Action of propofol on central sympathetic mechanisms controlling blood pressure

Andrei V. Krassioukov MD PhD,*†
Adrian W. Gelb MB ChB FRCPC,‡
Lynne C. Weaver DVM PhD*†

This study was done using Wistar rats to determine if the actions of propofol (22 ± 1, 40 ± 2, 64 ± 3 and 102 ± 3 mg · kg^{-1} · hr^{-1}) decreased blood pressure and heart rate through depression of brain stem vasomotor centres. All rats were given atropine to block vagal influences on the heart. Propofol decreased renal nerve activity as well as blood pressure and heart rate in a dose-dependent manner. Infusion of the lowest dose of propofol (22 ± 1 mg · kg^{-1} · hr^{-1}) had no effect on blood pressure, heart rate and renal nerve activity. Infusion of propofol at 40 ± 2 mg · kg^{-1} · hr^{-1} decreased renal activity by 22 ± 4% (mean ± SEM) and at 64 ± 3 mg · kg^{-1} · hr^{-1} it decreased renal nerve activity by 36 ± 6%. Finally, infusion of the largest dose of propofol (102 ± 3 mg · kg^{-1} · hr^{-1}) decreased nerve activity by 50 ± 5%. The haemodynamic changes observed in our experiments during the infusion of propofol paralleled the changes in sympathetic firing, suggesting that hypotension was caused by central actions of propofol to depress sympathetic firing. In experiments with bolus injections of propofol, the renal nerve activity returned to normal before arterial pressure and heart rate recovered. Because decreases in blood pressure and heart rate were longer-lasting than changes in renal nerve activity, a part of the vasodepression and bradycardia caused by propofol likely resulted from direct actions on blood vessels and the heart. Sympathetic and cardiovascular responses to blocking neurons in the ventrolateral medulla with microinjection of glycine were depressed by propofol. However, responses to blockade of this important brainstem structure were elicited at all doses of propofol suggesting that, while it causes depression of CNS neurons responsible for control of resting arterial pressure and heart rate, this depression is not maximal and substantial control remains.

Cette étude a été réalisée avec des rats Wistar afin de déterminer si l'action du propofol (22 ± 1, 40 ± 2, 64 ± 3, et 102 ± 3 mg · kg^{-1} · h^{-1}) diminue la pression artérielle et la fréquence cardiaque par une dépression des centres vasomoteurs du tronc cérébral. Tous les rats ont reçu de l'atropine pour bloquer les effets vagaux sur le coeur. Le propofol diminue l'activité rénale d'origine nerveuse autant que la pression artérielle et la fréquence cardiaque d'une manière dose-dépendante. La perfusion de la plus faible dose de propofol (22 ± 1 mg · kg^{-1} · h^{-1}) n'a pas d'effet sur la pression artérielle, la fréquence cardiaque et l'activité d'origine nerveuse. Une perfusion de propofol à 40 ± 2 mg · kg^{-1} · h^{-1}) diminue l'activité rénale d'origine nerveuse 22 ± 4% (moyenne ± erreur type), à 64 ± 3 mg · kg^{1} · h^{-1}, elle diminue cette activité de 36 ± 6%. Finalement, l'infusion de la dose la plus élevée de propofol (102 ± mg · kg^{-1} · h^{-1}) diminue cette activité nerveuse de 50 ± 5%. Les variations hémodynamiques observées dans notre expérience pendant la perfusion de propofol se profilent aux modifications de décharges sympathiques suggérant que l'hypotension est causée par une action centrale de dépression sympathique par le propofol. Lors d'injections de propofol par bolus, l'activité rénale d'origine nerveuse se normalise avant la pression artérielle et la fréquence cardiaque. Puisque les diminutions de pression artérielle et de fréquence cardiaque ont duré plus longtemps que celle de l'activité rénale d'origine nerveuse, une part de la vasodépression et de la bradycardie causée par le propofol résulte vraisemblablement d'une action directe sur les vaisseaux sanguins et le coeur. Les réponses sympathiques et cardiovasculaires au blocage des neurones de la région ventrolatérale par des microinjections de glycine sont déprimées par le propofol. Cependant les réponses au blocage de cette importante structure du tronc cérébral sont obtenues pour toutes les doses de propofol. Ceci suggère que bien que le propofol amène une dépression des neurons du SNC responsables du contrôle de la pression artérielle et de la fréquence cardiaque, cette dépression n'est pas maximale et un contrôle substantiel subsiste.

Key words
ANAESTHETICS, INTRAVENOUS: propofol;
MEDULLA:
SYMPATHETIC NERVOUS SYSTEM.

From the Department of Stroke and Aging, The John P. Robarts Research Institute,* Department of Physiology† and Department of Anaesthesia,‡ The University of Western Ontario.

Supported by the Heart and Stroke Foundation of Ontario and the Medical Research Council of Canada/Canadian Hypertension Society.

Address correspondence to: Dr. Andrei Krassioukov, The John P. Robarts Research Institute, 100 Perth Drive, P.O. Box 5015, London, Ontario N6A 5K8.

Accepted for publication 16th April, 1993.

Propofol (2,6-diisopropylphenol, diprivan) produces a reduction in arterial blood pressure, cardiac output, and total peripheral resistance in man and experimental animals.[1-5] The changes in peripheral resistance are greater than those caused by the administration of other anaesthetic drugs and are thought to reflect the combination of a decreased sympathetic tone and direct actions on the vasculature.[3,6-9] Actions of this anaesthetic to decrease sympathetic tone could be caused by depression of central nervous system "vasomotor" neurons but the central actions of propofol on structures involving vasomotor regulation have never been studied. Several areas of the brainstem, especially the ventrolateral medulla, are known to control resting blood pressure and heart rate through actions on the sympathetic nervous system.[10] Depression of ongoing firing of neurons in the rostral ventrolateral medulla by drugs or inhibitory neurotransmitters leads to profound decreases in sympathetic tone, heart rate and arterial blood pressure, illustrating that this region is a major vasomotor centre.[11-13] The aim of this study was to determine if the actions of propofol to decrease blood pressure and heart rate are mediated through depression of central neural structures involved in resting and reflex control of blood pressure. Specifically, we determined the effects of different doses of propofol given either as bolus injections or by continuous infusion on blood pressure and heart rate and resting sympathetic discharge. To evaluate the depression of the medullary vasomotor centre by different doses of propofol, we investigated well-known sympathetic and cardiovascular responses to microinjection of the inhibitory amino acid glycine into the rostral ventrolateral medulla.[12,13] A depressant action of the anaesthetic on these medullary neurons would lead to smaller responses to the amino acid blockade.

Methods

Surgical preparation of animals

After approval by the University of Western Ontario animal care committee, experiments were performed on male Wistar rats weighing between 200–400 g. Anaesthesia was induced in all rats with pentobarbital (40 $mg \cdot kg^{-1}$, intraperitoneally) and the animals were then tracheotomized and their lungs artificially ventilated. They were paralysed during surgical preparation with gallamine triethiodide (20 $mg \cdot kg^{-1}$ initially, followed by doses of 10 $mg \cdot kg^{-1}$ as needed). Before each supplemental dose of gallamine was given, the animal's plane of anaesthesia was assessed by examination of palpebral and withdrawal reflexes. After completion of surgical preparation (approximately two hours), the use of the muscle relaxant was discontinued. Atropine sulphate (1 $mg \cdot kg^{-1}$, bolus, Sigma Chemical Company, USA) was given *iv* every two hours to block vagal influences on the heart. Parasympathetic blockade was done to permit the effects of propofol on cardiac sympathetic tone to be assessed. Both jugular veins were cannulated, one was used for the bolus injection and infusion of propofol while the other was used for the continuous infusion of normal saline (0.01 $ml \cdot min^{-1}$) and for the administration of other drugs as required. The femoral artery was cannulated to monitor arterial blood pressure and to obtain samples for blood gas tension measurement (blood gas analyzer, model 170, Corning Medical, USA). Arterial pH and blood gases were kept in the normal ranges (pH: 7.35 – 7.45, PaO_2 > 100 mmHg; $PaCO_2$: 25–40 mmHg) by adjusting the respiratory rate or volume or by occasional small bolus injections of sodium bicarbonate as required. Rectal temperature was maintained at 37°C with a heating pad. Rats were divided into two treatment groups.

In the first group (18 rats) anaesthesia was continued with an intravenous infusion of propofol at 50 $mg \cdot kg^{-1} \cdot hr^{-1}$ (I.C.I. Pharma, Mississauga, Ontario, Canada) as soon as effects of the pentobarbital anaesthesia began to abate. This dose provided adequate continued surgical anaesthesia. These rats were tested for responses to infusion of different doses of propofol (18 rats) and to microinjection of glycine into the rostral ventrolateral medulla during these infusions (seven rats, 17 microinjections). In a second group of six rats anaesthesia was maintained with supplemental intravenous injection of pentobarbital (5 $mg \cdot kg^{-1}$). In this group of animals responses to bolus injections of propofol (five rats) as well as responses to blockade of the rostral ventrolateral medulla by glycine were tested (three rats, five microinjections). The integrity of a vasomotor reflex mediated through the rostral ventrolateral medulla and completeness of blockade of cardiac muscarinic receptors by atropine was assessed in both groups of rats by activating the arterial baroreceptor reflex and monitoring heart rate and sympathetic responses. Arterial blood pressure was increased by 60–70 mmHg by a bolus injection of phenylephrine (1–3 μg, *iv*) to stimulate carotid sinuses and aortic arch baroreceptors. This stimulation is known to cause immediate reflex inhibition of sympathetic nerve activity and abrupt, vagally-mediated bradycardia if cardiac muscarinic receptors are functioning.

The rats were placed in a stereotaxic frame and, in the ten rats in which glycine was microinjected into the RVLM, a section of the intraparietal bone was removed to expose the medulla. This exposure was done in preparation for microinjections of the inhibitory amino acid glycine into the ventrolateral medulla. The brain surface was kept moist with saline-soaked gauze until immediately before microinjection. The left postganglionic

renal nerve was exposed in all rats via a retroperitoneal approach. The central end of the nerve was placed on a stainless steel bipolar electrode for recording multifibre electrical activity. To isolate the renal nerve and electrode from the surrounding tissue and to prevent dehydration of the exposed nerve, the nerve and uninsulated electrode tips were covered with dental impression medium (Perfourm, Cutter Dental, USA). Also, to eliminate artifacts in the neural recordings caused by respiratory movements a pneumothorax was made by incising the diaphragm in all animals.

Neural discharge was amplified (Grass P511 amplifier; Grass Instrument Co., USA) at a bandwidth of 30 Hz–3 kHz. The signals after amplification were monitored on an oscilloscope and recorded on magnetic tape. Moreover, blood pressure was determined using a pressure transducer (Statham Instruments, Inc., USA) and heart rate was determined using a Grass tachograph triggered by the systolic phase of each arterial pressure pulse. Heart rate and arterial pressure were displayed continuously on a Grass polygraph.

Experimental protocols

At least four hours were allowed to elapse after the induction with pentobarbital before the study of propofol commenced in the first group of 18 rats. Before beginning a procedure to evaluate the effects of propofol, the infusion of propofol was stopped and a period of ten minutes allowed to elapse. This time interval was taken from information in the literature[2] demonstrating recovery from maintenance levels of propofol anaesthesia at 8–12 min. Again, the rats' reflexes were monitored so that complete recovery was not permitted and the rats were in a light plane of anaesthesia before assessing cardiovascular and CNS effects of the test doses of propofol. Criteria for the adequacy of anaesthesia were absence of palpebral or corneal reflexes, stable blood pressure and heart rate, and depressed withdrawal of the hindlimb in response to a noxious pinch of the toe or footpad.

Responses to intravenous infusion of propofol

Propofol was infused for 35 min at one of four rates: dose 1, 22 ± 1 $mg \cdot kg^{-1} \cdot hr^{-1}$; dose 2, 40 ± 2 $mg \cdot kg^{-1} \cdot hr^{-1}$; dose 3, 64 ± 3 $mg \cdot kg^{-1} \cdot hr^{-1}$; dose 4, 102 ± 3 $mg \cdot kg^{-1} \cdot hr^{-1}$. Changes in renal sympathetic nerve activity, arterial pressure and heart rate were monitored. More than one dose often was tested in each rat but a recovery period as described above was allowed between each dose. The animals were not permitted to regain consciousness and anaesthesia was resumed when a light plane of anaesthesia was reached. Recovery of these variables was studied only after terminating the infusion of dose 2 and dose 4 of propofol. Recording was discontinued when blood pressure, heart rate and renal nerve activity reached initial control levels or when the level of these parameters reached that which had been recorded during the infusion of dose 1. This usually occurred 10–15 min after stopping the infusion.

Responses to bolus injections of propofol

This series of experiments was done on the second group of rats who were under light pentobarbital anaesthesia. Control values of blood pressure, heart rate, and renal nerve activity were obtained and then responses to intravenous bolus injections of propofol 5 $mg \cdot kg^{-1}$, 7 $mg \cdot kg^{-1}$ and 12 $mg \cdot kg^{-1}$ were assessed.

Effects on sympathetic and vasomotor control by the rostral ventrolateral medulla

To determine actions of propofol on the medullary "vasomotor" group of neurons, responses to microinjection of glycine into the rostral ventrolateral medulla were evaluated in one group of animals anaesthetized with doses 1, 2 and 4 of propofol and in a second group under light pentobarbital anaesthesia. Each rat under propofol anaesthesia received all doses of the anaesthetic with an appropriate recovery period (*vide supra*) between each dose.

Small volumes (50–80 nl) of 1.0 M glycine in normal saline (pH 7.4) were pressure-injected into one side of the rostral ventrolateral medulla through glass micropipettes pulled to produce a tip size of approximately 25 μm. These pipettes were positioned in the rostral ventrolateral medulla using stereotaxic methods according to the stereotaxic atlas of Paxinos and Watson.[14] Ejection pressure and pulse duration during microinjection were controlled by a picospritzer (General Valve Corporation, USA). After the experiments, the rat brains were removed for histological verification of the sites of microinjection of glycine into the rostral ventrolateral medulla. Details of methods for these microinjection and histological procedures have been described previously.[12,13] Injections of vehicle were not done in the present study as previous investigations in our laboratory have shown that microinjecting 1.0 M NaCl (180 nl) into the rostral ventrolateral medulla in rats causes no sympathetic or cardiovascular responses.[13]

Analyses of data

Sympathetic discharge was quantified by cumulative integration of the voltage recorded after subtraction of electronic noise in the signal. This noise was determined at the end of the experiment by obtaining a sample of background electronic noise after the animal had been given a lethal dose of urethane. The voltage was full-wave rectified and integrated in ten-second intervals using a pro-

gramme prepared by R.C. Electronics Inc. (USA). Nerve activity was expressed in μV's and control periods consisted of six ten-second samples. Differences in control baseline voltages of multifibre nerve activity recorded extracellularly may reflect differences in the size of the nerve bundle dissected (i.e., number of axons) and the contact of the nerve with the recording electrode and cannot be assumed to reflect differences in the physiological state of the rat. Therefore, little significance can be attributed to such differences between rats or between groups of rats in this study. To determine statistical changes in neural activity, blood pressure and heart rate, a one-way analysis of variance (ANOVA) with repeated measures was used: (1) to compare effects of different doses of propofol on these variables, (2) to compare responses to stimulation of baroreceptors and (3) to compare responses to microinjection of glycine into the rostral ventrolateral medulla.[15] Comparisons between percentage changes in nerve activity were made after square root normalization of percentage values. When all measures were not available in all animals, a completely random ANOVA was used.[15] Tukey's test was used for comparisons of mean values.[15] All the data in the text are presented as mean ± SEM. In the figures, variability in each group is expressed as a pooled standard error. By convention, if a response is described as a change, the assumption should be made that the change is statistically significant. Differences were considered significant when $P < 0.05$ and variability is expressed as a pooled standard error derived from the ANOVA.

Results

Completeness of muscarinic blockade by atropine was confirmed in rats anaesthetized with either propofol or pentobarbital. Baroreceptor reflexes were induced by pressor responses (±60–70 mmHg) to *iv* injection of phenylephrine 1–3 mg and these reflexes were accompanied by insignificant changes in heart rate indicating that the vagolytic effects of atropine were present throughout the experiments. In contrast, the peripheral and brainstem pathways for this reflex were intact because the baroreceptor-induced decrease from control in renal nerve activity during infusion of propofol at dose 1 was 71 ± 5%, at dose 2 was 59 ± 6%, and at dose 4 was 70 ± 3%. In rats during pentobarbital anaesthesia this baroreceptor test decreased renal sympathetic activity by 80 ± 5%.

Effect of continuous infusion of propofol on renal nerve activity, mean arterial blood pressure and heart rate

The responses of renal sympathetic nerve activity, arterial blood pressure and heart rate in rats during infusion of propofol at different doses are shown in Figure 1. Propofol decreased renal activity as well as blood pressure and heart rate in a dose-dependent manner. After 35 min of infusion, the low dose of propofol (dose 1) had no effect on blood pressure and heart rate and caused very small decreases in renal nerve activity. Infusion of the next higher dose (dose 2) decreased renal nerve activity by 22 ± 4% and decreased arterial pressure from 108 ± 3 mmHg to 88 ± 4 mmHg (17 ± 3%) and heart rate from 391 ± 14 bpm to 368 ± 13 bpm (6 ± 2%). The third dose rapidly decreased renal nerve activity by 36 ± 6%, decreased blood pressure from 106 ± 4 mmHg to 70 ± 3 mmHg (30 ± 3%) and decreased heart rate from 368 ± 14 bpm to 304 ± 12 bpm (17 ± 2%). The

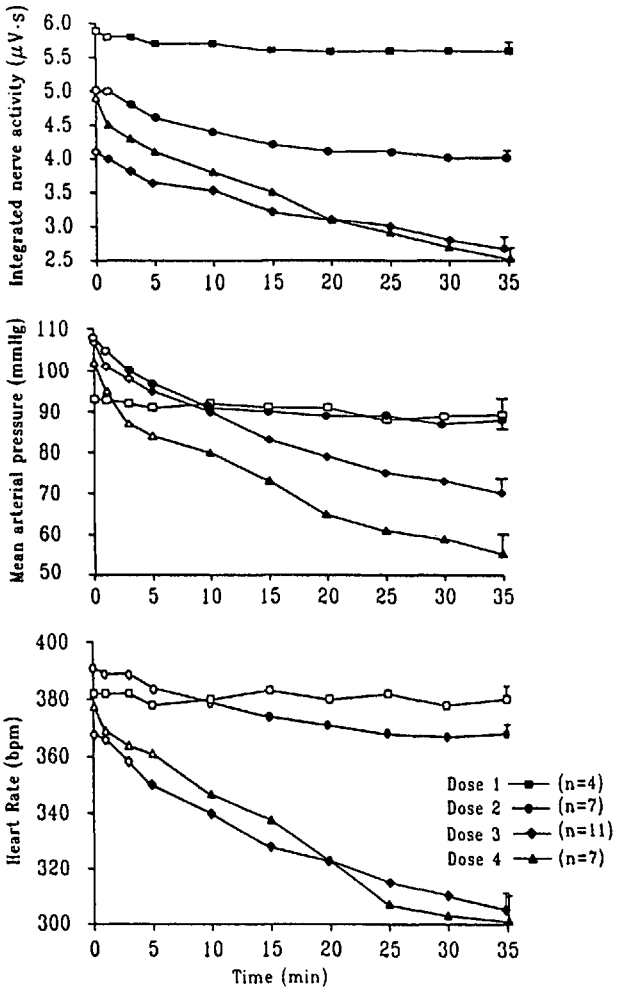

FIGURE 1 Mean values of renal nerve activity, mean arterial pressure and heart rate during 35 min infusion of different doses of propofol. Symbols for different doses of propofol are shown on the figure. Open symbols indicate values not different from control and closed symbols indicate values significantly different from control. Number of animals in each group is in brackets. Time zero is the beginning of the infusion of propofol. Variability in each group is expressed as a pooled standard error calculated from the analysis of variance of each data set.

infusion of the largest dose of propofol (dose 4) decreased nerve activity by 50 ± 5%, decreased blood pressure from 103 ± 9 mmHg to 54 ± 3 mmHg (48 ± 2%), and decreased heart rate from 378 ± 15 bpm to 301 ± 16 bpm (20 ± 4%). Changes in the blood pressure and heart rate caused by infusion of different doses of propofol occurred later than the changes in sympathetic nerve activity. Significant changes in renal nerve activity were recorded usually three to five minutes after the infusion of doses 1 and 2, and immediately after infusion of doses 3 and 4. Blood pressure and heart rate changed only after 10–15 min of infusion (Figure 1).

Duration of actions of propofol

The recovery of sympathetic activity, arterial pressure and heart rate after terminating the infusion of propofol was investigated after infusion of dose 2 and dose 4 (Figure 2). Renal nerve activity increased rapidly from its lowest level, by 35 ± 4% and 49 ± 4%, respectively, within 15 min of stopping the infusion of doses 2 and 4. Arterial pressure increased from 80 ± 5 mmHg to 98 ± 4 mmHg (22 ± 4%) and from 57 ± 6 mmHg to 95 ± 5 mmHg (67 ± 3%) within 15 min of terminating the infusion of these two doses. Heart rate increased from 362 ± 7 bpm to 400 ± 4 bpm (11 ± 6%) and from 283 ± 3 bpm to 341 ± 4 bpm (21 ± 7%). Increases from the lowest value of renal nerve activity, blood pressure and heart rate were recorded at three minutes after stopping the infusion of dose 2, and at five minutes after stopping the infusion of dose 4.

Effect of bolus doses of propofol

Responses of renal nerve activity and cardiovascular changes caused by *iv* bolus doses of propofol (5 mg · kg^{-1}, 7 mg · kg^{-1} and 12 mg · kg^{-1}) were measured in animals during light pentobarbital anaesthesia. Responses to injection of a bolus dose of 12 mg · kg^{-1} of propofol are shown in Figure 3. All three doses produced an initial inhibition of renal nerve activity and a hypotensive effect that was accompanied by bradycardia. Renal nerve activity was inhibited by 26 ± 3%, 35 ± 7% and 43 ± 8%, respectively, after bolus injection of propofol at 5, 7 and 12 mg · kg^{-1}. Blood pressure and heart rate were decreased by these bolus injections by 26 ± 4% and 9 ± 5% (5 mg · kg^{-1}), 35 ± 4% and 13 ± 7% (7 mg · kg^{-1}), 64 ± 4% and 17 ± 8% (12 mg · kg^{-1}), respectively. Sympathetic activity recovered rapidly, within five minutes after bolus injection of 5 mg · kg^{-1} and 7 mg · kg^{-1} propofol, and arterial pressure and heart rate reached initial levels only after ten minutes. Recovery after the bolus of 12 mg · kg^{-1} occurred at about ten minutes for sympathetic activity and 15–20 min for the cardiovascular responses.

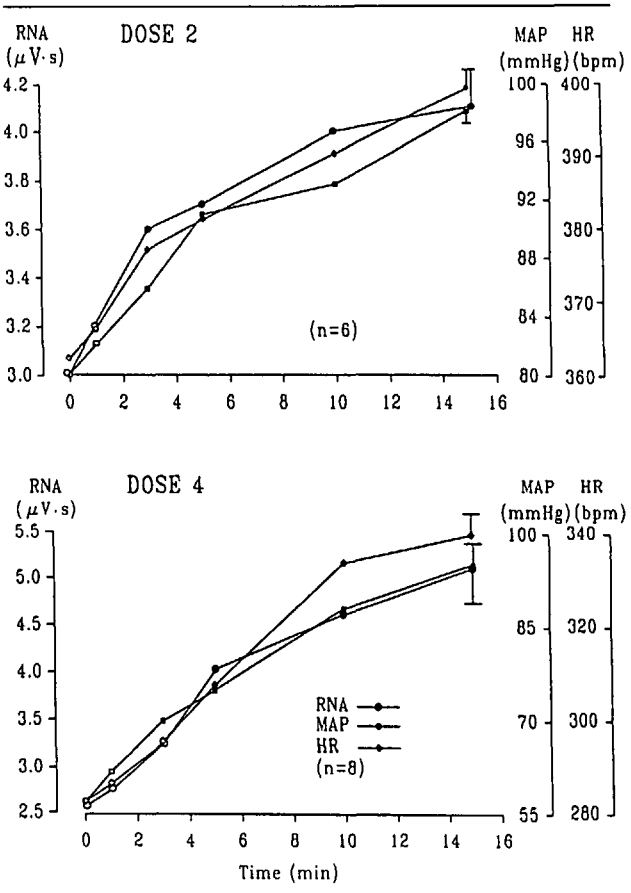

FIGURE 2 Recovery of renal nerve activity (RNA), mean arterial pressure (MAP) and heart rate (HR) after dose 2 and dose 4 of propofol. Time zero is the moment of stopping the infusion of propofol. Format is similar to that of Figure 1.

Sympathetic responses to blockade of the rostral ventrolateral medulla under propofol or pentobarbital anaesthesia.

Figure 4A illustrates a typical example of the changes in blood pressure, heart rate and renal nerve activity produced by an injection of glycine into the rostral ventrolateral medulla in a rat anaesthetized by dose 1 of propofol. Glycine injection into the rostral ventrolateral medulla produced the anticipated prolonged decreases in blood pressure, heart rate and sympathetic nerve activity.[12,13] Decreases in renal nerve activity caused by glycine injections into the rostral ventrolateral medulla were tested during infusion of three doses of propofol and under pentobarbital anaesthesia (Figure 4B). In rats during pentobarbital anaesthesia, nerve activity decreased by 48 ± 4% after this medullary blockade by glycine. This medullary blockade decreased nerve activity in rats after infusion of dose 1 of propofol by 49 ± 4%, after dose 2 it decreased by 35 ± 3% and after dose 4 it decreased by 27 ± 5%.

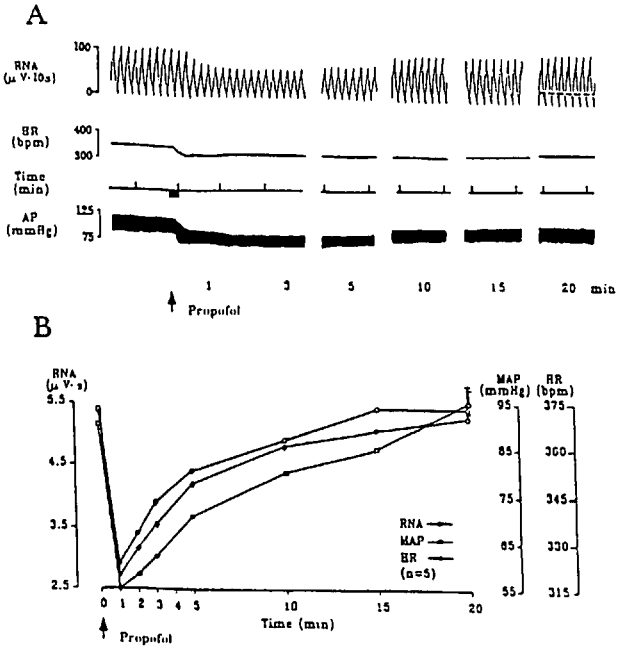

FIGURE 3 Effect of *iv* bolus injection of 12 mg · kg^{-1} propofol on renal nerve activity, arterial pressure (AP) and heart rate. A: polygraph recording of typical sympathetic and cardiovascular responses to this dose. The top panel illustrates the cotinuous record of integrated RNA. The integrator reset at 10-s intervals and the amplitude of each epoch prior to resetting indicates the integrated voltage in 10 s. Level of noise in the signal recorded from the nerve is shown by the broken line on the integrated renal nerve activity at the 20 min sample of recording. B: mean values of RNA, MAP and HR after this injection. Format is similar to that of Figure 1. Arrows show moment of the *iv* bolus injection of propofol.

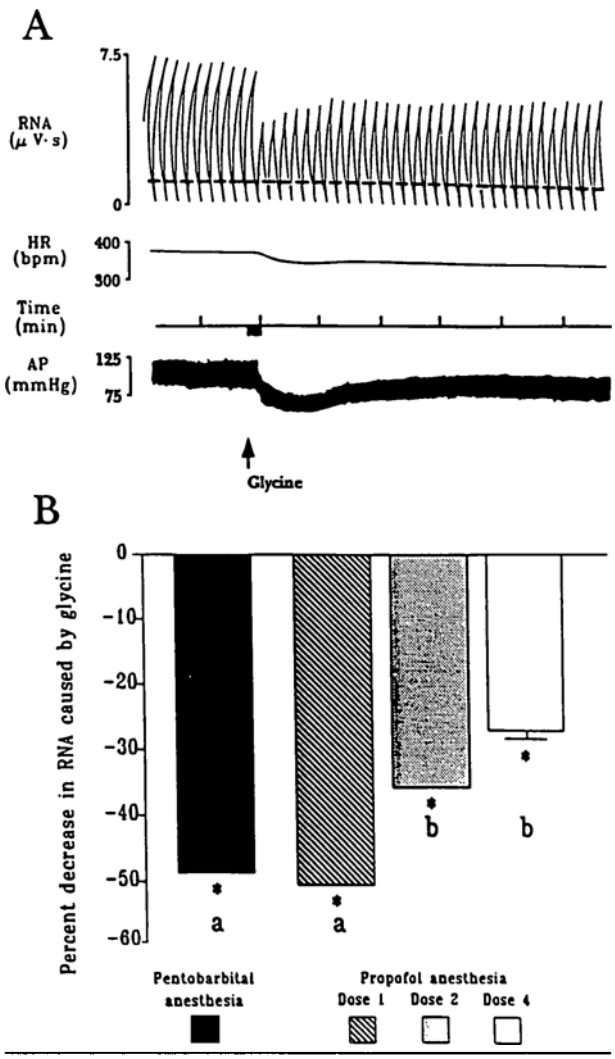

FIGURE 4 Effect of different doses of propofol on responses to microinjection of glycine into the rostral ventrolateral medulla. A: polygraph recordings of the sympathetic and cardiovascular responses to unilateral microinjection of glycine into the rostral ventrolateral medulla during infusion of dose 1 of propofol. Format is similar to that of Figure 3. Arrow shows moment of the injection of glycine. B: mean percent decrease of renal nerve activity after microinjection of glycine into the rostral ventrolateral medulla during pentobarbital anesthesia (five injections in three rats) and during infusion different doses of propofol (17 injections in seven rats). Asterisks indicate responses significantly different from control values. Bars labelled with the same letter (a or b) indicate responses not different from each other.

Changes in the magnitude of blood pressure responses to this blockade under pentobarbital and at different doses of propofol occurred in parallel to the changes in renal nerve activity. In the group under light pentobarbital anaesthesia, medullary blockade decreased blood pressure 30 ± 3 mmHg (from 95 ± 3 mmHg) and heart rate was decreased by 25 ± 6 bpm (from 375 ± 8 bpm). This response lasted 45 ± 4 min after the glycine injection. The depressor responses to medullary blockade under doses 1, 2 and 4 of propofol were 34 ± 5 mmHg, 24 ± 4 mmHg and 18 ± 4 mmHg, respectively. Heart rate during infusion of these doses was decreased by medullary blockade by 28 ± 7 bpm, 32 ± 4 bpm and 29 ± 9 bpm, respectively. The cardiovascular responses to medullary blockade lasted longer in the presence of dose 4 of propofol (57 ± 8 min) than during doses 1 and 2 (35 ± 5 min and 38 ± 5 min, respectively).

Histological verification of sites of glycine injection into the RVLM

The locations of histologically verified injection sites in the RVLM, plotted on stylized drawings (from Paxinos & Watson[14]) of transverse sections of the rat medulla, are shown in Figure 5. The sites of glycine microinjections were located within the well-known area, which was described previously as a "vasomotor centre" and named the RVLM.[10,11,13] This area is located 500–800 μm from the ventral surface of medulla, and extends from the caudal part of the facial nucleus to the rostral one-third of the inferior olive.

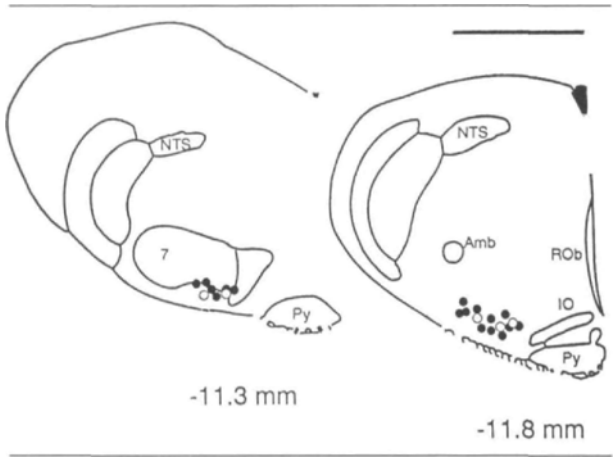

FIGURE 5 Stylized transverse sections of the rat medulla 11.3 and 11.8 caudal to bregma. Filled circles represent glycine injection sites in rats anaesthetized by propofol and open circles represent injection sites in pentobarbital anaesthetized rats. Amb. – nucleus ambiguus, IO – inferior olive, NTS – nucleus tractus solitarii, Py – pyramidal tract, ROb – raphne obscurus nucleus, 7 – facial nucleus. Calibration is 2 mm.

Discussion

The major findings of our study were that propofol caused a dose-dependent decrease in the firing of sympathetic nerves which was associated with depression of neurons in the medullary vasomotor centre. The changes in sympathetic firing were parallelled exactly by decreases in arterial pressure demonstrating that the central nervous system effects are, at least in part, responsible for the hypotension that is produced by this drug.

The haemodynamic changes observed in our experiments during the infusion of propofol were comparable to those found in previous studies, with the exception that we observed consistent decreases in heart rate. Propofol, in doses necessary to produce anaesthesia, has been shown to cause decreases in blood pressure and variable changes in heart rate.[5,16,17] As our rats were treated with atropine, the bradycardia produced by propofol must have been caused by depression of sympathetic cardioaccelerator tone or by direct depressant actions of propofol on the heart.[3,16,18] Several reports in the literature have suggested direct actions of propofol on the heart and peripheral vasculature and these actions also may play an important role in the hypotension that can be caused by this anaesthetic. Investigations of haemodynamic effects of propofol have yielded conflicting results as some investigators have shown that propofol decreases systemic vascular resistance without reducing stroke volume or cardiac output[6,16] whereas others have shown evidence of depressed cardiac function.[18] *In vitro* studies demonstrated no effect of propofol on myocardial contractility or on isometric relaxation in perfused isolated rabbit heart.[19,20] In contrast, changes in peripheral vascular resistance measured *in vivo* and *in vitro* have demonstrated a direct effect of the drug on the vasculature.[3,16,21–23]

Changes in peripheral vascular resistance may be direct or via peripheral or central neural mechanisms. Our experiments were designed especially to test the extent of medullary depression by evaluating the effect of complete unilateral blockade of the rostral ventrolateral medulla with an inhibitory amino acid (glycine) during different depths of propofol anaesthesia. If propofol depressed firing of these important "vasomotor" neurons, the effect of the blockade by glycine would become smaller. The sympathetic and blood pressure responses to glycine did become smaller as the depth of anaesthesia was increased but the responses under the light pentobarbital and dose 1 of propofol were substantial and the response even under dose 4 was still relatively large. That considerable responses to blockade of this important brainstem structure were elicited at all doses suggests that, while propofol does cause depression of CNS neurons responsible for control of resting arterial pressure, this depression is not maximal and substantial control remains.

The effects of propofol on arterial pressure were almost identical to its effects on tonic sympathetic vasomotor firing and, in turn, the depression of tonic firing of sympathetic nerves was approximately the same as the depression of the medullary vasomotor neurons. For example, dose 2 of propofol decreased tonic sympathetic firing by 22% and the response to medullary blockade was reduced by 25%. The known GABA-like actions of propofol[24,25] could lead to depression of medullary neurons generating sympathetic tone, as GABA is one of the inhibitory amino acids known to act in the rostral ventrolateral medulla.[26,27]

As propofol acted first on sympathetic outflow and then caused vasodepression a few minutes later, actions of this anaesthetic on the nervous system must precede any direct effects on the vasculature. One of the findings of our investigation adds to conclusions about the direct effects of propofol on the vasculature. Because propofol is often administered as bolus injections in clinical anaesthesia,[28] we investigated the effect of bolus injections of different doses of propofol on renal nerve activity as well as on blood pressure and heart rate. The doses used for the bolus injections in our experiments were those that have been used in previous investigations in rats.[2,7] These doses were chosen from previously published studies of the effects of propofol in animals.[2,3,5,7,29] The doses of propofol in the rat studies were much higher than doses used in humans, perhaps due to the rapid hepatic metabolism of propofol in rats.[30] Renal nerve activity, after bolus injections of propofol, returned to normal before arterial pressure and heart rate recovered. For example,

boluses of 12 mg · kg^{-1} propofol maintained blood pressure and heart rate at lowered levels for 20 min, but renal nerve activity returned to control values in ten minutes. Because decreases in blood pressure and heart rate were longer-lasting than changes in renal nerve activity, a part of the vasodepression and bradycardia caused by propofol must result from direct actions on blood vessels and the heart. However, the reasons why the direct actions are more long-lasting than those on the sympathetic nervous system remain to be determined. This dual time course of recovery from the actions of propofol was not observed after long-term infusions, possibly because of cumulative CNS effects that had a recovery time course similar to that of the peripheral effects.

One limitation of our study was that the effects of propofol were superimposed upon a pre-existent light level of anaesthesia. This was provided either by the lowest dose of propofol or low doses of barbiturate. Statements cannot be made that the same actions would have been observed if the experiments had begun from the conscious state but the methods used would have been difficult to carry out in conscious rats and a reasonable assumption is that vascular or CNS actions of propofol would have been at least as apparent in the absence of the initial basal anaesthesia.

The effects of propofol on different measures of central nervous system function have been shown in previous investigations.[2,31,32] Glen[7] described rapidly reversible depression of the electroencephalogram caused by anaesthetic doses of this drug. This investigator also reported dose-related, widespread decrease of cerebral blood flow and depression of cerebral metabolism caused by propofol. However, as shown by Dam *et al.*[31] propofol decreases central metabolism more in the forebrain than in the hindbrain, and the level of these metabolic changes resembled those observed after barbiturate, althesin, and etomidate anaesthesia. Nevertheless, these authors speculated very cautiously about the relationship between anaesthetic actions and regional metabolic changes in the brain. These data may be considered evidence for actions of propofol on forebrain and cortical neurons. Similarly, propofol may act on reticular formation neurons or other neurons in the pons, diencephalon or even cortex that contribute to cardiovascular control. We can do no more than speculate that such actions may exist as our experiments were designed to examine only actions on the well-known brainstem region crucial for blood pressure control.

In conclusion, our experiments have demonstrated that propofol can cause hypotension and bradycardia, in part, by actions on the central nervous system leading to decreased sympathetic nerve discharge. Despite these actions, control from the important vasomotor centre in the medulla is not disrupted in a major way. Moreover, as cardiovascular changes had a longer time course than did the sympathetic responses, propofol also appears to have direct actions on blood vessels and/or the heart.

Acknowledgements

This research was supported by grants from the Heart and Stroke Foundation of Ontario and the Medical Research Council of Canada/Canadian Hypertension Society. L.C. Weaver is the recipient of a Career Investigator Award from the Heart and Stroke Foundation of Ontario and A.V. Krassioukov holds a Fellowship from the Medical Research Council of Canada/Canadian Hypertension Society. The propofol (Diprivan) used in this study was kindly donated by I.C.I. Pharma, Mississauga, Ontario, Canada. The authors are grateful to Cathy Nutt for assistance with preparation of this manuscript.

References

1 *Aun C, Major E.* The cardiorespiratory effects of ICI 35 868 in patients with valvular heart disease. Anaesthesia 1984; 39: 1096–100.

2 *Glen JB, Hunter SC.* Pharmacology of an emulsion formulation of ICI 35 868. Br J Anaesth 1984; 56: 617–25.

3 *Goodchild CS, Serrao JM.* Cardiovascular effects of propofol in the anaesthetized dog. Br J Anaesth 1989; 63: 87–92.

4 *Mackenzie N, Grant IS.* Comparison of propofol with methohexitone in the provision of anaesthesia for surgery under regional blockade. Br J Anaesth 1985; 57: 1167–72.

5 *Sebel PS, Lowden JD.* Propofol: a new intravenous anaesthetic. Anesthesiology 1989; 71: 260–77

6 *Blake DW, Jover B, McGrath BP.* Haemodynamic and heart rate reflex responses to propofol in the rabbit. Br J Anaesth 1988; 61: 194–9.

7 *Glen JB.* Animal studies of the anaesthetic activity of ICI 35 868. Br J Anaesth 1980; 52: 731–41.

8 *Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M.* The haemodynamic effects of intravenous induction. Comparison of the effects of thiopentone and propofol. Anaesthesia 1985; 40: 735–40.

9 *Prys-Roberts C, Davies JR, Calverley RK, Goodman NW.* Haemodynamic effects of infusions of diisopropyl phenol (ICI 35 868) during nitrous oxide anaesthesia in man. Br J Anaesth 1983; 55: 105–11.

10 *Calaresu FR, Yardley CP.* Medullary basal sympathetic tone. Annu Rev Physiol 1988; 50: 511–24.

11 *Feldberg W.* The ventral surface of the brain stem: a scarcely explored region of pharmacological sensitivity. Neuroscience 1976; 1: 427–41.

12 *Beluli DJ, Weaver LC.* Differential control of renal and

splenic nerves without medullary topography. Am J Physiol 1991; 260: H1072–9.

13 *Hayes K, Weaver LC.* Selective control of sympathetic pathways to the kidney, spleen and intestine by the ventrolateral medulla in rats. J Physiol (Lond) 1990; 428: 371–85.

14 *Paxinos G, Watson C.* The Rat Brain in Stereotaxic Coordinates. 2nd ed. Orlando: Academic Press, 1986.

15 *Snedecor G, Cochran WG.* Statistical Methods. 8th ed. Ames IA: The Iowa State University Press, 1989.

16 *Claeys MA, Gepts E, Camu F.* Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 1988; 60: 3–9.

17 *Monk CR, Coates DP, Prys-Roberts C, Turtle MJ, Spelina K.* Haemodynamic effects of a prolonged infusion of propofol as a supplement to nitrous oxide anaesthesia. Br J Anaesth 1987; 59: 954–60.

18 *Stowe DF, Bosnjak ZJ, Kampine JP.* Comparison of etomidate, ketamine, midazolam, propofol and thiopental on function and metabolism of isolated hearts. Anesth Analg 1992; 74: 547–58.

19 *Baron JF, Soughir S, Arthaud M, Mouren S, Viars P.* Effects of propofol on coronary circulation and myocardial performance of an isolated rabbit heart. Anaethesiology 1990; 73: A561.

20 *Lin Y, Lee C, Lee T, Virtusio L, Wu SJ.* Negative inotropic effects of propofol vs thiopental: assessment in an isolated ventricular septum model. Anesthesiology 1990; 72: A564.

21 *Bentley GN, Gent JP, Goodchild CS.* Vascular effects of propofol: smooth muscle relaxation in isolated veins and arteries. J Pharm Pharmacol 1989; 41: 797–8.

22 *Muzi M, Berens RA, Kampine JP, Ebert TJ.* Venodilation contributes to propofol-mediated hypotension in humans. Anesth Analg 1992; 74: 877–83.

23 *Gelb AW, Zhang C, Hamilton JT.* The in vitro cerebrovascular effects of propofol are due to calcium channel blockade. Anesthesiology 1992; 77: A774.

24 *Concas A, Santoro G, Mascia MP, Serra M, Sanna E, Biggio G.* The general anesthetic propofol enhances the function of γ-aminobutyric acid-coupled chloride channel in the rat cerebral cortex. J Neurochem 1990; 55: 2135–8.

25 *Robertson B.* Action of anaesthetics and avermectin on $GABA_A$ chloride channels in mammalian dorsal root ganglion neurones. Br J Pharmacol 1989; 98: 167–76.

26 *Urbanski RW, Sapru HN.* Putative neurotransmitters involved in medullary cardiovascular regulation. J Auton Nerv Syst 1988; 25: 181–93.

27 *Willette RN, Barcas PP, Krieger AJ, Sapru HN.* Vasopressor and depressor areas in the rat medulla. Neuropharmacology 1983; 22: 1071–9.

28 *Sellgren J, Pontén J, Wallin BG.* Percutaneous recording of muscle nerve sympathetic activity during propofol, nitrous oxide, and isoflurane anesthesia in humans. Anesthesiology 1990; 73: 20–7.

29 *Adam HK, Glen JB, Hoyle PA.* Pharmacokinetics in laboratory animals of ICI 35 868, a new i.v. anaesthetic agent. Br J Anaesth 1980; 52: 743–6.

30 *Rhodes G, Longshaw S.* Autoradiographic distribution study of a short acting anaesthetic ICI 35 868. Acta Pharmacologica et Toxicologica 1977; 41: 132–3.

31 *Dam M, Ori C, Pizzolato G, et al.* The effects of propofol anesthesia on local cerebral glucose utilization in the rat. Anesthesiology. 1990; 73: 499–505.

32 *Van Hemelrijck J, Fitch W, Mattheussen M, Van Aken H, Plets C, Lauwers T.* Effect of propofol on cerebral circulation and autoregulation in the baboon. Anesth Analg 1990; 71: 49–54.