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Modulation of Cardiac Calcium Channels by Propofol

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Background: **Propofol elicits a rapid depression of transsarcolemmal Ca^{2+} influx and myocardial contractility. However, the mechanism underlying this action has not been well described. The present study was designed to test the hypothesis that propofol acts as an antagonist of L-type calcium channels.**

Methods: **Experiments monitored effects of propofol on (1) the binding of [^{3}H]nitrendipine (a 1,4-dihydropyridine calcium channel antagonist) to rat myocardial membranes; (2) L-type calcium current ($I_{Ca,L}$) as determined using whole-cell patch-clamp techniques in intact rat cardiomyocytes; and (3) myocardial contractility as examined in isolated rat papillary muscle.**

Results: **Propofol, in concentrations as low as 6 μM, increased the apparent dissociation constant (K_d) for [^{3}H]nitrendipine without affecting binding-site density (B_{max}). This decrease in dihydropyridine-binding affinity was associated with a depressed $I_{Ca,L}$ in cardiomyocytes and diminished myocardial contractility. Other experiments showed that etomidate has no effect on [^{3}H]nitrendipine binding, whereas ketamine enhances dihydropyridine binding.**

Conclusion: **Results suggest that propofol may inhibit cardiac L-type calcium current by interacting with the dihydropyridine-binding site. (Key words: Anesthetics, intravenous: propofol. Animal: rat. Heart: myocardial contractility. [^{3}H]nitrendipine binding. L-type calcium current.)**

CLINICAL use of propofol is associated in some reports with adverse cardiovascular effects, including decreases in cardiac output and arterial blood pressure.[1-4] This depression in cardiovascular function appears to result primarily from a decrease in sympathetic nerve activity and a reduction in baroreceptor control.[5,6] However, studies have also described a direct inhibitory effect of propofol on myocardial contractility, especially with relatively high concentrations such as those that may occur during rapid bolus injection.[7-9] The exact mechanism underlying this action has not been elucidated. Previous studies in our laboratory have shown that the cardiac action *in vivo* may be mediated in part by a propofol-induced antagonism of β-adrenoceptor binding.§ However, it seems likely that other mechanisms are involved in the direct negative inotropic effect. Because L-type calcium channels play a critical role in cardiac excitation-contraction coupling,[10] it is reasonable to postulate that disturbances in these calcium channels may contribute to the cardiac dysfunction. Indeed, propofol has been shown to inhibit calcium influx across plasma membranes as well as calcium release from the sarcoplasmic reticulum.[11-13] In addition, studies in guinea pig myocytes have indicated that propofol inhibits L-type calcium current ($I_{Ca,L}$).[11,14,15] The present study was designed to determine if the negative inotropic action of propofol in rat cardiac muscle is associated with effects on voltage-dependent L-type calcium channels. Radioligand techniques were used to examine effects of propofol on dihydropyridine binding in membranes prepared from rat ventricular myocardium, whole-cell patch-clamp techniques were used to monitor anesthetic effects on $I_{ca,L}$ in rat cardiomyocytes, and inotropic actions were evaluated in rat papillary muscle.

Materials and Methods

All protocols in this study were approved by the Institutional Animal Care and Use Committee at the University of Arkansas for Medical Sciences and were in accordance with the *Guide for the Use of Laboratory Animals* issued by the U.S. Department of Health and Human Services.

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Materials

Propofol (2,6-di-isopropylphenol) was purchased from Aldrich Chemical Company (Milwaukee, WI). [^{3}H]Nitrendipine (87 Ci/mmol) was purchased from Du Pont (Boston, MA). Ketamine and other chemicals were from Sigma Chemical Company (St. Louis, MO).

Membrane Preparation

Partially purified membranes from rat ventricular myocardium were prepared using a modification of a previously described procedure.[16] Briefly, hearts were isolated from male Sprague-Dawley rats weighing 300–350 g and perfused immediately through the aorta with Krebs-Henseleit buffer saturated with 95% oxygen and 5% carbon dioxide. After the perfusate was free of blood, the ventricles were homogenized in 50 mM TRIS HCl, 2 mM $MgSO_4$, *p*H 7.3 (4°C) using three 30-s bursts of a Polytron at a setting of 6 followed by six strokes of a manual glass/glass homogenizer. The homogenate was centrifuged at 800*g* for 20 min. The resulting pellet was discarded, and the supernatant was centrifuged at 2,500*g* for 20 min. From this second supernatant, a pellet was isolated by two sequential centrifugations at 30,000*g* for 20 min, with intermediate washing of the pellet using the homogenizing buffer. The final membrane pellet was resuspended in 50 mM TRIS HCl, 2 mM $MgSO_4$ buffer to make a final suspension of 0.5 mg protein per milliliter. Protein concentration was determined by the method of Bradford[17] using bovine serum albumin as the standard.

Radioligand Binding Assay

Membranes (250 μl final volume) were incubated with varying concentrations of [^{3}H]nitrendipine ($\approx$0.06–5 nM) in the presence and absence of propofol, etomidate, ketamine, butylated hydroxytoluene, or verapamil. A final concentration of 0.1% ethanol was included in all reaction tubes; preliminary studies showed that this solvent had no significant effects on binding. After 1 h at 24°C, the reaction mixture was diluted with 3.5 ml of ice-cold normal saline containing 0.2% bovine serum albumin and immediately filtered through GF/C filters using a vacuum filtration manifold. The filters were washed three times with 3.5 ml each of normal saline containing 0.2% bovine serum albumin, and the radioactivity remaining on the filters was measured by liquid scintillation spectrometry. Specific [^{3}H]nitrendipine binding was defined as the difference between binding monitored in the presence and absence of 10 μM unlabeled nifedipine. Data were analyzed using a microcomputer version of LIGAND[18] to calculate binding-site density (B_{max}) and the apparent dissociation constant (K_d); a one-site model provided the best fit for all experiments.

Cell Culture

Isolated ventricular myocytes were obtained by enzymatic dispersion of hearts isolated from male Sprague-Dawley rats weighing 300–350 g and were cultured in 60-mm culture dishes containing 60% medium 199 (GIBCO, Grand Island, NJ), 36% Earle's balanced salt solution, and 4% fetal bovine serum (GIBCO) as described previously.[19] After 24–48 h incubation at 37°C with 5% carbon dioxide and 95% air, rod-shaped cells with clear striations were used for electrophysiologic experiments.

Electrophysiologic Measurements

L-type calcium current was measured as described previously.[20] Briefly, rat ventricular myocytes attached to culture dishes were mounted on the heated stage of an inverted microscope and perfused with a Tyrode solution consisting of 145 mM NaCl, 5.4 mM KCl, 0.8 mM $MgCl_2$, 1 mM $CaCl_2$, 5.6 mM glucose, 5.8 mM HEPES, and 4.2 mM TRIS base (*p*H 7.4 at 37°C). Whole-cell currents were recorded using patch-clamp techniques with glass electrodes (tip resistance, 2–4 MΩ). To separate the calcium current from other transmembrane currents, a standard Na^+- and K^+-free pipette solution was used (100 mM CsOH, 70 mM aspartate, 11 mM CsCl, 15 mM tetraethylammonium chloride, 2 mM $MgCl_2$, 5 mM $TRIS_2$-phosphocreatine, 0.3–0.4 mM Li_4-GTP, 5 mM HEPES, and 5 mM TRIS base (*p*H adjusted to 7.2 with CsOH). Recorded currents were sampled at 5 kHz, filtered at 1 kHz, and analyzed using pClamp 6.0 software (Axon Instruments, Inc., Foster City, CA) and an Axon TL-1 LabMaster DMA acquisition system in a PC/AT computer. Because capacitance and leakage may not be linear under the conditions of this experiment, there was no attempt at correction. Cells were clamped at −70 mV and superfused with an external solution consisting of 148 mM N-methyl-D-glucamine chloride, 2 mM $CaCl_2$, 0.8 mM $MgCl_2$, 5.6 mM glucose, 5.8 mM HEPES and 4.2 mM TRIS base (*p*H 7.4). After a 10–15-min equilibration period, calcium currents were evoked by 200-ms depolarizing pulses from the holding potential of −70 mV to potentials between −60 and +80 mV. After baseline measurement in the presence of 0.1% ethanol, the external solution was exchanged with a solution containing 25 or 50 μM propofol (dissolved in ethanol to

produce a final ethanol concentration of 0.1%; preliminary studies showed that 0.1% ethanol decreases $I_{Ca,L}$ by no more than 10%). Recovery of $I_{Ca,L}$ was examined by returning to the drug-free solution.

Isolated cardiac muscle preparation. Papillary muscle was prepared as described previously.[20] Briefly, hearts isolated from 300–350 g male Sprague-Dawley rats were immediately perfused through the aorta with a Krebs-Henseleit solution composed of 118 mM NaCl, 27.1 mM $NaHCO_3$, 3.7 mM KCl, 1.4 mM $CaCl_2$, 1.2 mM $MgCl_2$, 1 mM KH_2PO_4, and 11.1 mM glucose. This solution was buffered to *p*H 7.4 by saturation with 95% oxygen and 5% carbon dioxide gas and maintained at 37°C.

After the heart was free of residual blood, a papillary muscle (<0.7 mm diameter) was dissected and hung vertically in a tissue bath (37°C) containing the oxygenated Krebs-Henseleit solution described before. Nadolol (3 μM; a β-adrenergic antagonist) was included in the buffer to prevent potential effects of endogenous catecholamines. Preparations were paced through platinum contact electrodes at a frequency of 1 Hz by 1 ms square wave pulses set at 150% threshold voltage. Force of resting tension and isometric contraction was monitored by force-displacement transducers and recorded continuously on a polygraph. A length-tension relation was determined for each preparation, and resting tension was subsequently maintained at that level, which elicited 90% of maximum observed contractile force (approximately 0.7 g). Tissues were equilibrated for 60 min, during which time the bathing solution was changed every 15 min.

After equilibration, dose-dependent actions of propofol were examined by cumulative addition to the Krebs-Henseleit solution. The next higher concentration of the anesthetic was added only after tissues reached a steady-state response at the previous level (~5 min). The highest final concentration of ethanol in the tissue baths was 0.1%. Preliminary studies showed that this concentration did not significantly affect contractility (a decline in developed tension of less than 5% was observed in some preparations).

Statistical Analysis

Data were evaluated by Student's *t* test or analysis of variance (when comparing more than two groups). Differences were considered statistically significant when $P < 0.05$. All data are expressed as means ± SEM.

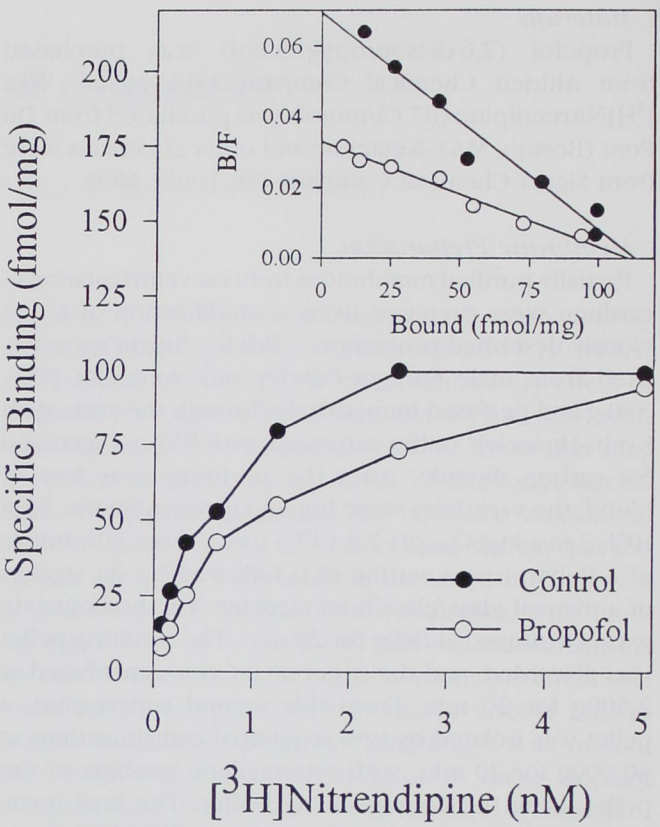

Fig. 1. Representative plots showing saturation binding and Scatchard analysis (inset) of [^{3}H]nitrendipine binding to rat ventricular membranes in the absence (closed circles) and presence (open circles) of 50 μM propofol.

Results

[3H]Nitrendipine Binding

As reported by others[21–23] but not all[24] investigators, [^{3}H]nitrendipine binding to rat ventricular membranes showed a single population of high-affinity binding sites (fig. 1). Propofol antagonized this binding in a competitive manner, decreasing the slope of the Scatchard plot while having no effect on the x intercept (fig. 1). As shown in table 1, the K_d for [^{3}H]nitrendipine was increased by propofol in a concentration-dependent fashion (6–200 μM), while no significant effect on B_{max} was observed.

Data in table 2 compare effects of propofol with those of other drugs. Consistent with results shown in figure 1 and table 1, 25 μM propofol inhibited [^{3}H]nitrendipine binding by approximately 54% and 46% when monitored at free ligand concentrations of 0.3 and 0.6 nM, respectively. Butylated hydroxytoluene, structurally

Table 1. Effects of Propofol on Specific [^{3}H]Nitrendipine Binding to Partially Purified Membranes Prepared from Rat Ventricular Myocardium (n = 4–7)

Propofol (μM)	K_d (nM)	B_{max} (fmol/mg protein)
0	0.68 ± 0.06	126.3 ± 5.6
1	0.56 ± 0.06	140.7 ± 8.4
6.3	1.29 ± 0.21*	134.3 ± 7.5
12.5	1.07 ± 0.08*	132.7 ± 9.1
25	1.26 ± 0.04*	124.1 ± 6.0
50	1.35 ± 0.11*	133.3 ± 6.2
100	2.19 ± 0.19*	120.5 ± 8.2
200	4.48 ± 0.94*	97.6 ± 19.4

*P < 0.05 *versus* control (0 μM propofol).

similar to propofol, and verapamil, a phenylalkylamine calcium channel blocker, also inhibited [^{3}H]nitrendipine binding. In contrast, etomidate did not alter binding, whereas ketamine elicited a slight increase in [^{3}H]nitrendipine binding.

Electrophysiologic Studies

To determine whether the propofol-induced decrease in [^{3}H]nitrendipine binding was paralleled by alterations in calcium channel activity, $I_{Ca,L}$ was measured in rat cardiomyocytes using whole-cell patch-clamp techniques. As shown in figure 2, propofol at 25 and 50 μM depressed $I_{Ca,L}$ by 28% and 57%, respectively. It did not change the voltage-dependence of peak L-type calcium current. When removing propofol, partial recovery was observed.

Inotropic Effects

Propofol elicited a concentration-dependent decrease in developed tension in rat papillary muscle when monitored at concentrations between 25 and 200 μM (fig. 3). This negative inotropic effect was reversible as contractile function returned to control values when the anesthetic was removed from the extracellular solution (data not shown).

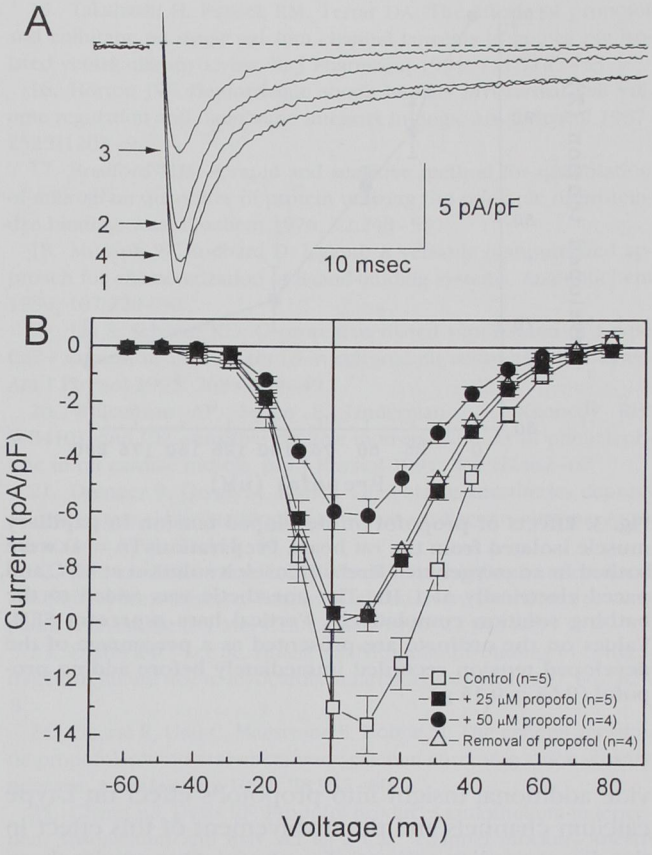

Fig. 2. (*A*) Representative current traces of $I_{Ca,L}$ in response to depolarizing pulses to 0 mM from a holding potential of −70 mV. These traces were obtained before exposure to propofol, during treatment with 25 μM and 50 μM propofol, and after recovery. (*B*) The current–voltage (I-V) relation of peak $I_{Ca,L}$ as monitored before and during exposure to propofol. Cultured rat ventricular myocytes were clamped at −70 mV. $I_{Ca,L}$ was elicited by 200-ms pulses from the holding potential of −70 mV to potentials between −60 and +80 mV in 10-mV increments.

Table 2. Effects of Various Drugs on [^{3}H]Nitrendipine Binding to Partially Purified Membranes Prepared from Rat Ventricular Myocardium (n = 4/condition)

	Specific [^{3}H]Nitrendipine Binding (fmol/mg protein)	
Condition	0.3 nM [^{3}H]Nitrendipine	0.6 nM [^{3}H]Nitrendipine
Control	40.4 ± 0.9	55.0 ± 1.9
Propofol (25 μM)	18.5 ± 0.8*	35.1 ± 1.7*
Ketamine (100 μM)	44.4 ± 2.9	64.6 ± 1.4*
Etomidate (40 μM)	37.7 ± 1.8	54.4 ± 3.1
BHT (100 μM)	21.1 ± 3.7*	29.4 ± 6.8*
Verapamil (10 μM)	15.8 ± 0.8*	22.4 ± 2.8*

BHT = butylated hydroxytoluene.

*P < 0.05 *versus* control.

Discussion

Studies using both patch-clamp techniques[11,14,15] and fluorescent calcium probes[13] have shown that propofol inhibits calcium influx in cardiomyocytes. Studies in other cells and tissues have also suggested that propofol acts as a calcium channel blocker.[24–26] Present data pro-

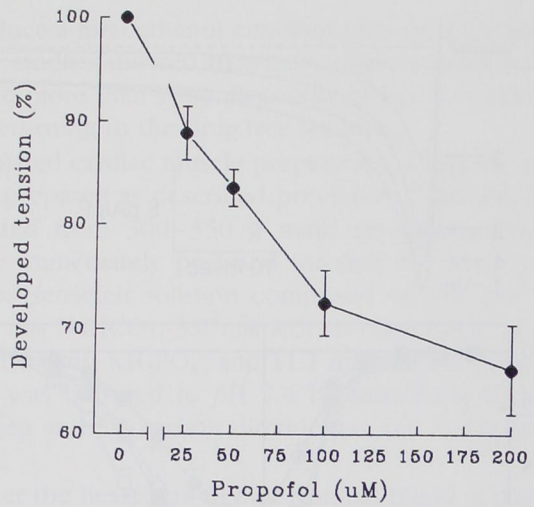

Fig. 3. Effects of propofol on developed tension in papillary muscle isolated from the rat heart. Preparations (n = 4) were bathed in an oxygenated Krebs-Henseleit solution at 37°C and paced electrically at 1 Hz. The anesthetic was added to the bathing solution cumulatively. Vertical bars represent SEM. Values on the ordinate are presented as a percentage of the developed tension recorded immediately before adding propofol (0.64 ± 0.15 g).

vide additional insight into propofol's effect on L-type calcium channels and the involvement of this effect in the direct cardiac actions of propofol. Our results show that propofol antagonizes specific dihydropyridine binding to rat ventricular myocardial membranes in a competitive manner. Dihydropyridines such as nitrendipine bind to the α subunit of the L-type calcium channel.[27] Thus the propofol-induced antagonism of [^{3}H]nitrendipine binding suggests that the anesthetic acts *via* the channel protein, possibly at the dihydropyridine binding site, to alter channel function.

Plasma concentrations of propofol during clinical use range from 3 to 90 μM (~0.7-20 μg/ml). A typical plasma concentration of propofol during general anesthesia is considered to be 35 μM (7.7 μg/ml).[28] However, because it has been estimated that this agent is 97-99% protein bound,[29] the effective free plasma concentration is probably less than 1 μM. Thus the concentrations used in this study are somewhat greater than those associated with the anesthesia achieved by continuous propofol infusion. For example, a significant increase in the K_d for dihydropyridine binding was observed at a concentration of 6 μM propofol, but not at 1 μM. It is possible, however, that plasma concentrations of free propofol approach those used in this study during bolus injection. Interestingly, etomidate showed no effect on dihydropyridine binding at 40 μM, a concentration well above peak clinical levels (*i.e.*, 10 μM).[30] In contrast, ketamine, which is associated with a cardiovascular stimulation during clinical use, slightly increased nitrendipine binding.

To determine if the propofol-induced modulation of [^{3}H]nitrendipine binding to myocardial membranes is associated with changes in channel function, electrophysiologic experiments in the present study monitored effects of the anesthetic on $I_{Ca,L}$ in intact cardiomyocytes. At 25 μM, propofol inhibited $I_{Ca,L}$ by approximately 28%, whereas 50 μM propofol inhibited the current by approximately 57%. Thus inhibitory effects of propofol on $I_{Ca,L}$ were observed at concentrations similar to those required to antagonize dihydropyridine binding. Propofol did not affect the voltage-dependence of the peak current.

Additional studies in rat papillary muscle were designed to determine if the concentration-dependent effects of propofol on dihydropyridine binding and $I_{Ca,L}$ were paralleled by changes in cardiac contractility. Results clearly showed that propofol diminishes myocardial contractility. This corresponds to previous studies showing that propofol is a cardiac depressant agent.[1-4,7-9] In addition, current data indicate that the negative inotropic action occurs over a concentration range that is similar to, although slightly higher than, the levels affecting $I_{Ca,L}$ and dihydropyridine binding. For example, 50 μM propofol decreased contractility by approximately 17% while causing a 57% reduction in I_{Ca} and about a twofold increase in the K_d for [^{3}H]nitrendipine binding. The cause of this disparity is not known, but the complex regulation of cardiac excitation-contraction coupling and the possible effects of propofol may explain some of the different action. Studies in our laboratory with the dihydropyridine calcium channel blocker nifedipine suggest that similar IC_{50} values are observed when examining effects on contractility in papillary muscle and I_{Ca} in cardiomyocytes (data not shown).

In summary, current results suggest that propofol acts directly on calcium channel proteins to diminish voltage-dependent $I_{Ca,L}$ and cardiac contractility. In view of our previous study showing that propofol antagonizes β-adrenoceptor binding,[10] it is conceivable that propofol's cardiac effects *in vivo* may be mediated *via* multiple mechanisms, especially during bolus injection. Further studies are required to determine if still other effects are involved in propofol's negative inotropic action.

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