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Halothane anesthesia suppresses reflex tachycardia caused by calcitonin gene-related peptide in dogs

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Abstract: Calcitonin gene-related peptide (CGRP) is known to produce vasodilation, hypotension, and tachycardia. To investigate the interaction between CGRP and anesthetics, the hemodynamic response to infusions of CGRP was studied in dogs anesthetized with halothane or pentobarbital. In halothane-anesthetized dogs given 0.4 μg·kg^{-1} of CGRP, mean arterial pressure (MAP) did not change significantly. However, there was a significant reduction in systemic vascular resistance (SVR) associated with significant increases in cardiac index (CI) and stroke volume index (SVI). Higher doses (4 and 40 μg·kg^{-1}) of CGRP produced dose-dependent decreases in MAP accompanied by a reduction in SVR. Further, both CI and SVI significantly increased at 4 μg·kg^{-1} CGRP but remained unchanged at the 40 μg·kg^{-1} infusion rate. Heart rate (HR) was not increased at all doses but was decreased at 40 μg·kg^{-1}. In pentobarbital-anesthetized dogs, CGRP at doses of 4 μg·kg^{-1} produced a qualitatively similar cardiovascular responses as that observed in halothane-anesthetized dogs, but with one exception: HR was significantly increased. The results show that the hemodynamic profiles induced by CGRP during halothane or pentobarbital anesthesia are a decrease in MAP accompanied by a reduction in SVR and no consistent alterations in CI. However, CGRP effects on HR showed in a different way. The results also show that HR response differs depending on the anesthetics used: HR increases during pentobarbital anesthesia, while it does not increase during halothane anesthesia.

Key words: CGRP (calcitonin gene-related peptide), Halothane, Pentobarbital, Systemic hemodynamics

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Introduction

Calcitonin gene-related peptide (CGRP) has been identified in the central nervous system [1,2], the cardiovascular system [3], and in various other tissues [4]. CGRP has been reported to induce vasodilation and hypotension in unanesthetized humans [5] and animals [6,7]. Hypotension induced by CGRP is accompanied by an increase in heart rate mediated through the arterial baroreflex in α-chloralose-anesthetized rabbits [8]. In addition, intracerebroventricular administration of CGRP has been shown to elevate the arterial pressure and to elicit tachycardia concommitant with a stimulation of a selective noradrenergic sympathetic outflow in unanesthetized rats [9]. However, intravenous administration of CGRP has been shown to cause vasodilation and hypotension in association with both positive chronotropic and inotropic actions, and an increase in cathecholamine release in unanesthetized humans [10,11]. Thus the mechanism of the reflex tachycardia may be due to the activation of an arterial baroreflex pathway, as shown by the rise in plasma norepinephrine levels after both central and peripheral administration of CGRP. However, these results were obtained in an unanesthetized condition. Anesthetics are reported to affect the cardiac vagal tone, resulting in changes in systemic hemodynamics [12] and the neural control mechanisms of heart rate, which are depressed by both pentobarbital and halothane anesthesia [13].

Halothane, in particular, inhibits autonomic reflex responses at multiple sites, including baroreceptors, both afferent and efferent, and the autonomic ganglia [14]. This study was performed to elucidate the possibility of using CGRP as a vasodilating agent during anesthesia. For the purposes of comparison, halothane and pentobarbital were chosen to study their interaction with CGRP.

Methods

Twenty-nine mongrel dogs weighing, 10–24kg, were randomly assigned to one of two groups as follows: (1) halothane-anesthetized dogs (n = 21); (2) pentobarbital-anesthetized dogs (n = 8). The procedures and protocol in this study were approved by the Animal Experiment Ethics Committee of Showa University, Fujigaoka Hospital.

Following intravenous pentobarbital ($25\,mg \cdot kg^{-1}$) and tracheal intubation, 21 dogs were anesthetized with halothane at an inhaled concentration of 0.9% delivered through an Ohmeda Vaporizer (BOC Health Care, Windlesham, UK). Another eight dogs were anesthetized with intravenous pentobarbital ($25\,mg \cdot kg^{-1}$) and anesthesia was maintained by pentobarbital at ($5\,mg \cdot kg^{-1} \cdot h^{-1}$) after tracheal intubation. The animals were mechanically ventilated with a constant-volume respirator (Harvard Instruments, Chicago, IL, USA) to maintain normocapnia, using 100% oxygen as a carrier gas at a flow of 3–5 $1 \cdot mi^{-1}$. The end-tidal halothane and CO_2 concentrations were continuously monitored with an infrared analyzer (Capnomac Ultima, Datex, Helsinki, Finland).

Instrumentation

Cannulae were placed in the left femoral artery for continuous systemic blood pressure (SBP) monitoring and blood sampling, and in the right femoral vein for administration of maintenance fluid (0.9% saline at $7\,ml \cdot kg^{-1} \cdot h^{-1}$) together with the infusion of CGRP. A 7-F balloon-tipped triple lumen pulmonary catheter (Baxter Healthcare, Irvine, CA, USA) was advanced into the pulmonary artery via the right external jugular vein and positioned by means of a pressure monitor in a branch of the pulmonary artery for the measurement of central venous pressure (CVP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and cardiac output (CO). CO was measured in triplicate using the thermodilution technique with a CO computer (Model MTC 6210, Nihon Kohden, Tokyo, Japan) followed by an injection of 5ml 0.9% saline at 0°C into the right atrium at end-expiration. Cardiac index (CI), stroke volume index (SVI), and systemic vascular resistance (SVR) were calculated using standard formulae. Mean arterial pressure (MAP) was determined by electric integration. Heart rate (HR) was calculated from Lead II of the electrocardiogram (ECG) using a cardiotachometer (Model AT 601G, Nihon Kohden) and was continuously monitored. Body temperature was monitored by a thermistor attached to the pulmonary artery catheter and was maintained at 37.0 ± 1.0°C with electric heating pads and lamps. All pressure-monitoring catheters were connected to a pressure transducer (UNIFLOW, Baxter Healthcare). SBP and ECG were monitored continuously by polygraph (Model RM 6200, Nihon Kohden) and recorded using an 8-channel recorder (Model VM-640G, Nihon Kohden).

Experimental protocol

The dogs anesthetized with halothane were assigned to three subgroups and were studied in the following manner: the low-dose group (n = 7) received $0.4\,\mu g \cdot kg^{-1}$ CGRP, the medium-dose group (n = 7) received $4\,\mu g \cdot kg^{-1}$ CGRP, and the high-dose group (n = 7) received $40\,\mu g \cdot kg^{-1}$ CGRP. The pentobarbital-anesthetized group (n = 8) received $4\,\mu g \cdot kg^{-1}$ CGRP. CGRP, dissolved in 0.1% bovine serum albumin in 50ml 0.9% saline, was infused for 60min into the left femoral vein with an infusion pump (Model STG-521, Terumo Tokyo, Japan) at constant rates in all groups. After completion of the surgical preparation, the animals were observed for approximately 60min to allow hemodynamic variables (SBP, MPAP and HR) to stabilize. Measurements of baseline values were obtained before infusion of CGRP. Hemodynamic variables were then measured at 5, 30, and 60min after the start of infusion of CGRP, and at 10, 30, and 60min after the end of infusion. We used Des-1-Ala, des-α-amino chicken CGRP (Asahi Chemical Industry, Tokyo, Japan). This CGRP has been identified as having a 4-amino-acid difference from human CGRP (α) [15].

Statistical analysis

All data are expressed as the mean ± SD. Intergroup differences were analyzed by a two-way analysis of variance from repeated measurements of identical variables followed by Dunnett's test where appropriate. A probability value of less than 0.05 was considered statistically significant.

Results

The baseline values of systemic hemodynamics, including MAP, HR, CI, SVI, and SVR, are presented in Table 1. These hemodynamic variables did not differ significantly among the groups. Cardiovascular changes during and after CGRP infusion, expressed as a percentage of baseline values (100%), are depicted in Figs. 1–4.

In halothane-anesthetized dogs, CGRP produced dose-dependent decreases in MAP and SVR which were not accompanied by a reflex tachycardia. With $0.4\,\mu g \cdot kg^{-1}$ CGRP, MAP did not change significantly.

With 4 μg·kg^{-1} CGRP, MAP progressively and significantly decreased from the baseline values of 112 ± 15 mmHg to a nadir of 75 ± 17 mmHg at 30 min into the infusion period. MAP gradually returned toward baseline values following termination of CGRP. With 40 μg·kg^{-1}, there was a marked, significant decrease in MAP during and after the infusion (Fig. 1). This hypotensive response to CGRP was related to a reduction in SVR at all doses of CGRP. However, the maximal percentage changes in SVR were identical at both 4 μg·kg^{-1} CGRP (50 ± 14%, $P < 0.01$) and at 40 μg·kg^{-1} CGRP (49 ± 7%, $P < 0.01$) (Fig. 2). CI progressively and significantly increased with CGRP at 4 μg·kg^{-1} from the baseline values of 3.0 ± 0.7 l·min^{-1}·m^{-2} to a maximum of 152 ± 51% at 60 min into the infusion period, and remained significantly elevated at 10 min after termination of CGRP.

In contrast, CI did not significantly change during or after infusion of CGRP at 40 μg·kg^{-1} despite a significant reduction in SVR (Fig. 2). There was no increase in HR in halothane-anesthetized dogs despite hypotension induced by 4 and 40 μg·kg^{-1} CGRP (Fig. 1).

In pentobarbital-anesthetized dogs at 4 μg·kg^{-1} CGRP, MAP progressively and significantly decreased from the baseline values of 119 ± 17 mmHg to a nadir of 93 ± 13 mmHg at 60 min into the infusion period (Fig. 3). Hypotension was accompanied by an increase in CI, which reached a maximum of 137 ± 37% ($P < 0.01$), and by a reduction in SVR, with a nadir value 60 ± 15% ($P < 0.01$) during the infusion period (Fig. 4). HR was increased from the baseline values of 153 ± 26 beats per min to 162 ± 29 beats per min ($P < 0.05$), 172 ± 32 beats per min ($P < 0.01$), and 172 ± 28 beats per min ($P < 0.01$) at 5, 10, and 30 min into the infusion period, respectively (Fig. 3). These cardiovascular changes in pentobarbital-anesthetized dogs were qualitatively similar (an exception was the increase in HR) to those produced by 4 μg·kg^{-1} CGRP in halothane-anesthetized dogs.

Discussion

The results of the present study demonstrate that hemodynamic responses to CGRP infusion were similar during halothane or pentobarbital anesthesia. The hemodynamic profiles induced by CGRP during the use of both anesthetics are a decrease in MAP and a reduction in SVR, with no consistent alterations in CI. However, HR changes induced by CGRP showed a difference. Reflex tachycardia accompanied by a reduction of both MAP and SVR were not induced by CGRP during halothane anesthesia. This is in contrast to the observed tachycardia during pentobarbital anesthesia in the present study as well as in those reported previously [10,11,16,17].

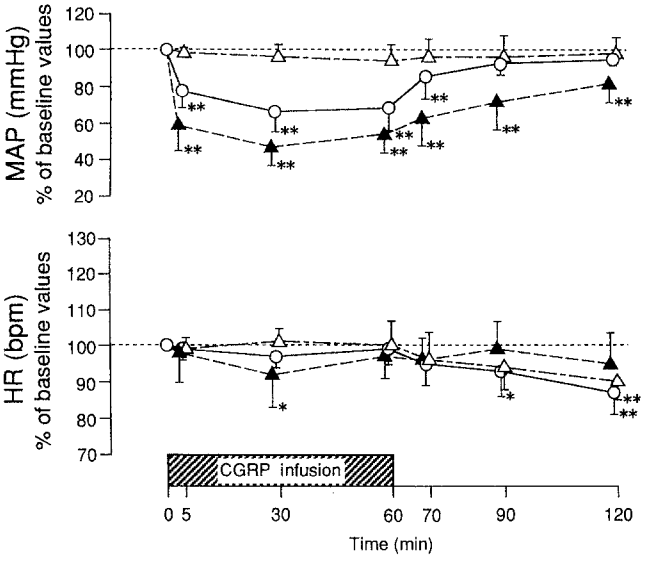

Fig. 1. Changes in mean arterial pressure (MAP) and heart rate (HR) during and after infusion of Des-1-Ala, des-α-amino chicken calcitonin gene-related peptide (CGRP) in halothane-anesthetized dogs. (*open triangles*, $n = 7$), 0.4 μg·kg^{-1}; (*open circles*, $n = 7$), 4 μg·kg^{-1}; (*solid triangles*, $n = 7$), 40 μg·kg^{-1}. Data are expressed as mean ± SD. *$P < 0.05$, **$P < 0.01$, significantly different from baseline value

Table 1. Baseline values of hemodynamic variables before infusion with calcitonin gene-related peptide (CGRP) (0.4, 4, 40 μg·kg^{-1}) in dogs under halothane or pentobarbital anesthesia

	Halothane			Pentobarbital
	0.4 μg	4 μg	40 μg	4 μg
MAP (mmHg)	118 ± 13	112 ± 15	113± 12	119 ± 17
HR (beats·min^{-1})	157 ± 31	155 ± 26	161 ± 17	153 ± 26
CI (l·min^{-1}·m^{-2})	2.7 ± 0.4	3.0 ± 0.7	3.7 ± 0.6	2.9 ± 1.1
SVI (ml·beat^{-1}·m^{-2})	18 ± 3	21 ± 8	23 ± 5	19 ± 6
SVR (dynes·s·cm^{-5})	5099 ± 439	4311 ± 1176	3426 ± 926	4421 ± 1370

Data are expressed as mean ± SD.
MAP, mean arterial pressure; HR, heart rate; CI, cardiac index; SVI, stroke volume index; SVR, systemic vascular resistance.

The increases in HR elicited by CGRP during pentobarbital anesthesia may be the results of two major mechanisms: one is the direct positive chronotropic action of CGRP on the heart [18], and the other is a reflex-mediated action on sympathetic tone in response to hypotension [10,11,19].

The lack of increase in HR during halothane anesthesia is a surprising observation. One possible explanation is that the differences in the effect of CGRP on HR appear to be due to differences in the properties of the anesthetics used during the experiments.

Halothane is well known to inhibit the baroreceptor pathways both centrally and peripherally [14]. In addition, halothane decreases the rate of spontaneous discharge of slow-action potentials in the sinoatrial node tissue and prolongs atrioventricuar conduction [20]. Further, it has recently been reported that in vivo, halothane inhibits sympathetic activity by decreasing the norepinephrine spillover rate into plasma [21]. These characteristics of halothane may therefore be an explanation for the suppression of the appearance of reflex tachycardia otherwise caused by CGRP through the sympathetic nerve endings, the arterial baroreflexes, and a direct effect on the sinoatrial node of the heart. Although pentobarbital, like halothane, also depresses the baroreceptor reflexes [13], the magnitude of the suppression may be less when compared with that seen with halothane.

Halothane-induced inhibition of CGRP reflex tachycardia may reduce myocardial oxygen demand. Further, it has been demonstrated that CGRP has a potent coronary vasodilator effect, causing notable dose-dependent decreases in coronary resistance and an increase in myocardial flow in the presence of decreased MAP [22]. If these findings can be extrapolated to a clinical setting, the combination of the reduction in myocardial oxygen demand induced by halothane and the coronary vasodilatory property of CGRP may be considered to be advantageous, especially in the treatment of abnormal hypertension during surgery in patients with coronary artery disease.

In summary, CGRP produces a decrease in MAP and SVR in association with no consistent changes in CI during halothane and pentobarbital anesthesia in dogs. No increase in HR is observed with CGRP administration during halothane anesthesia. It is suggested that

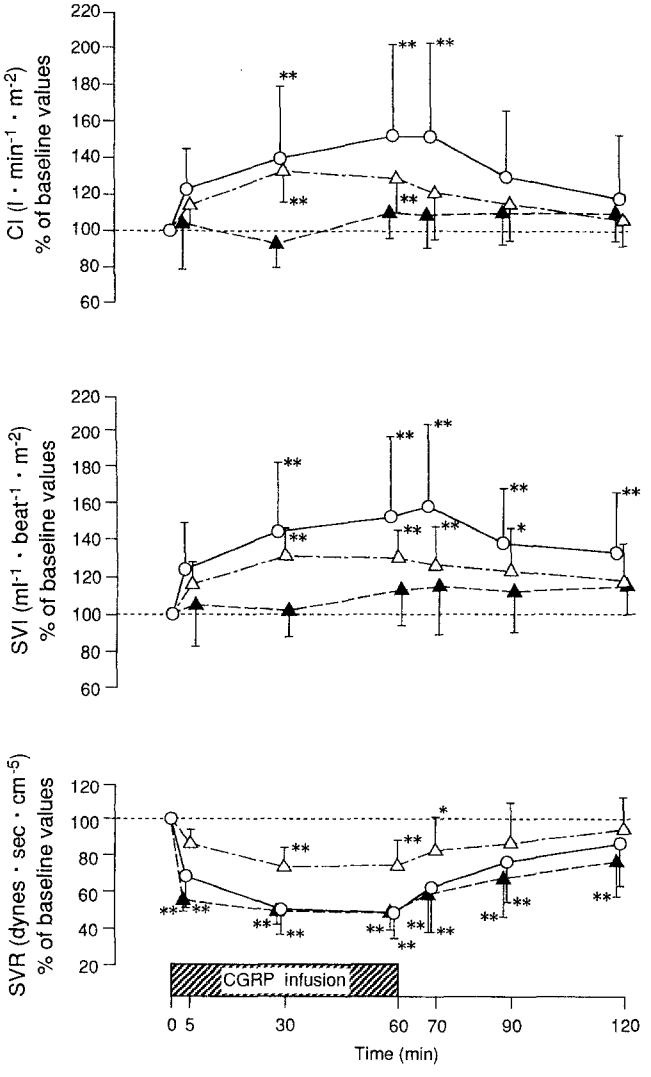

Fig. 2. Changes in cardiac index (CI), stroke volume index (SVI), and systemic vascular resistance (SVR) during and after infusion of Des-1-Ala, des-α-amino chicken CGRP in halothane-anesthetized dogs. (*open triangles*, $n = 7$), 0.4 μg·kg^{-1}; (*open circles*, $n = 7$), 4 μg·kg^{-1}; (*solid triangles*, $n = 7$), 40 μg·kg^{-1}. Data are expressed as mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$, significantly different from baseline value

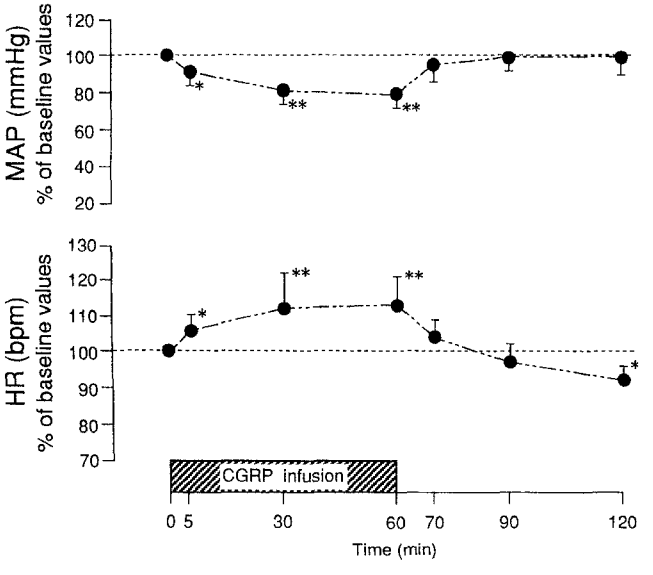

Fig. 3. Changes in MAP and HR during and after infusion of Des-1-Ala, des-α-amino chicken CGRP in pentobarbital-anesthetized dogs. (*solid circles*, $n = 8$), 4 μg·kg^{-1}. Data are expressed as mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$, significantly different from baseline value

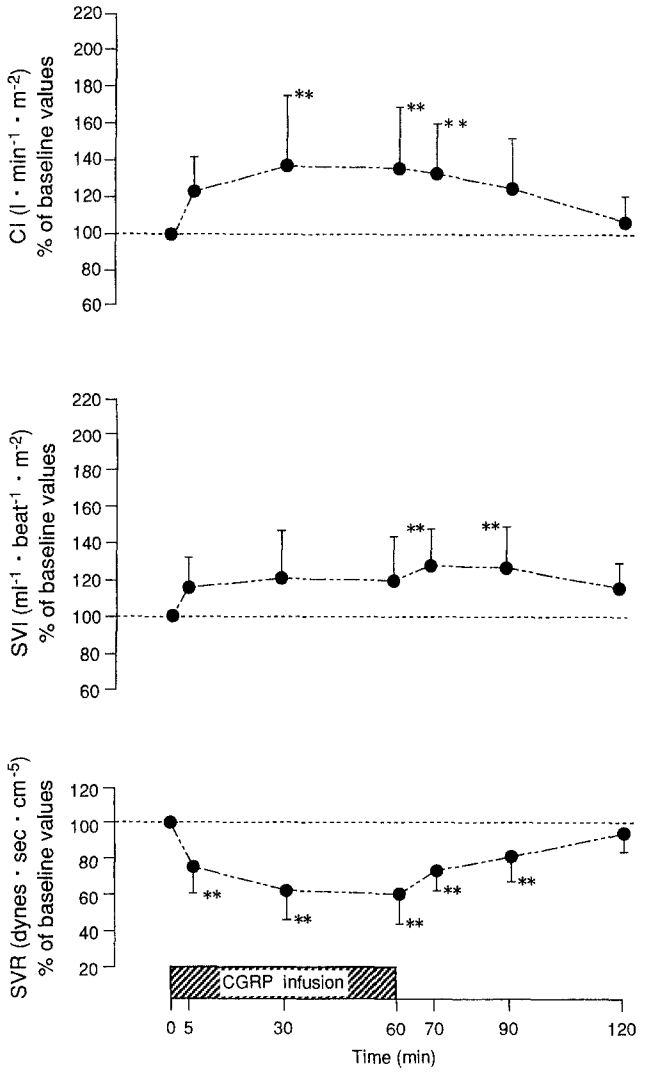

Fig. 4. Changes in CI, SVI, and SVR during and after infusion of Des-1-Ala, des-α-amino chicken CGRP in pentobarbital-anesthetized dogs. (*solid circles*, $n = 8$), $4\,\mu g \cdot kg^{-1}$. Data are expressed as mean ± SD. $^{**}P < 0.01$, significantly different from baseline value

CGRP may be a useful vasodilator during halothane anesthesia.

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