

Presynaptic and Postsynaptic Effects of the Anesthetics Sevoflurane and Nitrous Oxide in the Human Spinal Cord

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Background: Reduced spinal excitability contributes to the suppression of movement responses to noxious stimuli during the anesthetic state. This study examines and compares presynaptic and postsynaptic effects of two anesthetics in the human spinal cord.

Methods: The authors tested two parameters during the administration of 0.8 vol% sevoflurane or 40 vol% nitrous oxide compared with control states before and after drug administration: (1) the size of the soleus H reflex (integrating presynaptic and postsynaptic effects) at increasing stimulus intensities (recruitment curve) and (2) the amount of presynaptic inhibition on Ia afferents of the quadriceps femoris, evaluated by the heteronomous facilitation of the soleus H reflex caused by a conditioning stimulation of the femoral nerve. The study was performed in 10 subjects for each drug.

Results: At the chosen concentrations, the maximum H reflex was reduced by 26.3 ± 8.4% (mean ± SD) during sevoflurane and by 33.5 ± 15.6% during nitrous oxide administration. The averaged recruitment curves were similarly depressed under the influence of the two drugs. The reduction of H-reflex facilitation was significantly stronger for sevoflurane (28.8 ± 20.0%) than for nitrous oxide administration (6.2 ± 26.4%).

Conclusions: These results demonstrate in humans presynaptic effects of the volatile anesthetic sevoflurane but not of nitrous oxide. A possible explanation for this difference may be the different potency of the respective drugs in enhancing γ-aminobutyric acid type A (GABA_A) receptor–mediated inhibition, because presynaptic inhibition in the spinal cord involves this receptor subtype.

RESEARCH on spinal effects of anesthetics has become a focus of interest since the spinal cord was identified more than a decade ago as the primary target mediating the suppression of movement in response to noxious stimulation during the anesthetic state. In rats, neither decerebration1 nor hypothermic transection2 between the brain and the spinal cord altered the anesthetic requirements to suppress movement responses to noxious stimuli. It is commonly accepted that volatile anesthetics interact in the central nervous system with different ligand gated ion channels, at least glutamate, γ-aminobutyric acid type A (GABA_A), and glycine receptors.3 Although the primary molecular targets have been partly identified, the mechanisms by which anesthetics suppress movement responses are still not fully understood. Human in vivo studies have shown that the suppression of spinal motoneuron excitability, as assessed using the monosynaptic H reflex by volatile anesthetics and nitrous oxide, correlates well with the suppression of movement responses to noxious stimuli,4–6 which underlines the importance of anesthetic effects on the “final common pathway” for motor output in respect to the suppression of movement to noxious stimuli. In vitro studies on spinal cord slices have given evidence that anesthetics inhibit spinal motoneuron excitability by both presynaptic and postsynaptic actions.7–9 The relative contribution of presynaptic and postsynaptic effects, however, is not known.

The aim of the current study was to differentiate the amount of presynaptic and postsynaptic effects of anesthetics on spinal monosynaptic reflex excitability in humans. Therefore, we tested two parameters: (1) the size of the soleus H reflex (integrating both presynaptic and postsynaptic effects) and (2) the amount of ongoing presynaptic inhibition using the method first described by Hultborn et al.10. The soleus H reflex is facilitated by stimulating Ia afferents of the quadriceps femoris muscle in the femoral nerve, whose collaterals project monosynaptically onto soleus motoneurons. A simultaneous arrival of the excitatory postsynaptic potentials from soleus and quadriceps Ia fibers at soleus motoneurons leads to an increased H-reflex amplitude, because some motoneurons that would not be excited by the soleus Ia volley alone are excited by the additional excitatory postsynaptic potential from the conditioning stimulus. If the size of the test H reflex and the stimulus strength of the conditioning stimulus are kept constant, an increase of presynaptic inhibition is revealed by a decrease of H-reflex facilitation. Transmitters involved in these pathways are glutamate for the synaptic transmissions from the Ia afferents to the motoneurons and γ-aminobutyric acid (GABA) that mediates presynaptic inhibition on the Ia terminals. Whereas the nature of the postsynaptic receptors at the motoneuron remains uncertain—both N-methyl-D-aspartic acid (NMDA) and γ-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are...
possible candidates—the predominant role of GABA\textsubscript{A} receptors in presynaptic inhibition is undisputed.\textsuperscript{11}

To estimate the role of GABA\textsubscript{A} receptors in the mediation of presynaptic effects of anesthetics, we compared the presynaptic effects of the volatile anesthetic sevoflurane with those of nitrous oxide. Nitrous oxide is probably not exclusively, but mainly, mediating its effect \textit{via} glutamate receptors\textsuperscript{12,13} and can therefore serve as a control substance with little or no GABAergic effects. Both drugs were administered in concentrations that correspond to 0.4 minimum alveolar concentrations. We hypothesized that sevoflurane, like propofol,\textsuperscript{14} enhances presynaptic inhibition, whereas nitrous oxide shows no or little effect.

Materials and Methods

\textbf{Subjects}

After approval of the local ethics committee (Charité-Universitätsmedizin Berlin, Berlin, Germany), the study was performed in 24 (5 female) healthy volunteers, including 2 of the authors. Seven subjects received both drugs within a minimum time of 2 months between both measurements. All subjects gave their informed consent and were tested at least 1 day before the study to be suitable for this electrophysiologic procedure: Only volunteers whose H-reflex amplitude was facilitated by at least 15\% by the conditioning stimulus of the femoral nerve were included in the study.

During the entire study period, each subject was comfortably seated in a reclining arm chair, the hip semi-flexed at 120\°, the knees slightly flexed at 160\°, and the ankle at 110\°.

\textbf{General Experimental Arrangement}

We compared the H-reflex recruitment curve, especially the maximal H reflex and the amount of heteronymous H-reflex facilitation, during end-tidal concentrations of 45\% nitrous oxide and 0.8\% sevoflurane with the control values obtained before and at least 35 min after drug administration. In preliminary investigations, we have found that the inhalation of the chosen concentrations of both drugs results in a similar reduction of the unconditioned H reflex. Higher concentrations would cause such a reduction of the unconditioned H reflex that its size during drug administration could not be adjusted to its size during control conditions, which is essential for the method (see Heteronymous Ia Facilitation of the H Reflex). The chosen concentration also allows comparison with the previously published propofol study.\textsuperscript{14}

\textbf{Heteronymous Ia Facilitation of the H Reflex}

The underlying circuitry of the experiment and its rationale is explained in figure 1. The H reflex was elicited with a rectangular pulse of 1 ms duration (Digitimer DS7A; Digitimer Ltd., Welwyn Garden City, United Kingdom) by stimulation of the tibial nerve with the cathode (gold-plated half-ball electrode, 7.5 mm in diameter) in the popliteal fossa and the anode placed just above the patella. Reflex responses were recorded with paired adhesive Ag-AgCl electrodes (Medicotest A/S “blue point”; Istykke, Denmark) placed over the soleus muscle with an interelectrode distance of 2 cm. The electromyographic response was amplified 500-fold with a band pass filter ranging from 20 Hz to 2.5 kHz (Neuropack 4 mini; Nihon Kohden, Tokyo, Japan), digitalized with a sampling rate of 5 kHz (Mikro 1401 mk II; CED Ltd., Cambridge, England, United Kingdom), and stored on a mobile computer hard disk for further analysis. The peak-to-peak amplitude of the H reflex and M wave (direct muscle response due to motor fiber stimulation in the tibial nerve) was measured online using Signal 3.01 (CED Ltd.).

The sensitivity of the H reflex to inhibitory and facilitatory effects depends on its size.\textsuperscript{15} Hence, when measuring the effect of the conditioning stimuli, the size of the test reflex was kept at 15\% of the maximal motor response (M\textsubscript{max}) of the soleus muscle after electrical stimulation of the tibial nerve. M\textsubscript{max} was determined...
during each condition (before, during, and after drug administration) by increasing the stimulus current in steps of 10 mA (beginning at 40 mA) until further increase in stimulus current would not result in a further increase of the M-wave amplitude. The conditioning stimulus was applied to the ipsilateral femoral nerve. Therefore, the cathode (half-ball, 12.5 mm in diameter) was placed in the femoral triangle just lateral of the femoral artery, and the anode was placed on the back of the thigh. A rectangular pulse of 1 ms duration was delivered (Digitimer DS7A).

The stimulus intensity was adjusted to be approximately 15% above the threshold for the motor response in the quadriceps muscle. By choosing a stimulation current above the threshold, the stability of the conditioning stimulus could be monitored by measuring the amplitude of the direct quadriceps muscle response. Higher stimulation currents might have stimulated Ib fibers leading to contamination of the response. The stimulation current was kept constant throughout the experiment unless the quadriceps response changed abruptly because of leg movement. In this case, it was readapted to 15% of threshold of the motor response.

It is essential for the method that the investigated heteronymous facilitation be truly monosynaptic and not contaminated by any other effects such as Ib inhibition or oligosynaptic pathways. Only during the first 0.5 ms, facilitation from the femoral nerve onto the soleus motoneurons has been demonstrated to be purely monosynaptic.\(^\text{16}\) Therefore, we first established the earliest time interval between the soleus H-reflex stimulation (test volley) and the femoral nerve stimulation (conditioning volley) at steps of 0.1 ms (fig. 2).

To obtain a more sizeable facilitation within the time window of monosynaptic facilitation, the interval chosen for all measurements was 0.4 ms longer than the determined onset and remained unchanged throughout measurements. At that time interval, a series of approximately 100 unconditioned and of 100 conditioned H-reflexes, delivered every 6 s, was recorded for each experimental condition (before, during, and after drug administration). Conditioned and unconditioned reflexes were randomly alternated. Figure 3 shows the amplitudes of conditioned and unconditioned H-reflex responses in an exemplary subject. Corresponding raw tracings are presented in figure 4.

For statistical analysis, the size of every conditioned H-reflex response was normalized to the average unconditioned H-reflex response of the corresponding condition (before, during, and after drug administration) whose size was intentionally adjusted to be equal during each condition (figs. 3 and 4).

**Recruitment Curve**

Suppression of the H reflex may be dependent on stimulation intensity.\(^\text{17}\) Therefore, the recruitment curve was recorded under the conditions before, during, and after drug administration using the same recording and stimulation electrodes as for the test H reflex (see first sentence in Heteronymous Ia Facilitation of the H Reflex). The intensity of the stimulation pulses was increased stepwise from below the threshold of the H reflex up to M\(_{\text{max}}\). At least 10 of these sequences were performed.

To make the recruitment curves for all states comparable, the amplitude of both the H reflex and the M response were normalized to the maximum amplitude of the M response of the respective state. Stimulus intensity was normalized to the stimulus intensity at the threshold of the M response. After normalizing the recruitment curves for every subject, an average curve of all subjects was calculated for each state by assuming linear progressions between every two points of the measured recruitment curves.

The motor threshold was defined as the lowest stimulus producing an amplitude in the M-wave time window that differed from that of the static noise in all 10 measurements.

The H reflex as well as the excitation of motoneurons from supraspinal centers follows the general recruitment order from smaller to larger motoneurons.\(^\text{18}\): At small stimulus intensities, small motoneurons are excited, and larger motoneurons are contributing to the H reflex only at higher stimulus intensities. To better differentiate effects on smaller versus larger motoneurons, the relative suppression of the H reflex at different stimulus intensities was calculated by dividing the recruitment curve data of the steady state drug level by the average of the two control curves measured at the states before drug administration (figs. 3 and 4).

![Fig. 2. Exemplary time course of the heteronymous Ia facilitation of the soleus H reflex. By convention, the timing of the test pulse (soleus H reflex) is given with reference to the conditioning pulse (Ia afferents in the femoral nerve). * Significant increase in comparison with the unconditioned H reflex.](image-url)
Maximal H Reflex (H_max)

Because the maximal motor response M_max is evoked by the recruitment of all motor axons and provides an estimate of the response given by the whole motoneuron pool of the soleus muscle, the quotient H_max/M_max is an estimation of the maximal proportion of the soleus motoneurons that can be monosynaptically excited by Ia fibers in the spinal cord from the soleus muscle. Therefore, the ratio of the maximal H-reflex size divided by the maximal M-response size (H_max/M_max) was calculated at every state for every subject.

Statistical Methodology

Statistical calculations were performed using the SAS Version 9.1 (SAS Institute Inc., Cary, NC) data analysis and graphic package. Data were analyzed by a linear mixed effect model (PROC MIXED; SAS Institute Inc.). Basically, a mixed effect model handles two types of variability, i.e., variability between individuals and residual variability. Residual variability and variability between individuals both assumes a normal distribution. Implicitly, a random effect model takes correlation within individuals into account. Residual variability is dependent on several fixed effects, one of which is the drug effect. Model selection is based on Akaike information criterion; here the model with the lowest Akaike information criterion was chosen. The model is equivalent to linear regression fit with the administered drug and the time points of measurement (before, during, and after drug administration) used as independent variables.

The statistical model assumed the drug, time points, and the interaction of drug and the measuring point during administration as fixed effects. The intercepts are...
chosen as random effects, where subjects are the unit of analysis. This implies that simultaneously variability between subjects and correlation within subjects is taken into account.

Data of the sevoflurane group before drug administration were used as baseline. The difference between the drug effects of sevoflurane and nitrous oxide was modeled by an interaction term. Statistical significance of this interaction term indicates a significant difference in the drug effect within the random effect model. The assumption of normal distribution of the data were evaluated graphically. The mixed effect analysis was applied to both the Hmax/Mmax and the heteronymous facilitation data.

To test differences in relative suppression of the H-reflex recruitment curves at different stimulus intensities, we used a Friedman test for repeated measures.

Drug Administration and Monitoring

Subjects fasted at least 6 h before the beginning of the drug administration. Standard anesthesiologic monitoring (noninvasive blood pressure monitoring, electrocardiography, and pulse oximetry) and an intravenous access via a forearm vein were established before the study period.

End-tidal carbon dioxide was monitored with an anesthesia monitor (iMM Anesthesia Monitor, Datex Ohmeda S/5 FM; Helsinki, Finland).

Both anesthetics were administered using an anesthesia workstation (Primus or Zeus; both Dräger Medical, Lübeck, Germany) via a facemask, which was tightly fixed over the subject’s mouth and nose. The subjects breathed either 45 vol% nitrous oxide in 55% oxygen, or 0.8 vol% sevoflurane in a nitrogen–oxygen mixture with 60% oxygen. To accelerate the distribution of the drugs, higher concentrations were administered during the first 5 min.

End-tidal drug concentrations were measured continuously using the build-in infrared spectrophotometric analyzer of the anesthesia monitor (iMM Anesthesia Monitor, Datex Ohmeda S/5 FM). All measurements during drug administration were performed during steady state conditions, i.e., the end-tidal concentration was kept constant for at least 35 min before measurements commenced.

Results

Although 24 subjects were originally enrolled in the study, the complete study procedure could be accomplished in only 13 subjects (3 female, 10 male; age, 25.8 ± 3.9 yr; height, 180.4 ± 9.8 cm; weight, 69.2 ± 10.1 kg [mean ± SD]). These were finally included in the analysis. Seven of these 13 subjects received both drugs. In each group, 3 other subjects completed the study.

The 11 subjects who did not complete the study were not included for the following reasons: In the sevoflurane group, 4 subjects were not included in the study. Three of these subjects dropped out within the first 30 min of sevoflurane administration because of uncontrolled movement and consecutive displacement of stimulation electrodes. For 1 subject, the study was terminated because of vomiting. In the nitrous oxide group, 7 subjects were not included in the study. Five of these subjects dropped out because of nausea and vomiting accompanied by uncontrolled movement and electrode displacement, occurring within the first 30 min of nitrous oxide administration. In 2 other subjects, the inhalation of nitrous oxide had to be discontinued because these subjects experienced severe nightmares associated with uncontrolled movement.

Two individuals (0413FW and 0924FB) presented vomiting during registration of the H-reflex recruitment curve during sevoflurane administration. Administration of sevoflurane had to be discontinued, but the experiments were continued in these cases, although the recruitment curves are missing.

The effects of the only partially overlapping groups of subjects for both drugs were accounted for by the mixed model statistical analysis, which used “subject” as unit of analysis.

The end-tidal concentration of 0.8 vol% sevoflurane led to a deep sedation in all subjects (reactions to loud verbal commands were completely suppressed). Fifty percent nitrous oxide induced a state in which all subject could still respond to loud verbal commands but had intense dreams, seeing themselves being taken into “another world.” All subjects remembered these dreams and reported them afterward.

Heteronymous Ia Facilitation

The average reduction of facilitation amounted to 28.8 ± 20.2% (mean ± SD; facilitation is expressed as percentage increase of the average unconditioned H reflex during each time point) for sevoflurane and 6.2 ± 26.4% (mean ± SD) for nitrous oxide. Exemplary data from one subject who received sevoflurane is shown in figure 3. (The data of all individuals are available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org.) Based on the linear mixed model, the amount of heteronymous H-reflex facilitation is reversible and significantly reduced by sevoflurane and nitrous oxide (fig. 5). But the extent of reduction is far less during administration of nitrous oxide. This is reflected in the significant interaction term in table 1. Individual data are presented in table 2.
H_max/M_max reduction for sevoflurane (interaction term of −0.05, compared with a mixed model effect of sevoflurane of −0.17). For both drugs, the common estimate of reflex excitability H_max/M_max was reduced significantly during drug administration. Individual data are presented in table 3.

Recruitment Curve

The averaged recruitment curves are similarly depressed under the influence of the two drugs (fig. 6). The two control curves measured before and after administration of sevoflurane show a nearly identical course, whereas the control curves obtained before and after administration of nitrous oxide differ noticeably, which is probably due to movement that occurred frequently during nitrous oxide administration.

The averaged courses of the relative suppression of the H reflex at different stimulus intensities for sevoflurane and nitrous oxide (fig. 7) show that the relative suppression of the H reflex is dependent on the stimulus intensity for both drugs. This dependency is statistically significant (Friedman test for repeated measures, P < 0.001) for each drug.

Discussion

In this study, we examined the influence of the anesthetics sevoflurane and nitrous oxide on spinal reflex excitability, trying to separate presynaptic from postsynaptic effects. Our data demonstrate a reversible reduction of heteronymous Ia facilitation in the sevoflurane group, whereas no significant changes could be observed in nitrous oxide group.

Because the change of the facilitation reflects inhibitory presynaptic effects on Ia afferents from the quadriceps femoris, there is strong reason to assume that this drug equally affects soleus Ia afferent fibers. Therefore, we conclude that the suppression of spinal monosynaptic reflexes by sevoflurane is partly due to presynaptic effects, whereas the suppression mediated by nitrous oxide is predominantly due to postsynaptic effects.

Presynaptic effects of the volatile anesthetics enfurane9 and isoflurane20 have been demonstrated on glutamatergic synapses in spinal cord preparations. Kullmann et al.21 showed a presynaptic effect of the intravenous anesthetic thiopentone and the volatile anesthetic halothane on synaptic transmission at Ia afferents on motoneurons in cats in vivo. To our knowledge, the current study is the first study that attempts to quantify presynaptic effects of volatile anesthetics in humans.

Possible Presynaptic Molecular Targets

Today, it is generally accepted that GABA mediates presynaptic inhibition at axo-axonic synapses in the spinal cord.22,23 Pharmacologically, it has been documented that presynaptic inhibition is reduced by the GABA antagonists bicuculline and picrotoxin.24–26 Morphologic evidence of GABAergic axo-axonic synapses that mediate presynaptic inhibition has been provided at the synapse between the Ia afferent and the motoneuron in cats.27 On these afferents, the GABAA receptor, rather than the GABAB receptor (which is also present at the Ia terminals), plays the predominant role in presynaptic inhibition.28

Against this background, one possible explanation for the contrasting results of sevoflurane and nitrous oxide

Table 1. Effect of Sevoflurane and Nitrous Oxide on Heteronymous Facilitation Modeled by the Linear Mixed Effect Model

<table>
<thead>
<tr>
<th></th>
<th>Estimate of Effect</th>
<th>Error</th>
<th>df</th>
<th>t Value</th>
<th>Pr &gt;</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (before sevoflurane administration)</td>
<td>0.4013</td>
<td>0.03082</td>
<td>12</td>
<td>13.02</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Drug effect (sevoflurane and nitrous oxide group) compared with baseline</td>
<td>−0.1333</td>
<td>0.01426</td>
<td>5,631</td>
<td>−9.35</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Washout compared with baseline</td>
<td>−0.02550</td>
<td>0.01076</td>
<td>5,631</td>
<td>−2.37</td>
<td>0.0178</td>
<td></td>
</tr>
<tr>
<td>Nitrous oxide group compared with sevoflurane group</td>
<td>−0.06837</td>
<td>0.01192</td>
<td>5,631</td>
<td>−5.74</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Modification of (sevoflurane) drug effect due to nitrous oxide (interaction)</td>
<td>0.07104</td>
<td>0.01881</td>
<td>5,631</td>
<td>3.78</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>SD of random effects</td>
<td>0.13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The table presents the result of the linear mixed effect model for the various time points, the effect of the drugs, and their interaction. Effect is the heteronymous facilitation expressed as percentage increase of the average unconditioned H reflex during each time point. The difference in the drug effects of sevoflurane and nitrous oxide was tested using the interaction term. The results are also presented more descriptively in figure 5.

Pr = probability.
in changing heteronymous Ia facilitation primarily is their different affinity to the GABA_\alpha receptor. The GABA_\alpha receptor is a major molecular target of sevoflurane, whereas nitrous oxide shows little or no effect on this receptor. Sevoflurane might mimic the physiologic effect of GABA on the terminal of the Ia afferent and might therefore tonically reduce the transmitter release from that synapse. This view would be in line with other pharmacologic studies that also used the method applied in this study. We have shown recently\(^{14}\) that the intravenous anesthetic propofol whose main molecular target is the GABA_\alpha receptor also increases the presynaptic inhibition of Ia afferents. We compared the sevoflurane data presented here with the propofol data presented recently\(^{14}\) (five individuals participated in both studies). Comparison was performed on the basis of the same statistical method we used here (linear mixed effect model) to compare the effects of sevoflurane and nitrous oxide. Interestingly, the attenuation of the heteronymous facilitation in the propofol study was significantly higher than during sevoflurane administration in this study (the magnitudes of the modification of drug effect due to propofol (interaction term) corresponds to the magnitude of the sevoflurane effect compared to the baseline). H_{max}/M_{max} suppression did not differ significantly between the two drugs. The degree of presynaptic inhibitory effect on Ia afferents increases therefore in the order nitrous oxide < sevoflurane < propofol. Because the overall suppression of the H reflex was similar for all drugs, an opposite order has to be assumed for postsynaptic suppressive effects on the H reflex. A combination of both presynaptic and postsynaptic effects on the terminals of the Ia afferent and the motoneuron seem likely, especially for sevoflurane.

### Possible Postsynaptic Molecular Targets

In the current study, nitrous oxide suppressed the H-reflex recruitment curve without any significant pre-

### Table 2. Average Amount of Facilitation of All Subjects

<table>
<thead>
<tr>
<th>Individual</th>
<th>Before</th>
<th>N_2O</th>
<th>After</th>
<th>Reduction, %</th>
<th>Individual</th>
<th>Before</th>
<th>Sevoflurane</th>
<th>After</th>
<th>Reduction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1221VK</td>
<td>27.1</td>
<td>35.1</td>
<td>20.2</td>
<td>-48.4</td>
<td>1030VK</td>
<td>18.1</td>
<td>13.3</td>
<td>31.1</td>
<td>45.9</td>
</tr>
<tr>
<td>1228FB</td>
<td>13.6</td>
<td>11.6</td>
<td>8.6</td>
<td>-4.5</td>
<td>0924FB</td>
<td>34.0</td>
<td>17.8</td>
<td>29.9</td>
<td>44.3</td>
</tr>
<tr>
<td>1229VB</td>
<td>29.4</td>
<td>30.9</td>
<td>28.0</td>
<td>-7.7</td>
<td>0616VB</td>
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<td>22.3</td>
<td>31.6</td>
<td>33.8</td>
</tr>
<tr>
<td>1230CL</td>
<td>74.7</td>
<td>34.8</td>
<td>53.4</td>
<td>45.7</td>
<td>0514CL</td>
<td>41.1</td>
<td>17.7</td>
<td>40.7</td>
<td>56.7</td>
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<tr>
<td>0205VP</td>
<td>16.1</td>
<td>12.6</td>
<td>17.5</td>
<td>25.0</td>
<td>0928VP</td>
<td>17.7</td>
<td>16.8</td>
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<tr>
<td>0307VH</td>
<td>17.2</td>
<td>20.0</td>
<td>25.0</td>
<td>5.2</td>
<td>0619VH</td>
<td>42.1</td>
<td>37.3</td>
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<tr>
<td>0103JB</td>
<td>40.2</td>
<td>31.4</td>
<td>46.7</td>
<td>27.6</td>
<td>0608JB</td>
<td>81.1</td>
<td>41.3</td>
<td>64.7</td>
<td>43.3</td>
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<tr>
<td>0405TP</td>
<td>31.6</td>
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<td>16.8</td>
<td>8.7</td>
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<td>45.4</td>
<td>39.5</td>
<td>74.7</td>
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<tr>
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<td>34.3</td>
<td>22.8</td>
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<td>29.3</td>
<td>26.7</td>
<td>26.8</td>
<td>4.8</td>
</tr>
</tbody>
</table>

The table shows the individual amounts of facilitation in every tested condition and the reduction under influence of the drug compared with the two control states. Individuals VK, FB, VB, CL, JB, FW, and VH have been examined in both groups. N_2O – nitrous oxide.

### Table 3. Average H_{max}/M_{max} Values of All Individuals

<table>
<thead>
<tr>
<th>Individual</th>
<th>H_{max}/M_{max}, %</th>
<th>Individual</th>
<th>H_{max}/M_{max}, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>N_2O</td>
<td>After</td>
<td>Reduction, %</td>
</tr>
<tr>
<td>1221VK</td>
<td>35.3</td>
<td>31.4</td>
<td>44.2</td>
</tr>
<tr>
<td>1228FB</td>
<td>94.5</td>
<td>36.2</td>
<td>63.9</td>
</tr>
<tr>
<td>1229VB</td>
<td>74.9</td>
<td>54.0</td>
<td>78.5</td>
</tr>
<tr>
<td>1230CL</td>
<td>52.1</td>
<td>22.0</td>
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<td>0103JB</td>
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<td>86.2</td>
<td>66.7</td>
<td>91.5</td>
</tr>
</tbody>
</table>

The table shows the individual amounts of the maximal H reflex (H_{max}/M_{max}) in every tested state and the reduction under influence of the drug compared with the two control states. Individuals VK, FB, VB, CL, JB, and VH have been examined in both groups. H_{max}/M_{max} – nitrous oxide.
synaptic effects on Ia afferents, indicating a predominant postsynaptic site of action. Although the transmitter between the Ia afferent and the motoneuron is generally undisputed to be glutamate, the nature of the receptor mediating the glutamate effect on the motoneuron—NMDA or non-NMDA receptors—remains a matter of debate.

The most parsimonious explanation for the H-reflex suppression during nitrous oxide administration is its antagonistic action on one of those receptors. Antagonistic effects of nitrous oxide on NMDA receptors and to a lesser extent on non-NMDA receptors are well documented. The blockage of glutamatergic receptors either can attenuate the excitatory input from the activated Ia afferent on the postsynaptic side or it can decrease the excitability of the motoneuron by reducing tonic facilitatory input of different origins. Both effects would result in the observed H-reflex suppression.

Beside direct effects of nitrous oxide on motoneurons, also indirect effects via modulation of descending noradrenergic pathways deriving from the brainstem might contribute to the reduction of reflex excitability.

F-wave studies indicate that sevoflurane suppresses spinal reflex excitability also by postsynaptic effects on the motoneuron itself. Both antagonistic action on excitatory (NMDA and non-NMDA receptors) neurotransmission and agonistic action on inhibitory neurotransmission and via GABA<sub>A</sub> receptors and glycine receptors that are also expressed in motoneurons could contribute to a general reduction of motoneuron excitability.

Limitations of the Study
Although the transmitter of the examined pathway is well known, the interpretation of drug effects on even this simple pathway cannot lead to definite conclusions about specific drug effects. With the employed study design, it cannot be excluded that the effects on presynaptic inhibition and the reflex excitability are secondary to supraspinal effects of one or the other drug studied. Numerous studies give evidence for supraspinal control of the H reflex which has been partly explained by changes in presynaptic inhibition. Information about how supraspinal influences tonically modulate the H reflex or presynaptic inhibition in different states of awareness is rather scarce but would be of relevance for the current study. However, there are reports that the H reflex is depressed during rapid eye movement sleep and that it increases when the level of attention is supposed to be high. Evidence for tonic supraspinal effects on I afferents from muscle fibers is given from animal studies. These show that reversible spinalization in anesthetized cats rather decreases primary af-
ferent depolarization produced by muscle afferents. This has been interpreted as a suppression of a tonic descending facilitation acting on pathways mediating primary afferent depolarization on Ia afferents. Therefore, it can be concluded that tonic supraspinal effects of anesthetics would rather enhance than inhibit tonic presynaptic inhibition on Ia afferents.

Brainstem structures responsible for modulation of presynaptic inhibition receive descending inhibition from higher centers. However, Kullmann et al. did not find differences between intact and de cerebrated animals in the maximal decrease of excitatory postsynaptic potentials in motoneurons after Ia afferent stimulation. These findings demonstrate that the integrity of cerebrobulbar pathways is not crucial for the manifestation of presynaptic effects on Ia afferents.

The change of the H-reflex recruitment curve during drug administration provides further arguments that the H-reflex suppression itself is primarily of spinal origin. The H reflex as well as the excitation of motoneurons from supraspinal centers follow the general recruitment order from smaller to larger motoneurons. Von Dincklage et al. demonstrated a preferential suppression of early recruited motoneurons during sevoflurane and propofol administration, and we confirmed these results here for nitrous oxide (fig. 6). Assuming supraspinal suppressive effects on the H reflex, one would expect a preferential suppression of those motoneurons that are last recruited, because influences on motoneurons from supraspinal centers of the brain follow the recruitment size principle in the same way as other physiologic inputs. Therefore, excitability depression by supraspinal effects would affect those larger motoneurons first, which are last in the order of being excited, and so the most susceptible to depression.

The results of the current study cannot be extrapolated to higher concentrations of the anesthetics, and the mechanisms involved may not explain the suppression of movement responses to painful stimuli (surgical immobility). However, the H reflex itself is correlated with mobility). However, the H reflex itself is correlated with the observed effect presents one possible mechanism by which the H reflex can be suppressed by sevoflurane and nitrous oxide.

The current study demonstrates that the suppression of human spinal monosynaptic reflexes by sevoflurane is partly mediated by presynaptic effects. It may be hypothesized that this effect is mediated by GABAA receptors, because nitrous oxide, which has little influence on GABAA receptors, also shows no presynaptic effect. However, clinical studies like this cannot prove such a hypothesis.

References
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