Anesthesiology
1999; 91:1853–60


# *Interaction of Intravenous Anesthetics with Human Neuronal Potassium Currents in Relation to Clinical Concentrations*

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***Background:*** **Neuronal voltage-dependent potassium (K) currents are crucial for various cellular functions, such as the integration of temporal information in the central nervous system. Data for the effects of intravenous anesthetics on human neuronal K currents are limited. It was the authors' aim to evaluate the concentration-related effects of three opioids (fentanyl, alfentanil, sufentanil) and seven nonopioids (thiopental, pentobarbital, methohexital, propofol, ketamine, midazolam, droperidol) used in clinical anesthesia on neuronal voltage-dependent K currents of human origin.**

***Method:*** **K currents were measured in SH-SY5Y cells using the whole cell patch-clamp technique. Currents were elicited by step depolarization from a holding potential of −80 to −50 mV through +90 mV, and their steady state amplitudes were determined.**

***Results:*** **All drugs inhibited the K currents in a concentration-dependent and reversible manner. Because time dependence of inhibition differed among the drugs, effects were measured after 54–64 ms of the test pulse. The $IC_{50}$ values (concentration of half-maximal inhibition) for current suppression ranged from 7 μM for sufentanil to 2 mM for pentobarbital. Suppression of the K currents by the opioids occurred at 10-fold lower $IC_{50}$ values (concentration of half-maximal inhibition) than that by the barbiturates. As estimated from the concentration–response curves, K-current suppression at clinical concentrations would be less than 0.1% for the opioids and approximately 3% for the other drugs.**

***Conclusions:*** **Effects of intravenous anesthetics on voltage-dependent K currents occur at clinical concentrations. The $IC_{50}$ values for current inhibition of the nonopioid anesthetics correlated with these concentrations (r = 0.95). The results suggest that anesthetic drug action on voltage-dependent K currents may contribute to clinical effects or side effects of intravenous anesthetics. (Key words: Barbiturate; opioid; ketamine; propofol; K current; patch-clamp technique.)**

THERE is considerable controversy about the mechanisms underlying general anesthesia.[1,2] It is generally accepted that many molecular structures, such as ion channels, are altered in their function by general anesthetics. However, there is no agreement as to which of these anesthetic actions are relevant to anesthesia. One criterion that has been proposed requires that *in vitro* effects occur in the same concentration range in which relevant clinical effects are observed.[1] Although this seems to be a plausible criterion, it does not and cannot provide any guideline as to the necessary magnitude of the *in vitro* effect in relation to the clinical effect.[3] Nevertheless, the relation between concentrations necessary to alter the function of voltage-dependent potassium (K) currents and free clinical plasma concentrations of intravenous anesthetics has never been evaluated systematically.

Another critical test suggested to judge the relevance of molecular targets for general anesthetic mechanisms evaluates the correlation between concentrations at which *in vitro* and *in vivo* effects are observed for a range of anesthetic agents.[4] Important to this approach is the evaluation of anesthetic agents belonging to different pharmacologic groups but producing similar clinical anesthetic effects. Based on this test γ-aminobutyric acid A ($GABA_A$) receptor channels have been argued to be relevant for anesthesia.[4] For example, the anesthetic

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Received from the Department of Anesthesiology and Intensive Care Medicine, University of Bonn, Bonn, Germany. Submitted for publication February 8, 1999. Accepted for publication July 8, 1999. Support was provided solely from institutional and/or departmental sources. Presented in part at the Wissenschaftliche Arbeitstage of the Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin, Würzburg, Germany, February 23–24, 1996; the annual meeting of the American Society of Anesthesiology, New Orleans, Louisiana,October 19–23, 1996; and the 5th International Conference on Molecular and Cellular Mechanisms of Anesthesia, Calgary, Alberta, Canada, June 18–20, 1997.

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concentrations necessary to double the relaxation times correlate well with the concentrations of these agents found in clinical anesthesia. No such test has been presented for K channels.

Neuronal voltage-dependent K channels are important for various cellular functions. They repolarize cell membranes after the firing of action potentials,[5] cause afterhyperpolarizations in some neurons,[6] and are critical for postsynaptic temporal integration of neuronal signals.[7,8] Alteration of voltage-dependent K channels, therefore, results in complex cellular changes. The inhibition of neuronal voltage-dependent K currents by some intravenous anesthetic agents has been reported, for example, in the frog node of Ranvier,[9] in demyelinated axons of *Xenopus laevis*,[10] and in oocytes expressing rat neuronal voltage-dependent K channels.[11] It has been shown that anesthetic actions may be species dependent[12] and subtype specific.[13–15] With the exception of etomidate,[16] the actions of intravenous anesthetic agents on neuronal voltage-dependent K currents of human origin have not been investigated. Therefore, we chose K channels of human origin to meaningfully correlate effective concentrations for *in vitro* effects with anesthetic concentrations observed in clinical anesthesia.

The aim of this study was to establish concentration–response curves for the effects on Shaw-like voltage-dependent K currents in human neurons[17] of a large number of intravenous agents used in clinical anesthesia. Complete concentration–response curves of three opioids (fentanyl, alfentanil, sufentanil) and seven intravenous nonopioid anesthetics (thiopental, pentobarbital, methohexital, propofol, ketamine, midazolam, droperidol) allowed comparison of *in vitro* effects with clinically relevant concentrations of intravenous anesthetics.

## Material and Methods

### *Cell Culture*

SH-SY5Y cells were grown in nonconfluent monolayer using RPMI medium (Biochrom, Berlin, Germany) at 37°C with 95% air and 5% carbon dioxide. Growth medium contained 10% fetal calf serum, glutamine (2 mM), penicillin (100 U/ml), and streptomycin (100 μg/ml). Neuronal differentiation was induced by exposure to retinoic acid (10 μM) for 3–7 days. Treatment of these cells with retinoic acid resulted in a reduction in cell division and neurite extension.[18,19]

### *Electrophysiologic Recordings*

Voltage-sensitive outward currents were recorded at room temperature (22–25°C) using an EPC-7 amplifier (List Electronic, Darmstadt, Germany) and pclamp software version 5.71 (Axon Instruments, Foster City, CA) using the whole cell patch-clamp technique.[20] Patch electrodes with an input resistance between 1.8 and 3 MΩ were pulled from borosilicate glass capillary tubes (World Precision Instruments, Saratoga, FL) and were filled with the following internal solution: KCl: 115 mM; $MgCl_2$: 1 mM; MgATP: 3 mM; HEPES: 10 mM; and EGTA: 10 mM. The pH was adjusted to 7.2 with potassium hydroxide. The extracellular solution contained 135 mM NaCl, 4 mM KCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$, 10 mM glucose, and 10 mM HEPES, and pH was adjusted to 7.4 with sodium hydroxide. Series resistance was measured to be 4.6 ± 2.1 MΩ (mean ± SD, n = 20) and was subsequently compensated for by 60%. The junction potential was measured to be 3.2 ± 0.9 mV (mean ± SD, n = 5) and was not corrected. Sodium and calcium currents also have been described in SH-SY5Y cells.[21,22,23] Only a minor percentage of the cells showed sodium currents but, at the holding potential of −80 mV, a substantial fraction of sodium channels was inactivated.[21] Because sodium currents generally were small compared with the K currents, they were not blocked. Furthermore, K-current inhibition was measured after 54 ms, when the remaining sodium currents were inactivated. Calcium channels were never seen with 2 mM extracellular $CaCl_2$.

The holding potential in all experiments was −80 mV, and the test potentials were rectangular pulses with durations of 84 ms increasing from −50 to +90 mV in 10-mV steps. The drugs were applied to the bath (2 ml) using a hydrostatic perfusion system (3 ml/min). The effect of the drugs was recorded after perfusing the bath for 2 min, and washout of drug effect was measured after perfusing for another 2 min with drug-free solution. This protocol was repeated at every concentration. The bath level was kept constant with a level control driven pump (MPCU-3; Lorenz, Lindau, Germany). The drugs were purchased from Parke-Davis (Freiburg, Germany; ketamine), Zeneca (Plankstadt, Germany; propofol), Janssen (Neuss, Germany; droperidol), Byk Gulden (Konstanz, Germany; thiopental), Lilly (Giessen, Germany; methohexital), Sigma (Deisenhofen, Germany; pentobarbital), and Hoffmann La Roche (Nutley, NJ; midazolam). The opioids (alfentanil, sufentanil, fentanyl) were a gift from Janssen. Intralipid, 10% (Fresenius, Bad Homburg, Germany), was used as a carrier for propofol, and etha-

**Table 1. Physicochemical Properties and Free Clinical Plasma Concentrations of the Drugs Investigated in This Study**

| Anesthetic Agent | Octanol–Water Coefficient | *p*ka | Protein Binding (%) | Free Plasma Concentration ($\mu$M) |
|---|---|---|---|---|
| Propofol | 5,011[32] | 11[32] | 98[32] | 1.7[24] |
| Etomidate | 1,260[32] | 4.1[32] | 76[32] | 2.4[26] |
| Ketamine | 151[32] | 7.5[32] | 26[32] | 15[27] |
| Droperidol | 3,100[32] | 7.4[32] | 85[32] | 0.2[28] |
| Thiopental | 561[32] | 7.4[32] | 82[32] | 14[25] |
| Pentobarbital | 106[32] | 8.0[32] | 56[32] | 88[29] |
| Methohexital | 691[32] | 8.4[32] | 93[32] | 6.3[30] |
| Midazolam | 1,862[33] | 6.2[32] | 96[32] | 0.4[31] |
| Alfentanil | 128[37] | 6.5[37] | 92[37] | 0.1[34] |
| Fentanyl | 816[37] | 8.4[37] | 84[37] | 0.0096[35] |
| Sufentanil | 1,757[37] | 8.0[37] | 93[37] | 0.0067[36] |

Values are taken from references 24–37.

nol was used as a carrier for pentobarbital and midazolam. The maximal concentration of ethanol was 0.0182 ml/ml (pentobarbital, 4 mM). Both carriers had no effect on the K currents in the concentrations used in this study. The concentration of propofol in the experimental chamber was measured by high-performance liquid chromatography (RF-10AXL; Shimatzu, Duisburg, Germany). The recorded signal was filtered at 3–10 kHz, digitized using an analog-to-digital converter (Digidata 1200; Axon Instruments, Foster City, CA), and stored on a personal computer with a sampling rate of 5 kHz for later analysis.

### *Clinical Concentrations and Physicochemical Properties*

The values of free clinical plasma concentrations and physicochemical properties of the intravenous anesthetics (table 1) were estimated from sources listed in table 1. Although values for partition coefficients for all anesthetic agents used in this study were published using the same condition (octanol–water, neutral form of the anesthetics), a comparable consistent set of anesthetic concentrations measured for the same clinical end point is not available. Ideally, in analogy to minimum alveolar concentration for inhalation anesthetics, the plasma concentration at which 50% of the patients respond to skin incision should be used. Information has been published only for propofol[24] and thiopental[25] (trapezius squeeze); for the other anesthetics a comparable concentration had to be estimated from a variety of pharmacokinetic and clinical endpoints.[26–37] The free clinical plasma concentrations are the best estimates of a set of consistent concentrations of intravenous anesthetics. We used free plasma concentrations because only the unbound concentration of the anesthetic is pharmacologically active.

### *Data and Statistical Analysis*

The K currents were measured as the average current during a 10-ms interval between the 54th and 64th ms of the test pulse. Inhibition of K current was measured at all test potentials between +10 and +70 mV. *Inhibition* was defined as the ratio of remaining current in the presence of the drug to the current in the absence of the drug subtracted from 1, and it was plotted as a function of anesthetic concentration. Voltage-dependence of inhibition was small and amounted to approximately a 10% difference in inhibition at concentrations close to the $IC_{50}$ values between test potentials from +10 to +70 mV. Each test potential contributed equally to the concentration–response curves, which were fitted using the Hill equation ($b/b_{max} = c^\gamma/[IC_{50}{}^\gamma + c^\gamma]$) using nonlinear regression[38] (SAS Institute, Cary, NC), where, b = inhibition, $b_{max}$ = maximal inhibition, c = anesthetic concentration, $\gamma$ = Hill coefficient, $IC_{50}$ = concentration of half-maximal effect. All data are given as the mean ± SD unless stated otherwise. The number is always the number of experiments. Linear regression analysis was performed using Sigma-Plot software (Kandel GmbH, Erkrath, Germany).

## Results

Voltage-dependent K currents in SH-SY5Y cells were elicited from a holding potential of −80 mV by stepping to depolarizing potentials between −50 and +90 mV (fig. 1, control currents). They activated at potentials more positive than −30 mV, with an activation midpoint of approximately +7 mV. At positive potentials, the K currents inactivated minimally during the 84-ms depolarization, with inactivation time constants of 5 s. The currents were sensitive to micromolar concentrations of tetraethylammonium and 4-aminopyridine.[17]

All intravenous anesthetics inhibited these K currents. Figure 1 shows K-current traces with the effect of one member of each pharmacologic group investigated. With some anesthetics, there was a substantial decrease of the K currents after they reached their maximum amplitude (compare, for example, the effects of thiopental and alfentanil in fig. 1B). This pronounced decrease of the currents was seen with all opioids, droperidol, and midazolam; it was small with propofol, and it was not seen with the barbiturates and ketamine. Current sup-

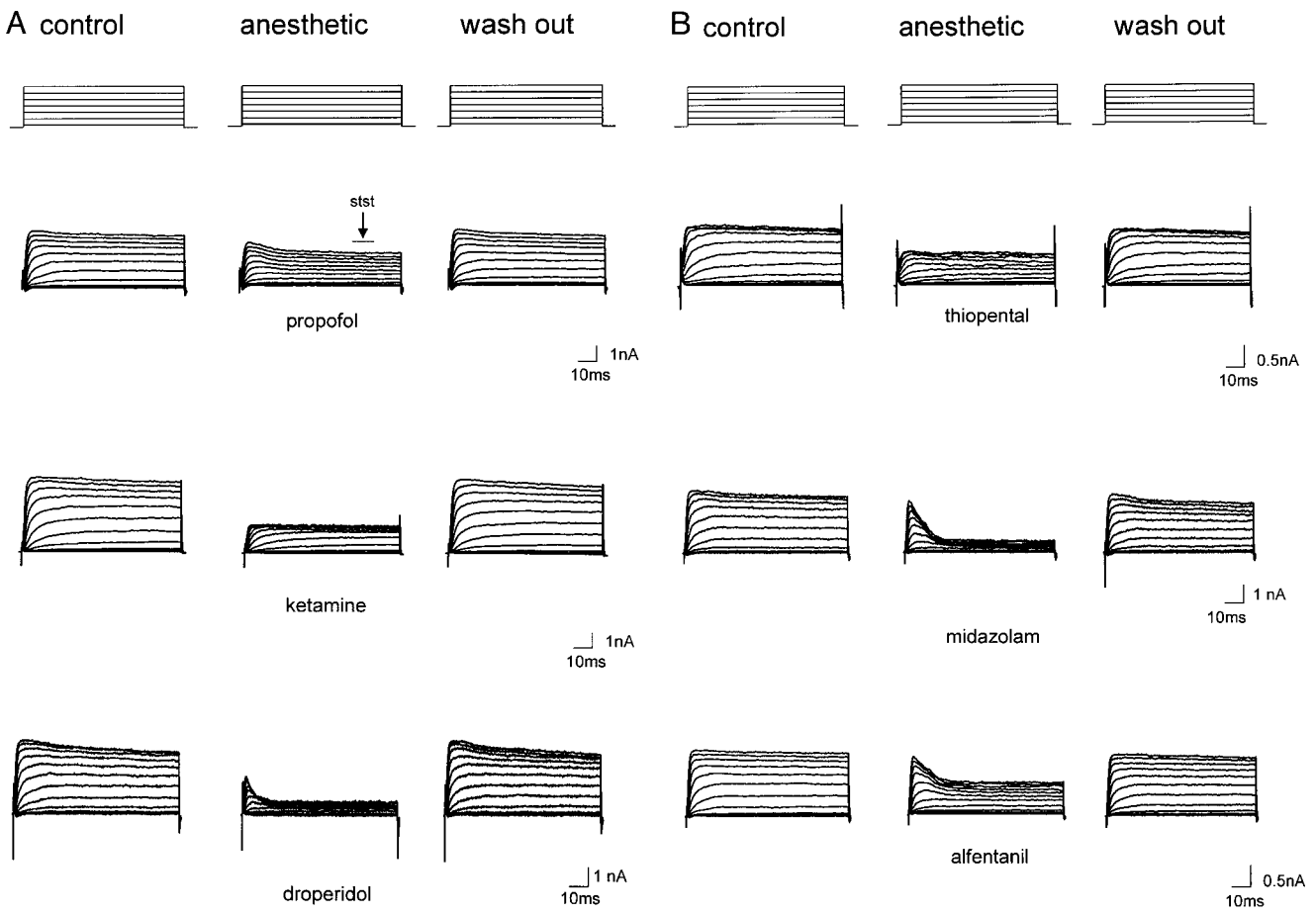


**Fig. 1. Superimposed traces of the voltage-dependent K currents evoked by depolarizing steps from a holding potential of −80 mV to test potentials from −50 to +70 mV. The interpulse duration was 1 s. Shown are the current traces during control conditions, the influence of the intravenous anesthetics on the K currents, and the currents after the drugs were washed out. The concentrations used were (*A*) 43 μM propofol, 290 μM ketamine, 66 μM droperidol, (*B*) 250 μM thiopental, 50 μM midazolam, and 100 μM alfentanil. Inhibition was measured during the steady state period (stst) of the K currents.**

pression by anesthetics was measured after 54 ms, when the (if any) pronounced decrease of K currents had reached a steady state (fig. 1A). Inhibition of the K currents was measured at seven different membrane potentials between +10 and +70 mV at all concentrations of each individual drug. This analysis resulted in good signal:noise ratios. It did not favor any specific membrane potential, and it also included membrane depolarization of physiologic relevance.

The current traces (figs. 1A and B) also show the reversibility of K-current inhibition, which was observed with all anesthetics. The concentration dependence of the drug effects was described mathematically by Hill functions (fig. 2). The $IC_{50}$ values for current suppression by the intravenous anesthetics ranged from 7 μM for sufentanil to 2 mM for pentobarbital (fig. 2, table 2). On average, the $IC_{50}$ values for opioids were 10 times lower than for the barbiturates. Despite the large range of $IC_{50}$ values, other parameters of the Hill functions were similar among the drugs (table 2). Hill coefficients were around unity for all intravenous anesthetics investigated, and the anesthetic agents almost completely blocked the K currents.

Hill functions were used to estimate what effect an intravenous anesthetic agent may have on K currents at free plasma concentrations encountered during clinical anesthesia (table 1). To check the validity of this procedure in a particular case, current inhibition by ketamine, as predicted by the Hill function, was compared with current inhibition experimentally determined at a clini-

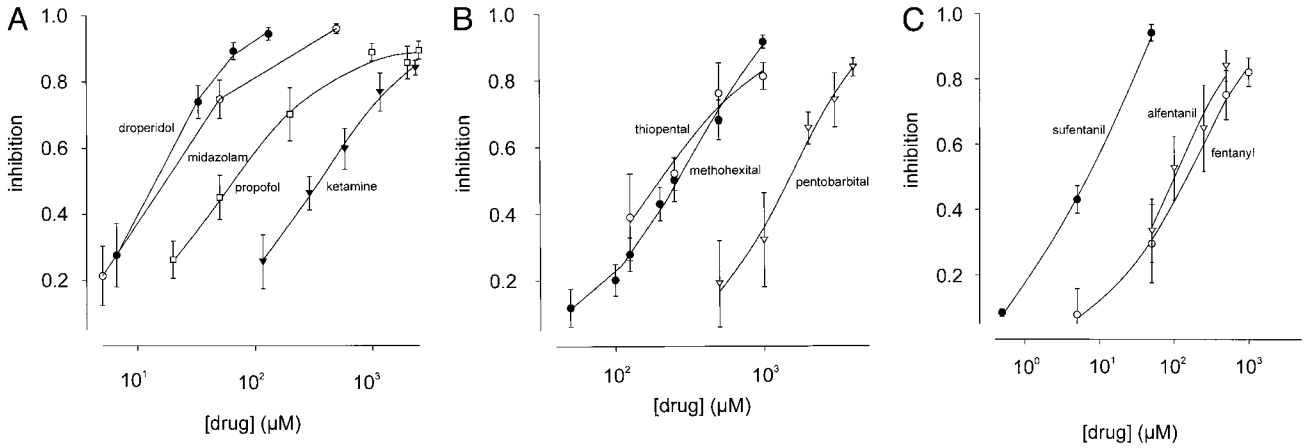


**Fig. 2. (*A*) Concentration–response curves for K-current inhibition by all intravenous anesthetics. Shown are mean values ± SD. For parameters of the Hill functions see table 2. (*B*) Grouped barbiturates. (*C*) Grouped opioids.**

cally relevant concentration of this drug (12 μM). At 12 μM ketamine, the Hill function (table 2) predicts a K-current inhibition of 4.4% with a 95% confidence interval of 2.4–7.5%; experimentally, an inhibition of 4.5 ± 4.5% (n = 8, 95% confidence interval 1.3–8.7%) was measured. It is noteworthy that both methods predicted the same inhibition, but the standard deviation of the experimental data point was as large as the data point itself. Even after eight experiments, the confidence interval for the experimental data points was still worse than that for the Hill function–derived estimate. The explanation may be that the Hill functions included more data points, most of which were measured at anesthetic concentrations that resulted in better signal: noise ratios. Therefore, the fitted Hill functions were used to estimate suppression of K currents by the other intravenous anesthetics at clinically relevant concentrations.

**Table 2. Hill Parameters Resulting from the Fit of the Concentration–Response Data According to the Hill Function**

| Anesthetic Agent | $IC_{50}$ ± SEM [μM] | Hill Coefficient ± SEM | $b_{max}$ ± SEM | n |
|---|---|---|---|---|
| Propofol | 43.6 ± 2.5 | 0.9 ± 0.1 | 0.92 ± 0.01 | 23 |
| Ketamine | 361 ± 39 | 0.9 ± 0.1 | 1.01 ± 0.04 | 28 |
| Droperidol | 14.4 ± 0.8 | 1.3 ± 0.1 | 1.01 ± 0.02 | 12 |
| Thiopental | 180 ± 86 | 1.15 ± 0.1 | 0.94 ± 0.23 | 18 |
| Pentobarbital | 1950 ± 695 | 1.3 ± 0.3 | 1.17 ± 0.25 | 19 |
| Methohexital | 307 ± 38 | 1.2 ± 0.1 | 1.10 ± 0.07 | 13 |
| Midazolam | 16.9 ± 1.4 | 1.1 ± 0.1 | 0.99 ± 0.02 | 7 |
| Alfentanil | 101 ± 6 | 0.9 ± 0.1 | 1.0 | 12 |
| Fentanyl | 138 ± 60 | 1.0 ± 0.1 | 0.8 ± 0.15 | 11 |
| Sufentanil | 7.35 ± 1.2 | 1.1 ± 0.05 | 0.97 ± 0.13 | 10 |

The $b_{max}$ value for alfentanil was set to 1 and the concentration–response data obtained with alfentanil were fitted with two open parameters.

SEM = standard error of the mean; $b_{max}$ = maximal inhibition; n = number of experiments.

## Discussion

The molecular structure of the K channels in SH-SY5Y cells has not been reported, but the properties of these channels are being characterized.[17] The high threshold of activation and the high sensitivity to tetraethylammonium and 4-aminopyridine[39] point to the predominant expression of a single family of voltage-dependent K channels[40] underlying the K currents in retinoic acid–differentiated SH-SY5Y cells.[41] The pharmacologic and biophysical properties of the K channels are similar to Shaw (Kv3) K channels.[40,42] K channels with activation and inactivation kinetics and pharmacologic profiles similar to SH-SY5Y cells determine the firing frequencies of neurons in the auditory system[7,8] and are found in the hippocampus.[43]

Concentration-dependent effects of some intravenous anesthetics on voltage-dependent K currents have been investigated in the frog node of Ranvier[9] and in *Xenopus* axons.[10] Despite similar qualitative effects, ketamine and etomidate[16] inhibited the K currents in SH-SY5Y cells with two- to threefold lower $IC_{50}$ values than in the frog node of Ranvier[9] or in *Xenopus* axons[10] (ketamine only). Species differences and K-channel subtype specificity in anesthetic pharmacology therefore might exist as already established for nonanesthetic drugs[42] and ethanol.[44]

Inactivation-like behavior of the K currents induced by

some of the anesthetic agents might reflect the kinetics of current block as established for open channel blockers.[45] However, inactivation-like behavior of K current induced by anesthetic agents may also result from different molecular mechanisms,[46] and our experiments do not allow discrimination among these mechanistic options.

Clinically and pharmacologically, intravenous anesthetic agents can be separated into at least two different classes: opioids and nonopioids. Opioids act *via* well-recognized specific receptor-mediated cellular mechanisms[47] at nanomolar concentrations, but no common receptor has been found at which the nonopioid intravenous anesthetics act with comparable potency. The separation of opioids and nonopioids is reflected by their actions on K channels in human neuronal SH-SY5Y cells. The ratio of the $IC_{50}$ values and the respective clinical concentrations are at least two orders of magnitude higher for the opioids than for the nonopioids (tables 1 and 2).

Concentrations for half-maximal *in vitro* effects on $GABA_A$ receptors previously were reported to have excellent correlation with clinical concentrations.[4] This argument has been used to emphasize the importance of $GABA_A$ receptors for clinical anesthesia. To our surprise, plotting $IC_{50}$ values for K-current suppression *versus* clinical concentrations[24–37] also resulted in an excellent correlation for the nonopioid intravenous anesthetics ($r = 0.95$, slope of the regression line = 1.15). This correlation is not simply a consequence of the well-known Meyer–Overton correlation[48] because K-current suppression by the nonopioid anesthetics correlates considerably more poorly with their octanol–water partition coefficients ($r = 0.65$; fig. 3). There is, however, a significant shift to the right from the line of unity for the correlation of $IC_{50}$ values and clinical concentrations.

The small effect of the nonopioid anesthetics at clinical concentrations (2.9% inhibition as estimated from the Hill equations) may suggest that inhibition of voltage-dependent K currents does not contribute to the hypnotic action of these drugs, despite the excellent correlation. If the inhibition of these voltage-dependent K currents produces excitatory side effects, it might be fortunate that the observed effects are so small. Conversely, Kv3 channels have, for example, been localized to GABAergic interneurones,[49] and excitation of these neurones would presumably result in overall depression. Not only does the localization of the K channels within a neuronal network determine whether their inhibition causes excitation or depression, but the network may also modulate the anesthetic response[50] and determine what degree of anesthetic inhibition is necessary to cause a significant perturbation of the network. In any case, the good correlation between clinical concentrations and $IC_{50}$ values suggests that these voltage-dependent K channels appear to be a biophysical target of intravenous anesthetics that may help to establish molecular determinants of anesthetic potency.

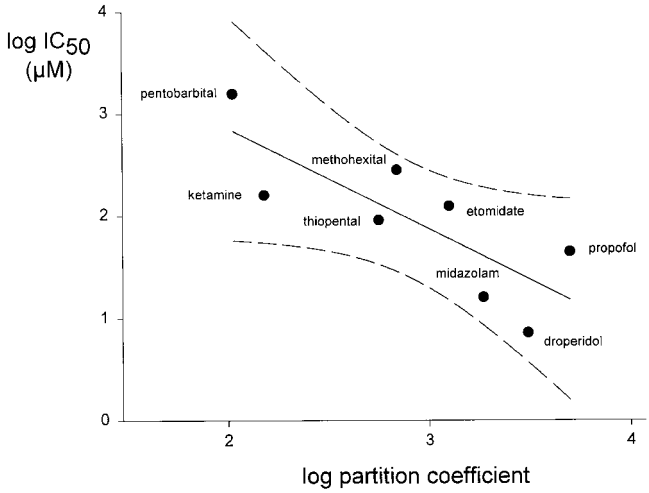


**Fig. 3. Double logarithmic plot of $IC_{50}$ values (table 2) and octanol–water partition coefficients (table 1) of the nonopioids according to the Meyer–Overton rule. The $IC_{50}$ value for etomidate is taken from the literature.[16] The regression line has a slope of −0.99 and the regression coefficient is 0.65 (n = 8). The dotted lines represent the 99% confidence interval.**

In summary, intravenous anesthetic agents reversibly inhibited voltage-dependent K currents from human neuroblastoma cells in a concentration-dependent manner. Effects of intravenous anesthetics already occurred at clinical concentrations and $IC_{50}$ values of K-current inhibition correlated with clinical concentrations. The results of our study suggest that understanding actions of intravenous anesthetics on voltage-dependent K currents might help to elucidate molecular mechanisms underlying anesthetic drug effects, and these actions need further investigation.

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