Inhibitory Effects of Propofol on Neuron Firing Activities in the Rostral Ventrolateral Medulla

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Abstract

The effect of propofol on neuronal activity in the rostral ventrolateral medulla (RVLM) is not well established. Therefore, we performed extracellular recording on neurons of the RVLM to investigate neuronal activity before and after administration of intravenous propofol. The mean systemic arterial pressure (MSAP), heart rate and integrated neuronal firing rate (INFR) in the RVLM were continuously recorded in anesthetized cats before and after intravenous injection of 2 mg/kg propofol or supplemental injections of 1, 2 and 4 mg/kg propofol that were given respectively. Additionally, we compared the MSAP, heart rate (HR), and INFR in the RVLM following intravenous injection of 2 mg/kg propofol or 12.5 μg/kg nitroprusside. Neuronal firing was dose-dependently and reversibly inhibited after the supplemental doses of 1, 2 and 4 mg/kg propofol. The control INFR was 14.2 ± 9.9 Hz, and this decreased to 12.1 ± 9.4 Hz after the first dose of propofol (P = 0.085 *vs*. control), and further decreased to 9.3 ± 7.7 Hz (P = 0.001 *vs*. control) and 7.5 ± 7.7 Hz (P < 0.001 *vs*. control) after the second and third doses of propofol, respectively. Besides, SAP and HR were dose-dependently decreased by propofol as well. However, the effects of propofol and nitroprusside on neuronal activity in the RVLM differed. Propofol inhibited neuronal firing, whereas nitroprusside activated neuronal firing. In conclusion, propofol may dose-dependently inhibit spontaneous neuronal activity and the baroreflex in the RVLM.

Key Words: hypotension, bradycardia, propofol, rostral ventrolateral medulla, extracellular recording

Introduction

Propofol (2,6-diisopropylphenol, diprivan) is a commonly used intravenously administered general anesthetic, or sedative agent, with the advantages of rapid onset, effective and rapid recovery (2, 16, 18). However, the major side effects of propofol include hypotension and bradycardia, especially in the elderly or critically ill patients (14, 20). Although these adverse effects can be induced peripherally by myocardial inhibition and vasodilatation (1, 13, 16), inhibition by the sympathetic nervous system also plays a crucial role in hypotension and bradycardia (10, 11, 21). An important integrating mechanism for the

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sympathetic nervous system resides in the medulla, especially in the rostral ventrolateral medulla (RVLM). Many studies indicate that the RVLM regulates tonic sympathetic outflow (3, 4, 9). For example, electrolytic lesioning or chemical inactivation of RVLM neurons by inhibitory substances, such as glycine and γ-aminobutyric acid, results in a depressor response (6, 7, 17). In contrast, electrical or chemical stimulation of RVLM neurons by excitatory substances, such as glutamate and angiotensin II, produces a pressor response (12, 15, 19). However, direct evidence of the action of propofol in the RVLM, especially concerning neuronal activity, is not well-established.

Nitroprusside is a pure vasodilator, and it doesn't have central Inhibitory effect. The mechanism of SAP decrease in nitroprusside is different with that in propofol. In this study we compare the effects of nitroprusside and propofol on neuron firing, SAP and HR. To further investigate the action of propofol in the RVLM, we hypothesized that propofol may inhibit the activity of RVLM neurons, thus causing hypotension and bradycardia. We subsequently used extracellular recording of neurons to directly assess neuronal firing in the RVLM and to investigate neuronal activity when neurons were exposed to different doses of propofol.

Materials and Methods

Preparation Experiments were performed in 42 cats of either sex (1.8 – 4.2 kg) anesthetized with a mixture of α-chloralose (40 mg/kg) and urethane (400 mg/kg) administered intraperitoneally. All experimental procedures followed were approved by the Committee of Animal Care and Use of the Institute of Biomedical Sciences following the Guidelines of National Science Council. The trachea was intubated to allow spontaneous respiration or artificial ventilation through a respirator (Harvard Apparatus, Holliston, MA, USA). Animals were paralyzed by intravenous administration of gallamine triethiodide (2 mg/kg). Respiratory rate and tidal volume were adjusted to an end expiratory CO_2 concentration of 3.5 –4.0%, monitored with a capnograph (Capnograph IV, Gould, OH, USA). Rectal temperature was maintained at 37 ± 0.5 °C with a homeothermic blanket system. A polyethylene catheter (No. 14) was inserted into the right femoral vein of each animal for administration of drugs or fluid, and into the right femoral artery for monitoring systemic arterial pressure (SAP), mean SAP (MSAP) and heart rate (HR).

The head of each cat was fixed in a David-Kopf stereotaxic apparatus. The pressor region in the RVLM was located stereotaxically at 3.5 –4.5 mm rostral, 3 –4 mm lateral, and 3 –4 mm ventral, to the obex of the medulla. The stereotaxic coordinates were based primarily on the cytoarchitectonic atlas of the brain stem, with modifications. The obex was used as a reference stereotaxic zero, and a tungsten electrode was inserted into the brain stem at an angle of 34°, which is perpendicular to the floor of the fourth cerebral ventricle (2).

Unit activity was amplified through a preamplifier (Neurolog system, NL 104, Digitimer, Welwy Garden City, UK) coupled to a filter (NL 126, bandwidth frequency 5 –3 kHz), and displayed on an oscilloscope (4050, Gould). Signals were transmitted to a window discriminator (WPI 121) to remove background noise. Spikes above the low level of the window discriminator were converted to a transistor-transistor logic pulse (TTL, 5 V, 1 ms) with the window discriminator, and then integrated using an integrator (sample/hold, Gould) with a reset time of 1 s.

The integrated neuronal firing rate (INFR) was measured in hertz (Hz). The absolute value of the INFR was calibrated by a series of pulses (5 V, 1 ms) generated from a function generator (Tektronix, FG 507). All data were recorded and stored on a PowerLab system coupled with chart software (AD Instruments) and a polygraph recorder (2800S, Gould) coupled with a tape recorder system (Neuro Data DR-890, Sony slv-400), for later analysis.

Recordings after a Clinical Dose of Propofol

Thirty spontaneous neuronal firings were recorded from RVLM neurons of 15 cats. Once neuron firings had been obtained, 10 min were allowed to pass for neuronal activity to stabilize. The MSAP, HR, neuronal firing rate (NFR), and INFR were recorded. Parameters measured for 2 min before the propofol injection were defined as the controls. Then, 2 mg/kg propofol was injected through the femoral vein. Recordings were taken continuously until the MSAP and NFR returned to control levels. The neuronal firing rate at a certain time was taken by averaging several measurements over one min.

Recordings after an Incremental Dose of Propofol

Thirty spontaneous neuronal firings were recorded from RVLM neurons of 15 cats. The same procedure was performed as described above, except that instead of a single injection of propofol, supplemental injections of 1, 2 and 4 mg/kg propofol were given at intervals of 2 min, respectively. The MSAP, HR, and NFR were recorded continuously until the MSAP and NFR returned to control values.

Comparing the Action of Propofol and Nitroprusside on Neuronal Firings of the RVLM

Twelve neuronal firings were recorded from

Table 1. Effects of 1 ml saline on NF, SAP and HR

	Control	saline	
		1 min after injection	2 min after injection
NFR	17.0 ±9.3	16.9 ±8.9	16.8 ±8.0
SAP	123.8 ±28.3	123.3 ±28.0	123.7 ±28.3
HR	184.0 ±36.4	183.7 ±35.7	183.5 ±35.1

Abbreviations: NFR, firing rate of neuron; SAP, systemic arterial pressure; HR, heart rate. Value are mean ± SD, n = 12 in each group.

RVLM neurons of six cats in this part of the study. To further study the actions of propofol in the RVLM, we compared the action of propofol at a dose of 2 mg/kg with the action of nitroprusside at a dose of 12.5 mg/kg. The nitroprusside was diluted with normal saline. The experiment was divided into two phases: the propofol phase and the nitroprusside phase. The order in which the drugs were administered was randomized.

Initially, extracellular recordings of spontaneous neuronal firings in the RVLM were allowed to stabilize for 10 min. Then, either nitroprusside or propofol was injected very slowly through the femoral vein. The MSAP, HR, NFR, and INFR were recorded before drug injection for 2 min (control) and after injection for 10 min.

After completion of the first phase, the study was temporarily interrupted for 30 min to stabilize the neuronal recording. The study then resumed for the second phase using the same procedure as that used for the first phase, except that the different drug was used.

Identification of the RVLM

At the end of the experiment, the anaesthetized cats were euthanased by overdose of pentobarbital. Brains were then prepared and sectioned in a series of 50 μm cryostat sections (2800 Frigocut E, Reichert-Jung, Germany). Needle tracks in the RVLM were identified under a 40 × microscope. The tip of needle track fitting the anatomical position of the RVLM was counted.

Statistical Analysis

Data are presented as means and standard deviations (mean ± SD). Differences in the MSAP, HR, and INFR before and after a single propofol injection were analyzed using the Student's paired *t* test. Differences in the MSAP, HR, and INFR before and after supplemental propofol injections were analyzed using repeated one-way ANOVA. Differences in the MSAP, HR, and INFR before, 1 min and 2 min after nitroprusside and propofol injections were also analyzed using repeated one-way ANOVA. Dunnett's test was performed if significant differences between means were observed using the repeated one-way ANOVA, and $P < 0.05$ was accepted as statistically significant.

Results

Recordings after Intravenous Administration of Normal Saline

Twelve neuronal firings from RVLM neurons of six cats were recorded after 1 ml normal saline had been administrated intravenously to examine the volume effect of the intravenous injection. The result revealed that the 1 ml normal saline injection did not influence the neuronal firing rate. Therefore, the volume effect of the intravenous injection could be excluded from this study (Table 1, Fig. 1).

Action of Propofol on Neuronal Firing

We recorded 30 spontaneous neuronal firings in anesthetized cats given 2 mg/kg propofol. The neuronal firing rate varied. Three neurons (3/30) were very sensitive to the clinical anesthetic dose of 2 mg/kg propofol and were rapidly blocked for a short period, after which they gradually regained their activity. Twenty-four neurons (24/30) were sensitive to the 2 mg/kg dose of propofol and their firing gradually decreased, but was not blocked. The remaining three neurons (3/30) were resistant to the dose of 2 mg/kg and showed no change in firing rate. The overall average NFR of the 30 neurons was 14.1 ± 9.9 Hz under control parameters and 9.7 ± 9.0 Hz for 10 min after the 2 mg/kg propofol injection. The recovery time of the firing rate of these 30 neurons was 36.4 ± 19.2 min.

Dose-Response Action of Supplemental Doses of Propofol

To determine the dose-response effect of propofol on medullary neurons, 30 spontaneous neuronal firings were recorded after supplemental doses of 1, 2 and 4

Table 2. Effects of propofol on NF, SAP and HR after 2 min injection

		1 mg/ kg	2 mg/ kg	4 mg/ kg
	Control			
NFR	14.2 ±9.9	12.1 ±9.4	9.3 ±7.7*	7.5 ±7.7*
SAP	122.9 ±21.1	117.7 ±22.2*	111.7 ±22.9*	101 ±21.9*
HR	178.3 ±32.2	173.7 ±32.4*	166.7 ±31.7*	155.5 ±30.8*

Values are mean ± SD, n = 30 in each group; *, $P < 0.05$ when compared with the Control.

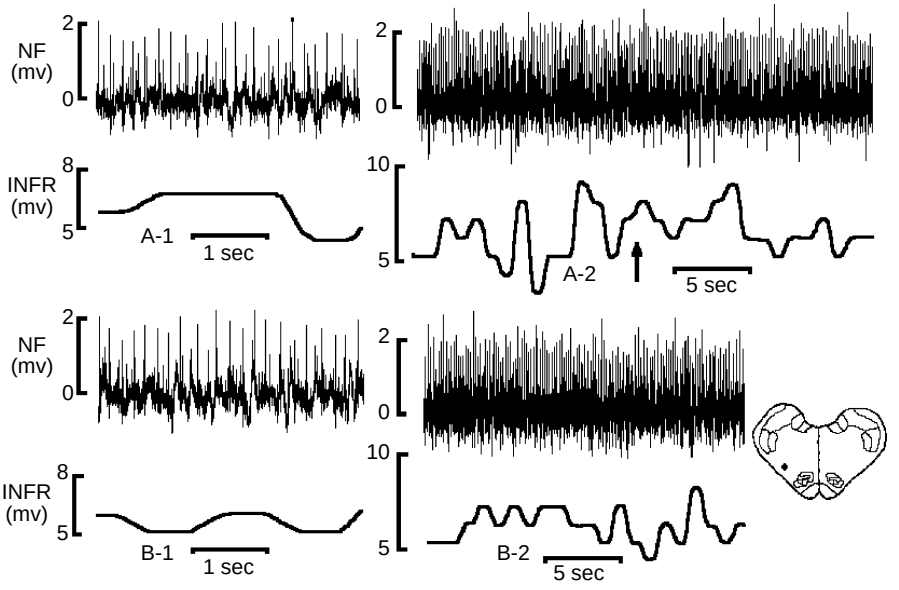

Fig. 1. Neuronal firing in the RVLM before and after intravenous administration of 1 ml normal saline. Panel A-1 shows a fast recording of NFR before the normal saline injection. The length of the bar is 1 s. Panel A-2 shows a slower recording of NFR, which shows no change in INFRs after the normal saline injection. The length of the bar is 5 s. Panel B-1 shows a fast recording of NFR about 2 min after the normal saline injection. Panel B-2 shows a slower recording of NFR around 2 min after the normal saline injection.

mg/kg propofol were given respectively. The firing of most neurons was gradually inhibited by each supplemental dose of propofol. The extent of this inhibition correlated with the total dose of propofol (Table 2, Fig. 2). The control NFR of 14.2 ± 9.9 Hz was depressed to 12.1 ± 9.4 Hz, 2 min after the first supplemental dose of 1 mg/kg propofol ($P = 0.085$) reached 9.3 ± 7.7 Hz, 2 min after the second dose of 1 mg/kg propofol ($P = 0.001$ *vs*. control), and decreased to 7.5 ± 7.7 Hz, 2 min after the third dose of 2 mg/kg propofol ($P < 0.001$ *vs*. control).

The MSAP and HR, which were 122.9 ± 21.1 mmHg and 178.3 ± 32.2 bpm, respectively, in the controls, were also dose-dependently inhibited by propofol. The MSAP and HR decreased to 117.7 ± 22.2 mmHg and 173.7 ± 32.4 bpm, respectively, 2 min after the first dose of propofol ($P < 0.001$), and then further decreased to 111.7 ± 22.9 mmHg and 166.7 ± 31.7 bpm, respectively, 2 min after the second dose of propofol ($P < 0.001$ *vs*. control), and to 101 ± 21.9 mmHg and 155.5 ± 30.8 bpm, respectively, 2 min after the third dose of propofol ($P < 0.001$ *vs*. control).

Although the extent of inhibition in different neurons varied, most neurons (27/30) were sensitive to propofol and were inhibited by the three intravenous supplemental propofol doses (comprising a total dose of 4 mg/kg). Three neurons were resistant to propofol and their firings were not affected by the drug.

Comparison of the Actions of Propofol and Nitroprusside on Neuronal Firings of the RVLM

The neuronal firing rate was significantly potentiated by nitroprusside. The firing rate was 16.8 ± 10.4 Hz in controls, increased to 21.8 ± 12.0 Hz 1 min after the injection ($P = 0.047$ *vs*. control), and was 18.5 ± 11.1 Hz 2 min after the injection ($P = 0.384$ *vs*. control; Table 3, Fig. 3). In contrast, the neuronal firing rate was significantly inhibited by propofol: it was 16.8 ± 9.7 Hz in controls and decreased to 12.3 ±

Table 3. Effects of intravenous injections of nitroprusside and propofol on NF, SAP and HR

	Control	Nitroprusside, 1 mg/ kg		Control	propofol, 2 mg/ kg	
		1 min after injection	2 min after injection		1 min after injection	2 min after injection
NFR	16.8 ± 10.4	21.8 ± 12*	18.5 ± 11.1	16.8 ± 9.7	12.3 ± 9.0*	11.1 ± 9.6*
SAP	125.8 ± 28.0	103.4 ± 25.9*	107.7 ± 24.5*	125.6 ± 27.8	118.0 ± 26.8*	113.7 ± 26.6*
HR	184.6 ± 38.2	203.4 ± 39.3*	193.5 ± 38.9*	184.9 ± 38.3	178.3 ± 37.4*	171.8 ± 35.5*

Values are mean ± SD, n = 12 in each group; *, $P < 0.05$ when compared with the Control.

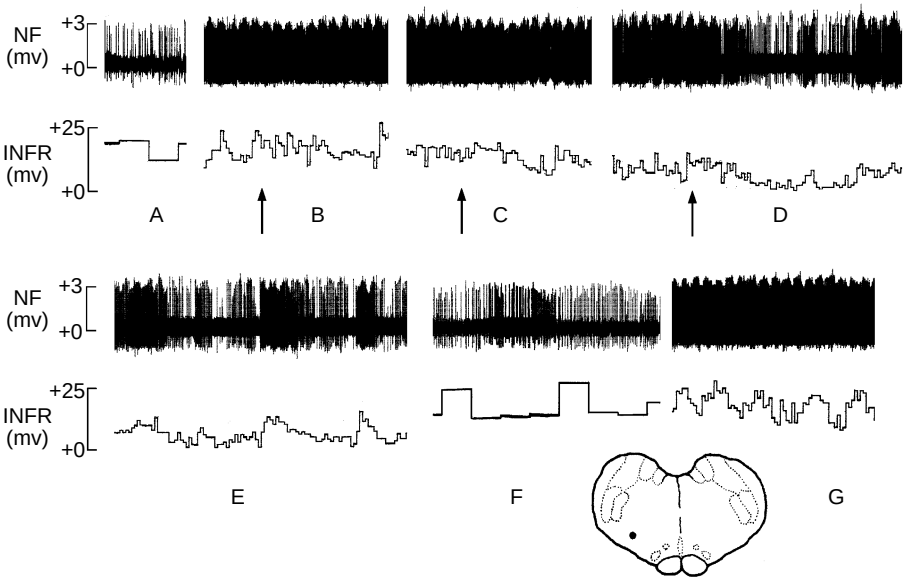

Fig. 2. Neuronal firing in the RVLM before and after intravenous administration of propofol in a cat. Panel A shows the neuronal firing rate (NFR) and integrated neuronal firing rates (INFRs) of the control with a chart speed of 10 mm/s. For panels B to E, the chart speed is 1 mm/s. Panel B shows the NFR immediately after the first dose of 1 mg/kg propofol *i.v.* (arrow). Panel C shows a mild decrease in NFR immediately after the second dose of 1 mg/kg propofol *i.v.* (arrow). Panels D and E show a marked decrease in NFR after the third dose of 2 mg/kg propofol *i.v.* (arrow). Panel D shows the NFR immediately after the propofol injection, and panel E the NFR around 2 min after the propofol injection. Panel F shows the NFR recovery from the third dose of propofol with a chart speed of 10 mm/s. Panel G shows the recording of panel F with a chart speed of 1 mm/s. The dot indicates the site of extracellular recording.

9.0 Hz 2 min after the 2 mg/kg propofol injection ($P < 0.001$ *vs*. control; Table 3, Fig. 3). SAP was not affected by either nitroprusside or propofol. In the nitroprusside group, the MSAP decreased from 125.8 ± 28 mmHg to 103.4 ± 25.9 mmHg 1 min after the injection, and to 107.7 ± 24.5 mmHg 2 min after the injection ($P < 0.001$ *vs*. control; Table 3, Fig. 3). In the propofol group, the MSAP decreased from 125.6 ± 27.8 mmHg in the control group to 118.0 ± 26.8 mmHg 1 min after the injection, and to 113.7 ± 26.6 mmHg 2 min after the injection ($P < 0.001$ *vs*. control; Table 3, Fig. 3).

The effects of nitroprusside and propofol on the HR were different. Propofol caused a decrease in HR, whereas nitroprusside produced an increase in HR. In the nitroprusside group, the HR increased from 184.6 ± 38.2 bpm in controls to 203.4 ± 39.3 bpm 1 min after the nitroprusside injection, and to 193.3 ± 38.9 bpm 2 min after the injection ($P < 0.001$ *vs*. control; Table 3, Fig. 3). In the propofol group, the HR decreased from 184.9 (38.3 bpm in controls to 178.3 ± 37.4 bpm 1 min after the propofol injection, and to 171.8 ± 35.5 bpm 2 min after the injection ($P < 0.001$ *vs*. control; Table 3, Fig. 3).

Discussion

Our major finding is that propofol dose-dependently inhibits neuronal firing in the RVLM. In addition, blood pressure and HR are dose-dependently inhibited by propofol. Nitroprusside causes vasodilatation, and therefore induces hypotension, without any anesthetic effect. To demonstrate that neuronal inhibition is unaffected by hypotension, we injected nitroprusside

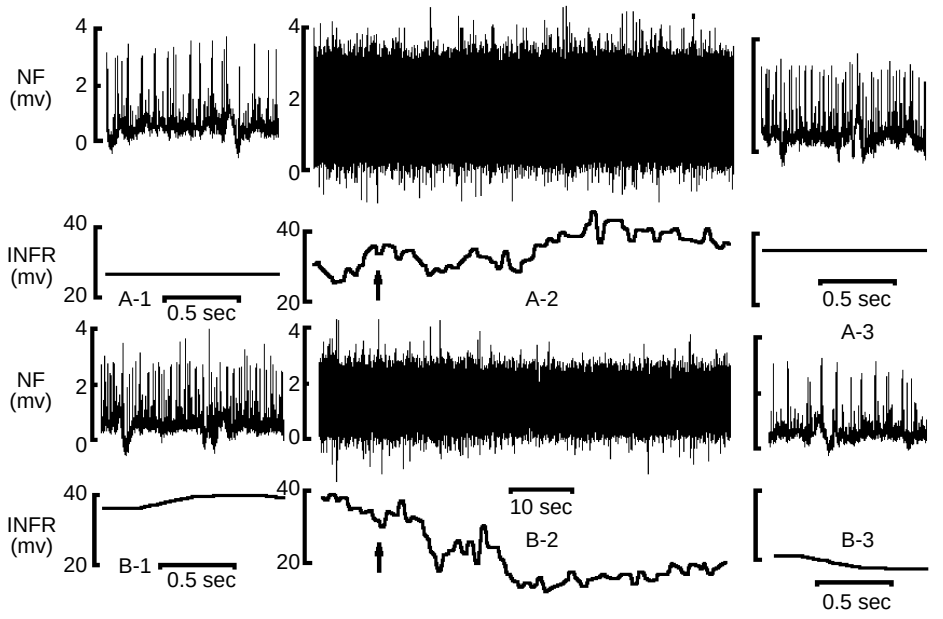

Fig. 3. Comparison of the action of propofol and nitroprusside on neuronal firing of the RVLM. Panel A-1 shows a fast recording of NFR before the nitroprusside injection. The length of the bar is 0.5 s. Panel A-2 shows a slow recording of NFR, which demonstrates the increase in INFRs after an intravenous injection of 12.5 μg/kg nitroprusside. The length of bar is 10 s. Panel A-3 show a fast recording of NFR 2 min after the nitroprusside injection. The length of the bar is 0.5 s. Panel B-1 shows a fast recording of NFR before the propofol injection. The length of the bar is 0.5 s. Panel B-2 shows a slow recording, which demonstrates a decrease in INFRs after an intravenous injection of 2 mg/kg propofol. The length of the bar is 10 s. Panel B-3 shows a fast recording of NFR 2 min after the propofol injection. The length of the bar is 0.5 s.

intravenously. Nitroprusside did not inhibit neuronal firing in the RVLM, nor did it inhibit HR. On the contrary, nitroprusside facilitated neuronal firing, perhaps through the baroreflex. These findings demonstrate that propofol directly inhibits neuronal activity in the RVLM, a result reflected in the falling of the SAP and the decrease in HR. Many studies indicate that the RVLM is the regulatory area for tonic sympathetic outflow (3, 4, 9). It is also a major mediator of SAP and HR. Therefore, the inhibitory action of propofol on the RVLM should play a crucial role in inducing hypotension and bradycardia. Findings show that propofol dose-dependently decreases SAP and HR as well as inhibits spontaneous neuronal activity in RVLM

Careful investigation using extracellular recording of neuronal firing reveals that firing activities of different neurons in the RVLM vary. For example, some neuronal firings are of high frequency and some are of low frequency. This reveals that different types of neurons exist in the RVLM and possibly display different functions. For example, some neurons are bulbospinal neurons that project to the spinal cord, whereas others are interneurons that project within the RVLM (5, 8). Neurotransmitters and receptors on neuronal membranes may also differ in RVLM neurons (3, 4, 9, 12). These variations among RVLM neurons may explain the different inhibitory effects of propofol on RVLM neurons. Some neurons are sensitive to propofol, whereas others are less sensitive. However, most neuronal firings in the RVLM are inhibited by intravenous propofol, demonstrating that the inhibitory effect of propofol has a major effect on spontaneous neuronal firing in the RVLM. We also found that some neurons are insensitive to propofol, which is possibly due to the inactivation of receptors on these neurons by propofol.

Administration of intravenous propofol also causes a dose-dependent inhibition of SAP and HR. However, this effect is less powerful than the inhibition of neuronal firing. This may be due to the following two reasons: (a) many types of neurons exist in the RVLM, (b) individual neuronal functions in the RVLM may differ. As a matter of fact, RVLM contains neurons that function in cardiovascular actions, but RVLM also contains neurons that are involved in other functions, such as sweating, urination, and bowel movement, *etc*.

The volume effect of the intravenous injection did not influence the extracellular recording of neurons in our study. We have recorded neuronal firings before and after injection of 1 ml normal saline and found no change in the firing rate before and after injection. Even a slight increase in the volume of the injection did not produce any effect. The following

two factors may produce better stabilization of recordings and prevent the occurrence of the volume effect: (a) appropriate anesthesia and paralysis, and (b) well-controlled ventilation with adequate muscle relaxant.

In conclusion, propofol dose-dependently directly inhibits neuronal firing in the RVLM. It is involved in producing cardiovascular effects, such as hypotension and bradycardia. The effect of propofol on neuronal firing rate and cardiovascular effects differs from that of the nitroprusside dose in RVLM.

Acknowledgments

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