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Effects of Methoxyflurane Anesthesia on Adrenal Medullary Catecholamine Secretion:

Inhibition of Spontaneous Secretion and Secretion Evoked by Splanchnic-nerve Stimulation

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The effects of methoxyflurane on catecholamine secretion by the adrenal medulla and on the pressor effect induced by stimulation of the splanchnic nerve were investigated in cats which had received pentobarbital as a basal anesthetic agent. Inhalation of a methoxyflurane–air mixture (0.3–0.6 per cent methoxyflurane) inhibited both spontaneous catecholamine release and the secretion evoked by splanchnic-nerve stimulation. During inhalation of 0.4 per cent methoxyflurane spontaneous releases of epinephrine and norepinephrine amounted to 17 and 6 per cent of the initial rates, respectively, and releases evoked by neural stimulation were reduced to 30 and 14 per cent of the initial rates. Under these conditions, the pressor effect induced by splanchnic-nerve stimulation was decreased by 42 per cent and, during inhalation of 0.6 per cent methoxyflurane, it was reduced by 79 per cent. These results indicate that the inhibition of catecholamine release by methoxyflurane is at least partially due to a direct effect on the chromaffin cell: the secretion-stimulating effect of acetylcholine, released from the splanchnic nerves, is inhibited. A comparison of these results with those previously obtained for halothane[3] indicates that both anesthetics act in the same manner on spontaneous catecholamine secretion and on the catecholamine output during splanchnic-nerve stimulation. (Key words: Anesthetics, volatile: methoxyflurane; Sympathetic nervous system: methoxyflurane.)

LI AND ASSOCIATES[1] have shown in dogs that the catecholamine concentration of blood from the adrenal vein is decreased during methoxyflurane anesthesia proportional to the concentration of the anesthetic; however, the mechanism of inhibition of catecholamine release by methoxyflurane remained unexplained.

To test whether a direct effect on the chromaffin cells of the adrenal medulla is involved in methoxyflurane-induced inhibition of catecholamine secretion, perfusion experiments were carried out on isolated bovine adrenal glands; these revealed that methoxyflurane is capable of inhibiting the release-stimulating action of acetylcholine almost completely.[2] Under physiologic conditions an increase in secretory activity of the adrenal medulla is elicited by acetylcholine released from the splanchnic nerves. Consequently, we investigated *in vivo* whether methoxyflurane is able to inhibit the increased catecholamine output from the cat adrenal medulla provoked by electrical stimulation of the splanchnic nerve. In addition, we tested whether methoxyflurane also counteracts the pressor effect of splanchnic-nerve stimulation.

In a previous study, effects of halothane on spontaneous catecholamine release and the release mediated by splanchnic-nerve stimulation were determined using the same methods.[3] To provide a basis for comparison of the effects of halothane and methoxyflurane, the spontaneous output from the adrenal medulla during methoxyflurane anesthesia was also measured.

Methods

The experiments were performed on cats of either sex (weights 1.7–4.0 kg). Tracheotomy and cannulation of the trachea were carried out 20 min after ip injection of pentobarbital (30 mg/kg) for basal anesthesia.

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Mechanical ventilation was initiated with a tidal volume of 35–65 ml and a respiratory frequency of 19/min. Thus, the animals were hyperventilated to the end of the experiments in order to prevent spontaneous respiration; injection of any neuromuscular blocking agent was avoided, since these substances are known to interfere with catecholamine secretion from the adrenal medulla.[2] The left femoral artery and vein were cannulated with polyethylene catheters for drawing blood samples and drug injection, respectively. The venous cannula was advanced until it rested in the vena cava. The right femoral artery was cannulated for recording blood pressure and pulse rate by means of a Statham pressure transducer. Spontaneous catecholamine secretion, secretion evoked by splanchnic-nerve stimulation, and the pressor effect of splanchnic-nerve stimulation were investigated in different groups of cats.

Investigation of Spontaneous Catecholamine Secretion

After midline laparatomy, the left adrenolumbar vein was cannulated from distal to proximal; the tip of the polyethylene catheter was kept 1–2 mm distant from the gland. At the end of the preparation, 2,500 units/kg (20 mg/kg) of heparin were injected into the femoral vein. Subsequently, the first blood sample was drawn from the adrenolumbar vein. During blood sampling the total outflow of the adrenal venous blood into the vena cava was blocked by a ligature on the adrenolumbar vein between the gland and the vena cava. This ligature was slipped off after termination of each blood sampling. The volume of blood samples was 4 ml, which could be drawn within 7 to 10 min. The blood volume removed was replaced with a corresponding volume of dextran solution (6 per cent).

Five cats received no methoxyflurane, in order to permit study of the influence of the basal anesthetic agent, pentobarbital, on catecholamine secretion. Methoxyflurane mixed with air was administered to eight cats after termination of the first blood sampling. The methoxyflurane vaporizer was inserted into a nonrebreathing system. During anesthesia blood sampling was started after 40 min of inhalation of each methoxyflurane concentration. Each concentration of methoxyflurane was administered for 50 min. Sixty minutes after cessation of methoxyflurane administration, the last blood sample was drawn from the adrenolumbar vein. The same time intervals were applied in the following series of experiments.

Catecholamine Secretion Evoked by Splanchnic-nerve Stimulation

After laparatomy the left splanchnic nerve was identified and a bipolar platinum electrode was fixed to the nerve 1.0–1.5 cm craniad to the left adrenal gland. Subsequently, the nerve was cut proximal to the electrode and the left adrenolumbar vein was cannulated (see above). In these experiments sampling of blood was started with the onset of stimulation and was continued for 10 min; thus, 7.5–11.5 ml of blood were drawn from the adrenolumbar vein. Electrical stimuli (4 V, 1 msec, 10 Hz, duration 5 min) were delivered to the splanchnic nerve from a square-wave generator. The voltage employed was submaximal, for the following reasons: When the effect of endogenous acetylcholine released by splanchnic-nerve stimulation is studied, a complete dose–response curve cannot be recorded. In this case the inhibitory effect of methoxyflurane can be measured most accurately when the acetylcholine concentration released causes catecholamine secretion which is about 70–80 per cent of the maximal rate, since in this range the dose–response curve is linear. Therefore, submaximal stimulation of the splanchnic nerve was employed; under control conditions, this increased catecholamine secretion by about 70–80 per cent of maximum.

In this series of experiments also, five cats received no methoxyflurane, in order to permit study of the effect of pentobarbital. Methoxyflurane mixed with air was administered to seven cats.

Pressor Effect of Splanchnic-nerve Stimulation

Preparation of the left splanchnic nerve was performed as previously described, and the same electrode was used for stimulation.

TABLE 1. Catecholamine Secretion from the Cat Adrenal Medulla during Pentobarbital Anesthesia*

Duration of Anesthesia (Min)	Spontaneous Secretion (ng/kg/min)		Secretion Evoked by Splanchnic-nerve Stimulation (ng/kg/min)	
	Epinephrine	Norepinephrine	Epinephrine	Norepinephrine
90	2.38 ± 0.34	4.36 ± 0.99	74.8 ± 28.5	99.8 ± 42.3
125	4.83 ± 2.96	4.77 ± 1.03	73.6 ± 16.7	79.5 ± 27.1
160	7.69 ± 4.31	6.71 ± 1.02	82.4 ± 16.1	69.9 ± 29.2
195	5.47 ± 3.25	9.64 ± 2.42	80.1 ± 18.2	96.8 ± 20.1

* Means ± SEM are given. The differences in either spontaneous catecholamine secretion (n = 5) or catecholamine secretion from the stimulated gland (n = 5) were not significant when the values of the corresponding groups were compared with each other.

The pressor effect of splanchnic nerve stimulation (lasting 5 min) was compared with that of an intravenous injection of norepinephrine (1 μg/kg) 5 min after the end of nerve stimulation. In nine cats submaximal stimuli (4 V, 1 msec, 10 Hz) were delivered to the nerve. Thus, the experimental conditions did not differ from those of the previous series of experiments.

Since blood pressure decreased considerably during methoxyflurane inhalation and since the stimulation threshold might be changed under these circumstances, five cats received infusions of dextran solution (6 per cent, 56–110 ml) during methoxyflurane administration in order to maintain blood pressures at approximately the initial levels. Submaximal stimulation of the splanchnic nerve was performed in these animals.

Finally, the possibility that methoxyflurane itself could raise the stimulation threshold of the splanchnic nerve had to be excluded. Therefore, in five cats supramaximal stimuli (20 V, 1 msec, 10 Hz) were delivered to the nerve.

Preparation of the Plasma Extracts and Analytical Methods

The blood samples for the determinations of catecholamine concentrations were collected in ice-cold tubes containing 0.5 ml 0.9 per cent saline solution with 1 per cent EDTA-disodium and 5 μg/ml of the MAO inhibitor, tranylcypromine. The samples were immediately centrifuged at about 10,000 × g for 10 min and maintained at 2 C. Subsequently, the blood plasma was sucked off and the proteins were precipitated with 4 N perchloric acid (0.1 volume of blood plasma). The acidified blood plasma was centrifuged at 10,000 × g for 10 min at 2 C, and the supernatants were frozen immediately thereafter at −16 C. The determinations of catecholamines were performed within a week. After thawing, the *p*H of the plasma extracts was adjusted with 5 N potassium carbonate to about 4, and the extracts were passed through Dowex 50 W X 8 columns (200–400 mesh, dimensions 20 mm² × 12 mm). The epinephrine and norepinephrine of the neutralized eluates (1 N HCl) were determined spectrofluorometrically with the trihydroxyindole method of Häggendal.[4] Recoveries of epinephrine and norepinephrine (20–100 ng) were 61.7 ± 8.6 per cent and 80.7 ± 6.8 per cent, respectively (n = 38, means ± SD). The catecholamine concentrations measured were corrected accordingly. The limit of sensitivity was in the range of 3 ng of each catecholamine per extract; this corresponded to adrenal medullary secretion of about 0.1 ng/kg/min.

*p*H, standard bicarbonate, and P_{CO_2} in arterial blood were measured with an Astrup micro apparatus AME 1. A Clark P_{O_2} electrode (type E 5046, Radiometer/Copenhagen) and an oxygen monitor (Model PHA 928, Radiometer/Copenhagen) were used to determine arterial and venous partial pressures of oxygen.

Statistics: In the tables and figures mean values are given, together with standard errors of the mean. For statistical evaluation of the data, Student's t test was used. Each cat served as its own control.

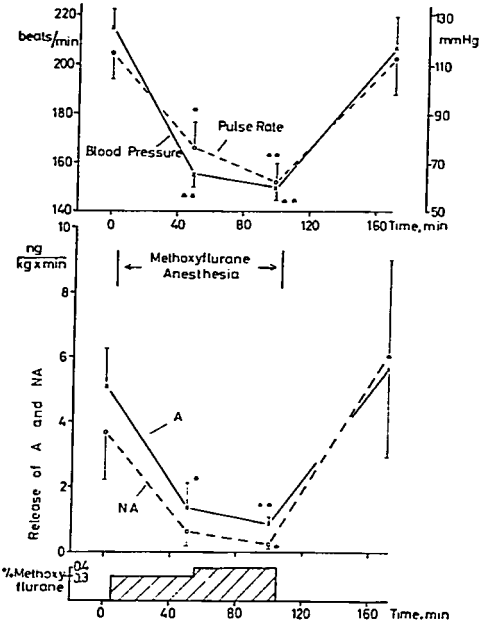

FIG. 1. *Lower graph:* Spontaneous release of epinephrine (A, *solid line*) and norepinephrine (NA, *broken line*) from the cat adrenal medulla *in situ* before, during and after inhalation of methoxyflurane–air mixtures (n = 8, means ± SEM). *Upper graph:* Mean arterial blood pressure and pulse rate in the same cats. $^{*}P < 0.05$; $^{**}P < 0.005$.

Results

Spontaneous Catecholamine Release and Hemodynamic Effects

In experiments on five cats without methoxyflurane, blood samples from the adrenolumbar vein were drawn four times at intervals of 35 min (table 1). Mean epinephrine and norepinephrine secretion tended to increase with time, but variations among cats increased considerably. Thus, the mean differences between sampling periods were not statistically significant.

Before administration of methoxyflurane, the amounts of epinephrine and norepinephrine secreted were 5.1 ng/kg/min and 3.7 ng/kg/min, respectively (fig. 1). After inhalation of 0.3 per cent methoxyflurane for 50 min, they were reduced to 36 and 17 per cent of the initial levels, respectively; upon continuation of the anesthesia with 0.4 per cent methoxyflurane, both epinephrine release and norepinephrine release declined further, to 17 and 6 per cent of the pentobarbital control values. After withdrawal of the inhalation anesthetic, secretion of both amines increased and, after an hour they reached levels slightly above preanesthetic values. Changes in pulse rate and blood pressure were directly related to changes in catecholamine secretion during and after methoxyflurane anaesthesia (fig. 1).

Splanchnic Nerve Stimulation

Experiments on five cats that had not received methoxyflurane indicate that the output of catecholamines from the adrenal gland during electrical stimulation of the splanchnic nerve remained remarkably con-

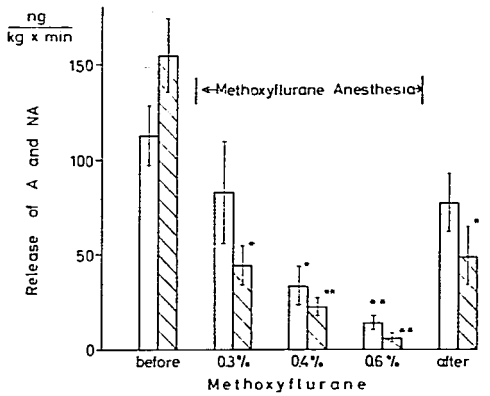

FIG. 2. Release of epinephrine (*A, open columns*) and norepinephrine (*NA, shaded columns*) from the cat adrenal medulla *in situ* during splanchnic-nerve stimulation (n = 7, means ± SEM). Catecholamine secretion was measured before, during, and 60 min after inhalation of methoxyflurane–air mixtures. $^{*}P < 0.005$; $^{**}P < 0.001$.

stant over the duration of the experiment (table 1).

Electrical stimulation of the splanchnic nerve before methoxyflurane administration increased epinephrine and norepinephrine secretion to 112 and 154 ng/kg/min, respectively (fig. 2). The amounts of catecholamines released from the gland by splanchnic-nerve stimulation declined continuously during 50-min periods of inhalation of 0.3, 0.4, or 0.6 per cent methoxyflurane. At a concentration of 0.6 per cent methoxyflurane, the epinephrine output from the stimulated adrenal gland dropped to 12 per cent and that of norepinephrine to only 4 per cent of control. By 1½ hours after withdrawal of the inhalation anesthetic, catecholamine release from the nerve-stimulated organ had not recovered to the initial values.

ACID–BASE METABOLISM AND P_{O_2}

Changes in acid–base balance and P_{O_2} in blood are summarized in table 2. Due to the hyperventilation present throughout the experiments, the values reflect changes typical of compensated respiratory alkalosis. Pa_{O_2} remained in the upper range of normal throughout the experiments. Venous partial pressure of oxygen dropped gradually because of repeated removal of blood from the animals.

TABLE 2. Acid–Base Balance and Oxygen Partial Pressure in Blood*

	pH_a	Pa_{CO_2} (mm Hg)	Standard Bicarbonate (mEq/l)	Pa_{O_2} (mm Hg)	Pv_{O_2} (mm Hg)
Before methoxyflurane	7.49 ±0.01	22.0 ± 1.0	19.9 ± 0.7	103 ± 4	33 ± 2
Methoxyflurane, 0.3 per cent	7.47 ±0.02	22.6 ± 1.3	19.1 ± 1.1	101 ± 5	31 ± 2
Methoxyflurane, 0.4 per cent	7.48 ±0.02	18.2 ± 1.2	17.9 ± 0.8	110 ± 4	28 ± 1
After methoxyflurane	7.47 ±0.02	18.8 ± 1.2	17.5 ± 0.8	110 ± 4	26 ± 1

* Values are means ± SEM from the cats of figures 1 and 2 (n = 15); blood samples for these measurements were drawn immediately after those for catecholamine determinations.

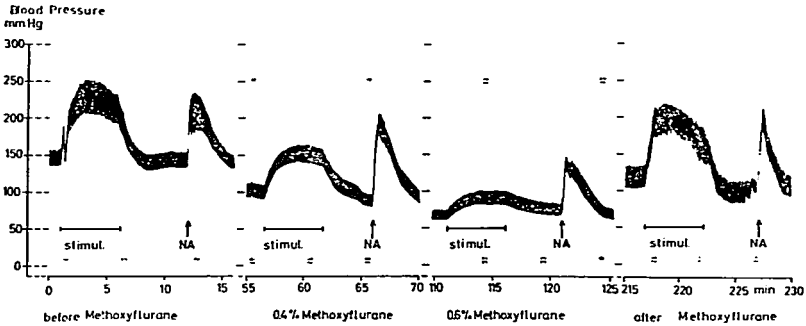

FIG. 3. Pressor effects evoked by splanchnic-nerve stimulation (*stimul.*) and by iv injection of norepinephrine (NA, 1 μg/kg) in a cat.

TABLE 3. Pressor Effects of Splanchnic-nerve Stimulation and Norepinephrine*

		Mean Arterial Blood Pressure before Stimulation (mm Hg)	Increase in blood pressure	
			Splanchnic-nerve Stimulation	Norepinephrine (1 μg/kg)
Series A Stimulation of splanchnic nerve with 4 V (9 cats)	Before methoxyflurane	92 ± 10 (100%)	95 ± 10 (100%)	67 ± 5 (100%)
	Methoxyflurane, 0.4 per cent	42 ± 10 (46%†)	58 ± 5 (61%†)	68 ± 12 (101%)
	Methoxyflurane, 0.6 per cent	27 ± 6 (29%‡)	21 ± 5 (22%‡)	48 ± 9 (72%)
	60 min after methoxyflurane	83 ± 13 (90%)	78 ± 8 (82%)	80 ± 11 (119%)
Series B Infusion of dextran solution during methoxyflurane anesthesia; stimulation of splanchnic nerve with 4 V (5 cats)	Before methoxyflurane	100 ± 9 (100%)	75 ± 10 (100%)	57 ± 6 (100%)
	Methoxyflurane, 0.4 per cent	93 ± 3 (93%)	31 ± 8 (41%†)	54 ± 11 (95%)
	Methoxyflurane, 0.6 per cent	79 ± 7 (79%)	26 ± 9 (35%†)	65 ± 10 (114%)
	60 min after methoxyflurane	104 ± 12 (104%)	48 ± 8 (64%)	69 ± 9 (121%)
Series C Stimulation of splanchnic nerve with 20 V (5 cats)	Before methoxyflurane	90 ± 5 (100%)	129 ± 9 (100%)	67 ± 6 (100%)
	Methoxyflurane, 0.4 per cent	55 ± 3 (61%‡)	84 ± 9 (65%‡)	78 ± 10 (116%)
	Methoxyflurane, 0.6 per cent	44 ± 4 (49%‡)	43 ± 8 (33%‡)	79 ± 8 (118%)
	60 min after methoxyflurane	75 ± 5 (83%)	96 ± 7 (74%)	84 ± 14 (125%)

* Values are means ± SEM. † $P < 0.01$. ‡ $P < 0.001$.

Pressor Effect of Splanchnic-Nerve Stimulation

The pressor effects of splanchnic-nerve stimulation and norepinephrine injection are shown in figure 3 and table 3. Before initiation of methoxyflurane anesthesia, submaximal stimulation (4 V) of the splanchnic nerve caused mean arterial blood pressure to rise by 95 mm Hg (table 3A); the injection of norepinephrine (1 μg/kg) resulted in an elevation of blood pressure by 67 mm Hg. Following periods of 50 min of inhalation of 0.4 or 0.6 per cent methoxyflurane, mean arterial blood pressure decreased considerably, and the pressor effect of splanchnic-nerve stimulation declined to 61 and 22 per cent of the pentobarbital control, whereas the pressor effect of norepinephrine was not significantly decreased. When the drastic fall in blood pressure during methoxyflurane administration was prevented by infusion of dextran solution, the decrease in the pressor effect of splanchnic-nerve stimulation caused by methoxyflurane still amounted to 35 per cent of the pentobarbital control (table 3B); this percentage was not significantly different from that observed when dextran solution was not infused. The same result was obtained when supramaximal stimuli (20 V) were delivered to the splanchnic nerves of cats that had not received dextran infusion (table 3C).

Discussion

The results of the present investigation of cats confirm the finding of Li *et al.*[1] that methoxyflurane decreases spontaneous catecholamine secretion of the adrenal medulla. In addition, we found that this anesthetic also inhibits the catecholamine release induced by splanchnic-nerve stimulation. The methoxyflurane-induced inhibition of catecholamine release is of such a magnitude that the pressor effect of splanchnic-nerve stimulation is considerably decreased. This effect is not the result of reduced sensitivity of the cat heart or blood vessels to catecholamines, since the pressor effect of a standard dose of exogenous norepinephrine (1 μg/kg) is not significantly altered in intact animals.

In order to evaluate the effects of the basal anesthetic, pentobarbital, on adrenal medullary catecholamine secretion, experiments were carried out on cats which had received only pentobarbital for anesthesia. Contrary to the results obtained with methoxyflurane, no significant change in catecholamine secretion as a function of time was observed. In fact, catecholamine secretion tended to increase.

Earlier *in-vitro* investigations of isolated bovine adrenal glands revealed that the stimulating effect of acetylcholine (10^{-5} g/ml) on catecholamine secretion is decreased by methoxyflurane in a concentration-dependent fashion (50 per cent inhibition of catecholamine output at 2×10^{-5} g methoxyflurane/ml Locke's solution).[2] Thus, the inhibition of catecholamine secretion evoked by splanchnic-nerve stimulation in intact cats is probably the result of inhibition of the acetylcholine effect exerted at the chromaffin cells of the adrenal medulla. Whether or not methoxyflurane also inhibits the *release* of acetylcholine from the splanchnic nerves cannot be determined from the results of the present investigation. However, methoxyflurane does not exert considerable influence on the stimulation threshold of the splanchnic nerve, since the inhibitory effect of this anesthetic on the pressor effect of splanchnic-nerve stimulation is in the same range at supramaximal as at submaximal stimulation of the nerve. Moreover, the stimulation threshold does not seem to be raised by the drastic fall in blood pressure observed during methoxyflurane anesthesia, since inhibition of the pressor effect of splanchnic-nerve stimulation remains unchanged when the decrease in blood pressure is prevented by infusion of dextran solution.

Even in resting conditions, small amounts of acetylcholine are continuously released from the splanchnic-nerve terminals due to the tonic activity of the sympathetic efferents to the adrenal medulla, which is thus responsible for the baseline output of catecholamines from the gland.[5,6] Consequently, inhibition of the acetylcholine effect on the chromaffin cells caused by methoxyflurane should contribute to reduction of spontaneous catecholamine output from the gland.

TABLE 4. Inhibitory Effects of Halothane[3] and Methoxyflurane on Catecholamine Secretion by the Cat Adrenal Medulla*

	Spontaneous Secretion		Secretion Evoked by Splanchnic-nerve Stimulation		Pressor Effect	
	Epinephrine	Norepinephrine	Epinephrine	Norepinephrine	Splanchnic-nerve Stimulation	Norepinephrine (1 μg/kg)
Halothane,[3] 1.5 per cent (35 min)	26	12	15	7	48	81
Methoxyflurane, 0.4 per cent (50 min)	17	6	30	14	61	101

* Values are mean percentages of preanesthetic levels. Differences between the inhibitory effects of methoxyflurane and halothane were not significant.

Investigations of preganglionic sympathetic activity in cats indicate that the decrease in spontaneous catecholamine secretion during methoxyflurane anesthesia depends not only on inhibition of the acetylcholine effect on chromaffin cells but also on central nervous system inhibition of the sympathoadrenal system. Methoxyflurane depresses preganglionic cervical sympathetic activity and sympathetic discharge in splanchnic nerve.[7] In addition, this agent reduces the absolute increase in preganglionic cervical sympathetic activity caused by 2.5 and 5.0 per cent inspired carbon dioxide.[8]

Previous measurements of catecholamine concentrations in blood plasma revealed no significant change during methoxyflurane anesthesia.[1,9,10] As already pointed out by Li *et al.*,[1] this contradiction is due to the fact that the catecholamine concentration in blood plasma is influenced by several other factors, *e.g.*, metabolic degradation and uptake into adrenergically innervated tissues.[11,12,13] These processes are relevant for both norepinephrine and epinephrine, the latter being taken up at a slower rate than norepinephrine.[14] Thus, the catecholamine concentration in blood plasma is an unreliable indicator of adrenal medullary secretion.

Results complementary to those we obtained in the cat adrenal medulla were reported by Ovadia *et al.*[15] for sympathetic ganglia: In dogs anesthetized with chloralose and urethane, the left upper thoracic sympathetic chain was stimulated and the evoked postganglionic potentials were recorded; in these experiments methoxyflurane produced a dose-dependent blocking effect on ganglionic transmission. Since the adrenal medulla is embryologically, anatomically, and functionally homologous to the sympathetic ganglia, it is evident that drugs affecting adrenal medullary function usually act on sympathetic ganglia in the same manner.

Although it is difficult to judge to what extent normal catecholamine secretion from the adrenals contributes to the maintenance of blood pressure, heart rate, and myocardial contractility, it may be assumed that both the hypotensive effect of methoxyflurane and its negative actions on the myocardium are in part caused by the decrease in secretion of epinephrine and norepinephrine. During increased sympathoadrenal activity, the inhibition of adrenal medullary secretion may play a more important role in the depressive effects of methoxyflurane on cardiovascular system, since the pressor effect of splanchnic-nerve stimulation was found to be considerably inhibited by this anesthetic. In addition, the decreased catecholamine concentration at adrenergic receptor sites of the heart may contribute to the fact that methoxyflurane does usually not cause cardiac arrhythmia although it "sensitizes" heart muscle to the excitatory actions of catecholamines.[16]

Comparison of the results obtained with methoxyflurane with those obtained with halothane[3] indicates that both anesthetics act qualitatively in the same manner on spontaneous catecholamine secretion and on the catecholamine output during splanchnic-nerve stimulation (table 4). Both drugs inhibit

norepinephrine release to a greater extent than epinephrine release. This may be because epinephrine and norepinephrine are stored in separate cells of the cat adrenal medulla,[17,18] and the inhibitory effects of both anesthetics on norepinephrine-storing cells may be slightly more pronounced. Quantitatively, differences between the effects of methoxyflurane and halothane can be evaluated by considering MAC values. In cats, MAC values for halothane and methoxyflurane are 0.82 and 0.23 per cent, respectively.[19] Accordingly, concentrations of 1.5 per cent halothane and 0.4 per cent methoxyflurane may be regarded as roughly equivalent. Therefore, the inhibitory effects of 1.5 per cent halothane and 0.4 per cent methoxyflurane, inspired, on catecholamine secretion and pressor effect of splanchnic-nerve stimulation are listed in table 4; however, it must be considered that tissue equilibrium with the inhalation anesthetics was not obtained at the moment of blood sampling. At these concentrations, catecholamine secretion and pressor effect of splanchnic-nerve stimulation are inhibited to roughly the same extent by both anesthetics.

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