Preservation of Baroreflex Control of Vascular Resistance under Ketamine Anesthesia in Rats

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The aim of this study was to examine the effects of ketamine and pentobarbital on the baroreceptor reflex control of vascular resistance in rats. The gains of baroreflex were assessed by relating changes in arterial pressure to changes in hindlimb perfusion pressure, using an extracorporeal perfusion circuit with a delay system. Reflex-induced vasodilation or vasoconstriction in response to a rise or a fall in arterial pressure were elicited by injections of phenylephrine or nitroprusside, respectively. The gains of baroreflex were not altered by ketamine 1 and 5 mg/kg (i.v.), whereas those were depressed by pentobarbital 5 mg/kg (i.v.). The results suggest that ketamine preserves the baroreflex control of vascular resistance and pentobarbital depresses it. The preservation of the baroreflex control of vascular resistance may be advantageous for patients with hypovolemia to sustain the blood pressure. (Key words: baroreceptor reflex, ketamine, pentobarbital, vascular resistance)

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It is well known that blood pressure and heart rate are elevated under ketamine anesthesia in man and experimental animals[1,2]. The pressor response is considered to originate from stimulation of the sympathetic nervous system[3]. It is suggested that this occurs mainly centrally[4] and that it probably also includes a reflex increase in sympathetic discharge as a result of decreased sensitivity of the baroreceptors[5]. Blake and Korner[6,7] showed that ketamine produced marked depression of baroreceptor reflex control of heart rate in rabbits.

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On the other hand, the finding that moving pediatric patients in all positions during ketamine anesthesia showed no signs of orthostatic hypotension[8] suggests the preservation of baroreflex control of blood pressure in the human subject. Furthermore, it has been shown that ketamine did not block the baroreceptor reflex controlling sympathetic tone[9].

There is a possibility that the baroreflex control of vascular resistance is preserved even if that of heart rate is impaired[10]. Therefore, we designed, in this study, to examine the effect of ketamine anesthesia on the baroreceptor reflex control of vascular resistance in rats. Pentobarbital is used for comparison with ketamine.

Methods

Wistar Kyoto rats (n = 24), weighing 300–400 g, were used in this study. Un-

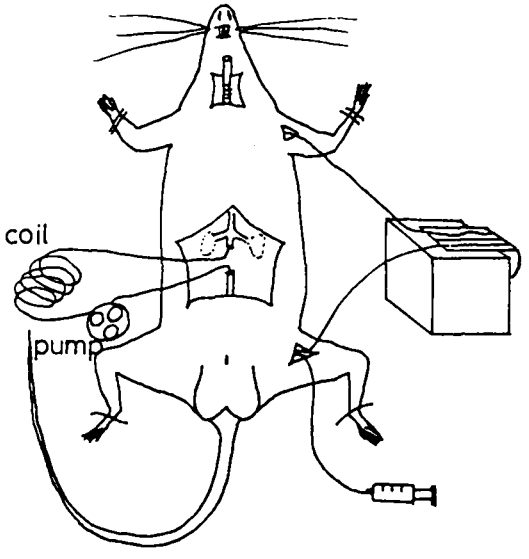

Fig. 1. A schema of surgical preparation for measurements of baroreflex control of hindlimb vascular resistance. See text for details.

der halothane anesthesia, rats were tracheotomized and ventilated with a Harvard small animal respirator. The experimental design to examine baroreflex control of hindlimb vascular resistance in rats was previously described[11]. Briefly, as shown in figure 1, a cannula was placed in the left axillary artery for continous recording of systemic arterial pressure. Another cannula was placed in the left iliac artery via the left femoral artery for the measurement of hindlimb perfusion pressure. The left femoral vein was cannulated for drug injection. The abdominal aorta was exposed through a midline incision. After the administration of sodium heparin (500 U/kg), the aorta was ligated at the distal portion to the renal arteries. Blood from the proximal aorta was withdrawn and pumped into the distal aorta perfusing the hindlimb, using a perfusion pump (Cole-Parmer Masterflex, model 7013). A delay system (20–30 sec) was included so as to prevent the direct vascular effects of drugs modifying reflex vascular changes. The delay system was immersed in a thermoregulated bath. The temperature of the bath was maintained at 37°C. The delay circuit was filled with approximately 3 ml of blood withdrawn from the aorta, and the equivalent volume of blood obtained from a donor rat was replaced intravenously. Blood flow to the hindlimb was adjusted initially so that the perfusion pressure closely approximated to the existing systemic arterial pressure. With this delay system, the maximal reflex change in hindlimb perfusion pressure occurred before an intravenously injected drug reached the perfused hindlimb. At constant flow, changes in perfusion pressure reflected changes in vascular resistance.

Systemic arterial and hindlimb perfusion pressures were measured with Statham pressure transducers (P23ID) and recorded on a Nihonkoden Medical Recorder. After completion of surgery, halothane administration was stopped and rats were ventilated with a mixture of nitrous oxide and oxygen (1:1) and immobilized with pancuronium bromide (0.2 mg/kg). A period of 20–30 min was allowed for stabilization before beginning the protocols. The experiments were done with rats placed on a heating pad to maintain body temperature around 37°C. Pa_{O_2}, Pa_{CO_2}, and pH were measured periodically, and it was confirmed that Pa_{CO_2} was between 30 and 40 mmHg, Pa_{O_2} above 200 mmHg and pH between 7.30 and 7.45.

Rats were divided into three groups based on anesthetic exposure; ketamine 1 mg/kg (n=8), ketamine 5 mg/kg (n=9) and pentobarbital 5 mg/kg (n = 7) intravenously. Baroreflex control of vascular resistance was examined before and 5 min after bolus injection of these anesthetics. To examine arterial baroreflex control of hindlimb vascular resistance, phenylephrine (2–4 μg) and sodium nitroprusside (1–2 μg) were injected intravenously. The dose of the drugs were adjusted to change arterial pressure by 40–60 mmHg. The volume of injection was 10–30 μl. An abrupt rise in arterial blood pressure evoked reflex-induced vasodilation, resulting in a decrease in perfusion pressure (fig. 2). On the other hand, a sudden fall in arterial blood pressure caused reflex-induced vasoconstriction, resulting in an increase in perfusion pressure (fig. 2). The gain of ar-

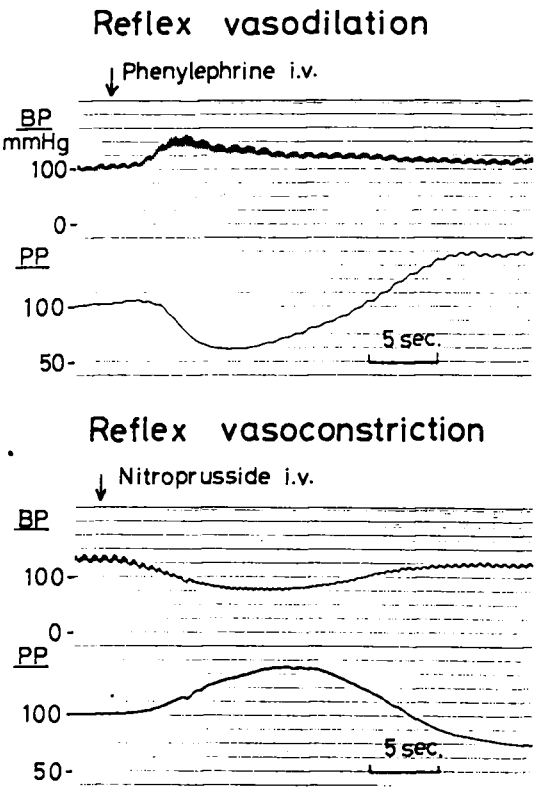

Fig. 2. Recordings of arterial pressure (AP) and hindlimb perfusion pressure (PP). Changes in perfusion pressure at a constant flow indicate changes in vascular resistance. An increase in arterial pressure by phenylephrine produced reflex vasodilation (upper) and a decrease in arterial pressure by nitroprusside reflex vasoconstriction (lower). (Reprinted from Hoka et al. (11), by permission of the American Heart Association Inc.)

terial baroreflex control of hindlimb vascular resistance was assessed by obtaining the ratio of the maximal change in hindlimb perfusion pressure to the maximal change in arterial pressure. The interval of injections of the drugs was at least 5 min. During that period the arterial pressure as well as hindlimb perfusion pressure, had returned to a baseline level.

All data were analysed to determine statistical significance from the control value (before anesthetic exposure of ketamine or pentobarbital) using Student's t-test for paired data. A probability less than 0.05 was considered statistically significant. All data are expressed as mean + SEM.

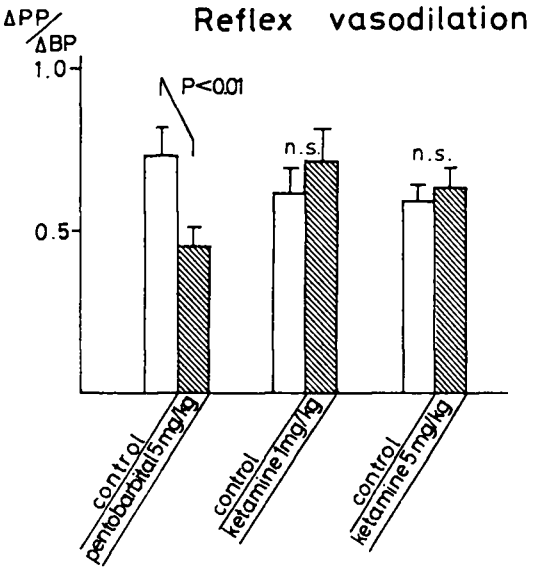

Fig. 3. The gain of arterial baroreflex control of hindlimb vascular resistance in response to phenylephrine (reflex vasodilation). Ketamine 1 and 5 mg/kg did not significantly alter the gain, while pentobarbital 5 mg/kg significantly decreased it.
n.s. = not significant

Results

Mean arterial pressures (MAP) before and after administration of ketamine 1 mg/kg were 132 ± 6 and 135 ± 3, and those of ketamine 5 mg/kg were 134 ± 6 and 136 ± 10 mmHg, respectively. MAP before and after pentobarbital 5 mg/kg were 142 ± 7 and 134 ± 7 mmHg, respectively. These values (before versus after) were not significantly different in all groups.

Figure 3 shows baroreflex gains following phenylephrine injection (reflex-induced vasodilation). The baroreflex gains in reflex vasodilation were 0.61 ± 0.08 and 0.71 ± 0.10 (not significant: n.s.) before and after ketamine 1 mg/kg, and 0.59 ± 0.05 and 0.63 ± 0.06 (n.s.) before and after ketamine 5 mg/kg, and 0.72 ± 0.09 and 0.45 ± 0.06 ($P<0.01$) before and after pentobarbital 5 mg/kg, respectively.

Figure 4 shows reflex gains following nitroprusside injection (reflex-induced vasoconstriction).The baroreflex gains in reflex vasoconstriction were 0.55 ± 0.14 and 0.62

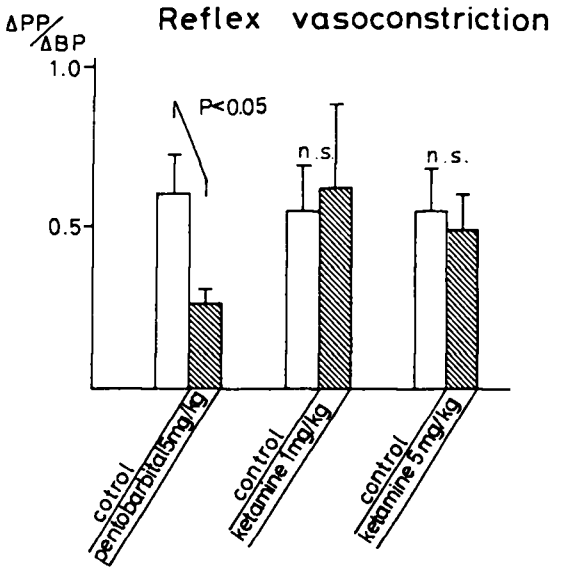

Fig. 4. The gain of arterial baroreflex control of hindlimb vascular resistance in response to nitroprusside (reflex vasoconstriction). Ketamine 1 and 5 mg/kg did not significantly alter the gain, whereas pentobarbital 5 mg/kg significantly decreased it.
n.s. = not significant

± 0.16 (n.s.) before and after ketamine 1 mg/kg, and 0.55 ± 0.13 and 0.49 ± 0.11 (n.s.) before and after ketamine 5 mg/kg, and 0.60 ± 0.13 and 0.25 ± 0.04 ($P<0.01$) before and after pentobarbital 5 mg/kg. Pentobarbital 5 mg/kg significantly depressed the baroreflex gains in reflex vasodilation as well as reflex vasoconstriction. However, ketamine 1 and 5 mg/kg did not significantly depress the baroreflex gains in control of hindlimb vascular resistance.

Discussion

The result presented in this study suggests that baroreflex control of hindlimb vascular resistance was maintained during ketamine anesthesia. By constrast, during pentobarbital anesthesia, baroreflex control of vascular resistance was significantly depressed. The maintenance of the baroreflex function may contribute to circulatory stability when anesthetizing hypovolemic patients with ketamine.

The gain of arterial baroreflex was assessed by relating changes in arterial pressure to reflex changes in hindlimb perfusion pressure. When the gain of arterial baroreflex is calculated in this way, it is influenced by the difference in vascular reactivity, or release of neurotransmitters. Thus, it may not represent the true gain of arterial baroreflex in terms of reflex control of sympathetic outflow. Therefore, we considered the possibility that the preservation of baroreflex control of vascular resistance by ketamine might be due to peripheral potentiation of sympathetic nerve responses which could have cancelled out the depressed baroreflex control of sympathetic outflow. However, this possibility is unlikely, since it has been shown that ketamine depressed the vasopressor response produced by stimulation of the lumbar sympathetic outflow and did not significantly affect the pressor response to intravenous noradrenaline administration[12].

The result of this study seems to be in accord with the reports of Wilson et al.[8] and McGrath et al.[9], but different from the findings of Dowdy and Kaya[5] and Blake and Korner [6,7]. Wilson et al.[8] reported moving pediatric patients in all positions during ketamine anesthesia without any sign of orthostatic hypotension, suggesting the preservation of baroreflex in the human subjects. McGrath et al.[9] showed that ketamine did not block the baroreflex controlling sympathetic tone. On the contrary, Dowdy and Kaya[5] showed that an increase in blood pressure by ketamine was due to the desensitization of carotid baroreceptor reflex in dogs. They concluded that ketamine inhibited the baroreflex function in the control of blood

pressure. They, however, did not examine the baroreflex sensitivity in response to changes in blood pressure, but revealed a depressed tonic inhibitory action of carotid sinus nerve by ketamine. Blake and Korner[6,7] showed that ketamine produced marked depression of baroreceptor reflex control of heart rate in rabbits. The reason why baroreflex control of heart rate is impaired whereas the control of vascular resistance is preserved is not clear, but may be explained in part by a different control of heart rate and vascular resistance[10]. There is no redundancy in the control of vagal neurons by aortic and carotid baroreceptors whereas there is significant redundancy in the control of sympathetic neurons[10]. Therefore, it is possible that there is preservation of reflex control of vascular resistance at a time when reflex control of heart rate is impaired.

This study also shows the depressive effect of pentobarbital on baroreceptor reflex control of vascular resistance. This is consistent with the previous investigators[13–15], though others have found its depressive effect to be minimal[16,17].

The doses of anesthetics in this study we used were relatively low compared to the previous reports[18,19]. The anesthetic doses of ketamine which raise arterial pressure in man and several animal species are of the order of 2–5 mg/kg (i.v.)[3,20,21] and higher doses could depress the cardiovascular system[3,21]. Therefore, we used 1 and 5 mg/kg of ketamine with the supplement of nitrous oxide. Consequently, it is possible that different results could be obtained with higher doses of ketamine.

Several reports[22–24] have suggested that ketamine may be the drug of choice for anesthesia during hypovolemia. The preservation of baroreflex control of vascular resistance by ketamine may contribute significantly to the maintenance of blood pressure in the subjects with hemorrhagic hypovolemia, since arterial baroreflex is considered to play an important compensatory role in such condition.

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