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The Effects of Ethrane on Arterial Pressure, Preganglionic Sympathetic Activity, and Barostatic Reflexes

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The effects of Ethrane on cervical preganglionic sympathetic nervous activity and on the responses of this activity to electrical stimulation of the aortic depressor nerve have been examined. Mean arterial blood pressure was also measured. Subjects of the experiments were cats anesthetized with nitrous oxide and immobilized with gallamine. Both ambient efferent sympathetic activity and mean arterial blood pressure declined as the concentration of Ethrane increased; however, both still responded with further decreases when the central end of the left aortic depressor nerve was stimulated electrically. The authors postulate that Ethrane, like halothane and the barbiturates, acts predominantly on the pressor elements of the medullary vasomotor center. The actions of this group of agents are compared with those of agents which cause sympathetic nervous activation (*e.g.*, diethyl ether). (Key words: Ethrane; Arterial pressure; Preganglionic sympathetic activity; Barostatic reflexes.)

Ethrane (Airco Compound 347) has been shown to have cardiovascular actions similar to those of halothane, namely, direct myocardial depression [1] and depression of blood pressure [2,3] and cardiac output.[2] However, total peripheral resistance increases during Ethrane anesthesia,[2] while with halothane it is diminished. Plasma norepinephrine concentrations have also been reported to increase during Ethrane anesthesia,[2] but since these measurements were made during both anesthesia and operation no clear-cut study of Ethrane's effect on the sympathetic nervous system has yet been executed. What follows is a report of an attempt to accomplish such a study. In addition, our experience in the past several years with five other inhalational and two intravenous anesthetics is reviewed, and certain generalizations concerning the means by which general anesthetic agents affect sympathetic nervous activity are made.

Methods

Subjects of the experiments were six cats weighing 2.2 to 3.3 kg. They were anesthetized initially with halothane by mask, while the trachea, a femoral artery, and a vein were cannulated. Halothane was then discontinued, and gallamine, 20 mg, was given immediately intravenously, then repeated at half-hourly intervals during the experiment. Respiration was maintained with a Phipps and Bird small-animal pump (nonrebreathing system). Flow to the respirator (50 per cent N_2O–50 per cent O_2) was 4 l/min.

Strands of the left cervical sympathetic trunk were used to record preganglionic-nerve responses. Electrical stimulation of the left aortic depressor nerve was used to measure barostatic reflexes. A more detailed description of the surgical preparation, nerve-response recording, and the basis for the stimulation voltages used has been reported elsewhere.[4]

Ethrane was vaporized in a Copper Kettle, the flow through which was adjusted, depending on its temperature, to produce a constant concentration. End-expired Ethrane concentrations were measured by gas chromatography (samples withdrawn in 4-ml increments into a 50-ml syringe).

Arterial pressures were sensed by a Statham P-23Db transducer attached to a femoral arterial cannula and recorded on a Grass re-

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TABLE 1. Effects of Ethrane on Preganglionic Cervical Sympathetic Activity and Femoral Mean Arterial Pressure in Normal and Baroreceptor-denervated Cats

	Normal Cats					Baroreceptor-denervated Cats				
	Control	Initial	0.9 Per Cent Ethrane*	1.7 Per Cent Ethrane*	Final	Control	Initial	1.1 Per Cent Ethrane*	2.0 Per Cent Ethrane*	Final
Sympathetic response frequency (impulses/sec)										
Cat 1	40	40	36	32	40	138	120	110	100	156
Cat 2	52	50	28	6	48	220	240	132	66	260
Cat 3	65	68	50	32	52	128	135	80	38	120
Cat 4	30	40	28	18	38	72	74	20	16	70
Cat 5	33	37	26	5	20	48	50	28	21	45
Cat 6	38	38	20	7	38	70	80	63	25	60
MEAN	43.8	45.8	31.3	16.7	41.8	112.7	116.5	72.2	44.3	108.5
SE	3.6	3.8	4.3	5.2	3.4	25.0	27.0	18.1	13.3	24.0
Mean arterial pressure (mm Hg)										
Cat 1	142	132	102	62	152	107	180	130	82	154
Cat 2	109	108	76	48	110	178	180	130	58	175
Cat 3	147	137	118	80	157	166	170	124	76	142
Cat 4	121	103	100	64	138	172	108	105	70	175
Cat 5	126	125	72	47	120	128	138	95	68	118
Cat 6	113	105	100	67	120	138	152	93	76	125
MEAN	126.3	118.0	94.7	62.8	133.8	156.5	164.7	112.8	72.3	147.8
SE	6.3	6.1	7.1	6.3	7.5	8.1	6.8	7.0	3.4	10.1

* Exact Ethrane concentrations: 0.9 per cent = 0.89 ± 0.06 per cent.
1.7 per cent = 1.74 ± 0.09 per cent.
1.1 per cent = 1.10 ± 0.09 per cent.
2.0 per cent = 2.01 ± 0.02 per cent.

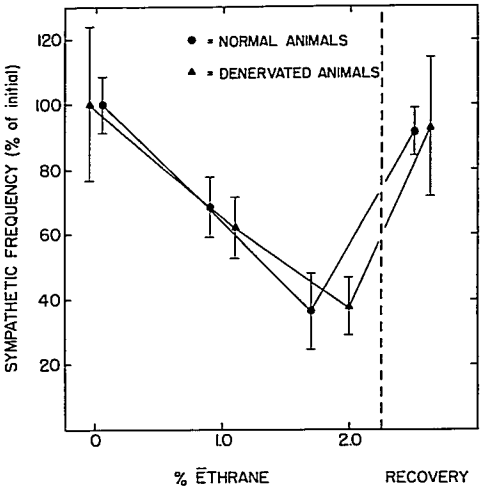

FIG. 1. Responses of sympathetic activity to increasing Ethrane concentrations, expressed as per cent of the initial value. Vertical bars represent ±SE. Ethrane end-expired concentration is given in volumes per cent.

corder. Mean pressures were obtained by electrical damping. End-tidal P_{CO_2} was measured continuously by a Godart capnograph (corrections were made for the spectral absorption caused by N_2O) and kept as close as possible to 5.4 per cent. Arterial blood samples (3 ml) were drawn at 60–90-minute intervals and analyzed in a I.L. electrode assembly for *p*H, P_{CO_2} and P_{O_2}. The blood withdrawn was replaced with an equal volume

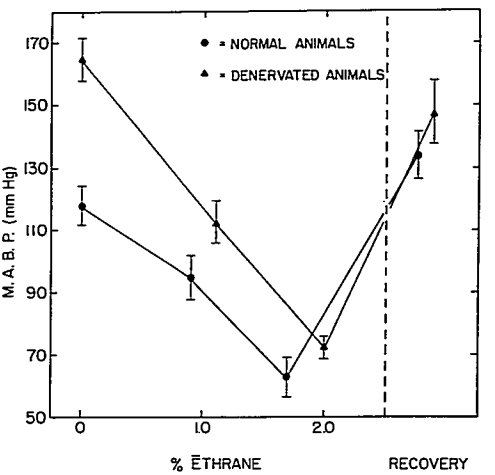

FIG. 2. Responses of mean arterial blood pressure to increasing Ethrane concentrations. Vertical bars represent ±SE. Ethrane end-expired concentration is given in volumes per cent.

TABLE 2. Effects of Ethrane on Responses of Sympathetic Nerves and Mean Arterial Blood Pressure to Electrical Stimulation of the Central End of the Left Aortic Depressor Nerve (Data Given as Per Cent Reduction)

	Initial	1.1 Per Cent Ethrane	2.0 Per Cent Ethrane	Final
Sympathetic response frequency (per cent reduction)				
Cat 1	40.0	50.0	44.0	51.2
Cat 2	27.5	70.4	78.6	45.5
Cat 3	28.6	37.5	28.1	23.7
Cat 4	20.7	25.0	40.0	28.6
Cat 5	20.7	31.8	33.3	37.7
MEAN	27.5	42.9	44.8	37.3
SE	3.5	8.0	8.9	5.1
Blood pressure (per cent reduction)				
Cat 1	15.0	24.0	11.0	29.8
Cat 2	2.3	14.8	7.1	4.9
Cat 3	15.6	11.0	6.8	8.1
Cat 4	11.4	14.0	15.3	2.9
Cat 5	4.3	12.6	9.7	10.1
MEAN	9.7	15.3	10.0	11.2
SE	2.7	2.3	1.5	4.8

of 0.9 per cent saline solution. The measured Pa_{O_2} exceeded 100 mm Hg in every sample. Metabolic acidosis, when present, was corrected with $NaHCO_3$ on the basis of base deficit × kg body weight × 0.3 mEq. Rectal temperature was measured with a Yellow Springs thermistor and maintained at 37–38 C with the aid of a "K-Pad" (Corman Rupp).

The results obtained were analyzed by Student's t test for paired data.

EXPERIMENTAL PROTOCOL

Six "normal" cats (only the left aortic depressor nerve was cut) were exposed to 1.5 per cent Ethrane for 15 minutes, after which mean arterial blood pressure (MABP), sympathetic nervous activity (SA), and end-expired Ethrane concentrations were measured. The inspired Ethrane concentration was then raised to 3 per cent for 15 minutes, after which the measurements were repeated. Ethrane was then discontinued and final measurements were made 25 minutes later. Baroreceptor denervation was then carried out; both vagi and the right aortic depressor nerve were cut and the carotid arteries were ligated above and below the sinus bulb. This increased sympathetic activity and arterial pressure and abolished the normal reflex depression in sympathetic activity that occurs when arterial pressure increases after injection of epinephrine. Ligation of the carotids is technically simpler than isolation and transection of the nerves, leads to the same result (abolition of the barostatic reflexes) and does not carry with it the risk of trauma to the nerve during dissection prior to exposure of "normal" cats to Ethrane.

When the changes in sympathetic activity and arterial pressure had stabilized after baroreceptor denervation, Ethrane was administered again in the same way as to the "normal" animal and the same measurements were made after the same time intervals, both during and after Ethrane administration. In addition, each cat was subjected to a 15-second period of baroreceptor stimulation (left aortic depressor nerve) every 5 minutes during administration of Ethrane; Cat 6, unfortunately, was unresponsive to baroreceptor stimulation, and the results from this animal have not been reported. The responses of arterial pressure to baroreceptor stimulation are expressed as maximal per cent depression observed during the 15-second stimulation period. For the sympathetic activity responses we have calculated the percentages of impulses deleted from the activity–time curve during stimulation; we find this value more meaningful than the maximal response, since sympathetic activity often failed to remain inhibited during the entire period of stimulation.

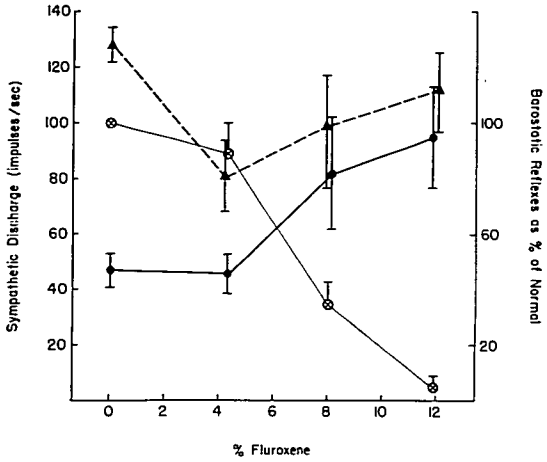

FIG. 3. Effects of fluroxene on sympathetic discharge and barostatic reflexes. ●, normal cats' sympathetic discharge rates in response to increasing fluroxene concentrations (left ordinate); ▲, denervated cats' sympathetic discharge rates in response to increasing fluroxene concentrations (left ordinate); ⊗, barostatic reflexes as per cent of normal at increasing concentrations of fluroxene (right ordinate). Vertical bars represent ±SE. Per cent fluroxene = end-expired concentrations in volumes per cent. (Data from reference 8.)

Results

Since the final level of sympathetic activity was significantly lower than the initial level in "normal" cats and the final blood pressure was significantly lower than the initial blood pressure in both "normal" and denervated animals, all changes in arterial pressure and sympathetic activity during administration of Ethrane have been compared with a "control" level calculated as the arithmetic mean of initial and final values. (The symbol ± indicates one standard error of the preceding mean.)

Results presented in table 1 are illustrated in figures 1 and 2.

"Normal" Cats

It is evident that arterial pressure and sympathetic activity both fell progressively with increasing Ethrane concentration in "normal" cats.

Denervated Cats

The effects of denervation on arterial pressure and sympathetic activity can be seen by comparing the final values in "normal" cats with the initial values in the denervated cats. The effects of Ethrane on arterial pressure and sympathetic activity in the denervated cats were similar to those in "normal" animals, that is, progressive depression at increasing depths of anesthesia. The results presented in table 2 are the responses of sympathetic activity and blood pressure to baroreceptor stimulation. It can be seen that neither 1 nor 2 per cent Ethrane altered the response significantly from its initial value.

Discussion

Substantial depression of blood pressure, increasing with increasing anesthetic depth, occurred during Ethrane anesthesia. Sympathetic activity was similarly affected, suggesting that at least part of the cardiovascular depression observed results from the reduction in sympathetic activity. In support of this is our observation during baroreceptor stimulation that in the presence of even maximal reductions of blood pressure and sympathetic activity (2.01 per cent Ethrane) further decreases in sympathetic activity were still followed by further reductions in blood pressure, indicating that the peripheral vascular response to sympathetic activity was preserved during Ethrane anesthesia as it is during methoxyflurane anesthesia.[5] In contrast, this response of arterial pressure to reflex reductions in preganglionic sympathetic activity was abolished by administration of halothane.[4]

In accordance with our previous method of interpretation, based on the findings of Alexander,[6] we propose that Ethrane apparently

depresses the "pressor" representation in the medulla or spinal cord, or both, without markedly depressing the "depressor" neurons. In this respect its actions resemble those of the barbiturates, halothane, and methoxyflurane. They contrast with those of cyclopropane, diethyl ether, chloroform, divinyl ether, trichloroethylene, and fluroxene. The latter agents all cause an increase in preganglionic sympathetic nervous activity that is accompanied by loss of the barostatic reflexes. We have postulated that this type of action is due to primary inhibition of the "depressor" neurons, the "pressor" elements remaining relatively unaffected.[7] Figure 3 shows an example of this type of action in response to the administration of fluroxene.[8] The most obvious analogy is that of a house with a broken thermostat that is unresponsive to heat; it is a paralytic hyperfunction (whether of furnace or sympathetic neurons) in which the checking mechanism has been destroyed, leading to uninhibited hyperactivity. Thus, we apparently can divide all the anesthetics studied by us so far into two major classes according to whether they inhibit (Group I) or preserve (Group II) the barostatic reflexes.

Anesthetics associated with sympathetic hyperactivity (Group I) have other actions which suggest release from normal inhibition at higher levels of the central nervous system. For example, they cause pupillary dilatation, delirium during induction of and emergence from general anesthesia, increased airway secretions and, in some patients, failure of the jaw muscles to relax. In addition, they tend to preserve whole-body oxygen consumption and temperature at normal levels, while preserving high-voltage EEG activity during anesthesia and favoring emesis during the recovery from anesthesia. In all these ways the agents comprising Group I differ in their actions from those in Group II.

It can be supposed that these other supramedullary actions represent either stimulation or release from inhibition at higher central nervous levels, such as the hypothalamic and limbic systems. Indeed, Brow and co-workers established long ago the dependence of cardiac arrhythmias during chloroform anesthesia on hypothalamic activation caused by this anesthetic,[9] and more recently Millar has produced evidence that cyclopropane and diethyl ether both cause excitation of the hypothalamus.[10] Since Bronk and associates[11] showed that electrical stimulation of the hypothalamus could simultaneously increase peripheral sympathetic activity and override the barostatic reflexes, it is even possible that the entire difference between our postulated Group I and Group II results from differences between their actions at the hypothalamic or other supramedullary subcortical levels of the central nervous system.

The exploration of the extent, origin, and significance of these differences between agents, which have been recognized to some extent for many years, will provide an exciting chapter in the unfolding story of neuropharmacology.

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