

# Propofol Modulates $\gamma$ -Aminobutyric Acid–mediated Inhibitory Neurotransmission to Cardiac Vagal Neurons in the Nucleus Ambiguus

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**Background:** Although it is well recognized that anesthetics modulate the central control of cardiorespiratory homeostasis, the cellular mechanisms by which anesthetics alter cardiac parasympathetic activity are poorly understood. One common site of action of anesthetics is inhibitory neurotransmission. This study investigates the effect of propofol on  $\gamma$ -aminobutyric acid–mediated (GABAergic) and glycinergic neurotransmission to cardiac parasympathetic neurons.

**Methods:** Cardiac parasympathetic neurons were identified *in vitro* by the presence of a retrograde fluorescent tracer, and spontaneous GABAergic and glycinergic synaptic currents were examined using whole cell patch clamp techniques.

**Results:** Propofol at concentrations of 1.0  $\mu\text{M}$  and greater significantly ( $P < 0.05$ ) increased the duration and decay time of spontaneous GABAergic inhibitory postsynaptic currents. To determine whether the action of propofol was at presynaptic or postsynaptic sites, tetrodotoxin was applied to isolate miniature inhibitory postsynaptic currents. Propofol at concentrations of 1.0  $\mu\text{M}$  and greater significantly ( $P < 0.05$ ) prolonged the decay time and duration of miniature inhibitory postsynaptic currents, indicating that propofol directly alters GABAergic neurotransmission at a postsynaptic site. Propofol at high concentrations ( $\geq 50 \mu\text{M}$ ) also inhibited the frequency of both GABAergic inhibitory postsynaptic currents and miniature inhibitory postsynaptic currents. Propofol at concentrations up to 50  $\mu\text{M}$  had no effect on glycinergic neurotransmission.

**Conclusions:** Propofol may vary heart rate by modulating GABAergic neurotransmission to cardiac parasympathetic neurons. At clinically relevant concentrations ( $\geq 1.0 \mu\text{M}$ ), propofol facilitated GABAergic responses in cardiac vagal neurons by increasing decay time, which would increase inhibition of cardioinhibitory cardiac vagal neurons and evoke an increase in heart rate. At higher supraclinical concentrations ( $\geq 50 \mu\text{M}$ ), propofol inhibits GABAergic neurotransmission to cardiac vagal neurons, which would evoke a decrease in heart rate.

**PROPOFOL** is an effective intravenous anesthetic agent widely used in surgical anesthesia and postoperative sedation and is characterized by its fast emergence and swift recovery. However, propofol can evoke changes in cardiovascular homeostasis, including a reduction in baroreceptor reflex responses<sup>1,2</sup> and decreases in blood

pressure<sup>3,4</sup> that depend on the depth of anesthesia. Changes of heart rate due to propofol are controversial, with increases,<sup>2</sup> decreases,<sup>5</sup> and no alteration in heart rate reported.<sup>6,7</sup>

Heart rate is controlled by the activity of premotor cardiac vagal neurons that originate in the brainstem.<sup>8,9</sup> Cardiac vagal neurons, which are located in nucleus ambiguus, are intrinsically silent, and their firing activity is determined by both excitatory synaptic inputs, such as glutamatergic and cholinergic pathways, and inhibitory pathways that include  $\gamma$ -aminobutyric acid–mediated (GABAergic) and glycinergic innervation. The GABAergic inhibitory pathway to cardiac vagal neurons has been shown to be an important target of anesthetic action. Pentobarbital at clinically relevant concentrations prolongs the duration of spontaneous GABAergic inhibitory postsynaptic currents (IPSCs) that impinge on cardiac vagal neurons. This action would augment the inhibition of cardiac parasympathetic neurons, reduce parasympathetic cardioinhibitory activity, and increase heart rate. Interestingly, expression of the GABA  $\epsilon$  subunit into cardiac vagal neurons alters the GABAergic receptors and confers barbiturate insensitivity to the inhibitory synaptic response.<sup>10</sup> The mechanism by which this anesthetic resistance occurs has not yet been elucidated. The  $\epsilon$  subunit may disrupt the anesthetic site on the GABA<sub>A</sub> receptor. Alternatively, the  $\epsilon$  subunit may prevent the allosteric interaction between GABA and anesthetic binding sites.

Although propofol has been reported to potentiate inhibitory  $\gamma$ -aminobutyric acid (GABA)- and glycine-induced currents and directly activate both GABA and glycine receptors expressed in xenopus oocytes,<sup>11,12</sup> hippocampal pyramidal,<sup>13</sup> and spinal neurons,<sup>14</sup> it is still unknown whether it has similar effects on parasympathetic neurons in the brainstem. This study examines whether propofol, at clinically relevant concentrations, alters the GABAergic and glycinergic neurotransmission to cardiac vagal neurons. The frequency, amplitude, and decay time of both spontaneous IPSCs and miniature IPSCs (mIPSCs) were examined to determine the site of action of propofol on cardiac vagal neurons.

## Materials and Methods

Experiments were performed in accordance with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association and the Na-

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tional Institutes of Health publication *Guide for the Care and Use of Laboratory Animals*<sup>15</sup> and are in compliance with the institutional guidelines at George Washington University (Washington, D.C.).

#### *Slice Preparation*

In an initial surgery, rats (2–6 days old) were anesthetized with ketamine and xylazine and hypothermia. The heart was then exposed through a right thoracotomy, and the retrograde fluorescent tracer rhodamine (XRITC; Molecular Probes, Eugene, OR; 2% solution) was injected into the pericardial sac and applied to the site of the terminals of preganglionic cardiac vagal neurons that are located in the fat pads at the base of the heart.<sup>16</sup> One to 3 days later, the animals were anesthetized with halothane and humanely killed by cervical dislocation. The brain was emerged in cold (4°C) buffer of the following composition: 140 mM NaCl, 5 mM KCl, 2 mM CaCl<sub>2</sub>, 5 mM glucose, and 10 mM HEPES, oxygenated continually with 100% O<sub>2</sub>. Under a dissection microscope, the cerebellum was removed, and the hindbrain was isolated. Slices of 400- $\mu$ m thickness were obtained using a vibratome and were transferred to the recording chamber and continuously perfused at 2 ml/min with a solution of the following composition: 125 mM NaCl, 3 mM KCl, 2 mM CaCl<sub>2</sub>, 26 mM NaHCO<sub>3</sub>, 5 mM dextrose, and 5 mM HEPES, aerated with 95% O<sub>2</sub>–5% CO<sub>2</sub> at a pH of 7.4. In experiments that examined mIPSCs, tetrodotoxin (1  $\mu$ M) was included in the perfusion to block action potential-dependent events. Individual cardiac vagal neurons in the nucleus ambiguus were identified by the presence of the fluorescent tracer, imaged with differential interference contrast optics, and studied using patch clamp electrophysiologic methodologies.

#### *Electrophysiologic Recordings*

Patch pipettes were pulled from glass capillaries (World Precision Instruments, Inc., Sarasota, FL) with an OD of 1.5 mm on a two-stage puller (PP-830; Narishige, Tokyo, Japan) and filled with solution of the following composition: 150 mM KCl, 2 mM MgCl<sub>2</sub>, 2 mM EGTA, 10 mM HEPES, and 2 mM Mg-ATP at a pH of 7.4. The membrane potential was held at –80 mV to examine spontaneous GABAergic and glycinergic IPSCs and mIPSCs. Electrophysiologic recordings were sampled at 200  $\mu$ s with a low-pass Bessel filter at 1 kHz.

#### *Experimental Protocols*

To isolate GABAergic synaptic events, slices were perfused with D-2-amino-5-phosphonovalerate (AP5; 50  $\mu$ M), 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 50  $\mu$ M) and strychnine (1  $\mu$ M) to block postsynaptic *N*-methyl-D-aspartate and non-*N*-methyl-D-aspartate glutamatergic and glycinergic receptors, respectively. Glycinergic events were isolated by perfusion with AP5 (50  $\mu$ M), CNQX (50  $\mu$ M),

and gabazine (50  $\mu$ M) to block postsynaptic *N*-methyl-D-aspartate and non-*N*-methyl-D-aspartate glutamatergic and GABAergic receptors, respectively. Propofol was applied by inclusion in the bath perfusion at concentrations of 0.1, 1, 5, 10, 50, and 100  $\mu$ M. Each dose of propofol was administered for 2 min. At the end of each experiment that examined GABAergic and glycinergic neurotransmission, gabazine (50  $\mu$ M) and strychnine (1  $\mu$ M) were applied to block the remaining GABAergic and glycinergic activity, respectively. GABAergic mIPSCs were isolated in the same solution as described above for isolating GABAergic neurotransmission, except tetrodotoxin (1  $\mu$ M) was included in the perfusate to block action potential-dependent events.

#### *Drugs*

Propofol (Diprivan) was obtained from Zeneca Limited (Macclesfield, Cheshire, United Kingdom). AP5, CNQX, strychnine, gabazine, and tetrodotoxin were purchased from Sigma Aldrich (St. Louis, MO).

#### *Data and Statistical Analysis*

Data were acquired using pCLAMP 8.0 software (Axon Instruments Inc., Union City, CA). Analysis of spontaneous synaptic currents was performed using MiniAnalysis (Synaptosoft, Decatur, GA; version 4.3.1) with amplitude thresholds of 20 pA for GABAergic IPSCs, 30–35 pA for glycinergic IPSCs, and 8 pA for mIPSCs. Values are expressed as mean  $\pm$  SEM. Statistic analysis was performed using analysis of variance or paired *t* test to detect differences between control and propofol-modulated GABAergic or glycinergic neurotransmission. A *P* value less than 0.05 was accepted as significantly different.

## **Results**

Propofol at a concentration of 0.1  $\mu$ M had no significant effect on GABAergic IPSC decay time or frequency. However, at concentrations from 1 to 100  $\mu$ M, propofol evoked significant increases in the decay time of spontaneous GABAergic IPSCs (fig. 1). The average IPSC decay time increased from 78.1  $\pm$  7.5 to 101.7  $\pm$  8.8 ms in the presence of propofol at a concentration of 1.0  $\mu$ M. The decay time was prolonged to 102.0  $\pm$  9.5, 110.2  $\pm$  11.0, 111.7  $\pm$  7.2, and 110.1  $\pm$  9.8 ms when propofol was applied at concentrations of 5, 10, 50, and 100  $\mu$ M, respectively.

To assess the reversibility of the effects of propofol on GABAergic IPSC decay time, changes in decay time were measured during application and on washout of 10  $\mu$ M propofol. Propofol increased the decay time of GABAergic IPSCs, and this increase in decay time persisted for 5

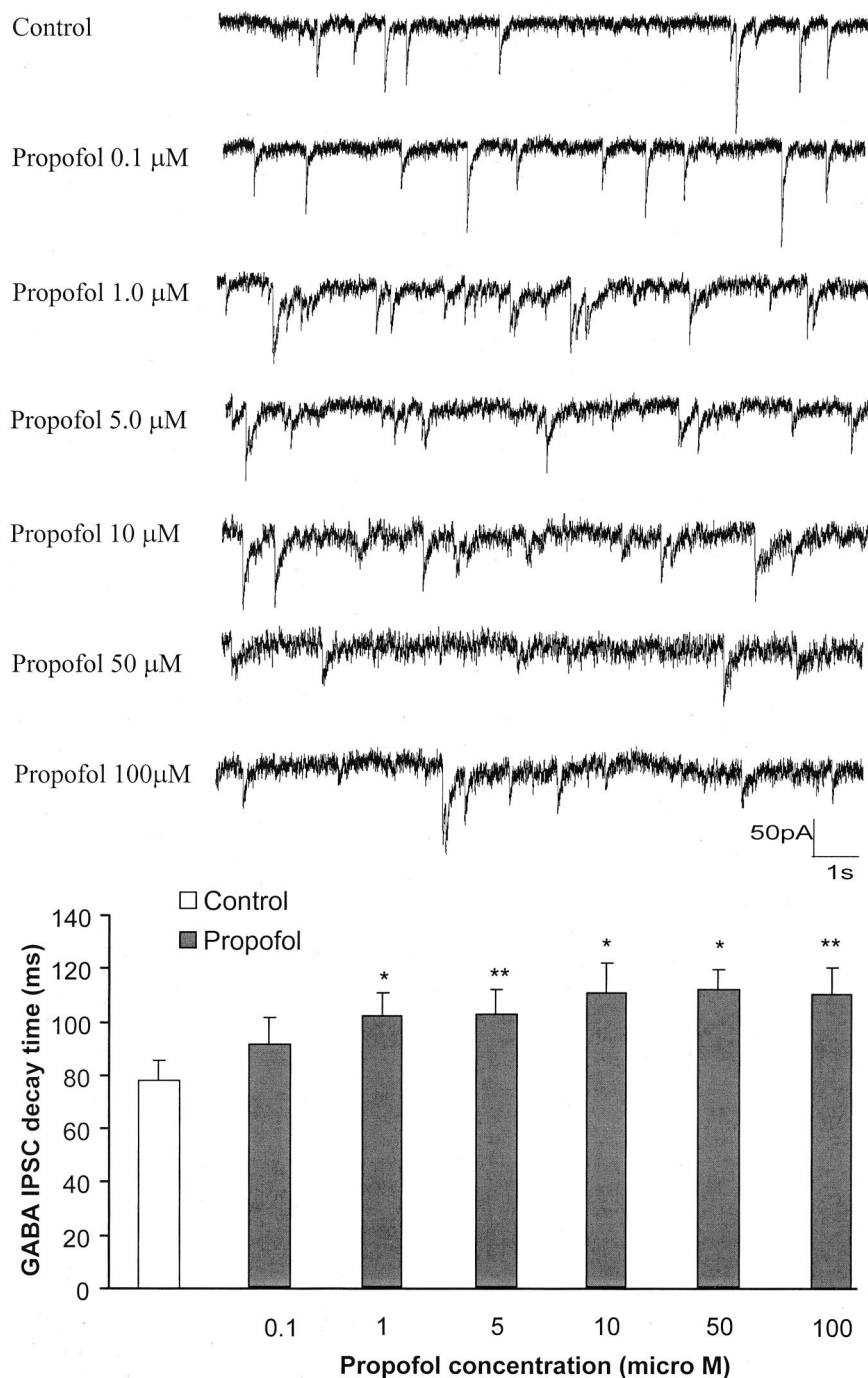


Fig. 1. Propofol at concentrations of 1  $\mu\text{M}$  and greater significantly increased the decay time of  $\gamma$ -aminobutyric acid (GABA)-mediated inhibitory postsynaptic currents (IPSCs) in parasympathetic cardiac vagal neurons. Representative traces of GABA-mediated IPSCs are shown in the top portion, at propofol concentrations of 0.1, 1.0, 5.0, 10.0, 50.0, and 100  $\mu\text{M}$ . The average results from seven cardiac vagal neurons are shown in the bottom portion. \*  $P < 0.05$ , \*\*  $P < 0.01$ .

min after propofol application (fig. 2). The effects of propofol were no longer significant 10 min after propofol application, and after 30 min, the decay time was indistinguishable from control values.

To examine whether this increase in GABAergic IPSC decay time could be caused by changes in the action potential in the preceding GABAergic neuron or whether the increase in decay time was action potential independent and likely due to postsynaptic changes, GABAergic mIPSCs were isolated in the presence of tetrodotoxin. Propofol at concentrations from 1 to 100  $\mu\text{M}$

but not 0.1  $\mu\text{M}$  significantly augmented the decay time of GABAergic mIPSCs (fig. 3). At concentrations of 1, 5, 10, 50, and 100  $\mu\text{M}$ , propofol increased the mIPSC decay time from  $77.6 \pm 7.4$  to  $93.8 \pm 8.0$ ,  $95.1 \pm 8.7$ ,  $98.8 \pm 11$ ,  $98.1 \pm 11$ , and  $92.9 \pm 4.6$  ms, respectively (fig. 3).

Propofol also seems to have presynaptic effects indicated by reductions in both GABAergic IPSC and mIPSC frequency, as shown in figure 4. GABAergic IPSC frequency was inhibited by 30% and 50%, and GABAergic mIPSCs were diminished by 50% and 70% with propofol concentrations of 50 and 100  $\mu\text{M}$ , respectively (fig. 4).



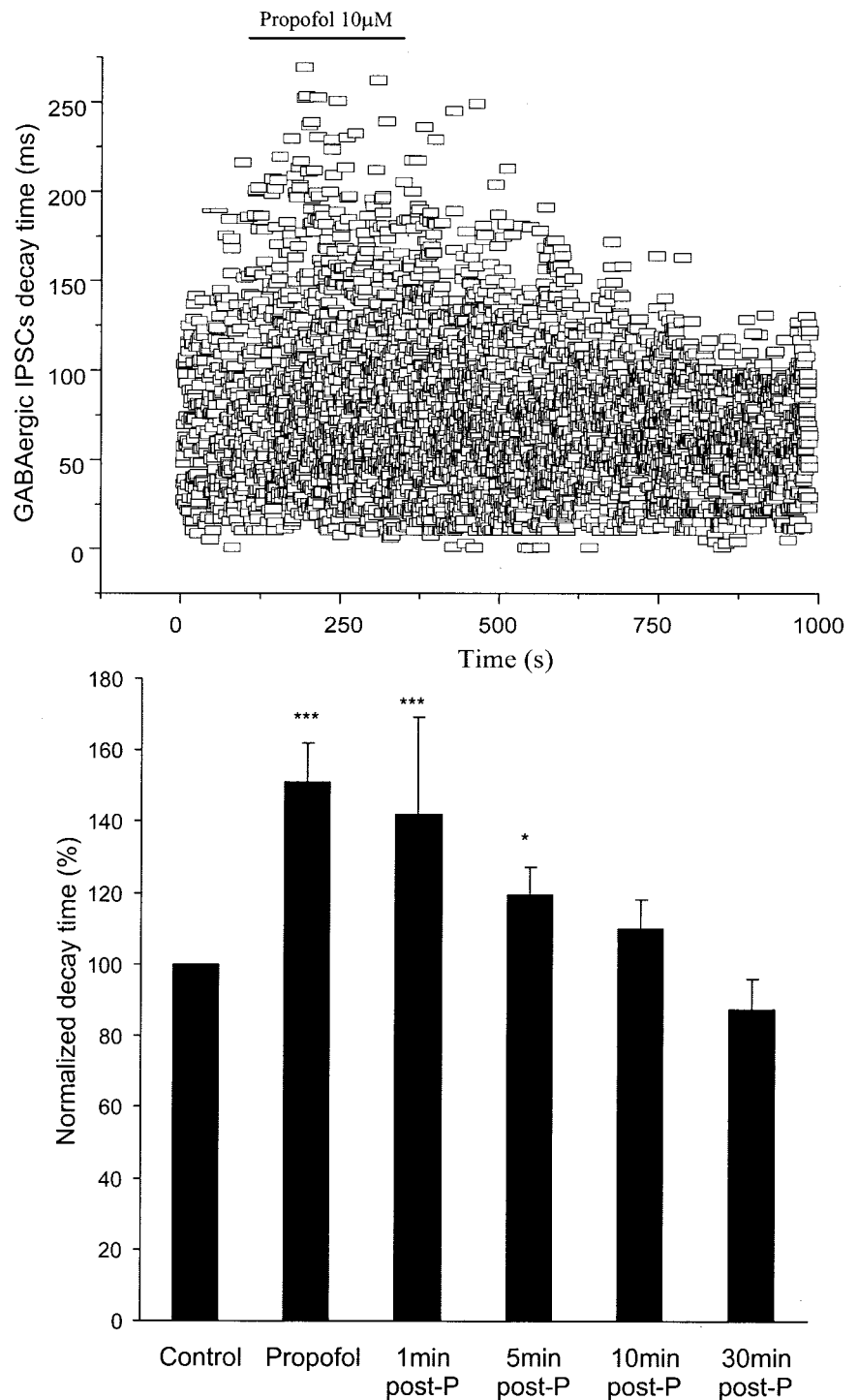


Fig. 2. Propofol at a concentration of 10  $\mu\text{M}$  significantly increased the decay time of  $\gamma$ -aminobutyric acid-mediated (GABAergic) inhibitory postsynaptic currents (IPSCs) in parasympathetic cardiac vagal neurons. The increase in decay time persisted for 5 min after washout of propofol, as shown in a representative experiment (*top*) and from the average results from seven cardiac vagal neurons (*bottom*). The effects of propofol were no longer significant 10 min after propofol application, and after 30 min, the decay time was indistinguishable from control values. \*  $P < 0.05$ , \*\*  $P < 0.01$ .

However, these presynaptic actions occurred at only propofol concentrations greater than 50  $\mu\text{M}$ . Propofol did not evoke any significant changes in the amplitude of either GABAergic IPSC or mIPSCs.

To test whether propofol acts at another important inhibitory pathway to cardiac vagal neurons, the effect of propofol on glycinergic neurotransmission to cardiac vagal neurons was examined. Even at concentrations up to 50  $\mu\text{M}$ , propofol did not elicit any significant alteration

of glycinergic IPSCs frequency, amplitude, or decay time (fig. 5).

### Discussion

Propofol has been reported to act on various receptors and ion channels in neurons and other neuronal preparations, including hippocampus CA1 pyramidal neurons,<sup>17,18</sup> cortical neurons,<sup>19</sup> cerebellar synaptosomes,<sup>20</sup>

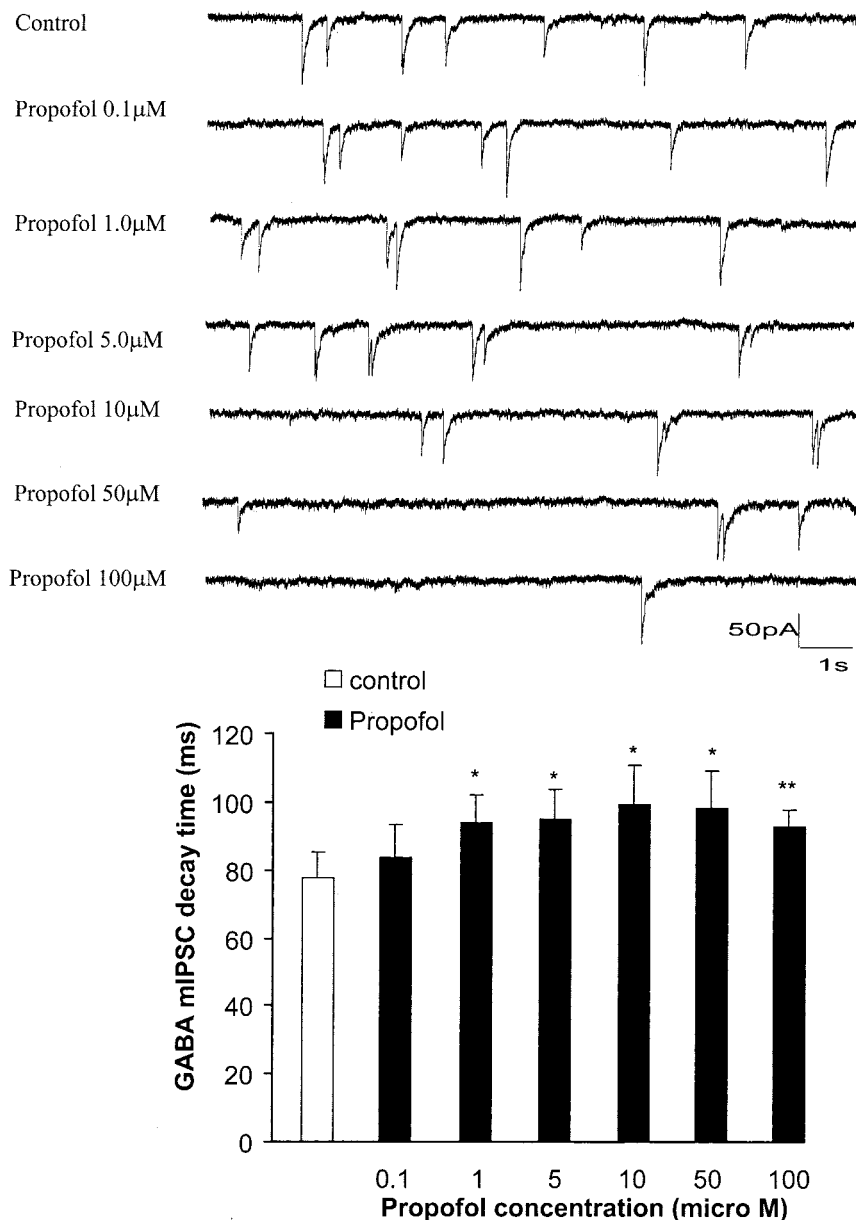


Fig. 3. In the presence of tetrodotoxin ( $1 \mu\text{M}$ ), propofol at concentrations of  $1 \mu\text{M}$  and greater significantly increased the decay time of  $\gamma$ -aminobutyric acid (GABA)-mediated miniature inhibitory postsynaptic currents (mIPSCs) in parasympathetic cardiac vagal neurons. Representative traces of GABA-mediated mIPSCs are shown in the top portion, at propofol concentrations of 0.1, 1.0, 5.0, 10.0, 50.0, and  $100 \mu\text{M}$ . The average results from eight cardiac vagal neurons are shown in the bottom portion. \*  $P < 0.05$ , \*\*  $P < 0.01$ .

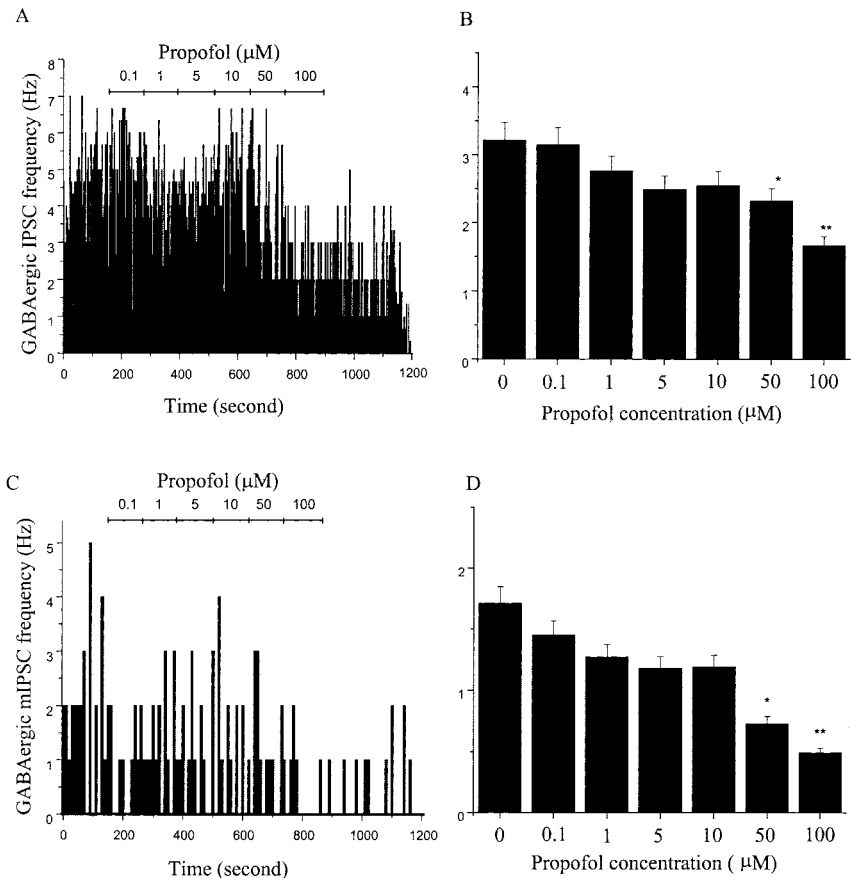
*Xenopus* oocytes<sup>12,21,22</sup> and in spinal cord.<sup>23</sup> However, the effect of propofol on neurons in the brainstem involved in cardiovascular homeostasis is particularly clinically relevant and has received little attention. This study examined the effects of propofol on parasympathetic cardiac vagal neurons in the nucleus ambiguus that dominate the control of heart rate.

Propofol at clinically relevant concentrations evoked changes in the GABAergic neurotransmission to cardiac vagal neurons. Propofol elicited a prolongation of both GABAergic IPSC and mIPSC decay times at concentrations of  $1 \mu\text{M}$  and greater. This alteration of decay time is consistent with what has been observed in other neurons within the central nervous system. Propofol has been shown to increase the duration of spontaneous and endogenous inhibitory synaptic responses by reducing

desensitization of postsynaptic GABA<sub>A</sub> receptors in cultured hippocampal neurons<sup>17,18</sup> and dissociated spinal dorsal horn neurons.<sup>24</sup> In primary cultured rat cortical neurons, propofol prolongs the decay phase of GABAergic mIPSCs and IPSCs at concentrations from 1 to  $10 \mu\text{M}$ .<sup>19</sup> It has been proposed that this prolongation of decay time is due to a reduction in postsynaptic GABA<sub>A</sub> receptor desensitization.

The results of this study show that in addition to an increase in decay time, at higher concentrations, propofol inhibits the frequency of GABAergic IPSCs and mIPSCs in cardiac vagal neurons. However, this inhibition of GABAergic frequency only occurred at higher concentrations of propofol ( $\geq 50 \mu\text{M}$ ). Because propofol decreased the frequency of action potential-independent GABAergic mIPSCs, the site of action of propofol is

**Fig. 4.** Propofol significantly inhibited the frequency of both  $\gamma$ -aminobutyric acid-mediated (GABAergic) inhibitory postsynaptic currents (IPSCs) and GABAergic miniature inhibitory postsynaptic currents (mIPSCs) in parasympathetic cardiac vagal neurons. However, significant inhibition of IPSC and mIPSC frequency only occurred at high concentrations of propofol, 50 and 100  $\mu\text{M}$ . The time course of a typical experiment examining GABAergic IPSCs is shown in *A*, and the results from seven experiments are shown in *B*. The effect of propofol on GABAergic mIPSCs is shown from a typical experiment in *C*, and the results from eight experiments are shown in *D*. \*  $P < 0.05$ , \*\*  $P < 0.01$ .



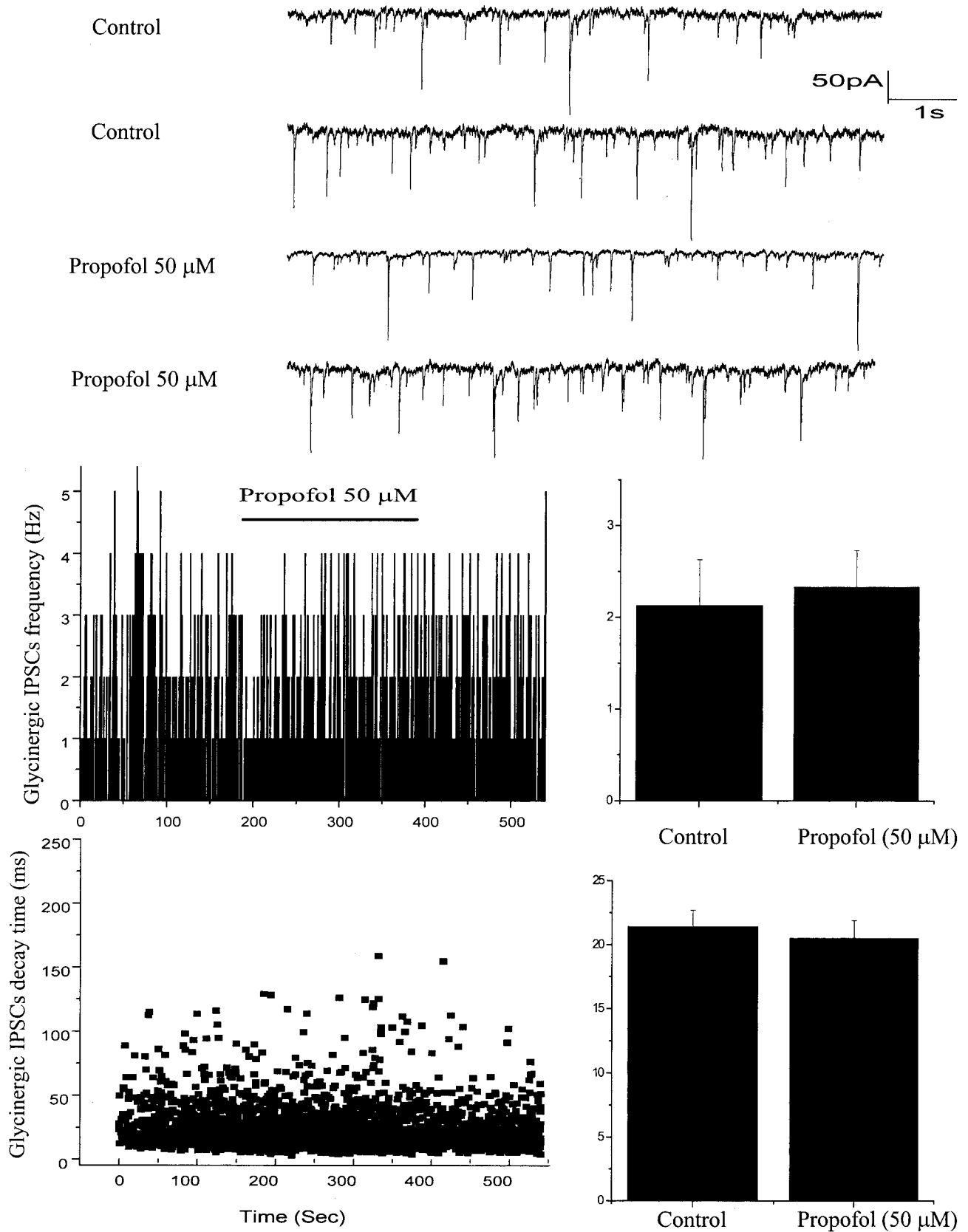
likely on the presynaptic GABAergic terminal. Other work has also shown that propofol can alter GABAergic frequency. Propofol at a concentration of 10  $\mu\text{M}$  increased the frequency of GABAergic mIPSCs in granule cells of the dentate gyrus.<sup>25</sup>

Studies on the effect of propofol on glycinergic receptors are controversial. Propofol (10  $\mu\text{M}$ ) prolonged the glycinergic mIPSCs in spinal cord by slowing desensitization and deactivation of glycinergic receptors,<sup>26</sup> and propofol has also been shown to inhibit glycinergic currents at high doses (100  $\mu\text{M}$ ).<sup>24</sup> Lower doses of propofol (1–10  $\mu\text{M}$ ) have been shown to enhance glycine-evoked responses in the optic nerve,<sup>27</sup> but in another study using human homomeric  $\alpha_1$  glycine receptors<sup>28</sup> in cultured hippocampal neurons, glycine-evoked currents were not altered by propofol.<sup>27</sup> In our study, propofol did not significantly alter glycinergic IPSCs in cardiac vagal neurons, suggesting propofol acts selectively on inhibitory GABAergic but not glycinergic neurotransmission to cardiac vagal neurons.

Clinically, propofol has been shown to increase heart rate when it is constantly infused intravenously at low doses (0.2–0.4  $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) to induce light sedation.<sup>2</sup> However, this situation does not occur commonly in clinical propofol anesthesia. A plasma propofol concentration of 1  $\mu\text{M}$  only produces sedation, and propofol concentrations of greater than 10  $\mu\text{M}$  are typically nec-

essary to achieve anesthesia when propofol is applied as the sole anesthetic agent.<sup>29</sup> Because propofol has a narrow therapeutic index and causes respiratory arrest when administered in excessive doses, it is usually administered with opioids or other volatile anesthetic agents in surgical anesthesia. Propofol is highly protein bound (as much as 98%) and plasma free propofol concentrations are typically maintained between 2 and 6  $\mu\text{M}$  when coadministered with other anesthetic agents in surgical anesthesia.<sup>29,30</sup> At comparable concentrations in this study (1 and 5  $\mu\text{M}$ ), propofol evoked an increase in GABAergic IPSC decay time, which would inhibit cardioinhibitory cardiac vagal neurons and elicit an increase in heart rate. At higher concentrations ( $\geq 50 \mu\text{M}$ ), propofol evoked a decrease in the inhibitory GABAergic frequency to cardiac vagal neurons, which would be expected to increase the activity of cardioinhibitory parasympathetic neurons, thereby decreasing heart rate. This is consistent with the clinical situations in which propofol anesthesia induces decreases in blood pressure, heart rate, and inhibition of respiratory rate if it is applied at high concentrations or if propofol is injected rapidly.<sup>6</sup> Experiments in animal studies also show that high doses of propofol induce bradycardia.<sup>5</sup>

In conclusion, this study showed that propofol at clinically relevant concentrations augments GABAergic activity to cardiac vagal neurons by increasing GABAergic



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**Fig. 5.** Propofol at a concentration of 50 μM had no significant effect on glycinergic decay time, frequency, or amplitude. Results from a typical experiment are shown in the *top portion*, and the summary from seven cardiac vagal neurons are shown in the *bottom portion*. IPSC = inhibitory postsynaptic current.

IPSC and mIPSC decay time. At higher concentrations (>50  $\mu\text{M}$ ), propofol also reduced GABAergic IPSC and mIPSC frequency. These propofol-induced alterations in the inhibitory GABAergic pathway to cardiac vagal neurons are likely involved in the cardiovascular changes that occur with propofol anesthesia.

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