Propofol Inhibits Neuronal Firing Activities in the Caudal Ventrolateral Medulla

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Background: Propofol is a potent intravenous anesthetic. The action of propofol on the medullary depressor area, the caudal ventrolateral medulla (CVLM), has not been well established. We therefore performed extracellular recordings to study the neuronal activity of the CVLM in cats before and after intravenous propofol administration, to investigate its influence on neuronal firings.

Methods: Experiments were performed on 31 cats anaesthetized with a mixture of α–chloralose and urethane administered intraperitoneally. Mean systemic arterial pressure, heart rate, and the neuronal firing (NF) rate were continuously recorded before and after intravenous injection of a single dose of 2 mg·kg^{-1} propofol or separate supplemental doses of 1, 2, and 4 mg·kg^{-1} propofol until those parameters had returned to the premedication level.

Results: Propofol dose-dependently and reversibly inhibited the NF rate after the supplemental doses of 1, 2, and 4 mg·kg^{-1} propofol. The control NF rate of 17.9 ±8.6 Hz was depressed to 15.8±8.5 Hz after the first dose of propofol ($p<0.05$ vs. the control), and was further depressed to 12.8±8.3 Hz ($p<0.05$ vs. the control) and 10.0±7.9 Hz ($p<0.05$ vs. the control) after the second and the third doses of propofol, respectively.

Conclusion: The dose-dependent inhibition of the spontaneous neuronal firing rate is the main pharmacological action of propofol in the caudal ventrolateral medulla of cats.

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Key words: **propofol, caudal ventrolateral medulla, extracellular recording.**

Much evidence indicates that the caudal ventrolateral medulla (CVLM) is a major tonic inhibitory area in the medulla oblongata, a cardiovascular control center. For example, electrolytic lesions in the CVLM or chemical inactivation of CVLM neurons by inhibitory substances such as glycine, γ-aminobutyric acid (GABA) or its angonist muscimol, or opioids result in a pressor response which increases blood pressure.[1-8] On the contrary, electrical or chemical stimulation of CVLM neurons by excitatory substances such as glutamate or angiotensin II produces a depressor response.[1,9-11] The CVLM has been demonstrated to project inhibitory neuronal transmission directly to the rostral ventrolateral medulla (RVLM) to modulate neuronal activities there.[12-15] Therefore, the CVLM is

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considered to be a depressor area, in contrast to the RVLM.

Propofol (2,6-diisopropylphenol, Diprivan™), is a widely used general anesthetic because of its good amnesic and anesthetic effect, and rapid onset and clearance.[16-18] However, it may still produce a few side effects such as hypotension or bradycardia.[19-23] The mechanisms for propofol's actions have been widely studied, but the central medullary action of propofol, particularly concerning spontaneous neuronal firing in the CVLM, has not been well established. We therefore performed extracellular recording in the CVLM of cats to study neuronal activities following systemic propofol administration. We also studied the effect of different doses of propofol on neuronal activities in the CVLM.

METHODS

Preparation

Experiments were performed on 31 cats of either gender (1.8-4.2 kg) anaesthetized with a mixture of 40 mg·kg^{-1} α-chloralose and 400 mg·kg^{-1} urethane administered intraperitoneally. The trachea of each cat was intubated to allow spontaneous respiration or artificial ventilation through a respirator (Volume Controlled Ventilator, Model 665, Harvard Apparatus, MA, USA). Animals were paralyzed intravenously with 2 mg·kg^{-1} gallamine triethiodide. The 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 measured and maintained at 37±0.5 ˚C with a thermostatically controlled heating pad. Polyethylene catheters (no. 14) were inserted into the right femoral vein for administration of drugs or fluids, and into the right femoral artery for monitoring the systemic arterial pressure, mean systemic arterial pressure (MSAP), and heart rate (HR). The head of the cat was fixed in a David-Kopf stereotaxic apparatus (David-Kopf, Tujunga, CA, USA). The pressor region in the CVLM was located stereotaxically at 1 mm rostral to, 1 mm caudal to, 3-4 mm lateral to, and 3-4 mm ventral to the obex zero of the medulla. The stereotaxic coordinates were based primarily on a cytoarchitectonic atlas of the brainstem with modifications: (1) the obex was used as a reference stereotaxic zero, and (2) the tungsten electrode was inserted into the brainstem at an angle of 34˚ which was perpendicular to the floor of the 4th cerebral ventricle.[24,25] Unit activity was amplified through a preamplifier (Neurolog system, NL 104) coupled with a filter (NL126, band frequency 5 Hz~3 kHz), and displayed on an oscilloscope (Gould 4050). Signals were transmitted to a window discriminator (WP1-121) to remove background noise. Spikes above the low level of the window discriminator were converted to a transitor-transitor logical pulse (5 V, 1 ms) by 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 Hz (spikes/s). The absolute value of the INFR was calibrated by a series of pulses (5 V, 1 ms) generated from a function generator (TEK, FG 507). All data were recorded on a polygraph (2800S, Gould) and stored on a tape recorder system (Neuro Data DR-890, Sony slv-400) for later analysis.

Recordings after intravenous normal saline

Twelve neuronal firings were recorded after 1 ml normal saline was administered intravenously to examine the volume effect of the intravenous injection. The result revealed that the 1 ml normal saline intravenous injection did not influence the neuronal firing rate. Therefore, the volume effect of the intravenous injection in our study can be excluded (data not shown).

Recordings after a clinical dose of propofol

Once neuron firings were obtained by extracellular recording, 10 min were allowed to pass in order for neuronal activity to stabilize. The MSAP, HR, neuronal firing (NF) rate, and INFR were recorded. Parameters measured 2 min before propofol injection were defined as the control. Then, 2 mg·kg^{-1} propofol was injected through the femoral vein. Thereafter, recordings were continuously taken until the MSAP and NF rate returned to their respective control levels. The recovery time of the NF rate was defined as the time needed for the firing rate to return to the control level. The firing rate at a certain time was taken as the value averaged over 1 min.

Recordings after an incremental dose of propofol

The same procedures were performed except that instead of a single injection, supplemental injec-

tions of 1, 1 and 2 mg·kg^{-1} propofol were given at intervals of 2 min. The MSAP, HR, and NF rate were recorded continuously until the MSAP and NF rate had returned to their respective control values. The firing rate at a certain time was also averaged over 1 min.

Identification of the CVLM

At the end of the experiment, the anaesthetized cats were sacrificed with a bolus injection of KCl. Brain sections in series of 50 μm were prepared using a cryostat (2800 Frigocut E, Reichert-Jung, Germany). The needle tracks in the CVLM were identified under a 10x microscope. The tip of the needle tract was confirmed to fit with the anatomical position of the CVLM, otherwise those recordings were excluded.

Statistical analysis

All data are presented as the mean and standard deviation (SD). The difference in the neuronal firing rate before and after the single propofol injection was analyzed using paired *t*-test. Differences in MSAP, HR, and the NF rate before and after supplemental propofol injections were analyzed using repeated-measures ANOVA. The Bonferroni multiple comparison was made to locate differences in the various doses. Statistical significance was defined as $p \leq 0.05$.

RESULTS

The action of propofol on neuronal firing

We recorded 32 spontaneous neuronal firings from 16 cats. Under the action of 2 mg·kg^{-1} propofol, the neuronal firing rate showed some variation. Some neurons (3/32) were very sensitive to a clinical anesthetic dose of 2 mg·kg^{-1} propofol. They were rapidly blocked for a short period of time and then gradually regained their firing activities. Most neurons (25/32) were less sensitive to 2 mg·kg^{-1} propofol; their firing activities gradually decreased but were not blocked. The remaining neurons (4/32) were resistant to 2 mg·kg^{-1} propofol, as evidenced by their firing rate remaining unchanged. The overall average neuronal firing rate of the 32 neurons was 16.6±9.0 Hz in the control and 11.2±8.8 Hz 10 min after propofol injection ($p < 0.001$). The recovery time of the firing rate of these 32 neurons was 37.1 ±18.3 min.

The dose-response action of supplemental doses of propofol

To further study the action of propofol on medullary neurons, 30 spontaneous neuronal firings from 15 cats were recorded to study the dose-response effect. The firing of most neurons was gradually inhibited by supplemental doses of propofol. The extent of firing inhibition correlated with the total dose of propofol (Table 1, Fig. 1). Repeated-measures ANOVA revealed that there was no significant interaction between cats and dose ($p = 0.640$). Dose had a significant effect on the response ($p < 0.001$). The Bonferroni multiple comparison indicated that the control firing rate was 17.9 ±8.6 Hz which was depressed to 15.8±8.5 Hz at 2 min after the first dose of 1 mg·kg^{-1} propofol ($p < 0.05$). It reached 12.8±8.3 Hz at 2 min after the second dose of 1 mg·kg^{-1} propofol ($p < 0.05$ vs. the control) and 10.0±7.9 Hz at 2 min after the third dose of 2 mg·kg^{-1} propofol ($p < 0.05$ vs. the control).

Again, the MSAP and HR were also dose-dependently inhibited by propofol. Repeated-measures ANOVA showed no significant interaction between cats and dose for the MSAP ($p = 0.514$) and HR ($p = 0.311$). A significant dose effect was seen

Table 1. Firing Rate of Neurons, Blood Pressure, and Heart Rate after Supplemental Doses of Propofol

	Control	Total dose of propofol (1 mg·kg^{-1})	Total dose of propofol (2 mg·kg^{-1})	Total dose of propofol (4 mg ·kg^{-1})	*p* (interaction; dose effect)
		2 min after injection	2 min after injection	2 min after injection	
Firing rate (Hz)	17.9± 8.6	15.8± 8.5*	12.8± 8.3*	10.0± 7.9*	0.640; < 0.001
Blood pressure (mmHg)	123.6±16.6	118.3±18.5*	113.3±18.7*	101.8±17.9*	0.514; < 0.001
Heart rate (bpm)	180.8±33.1	176.5±33.0*	169.6±31.7*	156.8±31.1*	0.311; < 0.001

Values are the mean±SD; N = 30 in each group.

*$p < 0.05$ when compared with the control according to Bonferroni multiple comparisons.

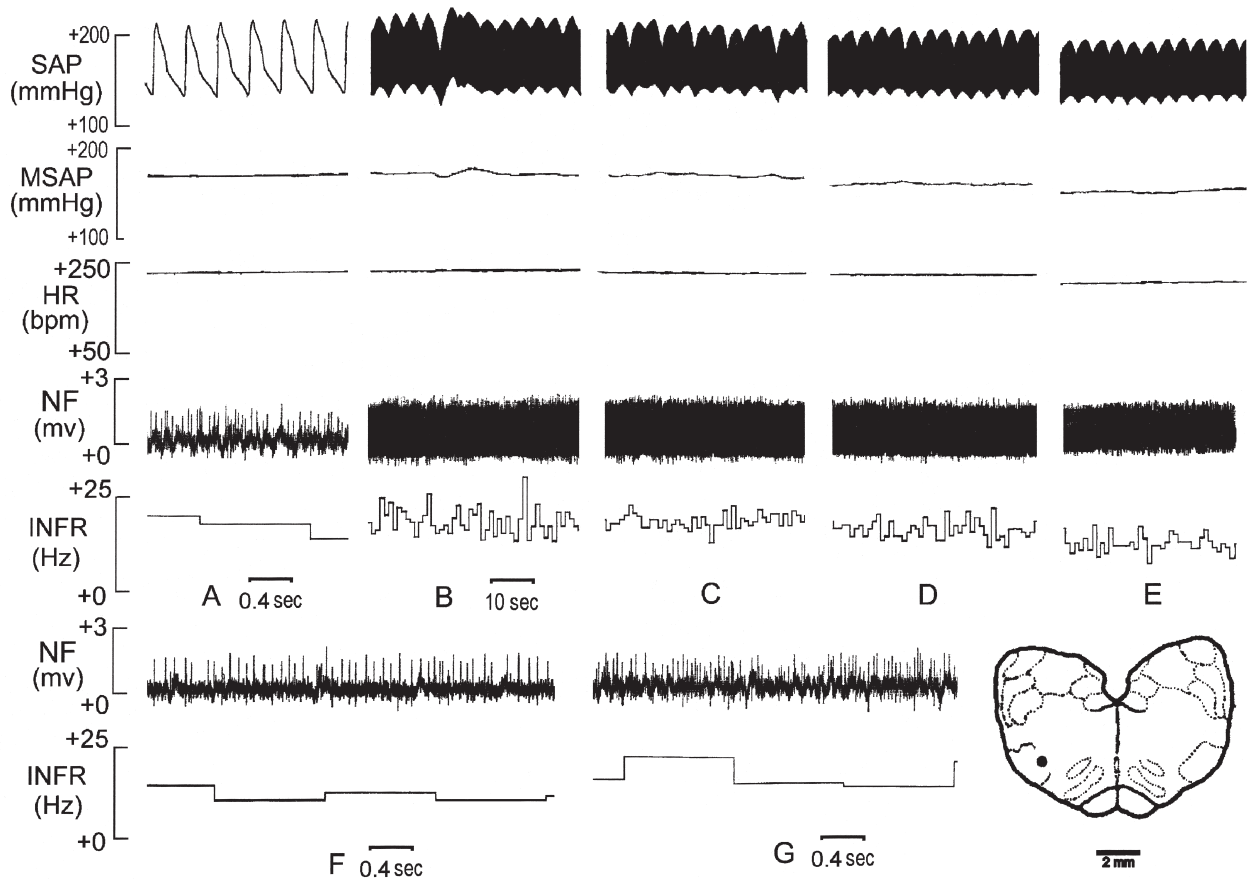

Fig. 1 Dose-response neuronal firing before and after intravenous administration of propofol in a cat. Panels A and B show the systemic arterial pressure (SAP), mean systemic arterial pressure (MSAP), heart rate (HR), neuronal firing (NF) rate, and integrated neuronal firing rate (INFR) of the control with chart speed of 25 and 1 mm·s^{-1}, respectively. In panels C to E, the chart speeds were all 1 mm·s^{-1}. Panel C shows the SAP, MSAP, HR, and NF rate 2 min after the first dose of 1 mg·kg^{-1} propofol i.v. Panel D shows a mild decrease in the SAP, MSAP, HR, and NF rate 2 min after the second dose of 1 mg·kg^{-1} propofol i.v. Panel E shows a marked decrease in the SAP, MSAP, HR, and NF rate 2 min after the third dose of propofol at 2 mg·kg^{-1} i.v. Panel F shows the rate and INFR of panel E with a chart speed of 25 mm·s^{-1}. Panel G shows the NF recovery from the third dose of propofol with a chart speed of 25 mm·s^{-1}. The dot indicates the site of extracellular recording.

in the MSAP ($p<0.001$) and HR ($p<0.001$). They were 123.6±16.6 mmHg and 180.8±33.1 bpm in the control, and decreased to 118.3±18.5 mmHg and 176.5±33.0 bpm, respectively, at 2 min after the first dose of propofol ($p<0.05$). They further decreased to 113.3±18.7 mmHg and 169.6±31.7 bpm at 2 min after the second dose ($p<0.05$ vs. the control), and to 101.8±17.9 mmHg and 156.8±31.1 bpm, respectively, 2 min after the third dose of propofol ($p<0.05$ vs. the control). Although the extent of inhibition in different neurons varied, most neurons (27/30) were sensitive to propofol, and were inhibited during all 3 intravenous propofol administrations (at a total dose of 4 mg·kg^{-1}). Three neurons were resistant to propofol, and their firings were not inhibited by propofol.

DISCUSSION

The major finding of our study is that propofol can dose-dependently inhibit spontaneous neuronal firing in the CVLM area of the medulla. Extracellular recordings in the CVLM revealed that the firing activities of different neurons can vary.

Some neuronal firings are of high frequency and some are of low frequency. This indicates that different types of neurons exist in the CVLM and possibly display different firing patterns or functions. For example, much evidence demonstrates that projecting neurons in the CVLM can transmit electrical signals to many different areas of the brainstem, midbrain, or spinal cord.[1] Also many interneurons exist in the CVLM. These neurons may also display different neuronal firing patterns. Our study also showed that the inhibitory effect of propofol on different neurons in the CVLM was not homogeneous, with some potent inhibitions and some mild inhibitions detected. We also found that some neurons were insensitive to propofol. This reveals that the cytoarchitecture of neurons in the CVLM is heterogeneous. Therefore, propofol may produce different effects on different neurons. However, most neuronal firings in the CVLM being inhibited by intravenous propofol demonstrates that the inhibitory effect of propofol still plays a major role in modulating spontaneous neuronal firing in the CVLM. Neuronal inhibition by propofol was dose dependent. The MSAP also decreased dose-dependently under the action of incremental propofol, but the extent of the MSAP decrease was less than that of the NF decrease (Table 1). There are 3 main possible reasons. 1. There are many factors influencing blood pressure changes; central control is not the only one. Peripheral factors such as vascular or cardiac functions also play an important role in blood pressure changes. 2. It has been demonstrated that the CVLM is the major inhibitory area in the medulla.[1,7,12,13] The major function of the CVLM is to project inhibitory neurotransmission to the RVLM to modulate tonic sympathetic activities.[1,13-15] In contrast to the RVLM, the CVLM is not a sympathetic generating center in the medulla.[1] Therefore, the neuronal firing changes induced by propofol might not be related to blood pressure changes. 3. Individual neuronal functions in the CVLM may differ. In addition to cardiovascular action, other functions such as sweating, urination, and bowel movement are also affected by neurons of the CVLM. Therefore, not all neurons in the CVLM are cardiovascularly related.

It has been demonstrated that the major role of the CVLM is to project tonic inhibitory neuronal transmissions to the RVLM to modulate the medullary sympathetic outflow.[10,14,15] Neurons in the CVLM are mainly GABAergic, in contrast to the glutamatergic neurons in the RVLM.[14] However, in our study, propofol displayed similar actions on neuronal firings in these 2 areas. In other words, propofol not only inhibited neuronal firings in the pressor area, the RVLM, but also inhibited neuronal firing in the depressor area, the CVLM. Therefore, inhibition of the neuronal firing rate causing a decrease in the neuronal activity is the main pharmacological action of propofol in these 2 areas of the medulla.

The volume effect was not found to affect extracellular recordings. We injected 1 ml normal saline instead of propofol to examine the possible volume effect on the neuronal firing rate. This volume of normal saline was more than the volume of the propofol we injected. The result revealed that this volume of normal saline induced no neuronal firing changes. Therefore, the volume effect of injected propofol in this study can be excluded. Adequate anesthesia with well-controlled ventilation may have helped to decrease the occurrence of the volume effect during the extracellular recording of neuronal firing.

Propofol (2,6-diisopropylphenol, Diprivan™), a GABA receptor agonist[16-18] characterized by its fast onset and clearance, has become a commonly used intravenous anaesthetic. The major side effects of propofol include hypotension and bradycardia especially in the elderly, those with volume deficits, or critically ill patients.[19-23] There are many reports describing the mechanisms responsible for the actions of propofol. Peripherally, it has been reported that propofol may produce vasodilatation, as well as negative chronotropic and inotropic actions.[20,26-29] Centrally, it has been reported that in rats, propofol may reduce sympathetic renal nerve activity and antagonize the inhibitory action of glycine in the RVLM.[30,31] We have also reported that propofol may directly modulate the vasomotor-integrating mechanisms in the RVLM through inhibiting pressor responses to microinjected glutamate.[27] Recently, we found that propofol inhibits spontaneous neuronal firing in the RVLM. The CVLM is a major inhibitory depressor area in the medulla. It directly modulates sympathetic outflow which is generated from the RVLM. However, the action of propofol in the CVLM, especially that concerning spontaneous neuronal firing, has not been well established. Our study provides the first evidence of neuronal firing

inhibition by propofol in the CVLM which may contribute to its central medullary mechanism.

In conclusion, propofol dose-dependently inhibited spontaneous neuronal activity in the CVLM, a major tonic inhibitory depressor area in the medulla. This effect may contribute to the central medullary mechanism of propofol.

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Propofol抑制延腦尾腹外側區的神經活性

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背 景： Propofol是一個強效的靜脈注射全身麻醉劑，然而它在中樞神經系統延腦尾腹外側區域 (caudal ventrolateral medulla, CVLM) 的作用尚未完全清楚，因此我們採用神經細胞外記錄的方法，記錄propofol靜脈注射前及靜脈注射後，延腦尾腹外側區域神經放電活性的變化。

方 法： 用31隻貓作爲研究的對象，使用-chloralose和urethane腹腔注射全身麻醉，在靜脈注射propofol 2 mg·kg^{-1}及連續追加劑量注射propofol後 (1, 1, and 2 mg·kg^{-1})，觀察紀錄平均血壓，心跳，及神經放電。一直記錄到神經放電回復到連續注射propofol前的水平。

結 果： 在連續注射propofol後 (1, 1, and 2 mg·kg^{-1})，神經放電活性呈現劑量依賴性及可逆性的抑制。對照組的神經放電頻率是17.9 ±8.6 Hz，在第1個劑量注射後，延腦尾腹外側區域的放電頻率減少到15.8 ±8.5 Hz ($p<0.05$ vs. the control)。在第2個劑量注射後，放電頻率減少到12.8±8.3 Hz ($p<0.05$ vs. the control)。在第3個劑量注射後，放電頻率更進一步減少到10.0 ±7.9 Hz ($p<0.05$ vs. the control)。

結 論： Propofol劑量依賴性及可逆性的抑制神經放電頻率，是它在延腦尾腹外側區域主要的藥理作用。

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關鍵字： propofol，延腦尾腹外側區，細胞外記錄。

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