Anesthetics and Response of Atria to Sympathetic Nerve Stimulation

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Isolated, sympathetically-innervated cat atria were used to examine the effect of anesthetic gases on the disposition of norepinephrine released by nerve stimulation. Increased rate of atrial beating in response to sympathetic stimulation at frequencies between 0.5 and 8 impulses/sec. was unaffected by cyclopropane, halothane, methoxyflurane or ether, although all had pronounced negative inotropic actions. It was concluded that the anesthetics had no observable action on the major pathway for inactivation of neurally-released norepinephrine, namely its re-uptake by sympathetic nerve endings. This conclusion was supported by the absence of effect of cyclopropane, halothane or ether on the retention of ^{3}H-norepinephrine in slices of cat ventricle.

THE ABILITY of certain hydrocarbon anesthetics to "sensitize" the myocardium to the arrhythmia-producing effect of catecholamines is well known. The exact mechanism of such anesthetic-induced myocardial supersensitivity to these amines remains unclear, despite considerable experimental investigation. Many reports, for example, indicate that cyclopropane or chloroform stimulate central sympathetic centers and cause arrhythmias; these are prevented by interruption of efferent sympathetic pathways by a variety of drugs and other procedures.[1-7]

Price *et al.*[7] suggested that cyclopropane-induced arrhythmias might follow liberation of excessive quantities of norepinephrine (NE) within the myocardium. It is known that high concentrations of exogenously-applied NE do cause a variety of arrhythmias.[8] In considering the link between anesthetic arrhythmias and catecholamines, little attention has been directed toward the effects of anesthetics on processes that inactivate these amines, particularly NE, within the heart. Should one or more of these processes be inhibited or reduced in efficiency by anesthetics, abnormally large amounts of NE in a functionally-active form could result; such a situation might be reflected in the production of arrhythmias.

The most important route for inactivation of neurally-released NE is re-uptake and binding of the amine at specific sites apparently within sympathetic nerve endings.[9, 10] Other pathways, that may be operative in some instances, are enzymatic deamination by monoamine oxidase (MAO) or 3-O-methylation by catechol-O-methyl transferase (COMT). Isolated sympathetically-innervated cat atria have been used to study the relative importance of each of the above mechanisms in terminating the effects of NE released on nerve stimulation.[11, 12] Inhibition of NE re-uptake by cocaine or imipramine potentiated the increase in frequency of beat, the response following sympathetic nerve stimulation. Since the potentiation was most pronounced at low frequencies of stimulation, the slope of the curve relating frequency of stimulation to response was decreased by inhibition of re-uptake.[12] In contrast, complete inhibition of enzymatic degradation by pheniprazine (MAO inhibitor) or tropolone (COMT inhibitor) failed to affect the slope of the frequency/response relationship.[12]

It was concluded, therefore, that drugs capable of inhibiting re-uptake would cause frequency-dependent potentiation of the atrial response to sympathetic nerve stimulation. As a corollary, it was argued[12] that frequency-de-

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TABLE 1. The Composition of Modified (Control) Krebs and Normal Krebs Medium

	Modified Krebs		Normal Krebs	
	G./L.	mM	G./L.	mM
NaCl	7.01	120	6.9	118.07
KCl	0.18	2.41	0.35	4.75
$CaCl_2$	0.19	1.71	0.28	2.54
$MgCl_2 6H_2O$	0.16	0.79	—	—
Na_2HPO_4	1.3	9.15	—	—
$NaH_2PO_4 H_2O$	0.22	1.59	—	—
KH_2PO_4	—	—	0.16	0.93
$MgSO_4$	—	—	0.14	1.19
$NaHCO_3$	—	—	2.1	25.0
Glucose	2.0	11.1	2.0	11.1
Total Na+	3.22	139.9	3.30	143.3
Total K+	0.09	2.41	0.23	5.87
Total Ca++	0.07	1.71	0.10	2.52
Total Mg++	0.02	0.79	0.03	1.16

pendent potentiation of the atrial response by a drug offered presumptive evidence that the drug could have caused such an effect by reducing efficiency of the NE re-uptake process.

Schneider and Gillis[11] observed that hypothermia caused arrhythmias in isolated, sympathetically-innervated cat atria at a time when re-uptake of neurally-released NE was depressed significantly. In addition, cocaine or imipramine, both of which more markedly inhibited re-uptake in the same preparation, were even more likely than hypothermia to cause arrhythmias.[12] Thus, there exists suggestive evidence pointing to a link between inhibition of NE re-uptake and cardiac arrhythmias. It seemed warranted therefore to study the possible influence of anesthetics that are known to cause arrhythmias on the process of NE re-uptake in cardiac tissue. This paper describes the results of such a study.

Methods

PREPARATION OF ATRIA

Isolated, sympathetically-innervated atria were prepared from 68 cats weighing between 1.7 and 4.4 kg. anesthetized with 30–40 mg. of pentobarbital per kg. intraperitoneally. The method of preparation was that described by Gillis *et al.*[13] The atria were placed in a bath containing 40 ml. of modified Krebs solution,* the temperature of which was controlled thermostatically at 37 ± 0.2° C. (the control medium). Atrial contractions were monitored by means of a Grass FT-03 force displacement transducer, the output of which was displayed on a Gilson polygraph.

To determine whether use of modified (*i.e.*, control) instead of normal Krebs medium influenced the function of the isolated atria, preliminary experiments were done in which the voltage and frequency response curves (v. infra.) for each preparation were determined first in normal and then in modified medium. Modified medium had no observable effect on the voltage or frequency response curves, when compared with those obtained in normal Krebs medium.

DETERMINATION OF VOLTAGE OR FREQUENCY/RESPONSE RELATIONSHIPS

Electrical stimulation was applied to a cleared 1–2 cm. length of the right cardioaccelerator nerve, distal to the stellate ganglion, via shielded platinum electrodes,[14] with a Grass model 4S stimulator. The atria were allowed to beat spontaneously until the rate/min. (rate /min. is described subsequently as "contraction rate") did not change by more than 2 to 4 beats/min. within a 10-minute period. At this point the contraction rate was considered to be constant.

The curve relating voltage to magnitude of response (*i.e.*, *maximum* rate increase) was determined, while the preparation was immersed in the Krebs medium. This was achieved by varying voltage using stimuli of 1 msec. duration and a frequency of 3 or 4/sec. In all cases, stimuli were sufficient to produce a maximum rate increase at the voltage used. Sufficient time was permitted between each period

* Modification of the Krebs medium[15] was necessitated by the requirement that CO_2 be absent from the solution (see Discussion). The modified solution was buffered with Na_2HPO_4 and NaH_2PO_4, in place of the usual $NaHCO_3$, and the medium was aerated with 100 per cent O_2 instead of 95 per cent O_2/5 per cent CO_2. The buffering capacity of this solution was excellent; *p*H (37° C.) remained at 7.39–7.41 while it was gassed for 30 min. with O_2 or O_2/anesthetics. The formula of normal Krebs and that of the modified medium used is given in table 1.

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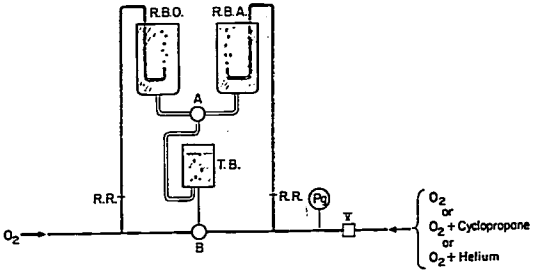

FIG. 1. Schematic diagram of arrangements used for aeration of modified Krebs medium with gas mixtures (see text for description).

of stimulation for the atrial contraction rate to return to control (prestimulation) values.

From the voltage/response curve so determined a submaximal voltage was selected (usually 50–70 per cent of maximum) to determine the frequency/response relationship. During the latter determination, 150 stimuli were delivered regardless of the frequency employed. Subsequently, the bathing medium was changed to modified Krebs solution aerated with anesthetic gas (or helium) and oxygen (the anesthetic medium). A 10- to 15-minute equilibration period was allowed, and then the frequency/response curve was again determined with voltage held constant at the previously determined submaximal value. Finally, anesthetic medium was replaced by control medium and a third determination of the frequency/response curve was made. The latter frequency/response relationship was compared with the first to assess any changes produced by a prolonged effect of the anesthetics or helium.

Determination of Concentration /response Curve Using Exogenous NE

When the spontaneous contraction rate in control medium was constant, varying concentrations of NE ** were added to the medium and the maximum rate increase measured. Thereafter the bath fluid was replaced by amine-free control medium. The atrial rate was permitted to return either to the rate before NE addition or to a constant value before addition of the next concentration of NE. NE concentrations were used in random order. Following determination of the concentration/response curve, control medium was replaced by anesthetic medium and determination of the relation between added NE concentration and response repeated, using the same amounts of NE. In some cases, the order of the experiments was reversed, anesthetics first, then control.

Aeration of Medium with Anesthetic Gases

A diagram of the arrangement used to supply gases is shown in Figure 1. Resistance regulators (RR) were placed between the gas supply and the reservoir bottles (RBO and RBA) and tissue bath (TB). The flow of gas was controlled at 100 cc./min. by means of the regulators. Prior to experiments the reservoirs RBO and RBA were gassed for at least 30 minutes with 100 per cent O_2 or the desired concentration of anesthetic gas (or helium) in O_2, respectively. Replacement, by overflow, of fluid in the bath by the alternate medium was achieved by appropriate positioning of stopcocks, A and B. One hundred per cent O_2, anesthetic gases or helium was bubbled simultaneously through the medium in the tissue bath. Halothane of methoxyflurane were delivered by Fluotec and Pentec vaporizers (V), respectively, using an oxygen flow of 5 l./min. Diethyl ether was delivered by means of a Copper Kettle vaporizer (V) with oxygen at a rate of about 6 l./min. Flowmeters (calibrated by the water-replacement method) of an anesthetic machine were used for delivery

** Norepinephrine hydrochloride—calculated as free base.

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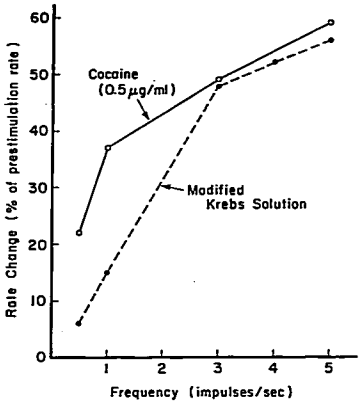

FIG. 2. The influence of cocaine (0.5 μg./ml. of modified Krebs solution) on the frequency/response curve of atrial preparation medium aerated with 100 per cent O_2. A total of 150 stimuli at submaximal voltage (8 volts) was delivered at each frequency.

of helium and cyclopropane. A pressure gauge (PG) was placed distal to the vaporizer, thus ensuring that the pressure within the latter could be held constant at one atmosphere. Each anesthetic was used at a concentration within the range of its minimum anesthetic alveolar concentration.[16]

Accumulation of ^{3}H-norepinephrine † by Cat Ventricle Slices

A method similar to that described by Dengler, *et al.*,[17] was used. Slices of cat ventricle, weighing between 75 and 125 mg., were prepared with a Stadie-Riggs microtome blade and placed in 10 ml. of previously-aerated control or anesthetic medium at 37°C. Fifteen minutes later ^{3}H-norepinephrine (^{3}H-NE) was added to give a concentration of 10 mμg. of base/ml. After incubation for an additional 30 minutes the slices were removed, washed twice in cold isotonic saline solution, blotted dry, and homogenized in 3 ml. of cold 0.4 *M* perchloric acid, containing 0.1 per cent sodium ethylene diamine tetra-acetate. The homogenates were allowed to stand in ice for two hours and then centrifuged at 28,000 × *g* for 15 minutes. One tenth of 1 ml. of the resulting supernatant was added to 10 ml. of Bray's phosphor[18] and counted for tritium in a Nuclear Chicago liquid scintillation counter that had a practical counting efficiency for tritium of 22–24 per cent. Correction was made for quenching which was determined, using tritiated water, by the internal-standard method. The effect of the anesthetics or the amount of tritium in tissues at the end of incubation was assessed by comparing the ratio,

$$R = \frac{\text{cpm} \times 10^4/g.\ \text{slice}}{\text{cpm} \times 10^4/ml.\ \text{medium}}$$

calculated for the anesthetics and the controls. The effect of each anesthetic was tested four or five times, each time using three to five slices. Some slices incubated in the control medium were used in every experiment.

† Chromatographically pure dl-norepinephrine hydrochloride-7-^{3}H (specific activity = 10.28 curies /m*M*.) was purchased from the New England Nuclear Corporation.

Results

Functional Characteristics of Isolated Sympathetically-Innervated Atria

Stimulation of the cardioaccelerator nerve, of suitable voltage, frequency, and impulse duration always caused an increased rate and force of contraction. All the anesthetics or helium however, decreased the spontaneous force of contraction (see below). Accordingly, only the positive chronotropic effect could be used as a measure of response to sympathetic nerve stimulation. The *response* was expressed as the percentage,

$$\frac{\text{increase in rate (beats/min.)}}{\text{prestimulation rate (beats/min.)}} \times 100$$

Since a primary aim of this study was to assess a possible action of the anesthetics on the re-uptake of NE, it was necessary to demonstrate that the functional consequence of inhibition of this process (*i.e.*, potentiation of the response to sympathetic nerve stimulation) could in fact be observed when the modified, rather than normal Krebs medium was used. Cocaine (0.5 μg./ml.) has been shown[12] to inhibit NE re-uptake in atria and simultaneously to potentiate the rate increases following

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sympathetic-nerve stimulation, particularly of low (0.5–3) impulses/sec.) frequency. Therefore, frequency/response curves in both the presence and absence of cocaine (0.5 μg./ml.) were determined in the same preparation. Potentiation, particularly at low frequencies, was produced by cocaine. The result of a typical experiment is illustrated in figure 2. Clearly, the use of control solution did not prevent frequency-dependent potentiation.

Effect of Changes in Oxygen Tension on Function of Atria

Since the anesthetics reduced the oxygen concentration of the gas mixtures used, we examined the effects of relative hypoxia on atrial function. In these experiments, a mixture of 50 per cent helium and 50 per cent oxygen was used for aeration of the control medium. Spontaneous contraction force decreased by approximately 40 per cent, within 25 minutes; the corresponding figure after 45 minutes was 50 per cent. The negative inotropic action was completely reversible within eight to ten minutes of re-exposure to the control medium. Despite the negative inotropic action, the frequency/response curve in the presence of helium/oxygen was identical with that determined in the control medium.

Effect of Anesthetics on Spontaneous Force of Contraction and on the Frequency/Response Curve

The results are summarized in table 2. Pronounced negative inotropic effects were observed with halothane, methoxyflurane and cyclopropane. In all but two experiments (methoxyflurane), the decreased contractile force was reversible on re-exposure to control medium.

Cyclopropane caused the most rapid decline in contractile force; reversal of this effect on changing back to control medium was also the most rapid of all. Only cyclopropane caused a slight decrease in the rate of contraction.

In none of the 50 experiments was any change observed in the slope or position of

Table 2. The Effect of Anesthetics on the Spontaneous Force and Rate of Atrial Contraction

Anesthetic	Concentration Used (% in O_2)	MAC*	Spontaneous Contraction Force (% of initial)	Spontaneous Rate** in O_2 (beats/min. ± SE)	N***	Spontaneous Rate** in Anesthetics (beats/min. ± SE)	N***
Halothane	0.25		60% in 30 min.	66 ± 1.0	5	65 ± 1.2	5
	0.25	0.87		109 ± 1.4	3	111 ± 0.7	4
	0.5		85% in 20 min.	93 ± 0.9	6	95 ± 0.7	6
	0.5			100 ± 0.9	3	104 ± 1.0	3
Methoxyflurane	0.1		75% in 30 min.	81 ± 0.6	4	77 ± 0.5	4
	0.23	0.23		94 ± 0.6	7	88 ± 0.4	6
	0.23		63% in 23 min.	70 ± 2.6	8	68 ± 1.7	7
	0.23			81 ± 0.6	4	72 ± 0.7	3
Cyclopropane	10.0		80% in 10 min.	99 ± 1.5	6	92 ± 1.9	6
	10.0	17.55		71 ± 2.3	5	73 ± 1.1	6
	20.0		70% in 10 min.	74 ± 1.9	6	68 ± 1.8	6
	20.0			111 ± 3.1	6	95 ± 3.0	3
	20.0			91 ± 0.5	5	83 ± 1.2	3
Diethyl Ether	2.0	3.04	none	132 ± 1.4	4	129 ± 1.2	4
	2.0		not determined	75 ± 0.9	3	78 ± 1.0	3
	2.0		not determined	100 ± 0.9	3	100 ± 0.9	3
	2.0		none	105 ± 0.9	4	107 ± 2.5	8

* Minimum anesthetic alveolar concentration.[16]

** The spontaneous rate was taken as that measured *between* each period of nerve stimulation at a time when the rate was constant.

***N refers to the number of values for spontaneous rate used to calculate the mean ± SE values shown.

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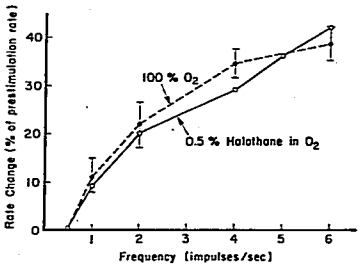

FIG. 3. The absence of effect of halothane on the frequency/response curve. A total of 150 stimuli at submaximal voltage (10 V.) was delivered at each frequency. The vertical bars indicate the range of percentage increases in rate during two separate determinations of the frequency/response relationship.

the frequency/response curve, when compared with that of the control curve for the corresponding atrial preparation. A typical result for halothane is illustrated in figure 3.

Effect of Anesthetics on the Concentration/Response Curve for Exogenous NE

When exogenous NE was added to the medium, atrial rate increased in proportion to the concentration used. No change in the slope of this line was produced by any of the anesthetics (fig. 4). Thus, anesthetics neither potentiated nor inhibited the effects of exogenous NE on atrial rate.

In this series of experiments, also, we noted that the spontaneous atrial contraction rate between the additions of NE was unaffected by halothane, methoxyflurane or ether. As mentioned above, however, cyclopropane slightly depressed the spontaneous rate.

Effect of Anesthetics on Accumulation of ^{3}H-NE by Ventricle Slices

Table 3 summarizes the results obtained. It can be seen that only methoxyflurane significantly decreased retention of ^{3}H-NE when compared with the control.

Discussion

Isolated sympathetically-innervated atria, as used in this study, could have yielded only presumptive evidence of an anesthetic action on the NE re-uptake process. Accordingly, only this possibility will be considered; it is recognized however that involvement of cathecholamines is only one of many mechanisms that may operate in the production of arrhythmia by anesthetics.

Carbon dioxide stimulates the sympathetic nervous system and liberates NE from sympathetic nerve endings in the myocardium of the intact animal.[19-20] Occasionally, however, the gas has been shown to protect the heart against cyclopropane-epinephrine arrhythmias *in vivo*.[22-24] Therefore we eliminated carbon dioxide from the bathing medium. This change in the medium (table 1) did not prevent the appearance of a frequency-dependent potentiation (and hence presumptive evidence for inhibition of NE re-uptake) in the presence of cocaine (fig. 2), similar to that reported when normal Krebs medium was used.[12] Furthermore, the *p*H of the medium was stable and the slope of the frequency/response curve determined in this medium was unaltered when compared with that in normal Krebs. It is apparent also that the slightly reduced concen-

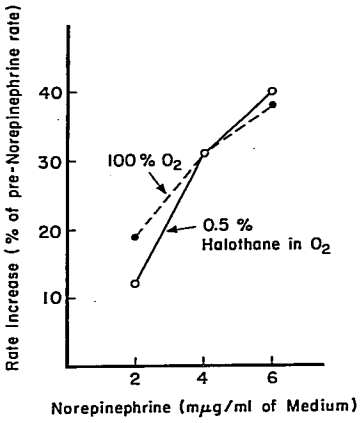

FIG. 4. The relationship between the increase in atrial contraction rate and the concentration of added NE. Both the control curve and that in the presence of halothane (0.5 per cent) were determined using the same atrial preparation.

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trations of K^+, Mg^{++} and Ca^{++} in modified Krebs did not affect the responses to either sympathetic nerve stimulation or exogenous NE.

The technique used to equilibrate anesthetic and medium seemed ample to achieve maximum concentrations of the dissolved gases. Paradise reported that halothane concentration in Krebs solution reached a steady level after five minutes of aeration of the solution.[25] Therefore, it is unlikely that the dissolved anesthetic concentrations were too low to influence re-uptake. In addition, the production of a marked negative inotropic action indicates that there was sufficient anesthetic to depress atrial function.

These considerations lead to the conclusion that the experimental conditions *per se* were such as to permit the appearance of a frequency-dependent potentiation of rate response if there was, in fact, inhibition by anesthetics of the re-uptake mechanism.

That none of the anesthetics changed the slope of the frequency/response curve or NE concentration/response curve suggests that these agents did not affect the re-uptake mechanism in atria. Such an effect may have been obscured, however, by the well-known depressant actions of these agents on the myocardium,[25-28] which were confirmed in this investigation. Accordingly, the ability of anesthetics to influence the uptake and retention of ^{3}H-NE by slices of cat ventricle was examined. In this system, functional depression caused by anesthetics cannot complicate interpretation of results. In these experiments, however, (table 3) no significant effect on ^{3}H-NE uptake was observed, except with methoxyflurane. We may conclude, therefore, that failure to observe frequency-dependent potentiation of atrial responses was not the result of a negative inotropic, and in some cases, negative chronotropic, effect of the anesthetics.

Finally, it must be noted that a decrease in oxygen tension was produced by introducing anesthetic gases. It is improbable, however, that this could account for the failure to observe frequency-dependent potentiation, since Gillis and Paton[29] found that even total anoxia for as long as 20 minutes failed to affect the retention of amine in the perfused cat heart.

TABLE 3. Effect of Anesthetics on Retention of ^{3}H-norepinephrine by Heart Slices

Gas Mixture	R (mean ± SE)	N
100% O_2 in Control Medium	3.14±0.18	21
0.5% Halothane	3.40±0.13	20
20% Cyclopropane	3.16±0.19	12
0.25% Methoxyflurane	2.64±0.13*	14
2.0% Ether	2.89±0.18	13

* $P < 0.05$ when compared with control medium. P value determined by weighted t test for groups of unequal size.

Summary and Conclusions

The effect of anesthetic gases on norepinephrine re-uptake, the major route for inactivation of neurally-released sympathetic transmitter, was examined in experiments utilizing sympathetically-innervated cat atria. Although cyclopropane, halothane, methoxyflurane, or ether had pronounced negative inotropic actions, they did not affect the positive chronotropic responses to sympathetic stimulation at frequencies from 0.5 to 8 cps. However, cocaine, at concentrations that markedly inhibit norepinephrine uptake, potentiated these responses, particularly to low-frequency (0.5–2 cps.) stimulation. With the exception of methoxyflurane, the anesthetics failed to influence the uptake and retention of ^{3}H-norepinephrine by slices of cat ventricle.

We conclude that anesthetics have little, if any, effect on the disposition of norepinephrine after its release from sympathetic nerve endings.

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