Title: **Propofol and Sevoflurane in Subanesthetic Concentrations Act Preferentially on the Spinal Cord: Evidence from Multimodal Electrophysiological Assessment**

Authors: *Thomas Kammer, M.D. Researcher* (corresponding author)
Department of Neurobiology, Max-Planck-Institute for Biological Cybernetics, Spemannstr. 38, D-72076 Tuebingen, Germany
Tel.: +44 7071 601593
Fax: +44 7071 601577
email: thomas.kammer@tuebingen.mpg.de

Benno Rehberg, M.D, Privatdozent.
Department of Anesthesiology, Charité Campus Mitte, Berlin, Germany, and Department of Anesthesiology, University of Bonn, Bonn, Germany

Dieter Menne, Ph.D. Director, Biomed Software
Biomed Software, Tuebingen, Germany

Hans-Christian Wartenberg, M.D., Staff Anesthesiologist
Ingobert Wenningmann, M.D., Staff Anesthesiologist
Bernd W. Urban, Ph.D., Professor,
Department of Anesthesiology, University of Bonn, Bonn, Germany

From: Department of Neurobiology, Max-Planck-Institute for Biological Cybernetics, Tuebingen, Germany

Support: Support was provided from the Max-Planck-Society, Munich, from Abbott GmbH, Wiesbaden, from the Dept. of Anesthesiology of the University of Bonn, and from the Deutsche Forschungsgemeinschaft, Bonn (Re 1534/2), all in Germany.

Presented in part at the "Molecular Mechanisms in Anesthesia"-meeting in Bonn, Germany, June 28-30, 2001.

Acknowledgements: The authors are grateful to Jean-Louis Griffoul, Drs. Martin Scholz and Goetz Wietasch for supplying the target-controlled infusion system, and to Hans-Guenther Nusseck for technical support. We also wish to thank Prof. Andreas Hoeft and Prof. Joachim Nadstawek for help with the organization of the study.

Abbreviated title: Preferential spinal effect of anesthetics

Brief summary: In human volunteers, subanesthetic concentations of propofol and sevoflurane profoundly affected spinal motor responses and muscle potentials evoked by transcranial magnetic stimulation. Cortical parameters of electroencephalography and auditory evoked responses were only slightly affected.

Abstract

Background:

Animal experiments in recent years have shown that attenuation of motor responses by general anesthetics is mediated at least partly by spinal mechanisms. Less is known about the relative potency of anesthetic drugs in suppressing cortical and spinal electrophysiological responses *in vivo* in humans, particularly those but not only those connected with motor responses. Therefore, we studied the effects of sevoflurane and propofol in humans using multimodal electrophysiological assessment.

Methods:

We studied 9 healthy volunteers in two sessions during steady-state sedation with either 0.5, 1.0, and 1.5 μg/l (targeted plasma concentration) propofol or 0.2 and 0.4 vol% (end-tidal) sevoflurane. Following a 15 min equilibration period, motor responses to transcranial magnetic stimulation (TMS) and peripheral (H-reflex, F-wave) stimulation were recorded, while electroencephalography and auditory evoked responses were recorded in parallel.

Results:

At concentrations corresponding to 2/3 of C_{50}awake motor responses to TMS were reduced by about 50%, H-reflex amplitude by 22%, F-wave amplitude by 40%, and F-wave persistence by 25%. No significant differences between sevoflurane and propofol were found. At this concentration the bispectral index was reduced by 7% and the middle-latency auditory evoked responses were attenuated only mildly (N_b latency increased by 11%, amplitude P_aN_b did not change). In contrast, the postauricular reflex was suppressed by 77%.

Conclusions:

The large effect of both anesthetics on all spinal motor responses, compared to the small effect on electroencephalography and middle-latency auditory evoked responses – assuming that they represent cortical modulation, may suggest that the suppression of motor responses to TMS is largely due to submesencephalic effects.

Introduction

Attenuation of motor responses induced by anesthetics is an essential component of the anesthetic state. The traditional definition of the potency of anesthetic drugs, the minimal alveolar concentration (MAC), is based on an effect on the motor system [1].

In recent years several animal experiments have demonstrated that important mechanisms by which anesthetics suppress motor reactions to painful stimuli, as measured in the MAC concept, are independent of forebrain structures and are putatively spinal in nature [2-4]. In contrast, devices available for clinical monitoring of anesthetic drug effects are based on cortical signals, i.e. most frequently electroencephalography or auditory evoked potentials [5]. It is not clear whether effects on electrophysiological responses at the cortical or at the spinal level have the same underlying mechanisms. Although clinical studies cannot directly address mechanisms, knowledge of *in vivo* concentration-response functions are important for comparisons with *in vitro* studies. Therefore, the aim of the present study was to compare the concentration dependence of anesthetic effects on spontaneous and on evoked electrophysiological responses at cortical as well as on spinal levels in humans.

Transcranial magnetic stimulation (TMS) offers an elegant approach for testing the excitability of the motor system in an integrative manner from the cortex level down to the muscle [6]. General anesthetics profoundly suppress the compound muscle action potential (CMAP) evoked by TMS of the motor cortex, (for review, see [7]). Only ketamine does not seem to suppress the muscle responses to TMS [8,9]. Several non-anesthetic drugs acting on the nervous system, e.g. antiepileptics, have been shown to alter excitability of the motor system exclusively at a cortical level [10]. It remains to be determined whether suppression, the main anesthetic effect on CMAPs, stems from modulation of cortical excitability, alteration of spinal transmission, or changes in the periphery.

Several authors have described profound effects at anesthetic concentrations on electrophysiological parameters characterizing the spinal level: the F-wave and the H-reflex [11-13]. A direct comparison of concentration-response functions of anesthetic effects in cortical and spinal systems is still lacking. The large effects seen at anesthetic concentrations suggest that profound changes occur at subanesthetic concentrations.

In this study we investigated low (subanesthetic) concentrations of two widely used general anesthetics, sevoflurane and propofol. The concentrations used (0.2 and 0.4 vol% sevoflurane, and 0.5, 1.0 and 1.5 μg/ml propofol) were chosen to cover a range extending to

two thirds of the C_{50}awake of both drugs (see methods). We used multimodal electrophysiological assessment including motor responses to TMS, H-reflex and F-waves. In addition, we recorded the electroencephalogram as a signal generated by forebrain structures, and auditory evoked potentials, which are composed of both cortical and subcortical components [14].

Materials and methods

Subjects

After institutional review board approval and written informed consent were obtained, 9 healthy volunteers (2 female, 7 male) were included in the study. They were paid for participation. Exclusion criteria included pregnancy, a history of alcohol and drug abuse and any CNS-active medication. Demographic data of the volunteers were a mean age of 29 years (range 24-38), a mean weight of 73 kg (range 59-93), and a mean height of 176 cm (range 160-187).

Anesthetic procedure

Subjects were seated in a quiet room. A cannula was inserted in a peripheral vein and noninvasive blood pressure, electrocardiography, and finger peripheral hemoglobin oxygen saturation were monitored continuously.

The volunteers were scheduled for the propofol and/or sevoflurane sessions in random order. Seven volunteers participated in both the propofol and sevofluran sessions with an interval of at least 24 hours between both sessions.

Sevoflurane was applied via a tight-fitting face mask. After application of the mask, end-tidal CO_2 was monitored continuously. Inspiratory sevoflurane concentration was adjusted to achieve constant end-tidal sevoflurane concentrations of 0.2 and 0.4 vol%. End-tidal anesthetic concentrations were measured using the infrared spectrophotometric analyzer of an anesthesia workstation (Julian, Dräger, Lübeck, Germany). Measurements were started after the end-tidal sevoflurane concentration had been constant for at least 15 minutes to allow for effect-site equilibration.

Propofol was infused intravenously via a computer-controlled infusion pump, programmed using the pharmacokinetic parameter set published by Gepts et al. [15] and adjusted to subject weight. Plasma concentrations were kept constant at 0.5, 1.0 and 1.5 µg/ml. Measurements were started after the calculated propofol plasma concentration had been constant for at least 15 minutes to allow for effect-site equilibration.

Electrophysiological monitoring

Electroencephalography and middle-latency auditory evoked potentials (MLAEPs)

For auditory evoked potential monitoring, the (bipolar) electroencephalogram was recorded between the left mastoid and a frontopolar electrode with the right mastoid as reference, using silver/silver chloride gel-filled electrodes (blue sensor, Medicotest S/A, Istykke, Denmark) and a Northwick Park evoked potential monitoring system (Northwick Park Hospital, Middlesex, Great Britain). Electrode impedance was kept below 5 kΩ. Analog filters were set at 0.5 and 400 Hz. The auditory stimulus was a binaural click at 70 dB above the average hearing threshold, delivered via close-fitting earpieces at a repetition rate of 6.5 Hz with a 5% rate variation.

Auditory evoked reponses were averaged in blocks of 256 sweeps. The amplitude of the postauricular response was measured by first averaging all sweeps recorded at a particular concentration of the anesthetic and by then determining the peak-to-peak amplitude P_0-N_a of the averaged response. To avoid distortion of the MLAEPs by the postauricular response only averages without postauricular responses were included in the analysis of amplitudes (P_a-N_b) and latencies (N_b) of the MLAEP. For this purpose, a positive postauricular response was defined as a peak-to-peak amplitude P_0-N_a larger than the amplitude N_a-P_a [16]. The fraction of discarded blocks had a wide interindividual variation of 0-90%. Latencies of earlier peaks were not evaluated because of limited time resolution of the recording system.

Continuous electroencephalography was recorded in a bifrontal montage using an Aspect A-1000 (Aspect Medical Systems, Natick, Mass.) electroencephalography monitor. The filter settings were 0.5 and 30 Hz. The spectral edge frequency at 95% of the power spectrum (SEF_{95}) and the bispectral index (BIS, version 3.22, Aspect Medical Systems, Natick, Mass.) as calculated by the monitor (averaged from both frontal leads) were recorded every five seconds on hard disk.

In addition to electrophysiological measurements the level of sedation was subjectively quantified using a modified Observer's Assessment of Alertness/Sedation Scale (OAA/S) [17]. The scores on this scale were defined as: 5 - responds readily to name spoken in normal tone, 4 - lethargic response to name spoken in normal tone, 3 - responds only after name is called loudly or repeatedly, 2 - responds only after mild prodding, 1 - responds only after painful trapezius squeeze, and 0 - no response to painful trapezius squeeze. Values were documented

periodically during a steady-state concentration period and mean values with one significant digit were calculated.

Motor system

Recordings of the compound muscle action potential (CMAP) were made with surface electrodes taped over the belly and tendon of the right abductor digiti minimi muscle (ADM) and the right soleus muscle. Signals were filtered (20-2000 Hz) and amplified with a stand-alone amplifier (Toennies DC/AC, Erich Jaeger, Würzburg, Germany). With a sampling rate of 5000 Hz (A/D device DAP 4200a, Microstar Laboratories, Bellevue, WA, USA) they were visualized and stored on a PC using DASYLab software (Datalog, Mönchengladbach, Germany). Additionally, a loudspeaker was used to monitor the signal acoustically. TMS was applied by one or two Magstim 200 modules (Whitland, Dyfed, UK) connected to a figure-of-eight coil (mean diameter of the two windings 70 mm each) via the Bi-stim module. The coil was placed tangentially on the left central region with the handle pointing backwards, and a position was carefully determined that evoked a maximal response of the CMAP in the relaxed ADM. For this purpose the handle was rotated about 45° to the left [18], perpendicular to the line of the central sulcus. This position, optimal for activating the corticospinal system trans-synaptically [19], was marked on the scalp with a pen to ensure an identical coil placement throughout the experiment.

The following parameters were determined:

a) TMS threshold in the relaxed ADM: the minimal stimulation power (in steps of 1%) to evoke at least 5 CMAPs ≥ 50μV out of 10 trials.
b) CMAP amplitude (peak-to-peak) in the relaxed ADM: mean of 10 responses at a stimulator output intensity of 1.3 times resting motor threshold.
c) TMS threshold in the active ADM: the minimal stimulation power to evoke a reproducible CMAP different from the background activity of a moderate innervation.
d) CMAP amplitude (peak-to-peak) in the active muscle: mean of 10 responses at stimulator output intensities of 1.1 to 1.6 times active motor threshold each (input-output function).
e) Amplitude and latency of the CMAP in response to supramaximal peripheral electrical stimulation of the ulnar nerve at the wrist (M-response).

f) Amplitude, latency, and persistence of the electrical responses recorded in the ADM following retrograde excitation of the spinal alpha-motoneurons through a supramaximal electrical stimulus at the wrist (F-waves).
g) Amplitude and latency of the electrical reflex responses recorded from the relaxed soleus muscle following stimulation of sensory fibers in the tibial nerve (H-reflex). Stimulus strength was adjusted individually to result in the maximal H response.

Aditionally, double TMS pulses were applied using the Bi-stim module. Results of these experiments are not reported here.

Data processing

To be able to compare effects of sevoflurane and propofol, the concentrations of the two drugs used were normalized to C_{50}awake, i.e. MACawake of sevoflurane (0.7 vol%, age-corrected for 29 years, [20]) and to CP_{50}awake of propofol (2.69 µg/ml for 21-30 years, [21]).

Statistical calculations were performed using the data analysis and graphics package R [22]. Data were analyzed by mixed-model ANOVA [23]. The model is equivalent to linear regression fits with the normalized concentrations of both drugs as independent parameters. A linear regression model but not a sigmoidal model was chosen since only 3 or 4 concentrations were tested, respectively. Quadratic terms have been tested in preliminary analysis, but did not improve the quality of the fit as measured with the Akaike Information Criterion [24]. The statistical model assumed $C_{50}awake$ and its interaction with *drug* to be fixed parameters; *subject* and *drug within subject* were used as random parameters. For each effect investigated a common slope over all subjects was estimated for each drug, with separate intercepts for each subject. The slopes of the regression lines corresponded to the effective specific potency of the drugs. The intercepts gave baseline estimates of the physiological parameters at a drug concentration of zero. The first parameter we evaluated in order to quantify drug responses was the slope of sevoflurane together with its confidence interval (CI_{95}) and *p*-value. If the value of zero was not contained in the confidence interval, we could infer that the physiological parameter showed a concentration-response relationship with sevoflurane. A large distance between the limit of the confidence interval and the value of zero corresponded to a low probability of error (*p*-value). The second parameter to be evaluated was the difference between the slopes of the regression lines for propofol and

sevoflurane. A significant difference between these slopes indicated that the concentration-response effect of propofol was different from that of sevoflurane.

Results

During application of the higher respective concentration of either propofol (target 1.5 µg/ml) or sevoflurane (0.4 vol%) most subjects were noticeably sedated, as reflected in average OAA/S-scores of 3.3 ±1.0 for both drugs (raw data in fig. 1). The lower concentrations resulted in OAA/S-scores of 4.0 ±0.6 at 0.2 vol% sevoflurane, 4.2 ±0.4 at 0.5 µg/ml propofol and 4.0 ±1.0 at 1.0 µg/ml propofol. Decrease in OAA/S-score correlated significantly with anesthetic drug concentration, no differences between both drugs were found (table 1). By definition of OAA/S as a scoring parameter describing vigilance one expects a slope of 2.5. The good agreement with the estimated slope of 3.01 (sevoflurane, table 1) shows that our population is close to the population mean used in the definition of C_{50}awake.

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insert fig. 1 and table 1 about here

Auditory Evoked Responses

Both propofol and sevoflurane induced a small but significant increase in the latency of the peak N_b (grand average in fig. 2, table 1). The amplitude of the principal peak of the middle latency auditory response P_a-N_b was not reduced at any concentration of propofol or sevoflurane used in this study (table 1, fig. 2). However, the amplitude of the postauricular response (peak P_0-N_a) was reduced markedly, at concentrations as low as at 0.5 µg/ml propofol and 0.2 vol% sevoflurane (fig. 2 and 3, table 1).

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insert fig. 2 and fig. 3 about here

Electroencephalogram

Increasing concentrations of propofol and sevoflurane elicited a significant decrease in the bispectral index (table 1). Changes in the spectral edge frequency SEF_{95} were not significant (table 1).

Motor Responses to Transcranial Magnetic Stimulation

Responsiveness of the motor system was tested by TMS. Motor threshold was determined at rest (resting threshold) and with slight preinnervation (active threshold), of the target muscle, i.e. a voluntary continuous contraction. Under control conditions preinnervation lowered the threshold (resting threshold: 49.0 ± 6.5%; active threshold 39.6 ± 6.8% of maximal stimulator output). Both sevoflurane and propofol increased resting threshold (fig. 4a, relative changes are shown). Active threshold increased significantly only with sevoflurane, but not with propofol (fig. 4b).

Motor responses to TMS were tested both in the relaxed muscle and in the active muscle. In the relaxed muscle, a stimulator intensity of 1.3 times resting threshold was chosen. Amplitudes were prominently decreased with increasing concentrations of sevoflurane and propofol (fig. 4a). In the active muscle six fixed stimulator intensity fractions (1.1, 1.2, 1.3, 1.4, 1.5, 1.6) of the active motor threshold were tested in order to measure the input-output function of the motor system. In fig. 5, an example of this input-output test is depicted. Under control conditions, the amplitudes increase with increasing TMS intensity and saturate at higher intensities. Amplitude changes at a stimulus level of 1.4 were chosen for statistical treatment (table 2) as amplitudes at this level showed the highest statistical correlation with C_{50}awake. Both sevoflurane and propofol decreased motor-response amplitudes (fig. 4b, table 2). In addition, the slope of the input-output function estimated with the center at 1.4 was significantly decreased (table 2).

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insert fig. 4, fig. 5 and table 2 about here

Motor responses to peripheral stimulation

Amplitudes and persistence of the F-waves were prominently reduced, while F-wave latency was not affected (example in fig. 6, mean values in fig. 7). A significant reduction was found for H-reflex amplitude (fig. 7). The latency of the H-reflex increased as well. All effects increased with increasing anesthetic concentration (table 2).

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insert fig. 6 and fig. 7about here

Neither latency nor amplitude of M-wave of ADM (stimulation at wrist) were affected by the drugs at any concentration (data not shown). No difference was found in the effects of sevoflurane compared to propofol for all motor responses to peripheral stimulation.

Discussion

The aim of this study was a comparison of anesthetic effects on cortical and subcortical/spinal signal processing in the human CNS. As measures for cortical processing we recorded spontaneous (BIS, SEF_{95}) and evoked (MLAEP) electroencephalogram signals. For the evaluation of spinal signal processing we selected the H-reflex and F-wave. In addition, we measured motor evoked potentials in response to TMS as an integrated response of the central and peripheral motor system.

It is well-known that these motor evoked potentials are suppressed at clinical concentrations of both propofol [25,26] and sevoflurane [19]. Therefore, we used sub-anesthetic concentrations. Sevoflurane and propofol were chosen as two widely used general anesthetics, representing both volatile and intravenous anesthetics. The concentrations of both drugs were selected to be equivalent with respect to a cortical behavioral response, i. e. being equal fractions of C_{50}awake.

The main finding of the study was a marked reduction in amplitudes of the motor-system responses elicited by TMS at the subanesthetic concentrations of sevoflurane and propofol used (up to 0.6 * C_{50}awake), still larger than the pronounced reduction of the spinal responses (F-wave and H-reflex) and much larger than the small changes in the cortical parameters measured by electroencephalogram and MLAEPs (Fig. 8 for summary of the effects).

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insert fig. 8 about here

General limitation of the study

We restricted this study to subanesthetic concentrations, at which motor responses are only partially suppressed and all effects could be quantitated and compared. In addition, it enabled us to record active motor threshold. Our subjects were at rest and reaction to painful stimuli was not assessed. Since only 3 or 4 concentration levels have been investigated, we used a linear approximation of the concentration-response relationship which has most likely a sigmoidal form. Therefore, any conclusions drawn from this study must be limited to the subanesthetic concentration range investigated in the absense of painful stimuli.

Profound effects on the spinal level

This study extends to the subanesthetic concentration range the previously reported profound suppression of spinal motor function and of motor responses to transcranial magnetic cortex stimulation at anesthetic concentrations [25].

The motor response to TMS requires intact cortical excitability, spinal integration of descending cortical motor signals, transmission of the signal via the peripheral motor nerve, and finally an intact neuromuscular junction. Therefore, changes in the motor response to TMS measured as the CMAP cannot be attributed to any specific level of signal transmission. It is well-known, however, that the last two levels are not affected by low concentrations of general anesthetics [27]. This is confirmed by our finding that neither M amplitude nor latencies of M-response nor F-wave were changed by propofol or sevoflurane.

To distinguish effects on the spinal integration level and cortical excitability, a direct measurement of corticospinal-tract signals would be appropriate. Unfortunately this requires implanted electrodes [28-31]. In a non-invasive approach, the F-wave and the H-reflex are commonly used to characterize spinal integration properties [4,12,13,32]. Our results suggest that the spinal level is indeed profoundly affected by both drugs at subanesthetic concentrations, as reflected by a decrease of F-persistence, F-wave amplitude as well as H-reflex parameters. Do these parameters exclusively mirror a direct pharmacological action at spinal cord neurons? The excitability of spinal cord circuitries as assessed by the F-wave and the H-reflex can additionally be modulated by supraspinal signals, as has been demonstrated with TMS (F-waves [33], H-reflex [34]). Nevertheless, two findings support the simple assumption that decreases in F-wave and H-reflex observed with general anesthetics indeed mainly stem from a direct modulation of spinal cord circuitries. First, an isolated suppression of cortical activity induced by repetitive TMS results in an increase of the H-reflex [35]. This indicates a tonic inhibitory control of cortical motor systems on spinal excitability. And second, in a goat model with separated circuitries for the head and the trunk, Antognini et al. [4] described that isoflurane applied to the spinal cord in the trunk circuit affected the F-wave in a lower concentration compared to the application to the head.

The suppression of spinal integration may be responsible for the entire reduction of the TMS response amplitude. It cannot be excluded, however, that additional cortical or subcortical effects contribute to the effect on the TMS response. The larger reduction of TMS amplitude compared to spinal-cord responses in our data might be interpreted as evidence for

such an additional supraspinal effect. A comparable observation based on F-waves and transcranial electrical stimulation has been made using anesthetic concentrations of isoflurane [32].

As mentioned above, descending motor cortex activity evoked by transcranial stimulation can be recorded invasively in the corticospinal tract using epidural electrodes over the spinal cord. It consists of a pattern of volleys at about 600 Hz, a D-wave and several I-waves. The D-wave represents "direct" synchronous activity of the fast conducting corticospinal fibers that are activated near the cell bodies in the cortex; I-waves represent the transsynaptic activation of corticospinal neurons ("indirect", for review see [36]). Invasive recordings in patients have shown that the I-waves but not the D-wave are suppressed by anesthetics such as isoflurane [37], sevoflurane [38,39], and propofol [39,40]. The simultaneous recording of corticospinal tract signals and muscle responses [40] confirmed previous animal studies that an isolated D-wave is not sufficient to evoke a muscle response but that a certain pattern of two or more waves is required.

So far, the modulation of D-waves and I-waves has not been studied in the subanesthetic concentration range we have chosen for our study. Therefore, we only can speculate whether I-wave suppression located in the motor cortex already occurs at low concentrations and has to be taken into account for the pronounced effects on CMAPs and spinal reflexes we observed.

The profound depression of F-wave amplitudes at subanesthetic concentrations calls into question the utility of this parameter as a tool for the prediction of involuntary movements for painful stimuli, as previously suggested [12].

Despite the profound effects at the spinal level the active TMS motor threshold remained unchanged with propofol, although it increased with sevoflurane. This dissociation did not occur in the relaxed muscle, where both drugs increased motor threshold. The unexpected difference with the active motor threshold suggests a complex physiological interplay between cortical and spinal levels.

Effects on electroencephalography and MLAEP

In order to estimate anesthetic effects on cortical function we acquired simultaneously MLAEP and electroencephalograpy data. The MLAEP and essential parts of the spontaneous electroencephalogram are generated by cortico-thalamic circuitries [14,41]. Both MLAEP and electroencephalogram were only slightly affected by the low concentrations of general

anesthetics used in our study, in contrast to the parameters of the motor system. The electroencephalography data do not stem from the motor cortex but rather from prefrontal areas. However, we take this continuous parameter as a general measure for cortical attenuation. At least, for the somatosensory cortex the pattern of electroencephalogram suppression is similar to the prefrontal areas [42].

Propofol [43-45] and sevoflurane [46] are known to alter MLAEPs in a concentration-dependent manner. However, few studies have analysed data during application of low, sedative concentrations. Tatsumi et al. [47] have found a nonsignificant reduction in Pa-Nb amplitude at 0.5 vol% sevoflurane and significant increases of P_a and N_b latencies at 0.25 vol%, but in their study, 50% nitrous oxide was used as an additional anesthetic. In a study by Tooley et al. [44] using propofol, the increase in latency of peaks Pa and Nb was not significant at 2 µg/ml.

The measured effects on the cortical level in our study are small compared to the effect on the spinal level described above. If one assumes that the measured effects on electroencephalogram and MLAEP reflect a general suppression of cortical function, than that suggests that at subanesthetic concentrations of sevoflurane and propofol spinal integration is more profoundly affected than cortical excitability. However, our approach of non-invasive measurement does not exclude a cortical contribution to the TMS modulation, i. e. a sizeable reduction in excitability in the motor cortex. The increase in TMS motor threshold might suggest such a cortical suppression effect. On the other hand, an increase in motor threshold would be expected with an isolated change in integration function at the spinal level as well.

Despite the profound suppression of spinal excitability at subanesthetic concentrations, patients may still move in response to surgical noxious stimuli despite being unconscious and having no recall at anesthetic concentrations. Apparently the inhibition at the spinal cord level can be overcome by still functional supraspinal circuits [4]. Spinal excitability itself might be changed due to high neuronal input during painful stimuli, permitting motor responses even at profoundly suppressed resting levels of spinal excitability.

Postauricular reflex as an analogue to spinal responses

The general finding that cortical function is less influenced by low concentrations of sevoflurane and propofol is supported by the differential effects seen in the auditory system. While the MLAEP is only slightly affected we found a drastic reduction in the amplitude of the postauricular response. In contrast to the MLAEP this response is mediated by a reflex

loop including the acoustic nerve and brainstem nuclei such as the upper olivear nucleus and facial nucleus [16,48]. It has been shown that brainstem auditory evoked potentials are resistant to anesthetics even in high concentrations [49]. Suppression of the postauricular reflex is thus likely to occur in the efferent part of the reflex arc. The postauricular response is comparable to the parameters F-wave and H-reflex in a sense that no cortical signal processing is involved. Brainstem nuclei and connections share structural properties with segmental spinal cord architecture. Supporting the analogy between spinal responses and the postauricular reflex is the relative stability of spinal components of somatosensory evoked potentials against anesthetics [50]. In both spinal and brainstem responses, the efferent part of the reflex arc is preferentially suppressed by anesthetics.

Comparison of propofol and sevoflurane effects

It has long been held that propofol is favorable compared to volatile anesthetics when monitoring the integrity of the spinal cord during surgery with either somatosensory evoked potentials [51] or motor evoked potentials [52]. Only recently, a direct comparison of both drug groups with adjusted concentrations has revealed similarities between suppression of somatosensory evoked potential amplitude by propofol and volatile anesthetics [53]. Our analysis also revealed no significant difference between the effects of calculated low concentrations of propofol and the measured low concentrations sevoflurane on the human motor system, with the exception of the active motor threshold with TMS [52].

In summary, our data from multimodal electrophysiological assessment show that at subanesthetic concentrations propofol as well as sevoflurane spinal responses of the motor system are profoundly suppressed. While cortical circuits represented by prefrontal electroencephalography and MLAEP are less affected, this doesn't prove yet that the cortical motor system is similarly less affected compared to the spinal level. The pronounced reduction of the postauricular reflex contrasted by slight MLAEP changes might suggest that a general pattern underlies the action of the drugs with a preferential suppression of submesencephalic efferences. In the absence of other potentially modulatory stimuli signal transmission from the cortex to the periphery is profoundly impaired as revealed by TMS. The similar high degree of suppression we found for both drugs already at subanesthetic concentrations may even suggest that neither drug is really suitable for TMS monitoring.

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Figure captions

Figure 1

Influence of propofol and sevoflurane on Observer's Assessment of Alertness/ Sedation Scale (OAA/S) as Trellis plots [54]. Raw data from 9 subjects are shown in boxes as circles. On the abscissa the concentration of the administered drug is given as a fraction of the C_{50}awake concentration: MACawake value of sevoflurane (lower row), CP_{50}awake value of propofol (upper row). Note that for propofol calculated concentrations were used. Data in corresponding boxes in the upper and lower row are from the same subject. Missing data are handled correctly by the mixed-model ANOVA which still works although sevoflurane data were not available in the second subject (blank box) and propofol was not administered in the sixth subject.

In the model used the slope is set as a fixed parameter for each drug, i.e. regression lines have the same slope for all individuals. For each effect, the drug with the steeper slope would be the more potent drug. In this plot of OAA/S, the slope of sevoflurane is significant (as tabulated in the second column in table 1). The difference between the slopes of the two drugs (as tabulated in the third column in table 1) is almost zero indicating that both drugs have similar potencies.

From the definition of the OAA/S and the normalization of concentrations to C_{50}awake we expect a slope of -2.5 (regression: -3.01) and an intercept of 5 (regression: 5.02) for both drugs, which agrees well with the values from the regression analysis and demonstrates that the C_{50}awake normalization we use is consistent with the data of the subjects in our study.

Figure 2

Grand average of auditory evoked potentials under control conditions and with 0.2 and 0.4 vol% sevoflurane (29% and 57% of C_{50}awake) . Labels indicate the evaluated peaks. Solid line: control condition, dashed: 0.2 Vol% sevoflurane, dotted: 0.4 Vol%. The postauricular response was evaluated as the amplitude difference P_0-N_a.

Figure 3

Modulation of electroencephalography and MLAEP parameters by sevoflurane (sqares) and propofol (stars). Drug effects are shown as changes relative to the control values in the absence of any drug. The abscissa is scaled relative to C_{50}awake for both drugs. Error bars indicate SD. Lat N_b -latency N_b; BIS - bispectral index (open symbols); PAR - postauricularis response (amplitude P_0-N_a).

Figure 4

Modulation of TMS parameters. A) Relative changes of threshold and amplitude in the resting muscle. Control values in the absence of the drugs are set to unity. B) Relative changes of threshold and amplitudes in the active, slightly preinnervated muscle. Amplitudes were evoked with a stimulator intensity of 140% of active motor threshold. The abscissa is scaled relative to C_{50}awake for both drugs. Error bars indicate SD.

Figure 5

Compound muscle action potentials (CMAPs) in response to transcranial stimulation with increasing stimulus intensity. Data from one subject (UH). A) with and without sevoflurane, B) with and without propofol. On the abscissa, stimulus intensity is given relative to maximum stimulator energy. The crosses left of the traces indicate active motor threshold under slight preinnervation. Motor responses were tested at six fixed fractions of motor threshold, 110% - 160%. The onset of each CMAP trace is shifted to its stimulus intensity applied on the abscissa. The scale bars indicate time in ms (abscissa) and voltage (ordinate) of the CMAP . Note that for propofol the target concentrations is used.

Figure 6

Modulation of spinal responses by sevoflurane. Representative traces from a single subject. A) F-waves. Twenty stimulations were recorded to estimate persistence (the fraction of positive responses). B) H-reflex. Due to the high reproducability of the response the single sweep shown is representative of a typical reflex.

Figure 7

Relative drug effects on F-wave and H-reflex. The abscissa is scaled relative to C_{50}awake for both drugs. Error bars indicate SD.

Figure 8

Summary of concentration-response slopes for selected parameters in the study, as measures of the effect specific potency of sevoflurane. Mean values and confidence intervals shown are from the second column in Table 1 and 2, normalized to the baseline values (column 5 in the tables) for easier comparison in the graph. If the boxes do not overlap with the line of zero, the effect is significant, as indicated in grey. For all parameters shown, propofol did not show a different effect compared to sevoflurane (see column 3 in Table 1 and 2).

Figure 1

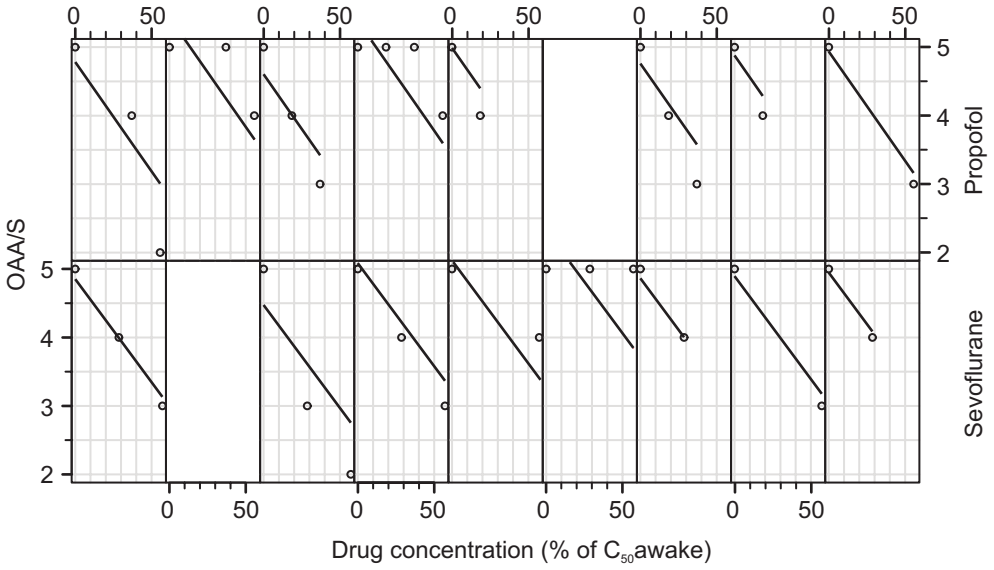

OAA/S
Propofol
Sevoflurane
Drug concentration (% of C_{50}awake)
0
50
2
3
4
5

Figure 2

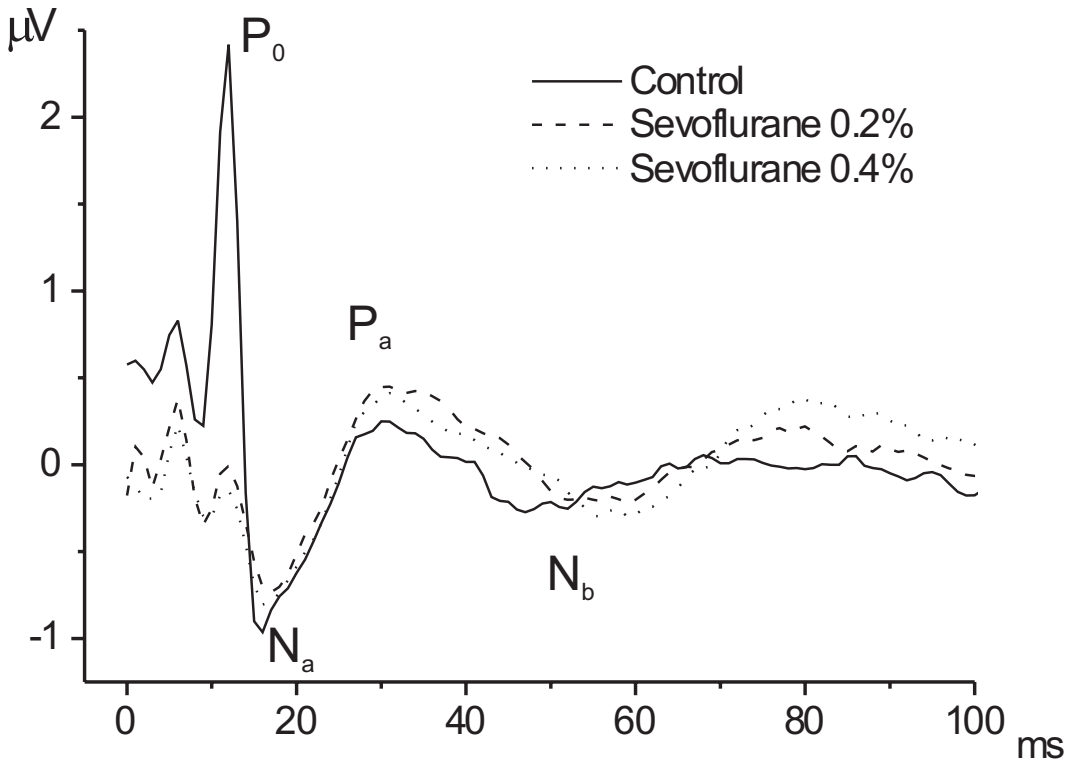

μV
2
1
0
-1
0
20
40
60
80
100
ms
P0
Pa
Na
Nb
Control
Sevoflurane 0.2%
Sevoflurane 0.4%

Figure 3

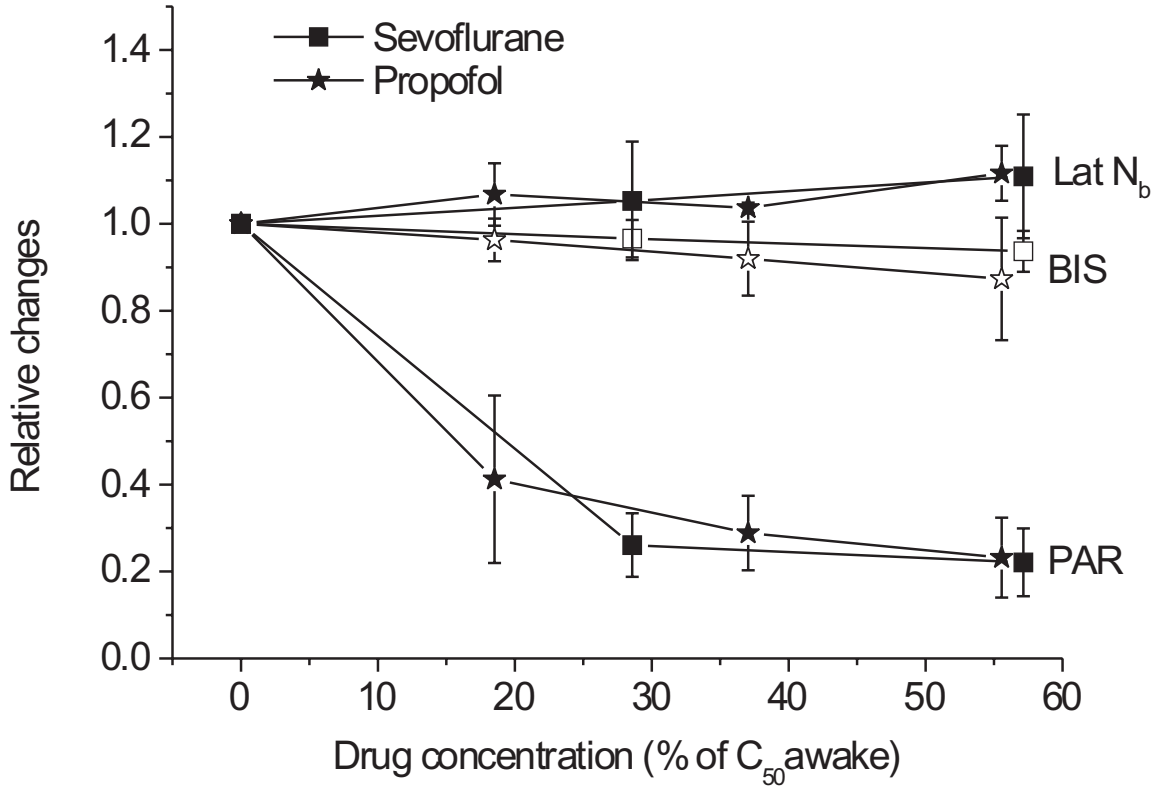

Sevoflurane
Propofol
Lat N_b
BIS
PAR
Relative changes
Drug concentration (% of C_{50}awake)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
0
10
20
30
40
50
60

Figure 4

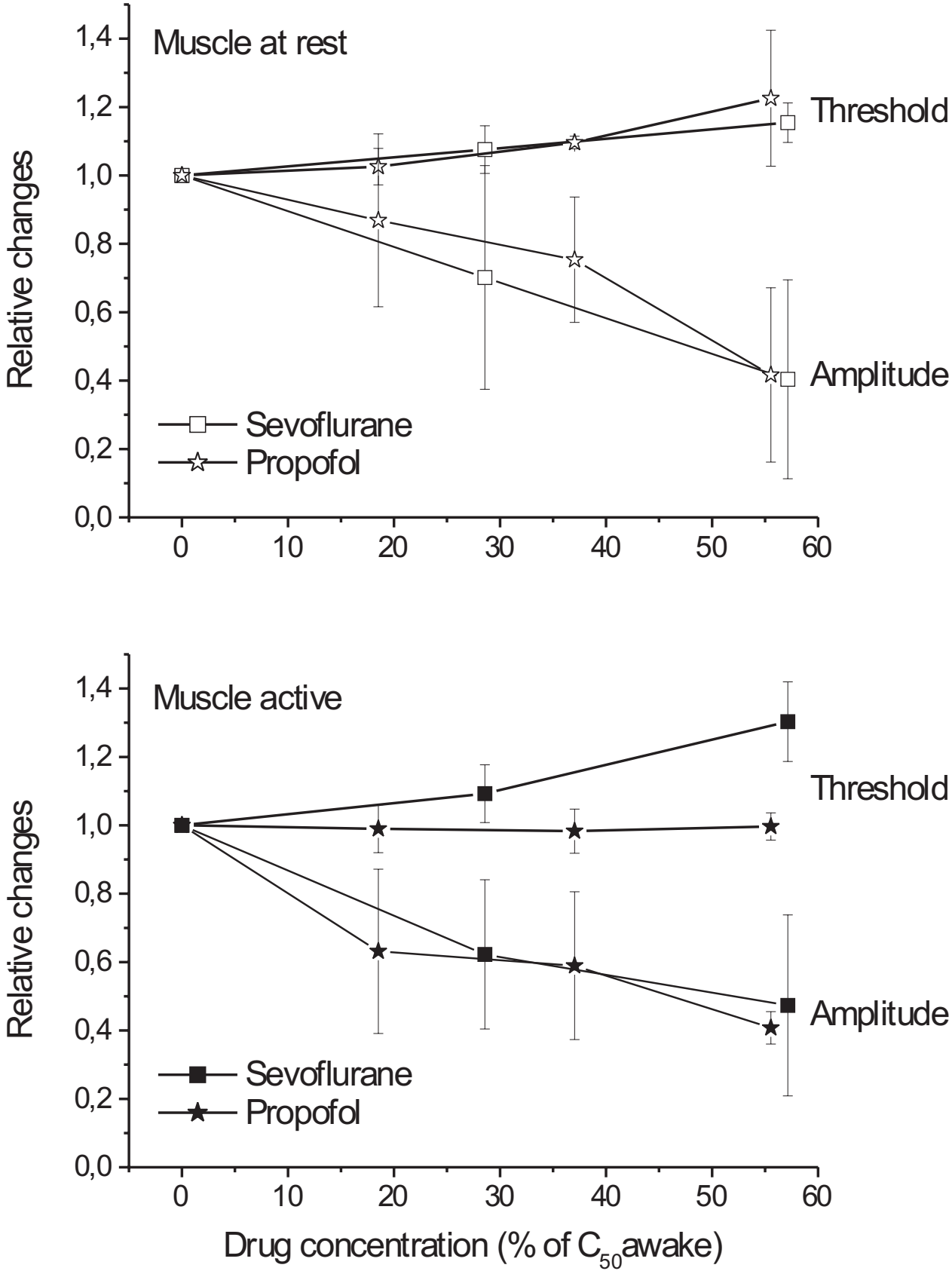

Muscle at rest
Threshold
Amplitude
Sevoflurane
Propofol
Muscle active
Threshold
Amplitude
Sevoflurane
Propofol
Relative changes
Relative changes
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
0
10
20
30
40
50
60
Drug concentration (% of C50awake)

Figure 5

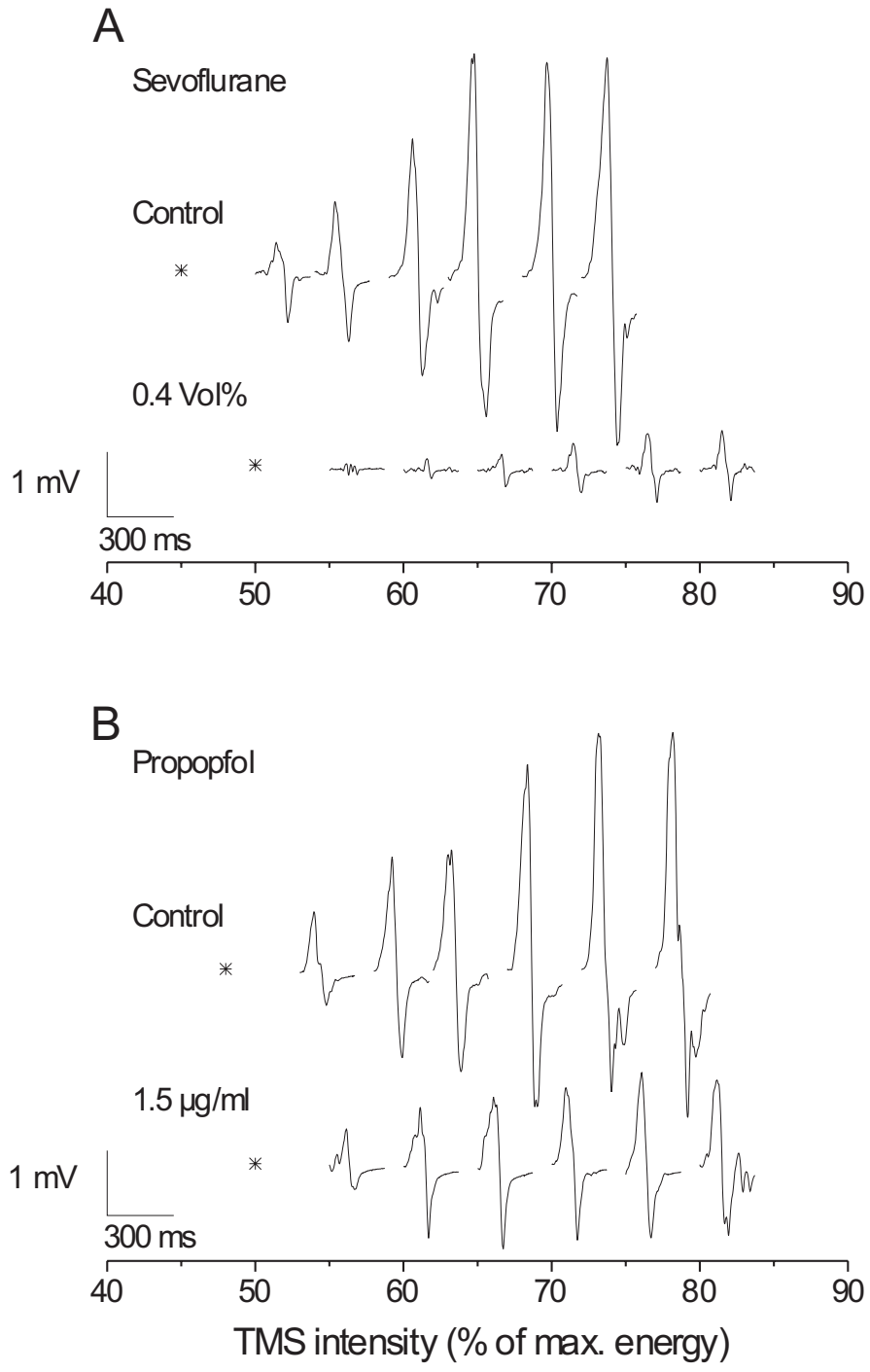

A
Sevoflurane
Control
0.4 Vol%
1 mV
300 ms
40
50
60
70
80
90
B
Propopfol
Control
1.5 µg/ml
1 mV
300 ms
40
50
60
70
80
90
TMS intensity (% of max. energy)

Figure 6

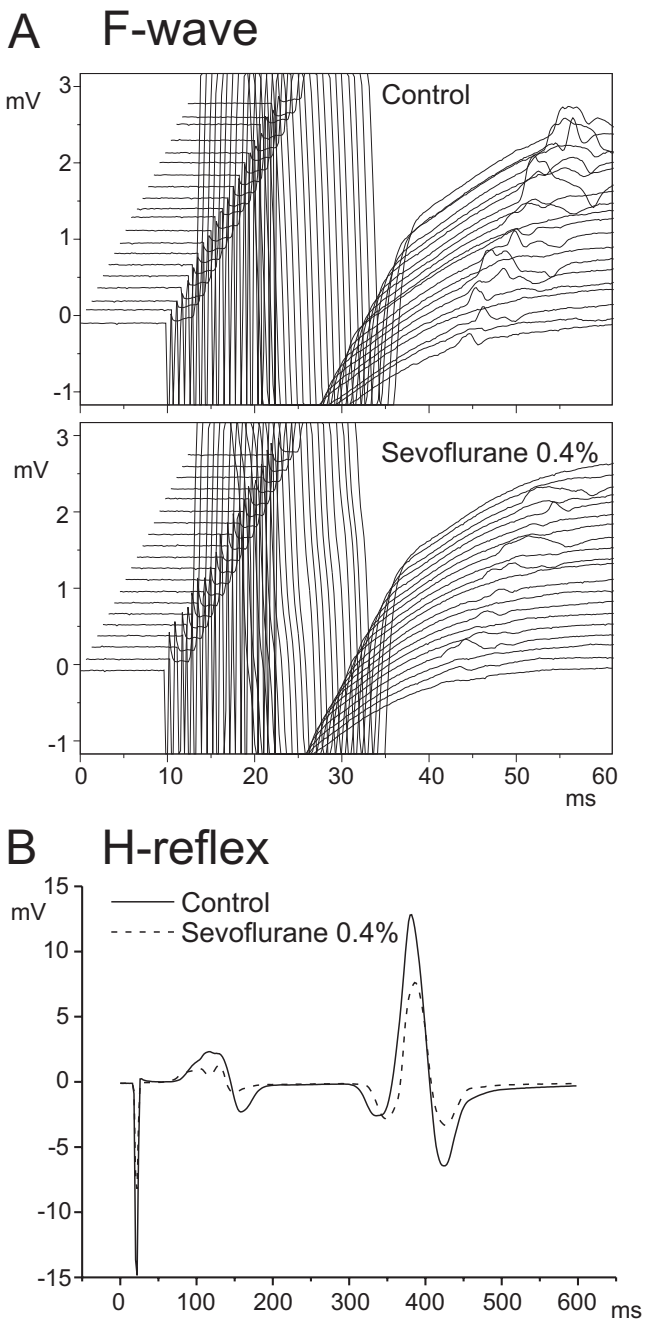
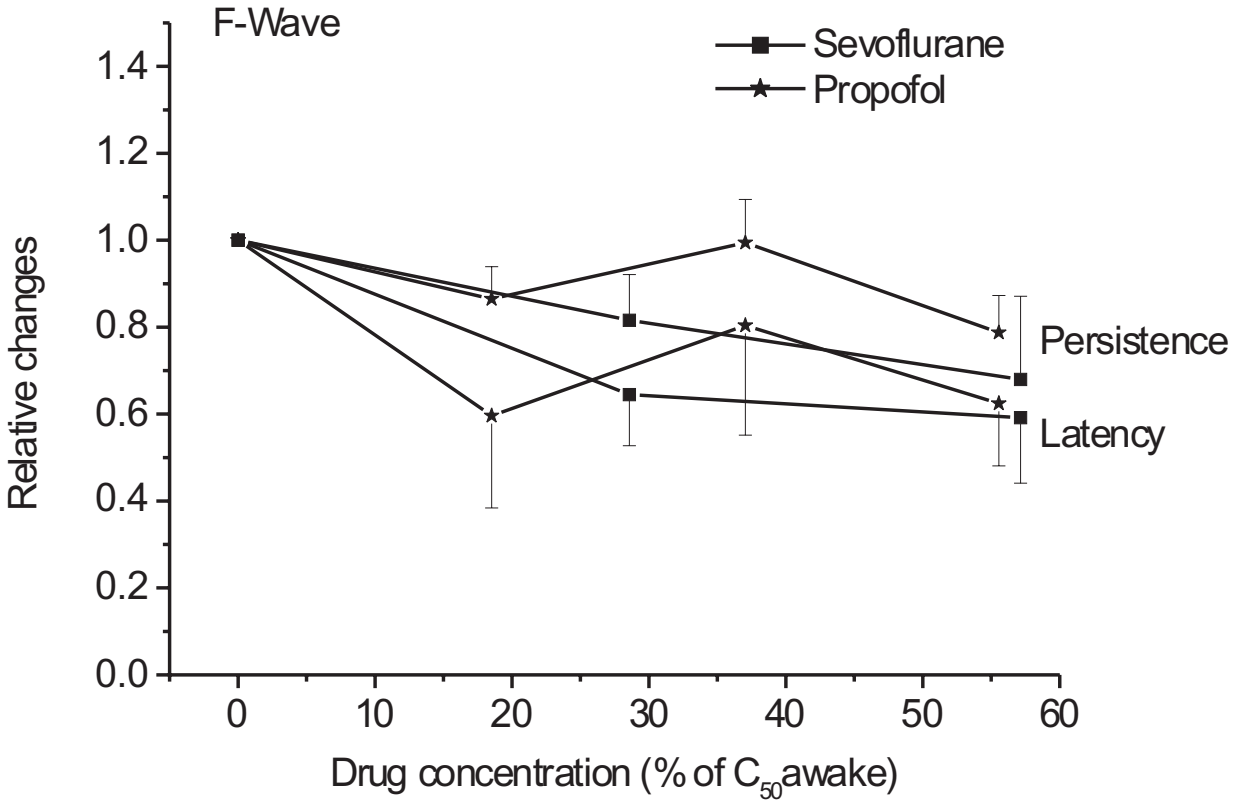

A F-wave
mV
3
2
1
0
-1
Control
Sevoflurane 0.4%
0
10
20
30
40
50
60
ms
B H-reflex
mV
15
10
5
0
-5
-10
-15
Control
Sevoflurane 0.4%
0
100
200
300
400
500
600
ms

Figure 7


F-Wave
Sevoflurane
Propofol
Relative changes
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Persistence
Latency
0
10
20
30
40
50
60
Drug concentration (% of C50awake)

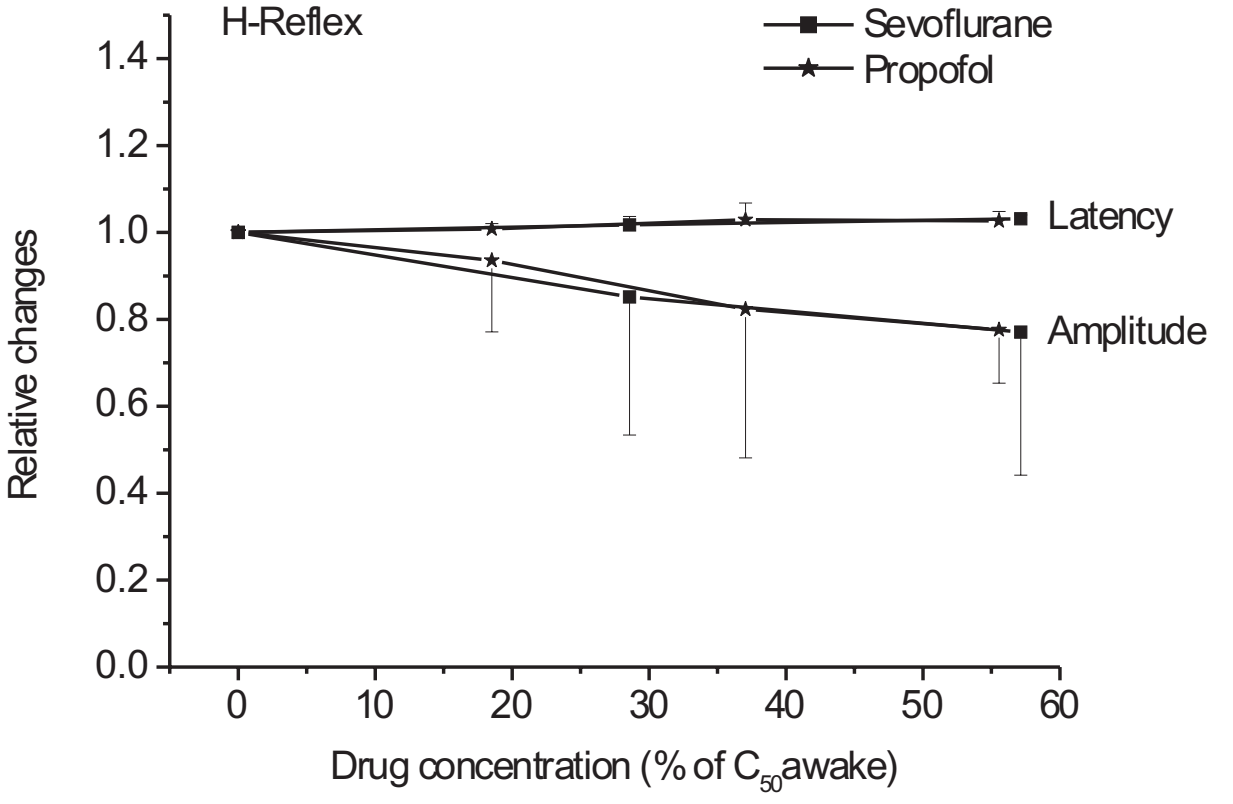
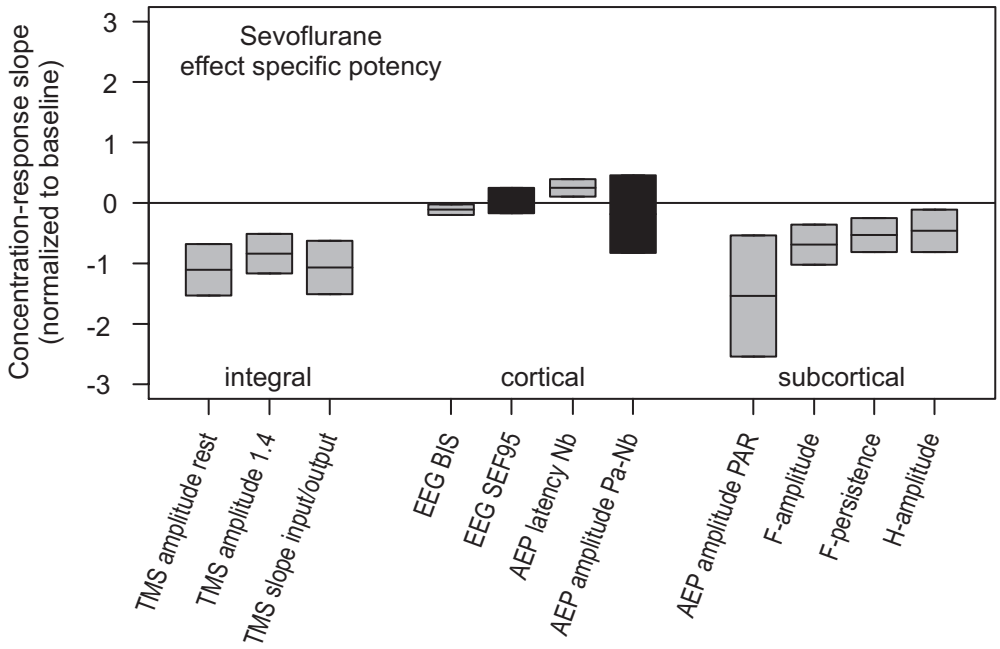

H-Reflex
Sevoflurane
Propofol
Relative changes
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Latency
Amplitude
0
10
20
30
40
50
60
Drug concentration (% of C50awake)

Figure 8


Sevoflurane
effect specific potency
Concentration-response slope
(normalized to baseline)
3
2
1
0
-1
-2
-3
integral
cortical
subcortical
TMS amplitude rest
TMS amplitude 1.4
TMS slope input/output
EEG BIS
EEG SEF95
AEP latency Nb
AEP amplitude Pa-Nb
AEP amplitude PAR
F-amplitude
F-persistence
H-amplitude