EFFECTS OF KETAMINE ON CENTRAL SYMPATHETIC DISCHARGE AND THE BARORECEPTOR REFLEX DURING MECHANICAL VENTILATION

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SUMMARY

In rabbits which were ventilated mechanically, with a background anaesthetic of pentobarbitone or after decerebration, ketamine depressed preganglionic sympathetic activity and arterial pressure. Conduction through central baroreceptor pathways, tested by depressor nerve stimulation, showed a selective inhibition of the heart rate response.

In man, ketamine causes cardiovascular stimulation (Domino, Chodoff and Corssen, 1965; Virtue et al., 1967; Bovill et al., 1971), whereas in animals it has been shown to produce responses which vary with the species and the experimental conditions employed. Thus, in dogs anaesthetized with pentobarbitone, Dowdy and Kaya (1968) described biphasic effects, whereas in conscious animals Traber, Wilson and Priano (1970) found only a pressor action. Chang, Chan and Ganendran (1969) reported depressor responses in conscious rats and those anaesthetized with pentobarbitone, whereas a pressor effect occurred after previous pithing. Many explanations have been suggested for such variability. The pressor response has been considered to involve the sympathetic nervous system (Dowdy and Kaya, 1968; Traber and Wilson, 1969), but the postulated sites of action are diverse, including a reflex increase in sympathetic discharge as a result of baroreceptor desensitization (Dowdy and Kaya, 1968), central sympathetic stimulation (Wong and Jenkins, 1974), or an increased efficacy of noradrenaline released from adrenergic nerve terminals as a result of blockade of neuronal re-uptake (Montel et al., 1973; Nedergaard, 1973). It has been suggested also that the pressor response is caused by a release of catecholamines from the adrenal medulla (Chang, Chan and Ganendran, 1969), or of corticosteroids from the adrenal cortex (Oyama, Matsumoto and Kudo, 1970). When a depressor response was found, it was attributed to a direct negative inotropic effect on the myocardium (Dowdy and Kaya, 1968).

We have investigated the effect of ketamine on central sympathetic discharge in the rabbit, to establish a possible correlation with the cardiovascular changes. Also, to this end we have looked for depression of central baroreceptor pathways, for comparison with the inhibitory action of several inhalation agents (Biscoe and Millar, 1966). A preliminary communication of the results has been published (McGrath, MacKenzie and Millar, 1975).

METHODS

Male New Zealand white rabbits, 2.8-3.5 kg, were anaesthetized with pentobarbitone or decerebrated. Pentobarbitone 30 mg/kg was given initially via the marginal ear vein, and subsequent doses of 4 mg/kg were administered every 40 min through a femoral vein cannula. A tracheal cannula was inserted soon after induction of anaesthesia.

Decerebration was carried out under anaesthesia with 3% halothane in oxygen; the accompanying low arterial pressure restricted bleeding and rendered carotid clamping unnecessary. At least 1 hr was allowed to elapse after stopping halothane before the effects of ketamine were examined.

Subsequent to the preparatory period, gallamine 1 mg/kg was given i.v. every 40 min. Mechanical ventilation (Harvard apparatus, Model 613) with 100% oxygen was adjusted to maintain the end-tidal carbon dioxide concentration at approximately 4%, monitored with a Beckman LB-2 carbon dioxide analyser. Arterial pressure was recorded via the femoral artery with a Bell and Howell pressure transducer, and heart rate was obtained from the pressure recording using a Devices instantaneous ratemeter. Heart rate, arterial pressure and the electronically meaned arterial pressure were displayed on a Devices MX-4 four-channel recorder. Rectal temperature was maintained at 38.5 ± 0.5 °C by means of a Palmer
homoeothermic blanket. Periodical analysis of arterial samples with an IL 227 meter showed that arterial pH remained within the range 7.35–7.49.

Activity was recorded from multifibre strands of the central end of the divided left preganglionic cervical sympathetic nerve, using bipolar platinum electrodes. The signal was amplified by a Tektronix Type 122 preamplifier, and displayed on a Tektronix Type D12 oscilloscope. The amplified signal was taken to a pulse height selector, whence the spikes were counted on a Panax ratemeter. Mean integrated sympathetic discharge rate was displayed on the Devices recorder, using time constants of 1–3 sec.

In each experiment 2 μg adrenaline was given i.v. to establish that the multifibre preparation was under baroreceptor control, and studies were undertaken only if nerve activity was reduced by the resulting increase in arterial pressure.

The desheathed central end of the divided left aortic depressor nerve was placed over a pair of silver wire electrodes for stimulation (0.1 msec pulse width, 50 Hz for 20 sec), using a Devices gated pulse generator and isolated stimulator. In all rabbits, the right aortic depressor nerve was divided, and in three experiments both carotid sinus nerves were cut. In three animals both vagi were divided in the neck, and the desheathed peripheral end of the left nerve was placed on silver electrodes to allow supramaximal stimulation (0.1 msec pulse width, 5 Hz for 20 sec).

Ketamine was given intravenously. Where several doses were administered to one rabbit, at least 30 min was allowed between each to allow complete recovery. Drugs used were: adrenaline acid tartrate (Macarthys), gallamine triethiodide (Flaxedil, May and Baker), pentobarbitone sodium (Nembutal, Abbott) and ketamine hydrochloride (Ketalar, Parke-Davis).

Adrenaline and ketamine are expressed as grams of the base, gallamine and pentobarbitone as grams of the salt.

RESULTS

Effects of ketamine on arterial pressure, heart rate and sympathetic activity

Animals with background anaesthesia of pentobarbitone. Figure 1 illustrates the effects of ketamine 5 mg/kg on arterial pressure and sympathetic discharge, which are both depressed, while heart rate is slightly reduced. A notable feature is the loss of respiratory modulations of sympathetic discharge, as seen previously with the inhalation anaesthetics (Millar and Biscoe, 1965). The effect on pressure and nerve activity is maximal at 2 min, and its magnitude is related to dose (fig. 2B and C). A dose–response plot for the three parameters shows similar reductions in arterial pressure and sympathetic activity (fig. 3), which are statistically significant with ketamine 5 and 10 mg/kg (figs. 2B, C and 3A). The reduction in heart rate caused by ketamine is not significant at any dose.
level for all experiments grouped together (figs. 2A and 3A). After doses up to 10 mg/kg, all three measurements returned to pre-existing values within 30 min, with no indication of a secondary pressor response. Ketamine 20 mg/kg profoundly depressed arterial pressure and sympathetic activity, causing circulatory collapse in four of five rabbits.

Decerebrate animals. In decerebrate rabbits the initial (pre-ketamine) values of mean arterial pressure (79 ± 6 mm Hg) and heart rate (324 ± 16 beats/min) did not differ significantly from those in the pentobarbitone group (89 ± 13 mm Hg and 312 ± 19 beats/min respectively).

The effects of ketamine were similar; thus both arterial pressure and sympathetic activity were depressed, while heart rate was not altered significantly (fig. 3b). The maximum change occurred within 2 min.

Three of four decerebrate rabbits died when ketamine 10 mg/kg was administered.

Baroreceptor denervation. Subsequent to division of both sinus and depressor nerves in two decerebrate

Fig. 2. Time course of the effects of intravenous ketamine (background anaesthesia: pentobarbitone). (A) Heart rate (HR); (B) mean arterial pressure (MAP); (C) cervical sympathetic discharge (CSA). Each parameter is expressed as a percentage of the pre-ketamine control value (mean ± SEM of five experiments). Doses: O = 1 mg/kg; △ = 2 mg/kg; ● = 5 mg/kg; ▲ = 10 mg/kg. Asterisks indicate *P* values by Student's *t* test: *P* < 0.05; **P** < 0.01; ***P*** < 0.001.
and one pentobarbitone-anaesthetized animals, ketamine showed effects similar to those in the groups with intact nerves, except that recovery of arterial pressure and sympathetic discharge occurred over a longer period.

Effects of ketamine on the baroreceptor reflex

Stimulation of the central end of the left aortic depressor nerve caused a reproducible decrease in arterial pressure, sympathetic activity and heart rate (fig. 1). Two min after ketamine 5 mg/kg, when arterial pressure and sympathetic discharge had been lowered by the drug, depressor nerve stimulation still reduced arterial pressure and sympathetic activity; although the absolute reductions were smaller than control, a similar base-line was reached as in the absence of the drug (figs. 1 and 4). Other doses of ketamine (1, 2 and 10 mg/kg) had similar effects on the arterial pressure and sympathetic components of the reflex, depressing the resting values to different extents, but leaving virtually unaffected the base-line achieved by baroreceptor stimulation.

In contrast, the heart rate component of the reflex was inhibited by ketamine, as illustrated for various doses in figures 1, 4, 5 and 6. This action, even at 1 mg/kg, is shown in figures 4 and 5, whereas the value to which arterial pressure can be reduced by baroreceptor stimulation remains closer to the pre-ketamine control.

Role of the vagus nerves in the reflex decrease in heart rate produced by depressor nerve stimulation

After section of both cervical vagi, and in the absence of ketamine, there was a smaller reduction in heart rate on depressor nerve stimulation (fig. 6). The residual response was unaffected by ketamine 5 mg/kg, which did cause inhibition when the vagi were intact.
Stimulation of the peripheral end of the divided left vagus nerve caused a reduction of heart rate to a degree similar to that evoked by depressor nerve stimulation before vagal section. This heart rate response was unaffected by ketamine 5 mg/kg (fig. 6).

DISCUSSION

In the mechanically ventilated rabbit, ketamine depresses preganglionic sympathetic discharge, in proportion to dose, and roughly in parallel with reductions in arterial pressure. This finding was unexpected, in view of the pressor action which has been reported in other species, and the common belief that ketamine stimulates sympathetic activity.

It remains a possibility that sympathetic activation by ketamine could originate in neurones influencing circulatory control, which are situated above the mid-collicular level, and are depressed by a background of pentobarbitone anaesthesia; if so, their influence would have been nullified in the present experiments, before the administration of ketamine.

Since the reflex responses of arterial pressure and sympathetic activity to depressor nerve stimulation were affected to a minimal extent by ketamine, the effects of the doses used on transmission through central baroreceptor pathways are more selective than those of moderate or high concentrations of the inhalation agents cyclopropane and diethyl ether which, under identical experimental conditions, stimulate sympathetic discharge and coincidentally inhibit all three measured components of the baroreceptor reflex (Biscoe and Millar, 1966). Figure 7, for example, shows the effect of 50% cyclopropane on the response to depressor nerve stimulation in a pentobarbitone-anaesthetized rabbit from the current series of experiments. Heart rate, arterial pressure and sympathetic activity are all increased after 7 min of cyclopropane administration, while the responses to depressor nerve stimulation are greatly reduced or abolished.
The inhibition by ketamine of the bradycardia produced by depressor nerve stimulation is of particular interest, and the findings suggest that this effect is exerted centrally on vagal pathways involved in the baroreceptor reflex. Since the decrease in heart rate produced by efferent vagal stimulation was not prevented by ketamine, the parasympathetic ganglion and postganglionic nerve endings do not appear to be critical sites of action of the drug. Recently, Brezenoff (1973) has observed that ketamine abolished the bradycardia produced by noradrenaline in the rat.

Several workers have noted that barbiturate anaesthesia can result in a "resetting" of the heart rate at higher values for a given arterial pressure (Morrison, Walker and Richardson, 1950; Price et al., 1952; Bristow et al., 1969). This could be a result of a selective inhibition of the parasympathetic compared with the sympathetic components of the baroreceptor reflex, as found here with ketamine.

Several anaesthetic agents, including barbiturates, have been shown to block postganglionic transmission of the cardiac vagus (Price, 1960). This was unlikely to have a serious influence on the present experiments, in view of the obvious vagal component in the baroreceptor responses of rabbits given pentobarbitone; also the size of the reflex response and the effects of ketamine were similar in pentobarbitone-anaesthetized and decerebrate rabbits. The central sympathetic component of the heart rate reflex was revealed by the bradycardia still evoked by depressor nerve stimulation subsequent to vagal section, confirming the observations of Kardon, Peterson and Bishop (1973).

The present studies, in which a pressor effect of ketamine was not seen, do not explain such a response in other species or conditions.

**Fig. 7. Effects of cyclopropane on the baroreceptor reflex in the rabbit (background anaesthesia: pentobarbitone). Left panel: depressor nerve stimulation (DS) prior to cyclopropane; centre: after 7 min of 50% cyclopropane administration; right: 12 min after discontinuing cyclopropane.**

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REFERENCES


**EFFETS DE LA KETAMINE SUR LA DECHARGE SYMPATHIQUE CENTRAL ET REFLEXE BARORECEPTEUR PENDANT LA VENTILATION MECANIQUE**

**RESUME**

Sur des lapins ventilés mécaniquement, ayant auparavant été anesthésiés au pentobarbitone ou après décérébration, la kétamine a réduit l'activité sympathique preganglionnaire ainsi que la tension artérielle. La conduction par des moyens barorécepteurs centraux, soumise à des essais par stimulation des nerfs depressives, a montré une inhibition sélective de la réponse des battements du cœur.

**WIRKUNGEN VON KETAMIN AUF DIE ZENTRALE SYMPATISCHE AKTIVITÄT UND DEN BAROREZEPTOR-REFLEX BEI MECHANISCHER BELÜFTUNG**

**ZUSAMMENFASSUNG**


**EFECTOS DE LA QUETAMINA EN LA DESCARGA DEL SISTEMA SIMPATICO CENTRAL Y EL REFLEJO BARORRECEPTOR DURANTE LA VENTILACION MECANICA**

**SUMARIO**

En conejos ventilados mecánicamente con un antecedente anestésico de pentobarbitona o después de la decerebración, la quetamina deprimió la actividad simpática preganglionar y la presión arterial. La conducción a través de vías de acceso barorreceptoras centrales ensayadas por la estimulación del nervio depresor mostró una inhibición selectiva de la respuesta del ritmo cardíaco.