to inspiratory premotor neurons. One MAC sevoflurane depressed neuronal activity by a combination of depression of overall glutamatergic excitation and an enhancement of overall GABAergic inhibition. The postsynaptic AMPA and NMDA receptor functions were not depressed, which allows the conclusion that sevoflurane reduced the presynaptic excitatory drive (fig. 7).
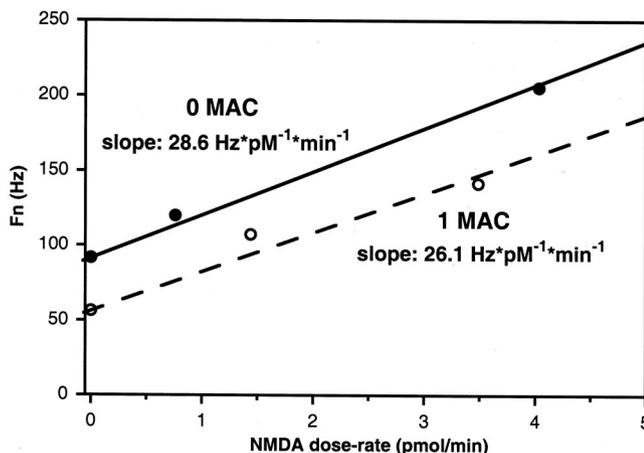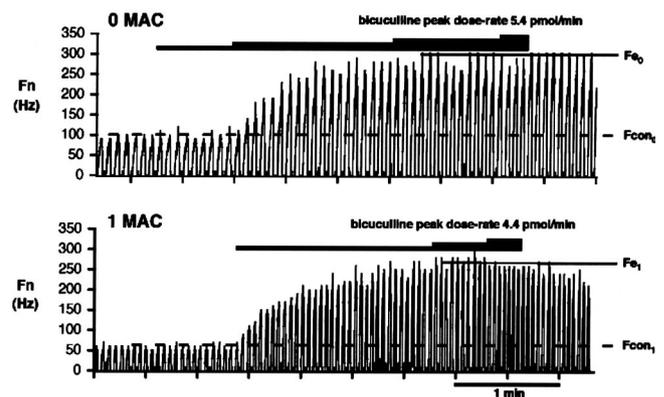

Fig. 3. Method used to analyze the effect of sevoflurane on postsynaptic glutamate receptor function. The graph shows the dose–response data of peak neuronal discharge frequency F_n to picoejection of *N*-methyl-D-aspartate (NMDA) onto the neuron shown in figure 2. Linear regression analysis was performed, where the y-intercept was constrained to pass through control frequency (F_{con}) at the zero dose rate. The slope at 1 minimum alveolar concentration (MAC) sevoflurane (*dashed line with open circles*) was normalized to the slope at 0 MAC (*solid line with solid circles*) to allow for pooled analysis of the data. The original slope values are given.

Fig. 4. Rate-meter recording (100 ms/bin) of the responses of the neuron shown in figure 1 to increasing doses of the γ-aminobutyric acid type A antagonist bicuculline at 0 and 1 minimum alveolar concentration (MAC) sevoflurane. When the increase in peak neuronal frequency had reached a plateau, the bicuculline dose rate was increased at least one more time to ascertain that the bicuculline effect was saturated, *i.e.*, that all γ-aminobutyric acid type A receptors were blocked. This frequency represents the overall excitatory drive (F_e) to the neuron. Stated are the maximal dose rates for bicuculline that were applied, while a maximal increase in neuronal discharge frequency was already achieved with much smaller dose rates. F_{con} = neuronal control frequency.
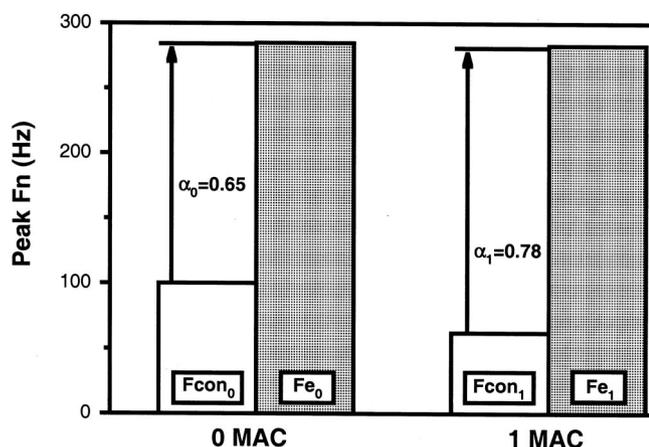
Fig. 5. Method of analysis for the effect of sevoflurane on overall neurotransmission. Peak neuronal frequency values were obtained from cycle-triggered histograms based on 5–10 respiratory cycles before picoejection of bicuculline (F_{con}) and at the maximal bicuculline response to determine overall excitation (F_e). The magnitude of the γ-aminobutyric acid–mediated input to the neuron, *i.e.*, overall inhibition (α), was calculated as $\alpha = (F_e - F_{con})/F_e$. In this neuron, 1 minimum alveolar concentration (MAC) sevoflurane increased overall inhibition α from 0.65 to 0.78, *i.e.*, by 20%.

Sevoflurane Does Not Depress Glutamate Receptor Function

The mechanism by which volatile anesthetics reduce glutamatergic neurotransmission is not fully resolved. Studies measuring glutamate release from rat synaptosomes[12,13] and neurotransmission in rat hippocampal slice preparations[14] suggest an anesthetic-induced decrease in glutamate release from presynaptic nerve endings rather than an anesthetic effect on the postsynaptic receptor. Recently, Wu *et al.*[15] have shown in calyx-type synapses in rat brainstem slices that 1–3 MAC-equivalent of isoflurane dose-dependently reduced a stimulation-evoked increase in presynaptic membrane capacitance. This was interpreted as a reduction in the number of
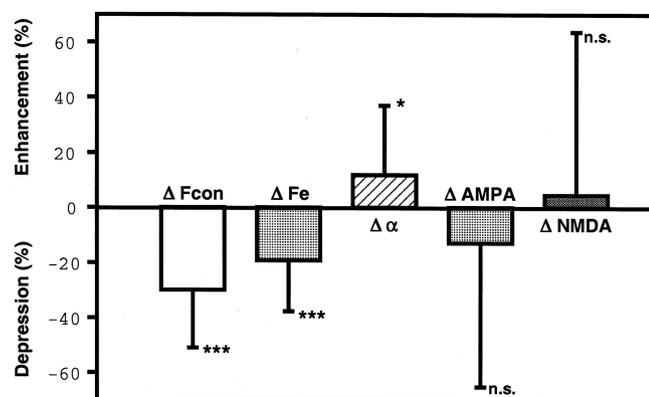

Fig. 6. Pooled summary data. Mean anesthetic-induced changes ± SD for control neuronal frequency (ΔF_{con}), overall excitation (ΔF_e), overall inhibition ($\Delta \alpha$), and the postsynaptic receptor response to α-amino-3-hydroxy-5-methylisoxazole-4-propionate (ΔAMPA) and *N*-methyl-D-aspartate (ΔNMDA) caused by 1 minimum alveolar concentration sevoflurane. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; n.s. = not significant; all relative to no change.

vesicles that fused with the presynaptic membrane and released glutamate, and correlated with a decrease in excitatory postsynaptic currents.[16] On the other hand, studies on glutamate receptor subtypes expressed in *Xenopus* oocytes showed that clinical concentrations of halothane, enflurane, and isoflurane depressed AMPA receptor (glutamate receptor 3) but enhanced kainate receptor (glutamate receptor 6) function.[17] Also, 0.5 MAC-equivalent isoflurane depressed NMDA receptor function by approximately 15% and AMPA receptor function by approximately 5%.[18]

In our previous studies, we found that 1 MAC halothane or sevoflurane depressed overall excitation of expiratory premotor neurons without affecting postsynaptic NMDA receptor function.[4,5] In contrast, 1 MAC halothane depressed AMPA and NMDA receptor function of inspiratory neurons by 19 and 22%, respectively.[2] Our previous hypothesis that glutamate receptors on inspiratory neurons belonged to subtypes that were differentially affected by anesthetics[2] is challenged by the current study, where sevoflurane did not depress AMPA or NMDA receptor function. We have previously shown that our method can reliably detect an anesthetic-induced change in receptor function of 20% with a power of 90%.[2] Therefore, it is possible that we were not able to discriminate real but smaller anesthetic-induced changes in receptor function due to method inherent variability. *In vitro* studies indicate that the anesthetic-induced changes in glutamatergic receptor function, unlike those for GABAergic function, may be of a rather small magnitude.[18]

Still, our data suggest that a decrease in presynaptic excitatory input is responsible in great part for the depression of overall excitatory drive. This decrease is likely the product of anesthetic effects on central chemodrive[19] as well as on neurotransmission at other levels upstream from the inspiratory premotor neurons (see fig. 1 in Stucke *et al.*[3]).

Sevoflurane Enhances Overall Inhibition

The moderate enhancement of overall GABAergic inhibition by sevoflurane in this study is similar to the results in expiratory premotor neurons but different from halothane, which did not change overall inhibition in inspiratory neurons. A more detailed discussion of this finding is provided in the companion article.[11]

Methodologic Considerations and Clinical Implications

Studies in the *in vivo* decerebrate dog model allow us to examine the effects of volatile anesthetics on respiratory neurotransmission under conditions that are as close as possible to the clinical application. In particular,

Fig. 7. Summary scheme of the effects of 1 minimum alveolar concentration sevoflurane on synaptic transmission to inspiratory premotor neurons in the caudal ventral respiratory group. The neuronal control frequency is depressed (*downward arrow*). This is due to a reduction of overall glutamatergic excitation (*downward arrow*) together with an increase in overall inhibitory input (*upward arrow*). Postsynaptic α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) and *N*-methyl-D-aspartate (NMDA) receptor responses were not changed (ø), which suggests that presynaptic excitatory drive is diminished (*downward arrow*). The inhibitory mechanisms (see *?*) are also investigated in this issue of ANESTHESIOLOGY.[11]
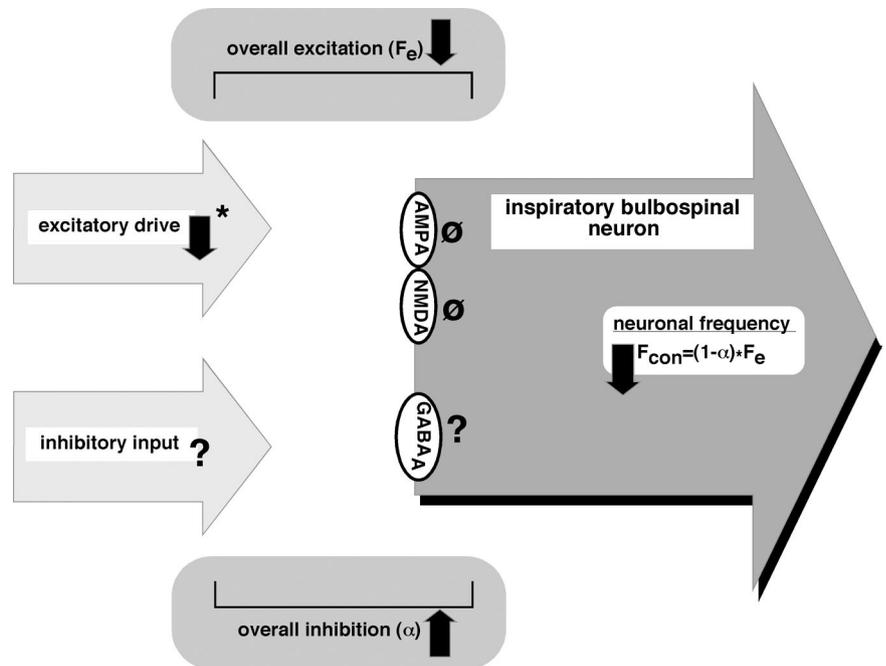
neurotransmitters will be present at physiologic concentrations and anesthetic levels in the tissues will be in the same range as during clinical anesthesia. The advantages and limitations of the decerebration method have been discussed before.[3,4] We have shown that the *in vivo* brainstem respiratory network of decerebrate dogs functions comparably to that of neuraxis-intact dogs, *e.g.*, the absolute magnitude of the neuronal control discharge frequency, overall excitatory drive, and overall inhibition to expiratory premotor neurons at 1 MAC halothane were similar in nondecerebrate[20] and decerebrate animals.[4,5]

The ability to pinpoint the specific sites or neuronal mechanisms affected by anesthetics with our methods is based on the fact that the endogenously active synaptic inputs to the premotor neurons are limited. Specifically, our previous studies conclusively showed that (1) tonic glutamatergic excitation was mediated by NMDA receptors to both inspiratory and expiratory neurons;[21,22] (2) phasic excitation was mediated by AMPA receptors only to the inspiratory neurons;[21] (3) the silent phase of both inspiratory and expiratory neurons was produced by phasic inhibition mediated by GABA_A receptors[23] and on inspiratory neurons in addition to a very minor degree by glycine receptors;[24] (4) GABA_A receptors also mediate a tonic inhibition that manifests itself as a gain modulation of underlying neuronal discharge patterns of both neuron types;[23] and (5) local application of acetylcholine,[24] norepinephrine, and serotonin produce no effect on the discharge of these neurons (unpublished observations, E. J. Zuperku, Ph.D., Milwaukee, Wisconsin, June to December 1995). Therefore, the discharge patterns of inspiratory and expiratory bulbospinal neurons during

their active phase are primarily the result of the interaction of ionotropic glutamate and GABA_A receptor–mediated excitation and inhibition, respectively. This contrasts with a multitude of neurotransmitters and neuromodulators known to control other respiratory neurons, in particular motoneurons. Accordingly, by blocking the GABAergic input, the full level of glutamatergic excitation is unmasked and can be quantified as well as the level of GABAergic inhibition.

Anesthetic-induced changes in nonsynaptic intrinsic properties of the neurons that may affect excitability seem negligible, at least in expiratory premotor neurons, because the response to exogenous local application of NMDA by 1 MAC halothane was unaltered.[4] For inspiratory neurons, the responses to exogenous AMPA and NMDA were both depressed by approximately 20% with 1 MAC halothane.[2] With our technology, we are not able to separate a direct effect on receptor function from an indirect effect *via* reduced excitability. Nevertheless, halothane had a postsynaptic effect on glutamatergic neurotransmission, which can be quantified. In contrast, the postsynaptic responses to exogenous application of the GABA_A receptor agonist muscimol were significantly enhanced for both neuron types (by approximately 75–110%).[3,11]

In summary, 1 MAC sevoflurane reduced inspiratory premotor neuronal activity by a depression of excitatory drive and an enhancement of overall inhibition. The postsynaptic glutamatergic receptor activity was not significantly affected by the anesthetic.

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