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Effects of Sevoflurane on Excitatory Neurotransmission to Medullary Expiratory Neurons and on Phrenic Nerve Activity in a Decerebrate Dog Model

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Background: **Sevoflurane is a new volatile anesthetic with a pronounced respiratory depressant effect. Synaptic neurotransmission in canine expiratory bulbospinal neurons is mainly mediated by excitatory *N*-methyl-D-aspartatic acid (NMDA) receptor input and modulated by inhibitory γ-aminobutyric acid type A ($GABA_A$) receptors. The authors investigated the effect of sevoflurane on these 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 (MAC; 2.4%) sevoflurane on extracellularly recorded neuronal activity was measured during localized picoejection of the glutamate agonist NMDA and the $GABA_A$ receptor blocker bicuculline in a two-part protocol. First, 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. In a second step, the neuronal response to exogenous NMDA was used to estimate sevoflurane's effect on postsynaptic glutamatergic neurotransmission.**

Results: **One minimum alveolar concentration sevoflurane depressed the spontaneous activity of 16 expiratory neurons by 36.7 ± 22.4% (mean ± SD). Overall glutamatergic excitation was depressed 19.5 ± 16.2%, and $GABA_A$ergic inhibition was enhanced 18.7 ± 20.6%. However, the postsynaptic response to exogenous NMDA was not significantly altered. In addition, 1 MAC sevoflurane depressed peak phrenic nerve activity by 61.8 ± 17.7%.**

Conclusions: **In the authors' *in vivo* expiratory neuronal model, the depressive effect of sevoflurane on synaptic neurotransmission was caused by a reduction of presynaptic glutamatergic excitation and an enhancement of $GABA_A$ergic inhibition. The effects on expiratory neuronal activity were similar to halothane, but sevoflurane caused a stronger depression of phrenic nerve activity than halothane.**

SEVOFLURANE is a volatile anesthetic of the ether group that has only recently gained wide clinical acceptance. *In vitro* studies demonstrate similarities between volatile anesthetics with respect to effects on synaptic neurotransmission but have also shown differences. For example, sevoflurane causes an open channel block of the γ-aminobutyric acid type A ($GABA_A$) receptor that seems different from other volatile anesthetics.[1]

In neuraxis-intact mammals, anesthetic concentrations of sevoflurane appear to cause more depression of the respiratory centers and normoxic ventilation than halothane.[2] Preliminary data in humans have suggested that sevoflurane and halothane might affect subgroups of respiratory neurons differently.[3]

Our canine decerebrate preparation[4] allows the study of the effects of volatile anesthetics on synaptic neurotransmission to single brainstem respiratory neurons *in vivo.* In previous studies, we found in the hyperoxic, vagotomized, and neuraxis-intact as well as in the decerebrate dog that the excitatory drive of expiratory premotor neurons in the caudal ventral respiratory group is primarily mediated by *N*-methyl-D-aspartatic acid (NMDA) receptors,[5] whereas the main synaptic modulator of neuronal activity is a $GABA_A$ergic inhibitory input.[6] We recently reported the effects of halothane on GABAergic and glutamatergic neurotransmission using this model.[7]

The current study was conducted to elucidate the effects of sevoflurane on overall inhibitory (*i.e.,* $GABA_A$ergic) and overall excitatory (*i.e.,* glutamatergic) neurotransmission to expiratory premotor neurons. Furthermore, we determined the effect of sevoflurane on postsynaptic glutamatergic receptor function. In addition to analyzing the effects at the premotor level, we measured the effects of sevoflurane on peak phrenic activity. These sevoflurane data were then compared with recently reported halothane data.[7]

Materials and Methods

Animal Preparation and General Methodology

The research was approved by the Medical College of Wisconsin Animal Care Committee (Milwaukee, WI) and conformed with standards set forth in the National Institutes of Health Guide for Care and Use of Laboratory Animals.

Anesthesia in dogs was induced by mask ventilation with sevoflurane, and the trachea was intubated with a cuffed endotracheal tube; from that time, the lungs were mechanically ventilated with an oxygen–sevoflurane (1.3–1.8 minimum alveolar concentration [MAC]) mix-

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ture throughout the surgical procedures. We have previously described the surgical preparation in detail.[7,8] In short, after bilateral vagotomy and bilateral pneumothorax the animals were decerebrated[9] and paralyzed (0.1 mg/kg pancuronium followed by 0.1 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}). The medulla oblongata and the phrenic nerve were prepared for recording. Esophageal temperature was maintained at 38.5 $\pm$ 1°C. Mean arterial pressure was kept above approximately 100 mmHg (if necessary, with 0.5–5 μg $\cdot$ kg^{-1} $\cdot$ min^{-1} phenylephrine). Protocols were performed only during steady-state conditions for blood pressure.

Neuron Recording Technique, Data Collection, and Experimental Conditions

Data recording and collection, as well as the drugs used, are described in detail in our previous study.[7] A multibarrel compound glass electrode was used to simultaneously record extracellular neuronal action potential activity before and during pressure ejection of respective neurotransmitters onto expiratory neurons of the caudal ventral respiratory group.[5,6,8] Bipolar hook electrodes were used to record multifiber activity from the C5 rootlet, and the phrenic neurogram was obtained from the moving average of this activity.

The protocols were performed under hyperoxic (fraction of inspired oxygen [F_{IO_2}] $>$ 0.8) and steady-state hypercapnic conditions (arterial carbon dioxide tension, 50–60 mmHg). A typical protocol consisted of two separate picoejection periods (part 1, 200 μM NMDA; part 2, 200 μM bicuculline) at each anesthetic dose level (*i.e.,* 0 MAC, 1 MAC sevoflurane, and 0 MAC end control).

Picoejection Protocol, Part 1: Effects of Sevoflurane on Postsynaptic Glutamatergic Excitation

The peak neuronal discharge frequency (F_n) was measured for 10–20 respiratory cycles during a preejection control period (F_{con}). Then the glutamate receptor agonist NMDA was applied in increasing dose rates until an increase in peak F_n of at least 40 Hz was achieved. Typically, picoejection durations of 6–8 min with 2 or 3 dose rates were needed. Sufficient time was allowed for F_n to return to the control level.

Statistical Analysis, Part 1

To quantify the effect of NMDA on the postsynaptic receptor, we determined the dose rate that caused a 40-Hz increase in peak F_n (*i.e.,* a 40-Hz net increase at 0 MAC sevoflurane) and designated it as D_{40Hz}. To confirm the linearity of the dose–response curves in this range, we also determined the net increase at half this dose rate and designated it as ½ D_{40Hz}. Next, we determined the corresponding net increases from the dose–response curves at 1 MAC sevoflurane. Then all net increases were normalized to the 40-Hz net increase at 0 MAC, which was assigned a value of 100%. A two-way, repeated-measures analysis of variance with main factors of level of anesthesia (0 or 1 MAC sevoflurane) and neurotransmitter status (preejection control *vs.* NMDA response) was performed (SuperANOVA; Abacus Concepts, Inc., Berkeley, CA).

Picoejection Protocol, Part 2: 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. Upon discontinuation of bicuculline, complete postejection recovery was awaited, which typically required 30–45 min. Then sevoflurane was introduced to a depth of 1.0 MAC (2.4 vol%),[10] and after an equilibration time of 15 min, both parts of the protocol were repeated in the same fashion. It was ensured that peak bicuculline dose rates during anesthesia always matched or exceeded those during the anesthetic-free run. After recovery from bicuculline, the anesthetic was discontinued, complete washout was awaited, and the picoejection protocol was repeated at 0 MAC to obtain end controls. A complete neuron protocol (0-MAC level, the anesthetic wash-in, the 1-MAC level, and the return to 0-MAC level end control) required approximately 4 h.

Statistical Analysis, Part 2

We defined the peak F_n for the preejection control period as F_{con}, and for the maximal F_n under bicuculline block as F_e. F_e is a measure of the uninhibited overall glutamatergic excitatory drive to the neuron, whereas F_{con} represents this drive reduced by the prevailing basal $GABA_A$ergic inhibition. To calculate the change in overall excitatory drive, the data were normalized to F_e at the 0-MAC level, which was assigned a value of 100%. A two-way, repeated measures analysis of variance with main factors of level of anesthesia (0 or 1 MAC sevoflurane) and blocking status (preejection control *vs.* maximal bicuculline block) was used.

The prevailing $GABA_A$ergic inhibition was described by the inhibitory constant α which is defined as follows: $\alpha = [F_e - F_{con}]/F_e$. 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. Then they were used in the calculation of the anesthetic-induced effects on overall excitation ($\Delta F_e = [F_{e1} - F_{e0}]/F_{e0}$) and overall inhibition ($\Delta\alpha = [\alpha 1 - \alpha 0]/\alpha 0$). All results are given as mean $\pm$ SD, and $P < 0.05$ was used to indicate significant differences unless stated otherwise.

Phrenic Nerve Data

Peak phrenic nerve activity (PPA), which is a neural index of the magnitude of the tidal volume,[11] was measured in arbitrary units as the peak height of the phrenic

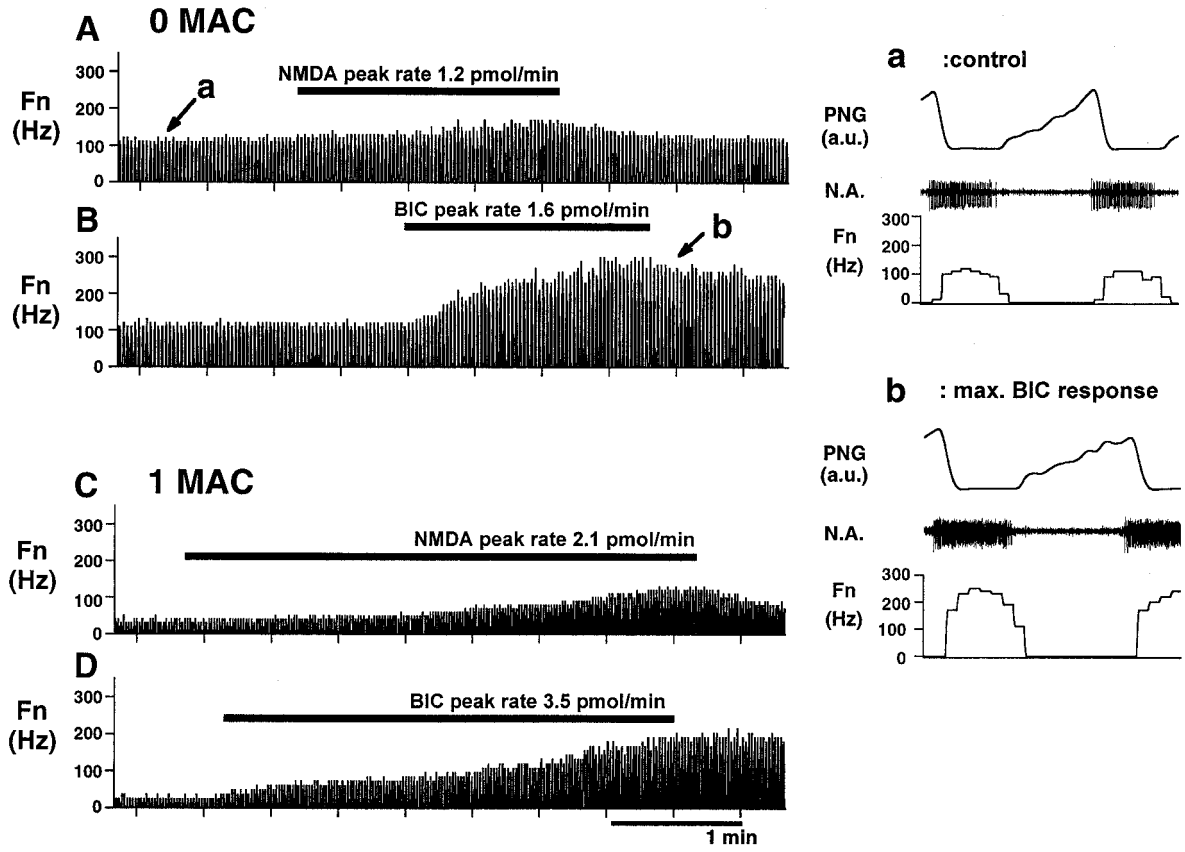

Fig. 1. Response of an expiratory neuron to picoejection of the glutamate receptor agonist *N*-methyl-D-aspartic acid (NMDA; traces *A* and *C*) and of the γ-aminobutyric acid type A receptor antagonist bicuculline (BIC; traces *B* and *D*) at 0 and 1 minimum alveolar concentration (MAC) sevoflurane. The picoejection response curves are shown as the rate-meter recordings of the neuronal discharge frequency F_n. The duration of the picoejection and the maximally ejected dose rate are marked. The traces *a* and *b* show time expanded views of two rate meter recordings (*a*, *bottom*, and *b*, *bottom*), together with the simultaneously recorded phrenic neurogram (PNG; in arbitrary units [a.u.]) and neuronal activity (N.A.). The detailed views are taken from the preejection control period (*a*) and at maximal increase of the neuronal discharge frequency (*b*). Also, note the increase in breathing frequency under 1 MAC sevoflurane (traces *A* and *B vs. C* and *D*).

neurogram in the anesthetic-free control state and during steady-state 1 MAC sevoflurane anesthesia. PPA data obtained from our previously published halothane study were similarly analyzed for comparison purposes. All PPA data were normalized to the values obtained during the anesthetic-free control state, which was assigned a value of 100%. These normalized data were used in the subsequent statistical analyses to compare the two agents.

Results

Twenty animals were studied, and 16 complete neuron protocols consisting of 0-, 1-, and 0-MAC end control levels were obtained.

Protocol, Part 1: Effects of Sevoflurane on Postsynaptic Glutamatergic Excitation

Figure 1 shows a representative example of an expiratory neuronal response to increasing picoejection dose rates of the glutamate receptor agonist NMDA before (trace A) and during (trace C) 1 MAC sevoflurane. A detailed analysis of these runs revealed that at 0 MAC a 40-Hz net increase was reached at a dose rate of 0.72 pmol/min. The net increase at the same dose rate at 1 MAC sevoflurane was 43.8 Hz even though F_{con} was profoundly depressed from 115 to 35 Hz (*i.e.,* by 70%).

The pooled normalized net increases in peak F_n, which were produced by NMDA, for 16 complete neuron protocols are summarized in figure 2. One MAC sevoflurane reduced the NMDA-induced net increase from 100 to 82.3 ± 53.7% at D_{40Hz}, but this was not statistically significant ($P = 0.17$). The 0-MAC end control value for D_{40Hz} (filled square in fig. 2) was 88.3 ± 53.6%, which was also not significantly different from the 0-MAC control (filled circle in fig. 2). The corresponding normalized ½ D_{40Hz} data were not statistically different. A slope analysis for the 0–½ D_{40Hz} and the ½ D_{40Hz}–D_{40Hz} values confirmed linearity of the NMDA responses over the full dose range.

Part 2: Effects of Sevoflurane on Overall Synaptic Neurotransmission

Figure 1 (traces B and D) shows the effects of bicuculline ejection on the same neuron as described earlier in

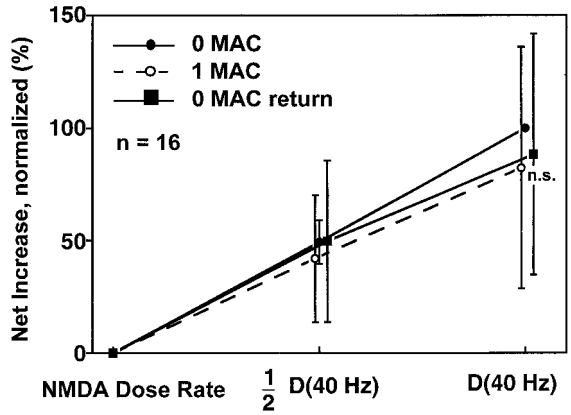

Fig. 2. Pooled summary data for protocol part 1, postsynaptic *N*-methyl-D-aspartatic acid (NMDA) response. Normalized mean values ± SD of net increase of peak F_n at the NMDA dose rates ½ D_{40Hz} and D_{40Hz} for 0-, 1-, and 0-minimum alveolar concentration (MAC) end control level (net increase = F_n at given NMDA dose rate − F_{con}). The values are normalized to the D_{40Hz} net increase at 0 MAC. At 1 MAC sevoflurane, the NMDA-induced net increase was nonsignificantly reduced from 100 to 82.3 ± 53.7% (n.s.; data staggered for clarity).

this study for the NMDA responses. At 0 MAC, bicuculline increased peak F_n from 115 to 247 Hz, yielding a $GABA_A$ergic inhibitory constant $\alpha_0 = 0.53$. This means that the prevailing endogenous $GABA_A$ergic inhibition attenuated neuronal output by 53% during the control state. At 1 MAC, bicuculline increased peak F_n from 35 to 162 Hz, yielding an α_1 value of 0.79. Thus, for this neuron, 1 MAC sevoflurane enhanced the GABAergic inhibition by 49%. The overall excitatory drive, which was measured in the absence of $GABA_A$ergic inhibition (*i.e.,* during maximal block with bicuculline) was decreased from 247 to 162 Hz or by 34%.

The pooled data for 16 complete neuron protocols are shown in figure 3. Analysis of the pooled data shows that 1 MAC sevoflurane increased the mean α value from 0.47 ± 0.07 to 0.56 ± 0.11 (*i.e.,* 1 MAC sevoflurane enhanced overall $GABA_A$ergic inhibition by 18.7 ± 20.6% ($\Delta\alpha$, fig. 3, *bottom*, center bar). At the same time, 1 MAC sevoflurane depressed overall excitation by 19.5 ± 16.2% ($P < 0.01$, ΔF_e, fig. 3, *bottom*, left). In addition, peak F_{con} was significantly reduced from 53.0 ± 6.4 to 36.6 ± 11.9% (fig. 3, *top*, F_{con}) (*i.e.,* by 26.7 ± 22.4% [ΔF_{con}, fig. 3, *bottom*, right).

Effects of Sevoflurane and Halothane on F_{con} and on Phrenic Activity

Phrenic data** were used when peak phrenic amplitude (PPA) for the 0-MAC end control period recovered to the preanesthesia control level. To maximize the number of data sets, we used phrenic data from several related studies with the same experimental setup (decerebration, mechanical ventilation, hyperoxic hypercapnia) and the same anesthetic sequence (0 MAC, 1 MAC, 0 MAC) but divergent picoejection protocols. We analyzed 20 protocols with sevoflurane, which were derived from 28 animals from the current study and an ongoing study. Twenty-four data sets with halothane were derived from 36 dogs, also from two studies (a study of halothane and expiratory neurons[7] and an ongoing study).

Both anesthetics significantly reduced PPA (fig. 4, *right*). Sevoflurane reduced PPA significantly more than halothane (60.1 ± 17.6% *vs.* 42.5 ± 18.4%, $P < 0.01$,

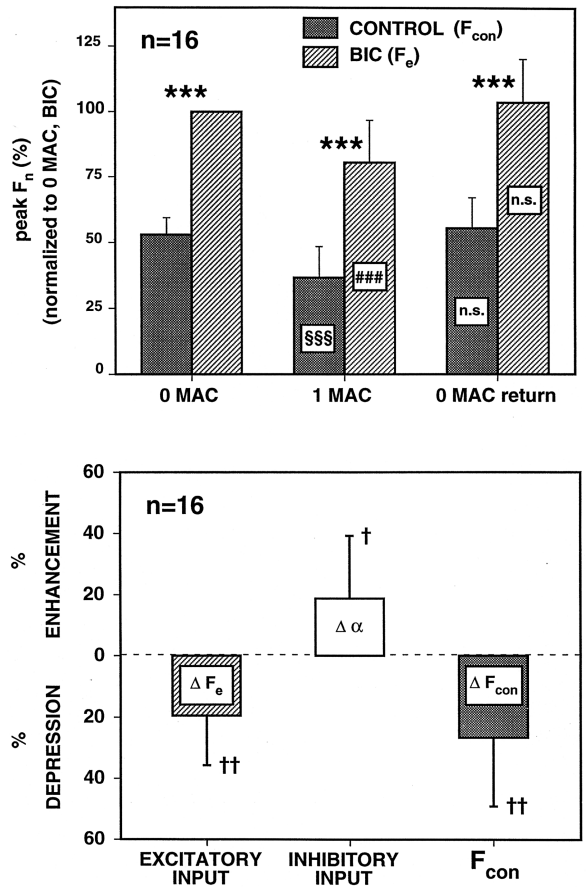

Fig. 3. Pooled summary data for protocol part 2, bicuculline (BIC) response. (*Top*) Mean values ± SD of normalized peak F_n (%) before (F_{con}) and during (F_e) maximal $GABA_A$ergic block with bicuculline for the 0-, 1- and 0-minimum alveolar concentration (MAC) end control level. At all MAC levels, F_e was significantly greater than F_{con} (*$P < 0.001$). 1 MAC sevoflurane caused a significant reduction of F_{con} (§§§$P < 0.001$) and F_e (###$P < 0.001$). The 0 MAC end control values for F_{con} and F_e were not significantly different (n.s.) from the initial 0 MAC values, indicating stability and reproducibility of the preparation. (*Bottom*) Mean values ± SD for depression of overall excitatory drive, ΔF_e, enhancement of inhibitory neurotransmission, $\Delta\alpha$, and the resulting depression of control frequency, ΔF_{con}, by 1 MAC sevoflurane in 16 neurons (†$P < 0.01$; ‡$P < 0.001$, relative to no change).**

** Phrenic data were obtained from several recent and ongoing studies as detailed.

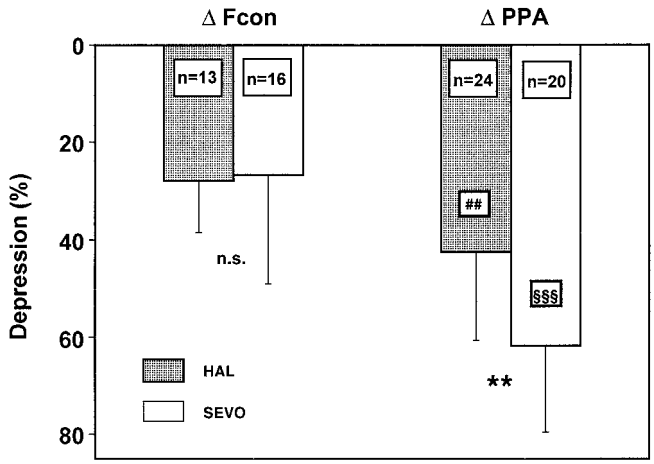

Fig. 4. Comparative effects of 1 minimum alveolar concentration (MAC) sevoflurane (SEVO; current study) and 1 MAC halothane[7] (HAL) on peak expiratory neuronal activity (ΔF_{con}, *left bars*) and peak phrenic nerve activity (ΔPPA (*right bars*). The depression of F_{con} by 1 MAC sevoflurane was not different (n.s.) from the depression by 1 MAC halothane. The depression of PPA by the anesthetic was significantly larger than the depression of F_{con}, both for 1 MAC halothane (*##P* < 0.01) and for 1 MAC sevoflurane (§§§*P* < 0.001). In addition, the depression of PPA was significantly larger with 1 MAC sevoflurane than with 1 MAC halothane (*P* < 0.01).**

unpaired two-sided *t* test). Both anesthetics depressed expiratory neuronal activity to a similar extent (ΔF_{con} [sevoflurane], 26.7 ± 22.4% *vs.* ΔF_{con} [halothane], 27.9 ± 10.6%[7] (fig. 4, *left*, nonsignificant). Both anesthetics depressed PPA significantly more than F_{con} (sevoflurane, $P < 0.001$; halothane, $P < 0.01$ [unpaired two-sided *t* test).

Discussion

The current study shows that sevoflurane reduced the activity of expiratory premotor neurons in the brainstem of decerebrate dogs. This reduction resulted from a depression of glutamatergic excitation without affecting the postsynaptic glutamate receptor excitability. Enhancement of $GABA_A$ergic inhibitory neurotransmission contributed approximately equally to the depressant effect of sevoflurane. The current study cannot address whether the $GABA_A$ergic effects are presynaptic or postsynaptic in nature.

The magnitude of the reduction of overall glutamatergic excitation by sevoflurane was not different than that found previously for halothane ($P = 0.08$, unpaired two-sided *t* test) [7]. Thus, it is likely that both anesthetics affect similar mechanisms that result in the inhibition of presynaptic glutamate release. These mechanisms may include a reduction in excitatory drive to the presynaptic neurons, as it has been described by Perouansky *et al.*[12] for the excitation of inhibitory interneurons, and inhibitory effects on one or more steps in the cascade that controls exocytosis of glutamate.[13]

Our *in vivo* study showed an enhancement of overall $GABA_A$ergic inhibition by 1 MAC sevoflurane, although we could not apportion the amount of presynaptic and postsynaptic contributions. Additional studies would be necessary to delineate the effects of sevoflurane and halothane on the postsynaptic $GABA_A$ receptor function in our respiratory neuron model.

An enhancement of the response to GABA and a small direct activation by sevoflurane have been described for the $GABA_A$ receptor.[1,14] In acutely dissociated rat hippocampal neurons during whole cell voltage clamp, Kira *et al.*[1] showed that sevoflurane alone could increase the Cl^- current (I_{Cl}). However, this effect is negligible at 1 MAC sevoflurane (*i.e.,* 0.35-mM concentration[15]) in aqueous solution and only becomes noticeable at bath concentrations of 3 MAC and greater. At 1 MAC, sevoflurane not only enhanced the GABA-induced I_{Cl},[14] but also accelerated the activation phase of I_{Cl}, suggesting an increase in the apparent affinity of the $GABA_A$ receptor to GABA.[1] Similarly, whole cell patch-clamp studies by Jenkins *et al.*[16] on mouse fibroblasts transfected with $GABA_A$ receptor subunits suggested a direct binding of sevoflurane to the receptor channel protein. In addition, the authors reported that there was no difference in the degree of $GABA_A$ergic potentiation between sevoflurane and halothane at 37°C. In accordance, we also found that there was no difference between the enhancement of overall inhibition by 1 MAC sevoflurane and 1 MAC halothane[7] in expiratory premotor neurons ($P = 0.18$, unpaired two-sided *t* test).

The phrenic neurogram represents the collective neuronal output of the phrenic motoneuron pool, and PPA is considered to be a good neural index for the magnitude of tidal volume.[11] Our data show that PPA is more depressed than expiratory premotor neurons (fig. 4). This suggests either a differential depression of inspiratory and expiratory premotor neurons by the anesthetics or additional depressant effects downstream at the phrenic motoneuronal level. However, we could show in an intact preparation that a 1-MAC halothane increase (from 1 to 2 MAC) depressed inspiratory and expiratory premotor neuronal activity to the same extent and significantly less than PPA.[17] Similarly, in the decerebrate preparation halothane depressed PPA more than expiratory premotor neuron activity. We assume that this differential depression is in part caused by an additional anesthetic-induced depression of synaptic transmission from the bulbospinal premotor neurons to the phrenic motoneurons, as well as direct depression of the phrenic motoneurons.

Recent *in vitro* studies have suggested the presence of voltage-independent, hyperpolarizing leak K^+ channels that are activated by inhalational anesthetics[18] and can be found in cerebral nuclei and with an especially high density in the membrane of motoneurons in the brainstem and spinal cord.[19] Talley *et al.*[19] found that in rat

hypoglossal motoneurons tandem-pore domain acid-sensitive K^+ (TASK)-1 channels contributed to a prominent pH-sensitive background K^+ current. Both halothane and sevoflurane increased the conductance of these K^+ channels, which produced dose-dependent hyperpolarizations that could be antagonized by decreasing the pH from 7.3 to 6.5.[20] It is possible that such anesthesia-induced K^+ channels contribute to the pronounced depression of phrenic motoneurons compared with the expiratory premotor neurons in our study.

Interestingly, Sirois et al.[18] found in hypoglossal motoneurons in a neonatal rat brainstem slice preparation that the outward K^+ current induced by 0.75% halothane (51.1 ± 6.5 pA) was 40% less than the current induced by 2.0% sevoflurane (71.3 ± 8.8 pA), which are considered equivalent anesthetic concentrations. These values suggest that sevoflurane may have a greater effect on TASK-1 channels than halothane. This could explain the finding that, in our preparation, at the 1-MAC level sevoflurane depressed phrenic motoneurons to a greater extent than halothane.

A similar, differential effect for the two anesthetics was reported by Doi *et al.,*[2] who recorded respiratory-related neuronal activity in the feline nucleus ambiguus and found a significantly greater depression of spontaneous neuronal activity with 1 MAC sevoflurane than with 1 MAC halothane. The nucleus ambiguus contains a high number of respiratory-related laryngeal and pharyngeal motoneurons,[21] and labeling reveals a high density of TASK-1 channels in this area.[19] We consider it likely that the neuron sample of Doi *et al.,*[2] contained mainly motoneurons and speculate that the greater depression of neuronal activity by sevoflurane was caused by a differential effect on TASK-1 channels.

TASK-1 transcripts are expressed at high levels in cranial and spinal motoneurons but not in all neurons. The role of these channels may be minimal in our premotor neurons, although direct data are lacking. Because activation of these channels was capable of producing up to a 50% increase in whole cell membrane conductance in hypoglossal motoneurons,[20] this effect would reduce neuronal excitability. However, the NMDA-induced excitation of our expiratory premotor neurons was not altered by sevoflurane (fig. 2) or halothane.[7] In addition, TASK-1 channels have been shown to be depressed by low pH, serotonin, and norepinephrine.[19] Ejection of serotonin, norepinephrine, and acidified artificial cerebrospinal fluid on expiratory premotor neurons in the thiopental-anesthetized intact dog does not alter neuronal frequency (unpublished data) as would be expected if TASK-1 channels were present and functional. Thus, it seems unlikely that in these canine expiratory premotor neurons an anesthetic-induced activation of inhibitory K^+ channels contributed to the changes in excitatory drive (*i.e.,* the depression of overall excitation).

Methodological Considerations

Many of the limitations of our methodology have been discussed in our previous publications[7,8] and elsewhere.[6,7] Decerebration allowed us to compare the effect of 1 MAC sevoflurane with an anesthesia-free control state. This may explain differences between our results and other studies. Mutoh *et al.*[22] studied the effect of sevoflurane on respiratory parameters in intact dogs under α-chloralose–urethane background anesthesia and also found that sevoflurane induced an increase in breathing frequency. In their model, however, this effect of sevoflurane could be abolished by vagotomy. In our decerebrate, vagotomized, and peripherally deafferented dogs sevoflurane still caused an increase in breathing frequency. Thus, we suggest that sevoflurane, like halothane, also has directly stimulating effects at the brainstem level, presumably in the rate-generating regions.[23]

In summary, sevoflurane depressed expiratory premotor neuron activity through a presynaptic reduction of glutamatergic excitation and an enhancement of $GABA_A$ergic inhibition. Sevoflurane depressed expiratory premotor neurons significantly less than phrenic motoneurons.

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