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THE MECHANISM BY WHICH N : N-DIBENZYL-CHLOROETHYLAMINE PROTECTS ANIMALS AGAINST CARDIAC ARRHYTHMIAS INDUCED BY SYMPATHOMIMETIC AMINES IN PRESENCE OF CYCLOPROPANE OR CHLOROFORM

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N : N-Dibenzyl-β-chloroethylamine (" Dibenamine ") protects animals against cardiac arrhythmias produced by cyclopropane-adrenaline (Nickerson and Goodman, 1947). The mechanism of this protection is obscure and will remain so until the nature of these arrhythmias is better understood. Meek (1940–1), Stutzman *et al.* (1947, 1949), and Allen *et al.* (1945) maintain that sympathomimetic amines having a catechol ring produce ventricular tachycardia in a dog under cyclopropane anaesthesia only when the heart is sympathetically innervated. They postulate the necessity of intact reflex pathways for both the dog and the cat since they found that decerebration, cardiac sympathectomy, and partial evisceration are procedures that prevent such arrhythmias. Meek and his collaborators do not consider the pressor effect of adrenaline of great significance in the production of arrhythmias under cyclopropane, for " when (ventricular) tachycardia was prevented by decerebration, ergotamine, or sympathectomy, often both the absolute rise in blood pressure and the angle of steepness of the rise were even greater than when tachycardia had previously been produced " (Meek, 1940–1).

Recently, Moe *et al.* (1948) have revived the idea that the pressor action of adrenaline is an important factor in the production of adrenaline-anaesthetic arrhythmias (see Allen, 1934 ; Shen, 1938 ; Shen and Marri, 1940). They found that if the pressor action of adrenaline was prevented by a pressure stabilizer there was marked—but not complete—protection against idioventricular activity under cyclopropane. Furthermore, they showed that a mechanical elevation of blood pressure after injection of adrenaline produces idioventricular rhythms in spite of pretreatment with an otherwise protective dose of dibenamine. In view of these findings and those of Acheson, Farah, and French (1947) and Nickerson and Goodman (1947) in which it was demonstrated that dibenamine does not inhibit the cardiac chronotropic and inotropic actions of adrenaline, Moe *et al.* concluded that the protective action of dibenamine could be explained on the basis of its ability to inhibit the peripheral, i.e., pressor, action of adrenaline. Furthermore, Moe and Freyburger (1950) found that protection against cyclopropane-adrenaline arrhythmia after upper thoracic sympathectomy is due to a reduction of blood

pressure after the operation and that protection is lost after restoration of blood pressure.

Nickerson and Nomaguchi (1949) conclude that the protective action of dibenamine on cyclopropane-adrenaline arrhythmias is chiefly due to a direct action on the myocardium which is independent of a transient "quinidine-like" activity. The prevention of the pressor response to adrenaline by dibenamine is not the main factor, since small doses of dibenamine can reverse the pressor response to adrenaline without protecting the heart against arrhythmia. Furthermore, N-*iso*propyl*nor*-adrenaline can produce arrhythmias under cyclopropane although it has only a vasodepressor action. On the other hand, Nickerson and Nomaguchi do not deny that the pressor action of adrenaline is a contributing factor in the production of arrhythmia, since larger doses of dibenamine were required to protect—although incompletely—against a standard dose of adrenaline if the blood pressure was raised mechanically by occlusion of the aorta after the injection of adrenaline.

Finally, Murphy, Crumpton, and Meek (1949) conclude that the pressor action of adrenaline "may have a favourable effect on the appearance of (ventricular) tachycardia"; their experiments utilizing a pressure stabilizer confirm the findings of Moe *et al.* (1948) only in part.

It appeared worth while to try to produce anaesthetic sympathomimetic amine arrhythmias in isolated mammalian hearts (heart-lung preparations) and to discover whether dibenamine exerts a protective action. In such a preparation reflex pathways are absent, and adrenaline causes but a slight rise in blood pressure. Furthermore, dibenamine could cause here no reversal of any pressor action of adrenaline. Moe *et al.* (1948) have produced multifocal ventricular discharges, but no fibrillation, in four dog heart-lung preparations by combining cyclopropane-adrenaline administration with a mechanical rise in blood pressure. They did not study the effect of dibenamine on such arrhythmias.

METHODS

Cyclopropane-adrenaline arrhythmias in heart-lung preparations

Male and female dogs ranging in weight from 5 to 9 kg. were used. Starling heart-lung preparations were made under sodium pentobarbital anaesthesia by the usual procedure. The temperature of the blood entering the heart was kept between 38 and 38.5° C. The blood volume was about 900 c.c. The resistance was maintained at 6.8 cm. Hg, and the blood pressure ranged between 10 and 12.5 cm. Hg. The venous inflow level was 9 cm. above the opening of the inferior vena cava. At the beginning of the experiment the venous inflow level was raised 10 cm., the output which was usually doubled was measured, and then the level was returned to and kept in the original position for 30 minutes. The level was now raised 10 cm. and kept in this position for the duration of the experiment. Pure O_2 was then introduced from a rubber bag to displace the air in the whole system, then a mixture of cyclopropane and O_2 was introduced from an 8-litre rubber bag. The concentration of cyclopropane was adjusted so that the system contained 40 ± 5 per cent cyclopropane in O_2. In order to ensure proper mixing of the gases and adequate oxygenation of the blood the following procedure was employed. The exhaled gas mixture from the pump passed through a soda-lime trap, then through a glass tube 15 mm. in diameter that reached to the bottom of the rubber bag. The inhaled gas passed from the bag into the pump through a second glass tube of the same width. Ten minutes after the introduction of the cyclopropane-oxygen

mixture 0.06 mg. adrenaline in 5 c.c. saline was injected within a period of two seconds into the venous cannula at a distance of 20 cm. from the heart.

When chloroform was used instead of cyclopropane, the method of Melville (1946) for producing ventricular fibrillation in intact dogs was followed. Here the venous inflow level was kept at a height of 9 cm.; 0.02 mg. adrenaline per kg. of the original weight of the dog was injected into the rubber tubing at a point as far from the heart as the usual distance from the point of injection in the femoral vein to the heart in the intact animal.

Electrocardiographic tracings, lead II, were taken in the usual manner.

Chloroform-sympathomimetic amine arrhythmias in intact dogs

Here the technique used by Melville (1946) was followed. Artificial respiration was kept at a moderate level so as not to influence the pre-existing blood pressure.

RESULTS

Isolated hearts

Experiments with cyclopropane.—Table I shows that arrhythmias can be produced in the isolated dog heart. Fig. 1 illustrates the production of ventricular fibrillation by cyclopropane-adrenaline. The increase in venous pressure and the

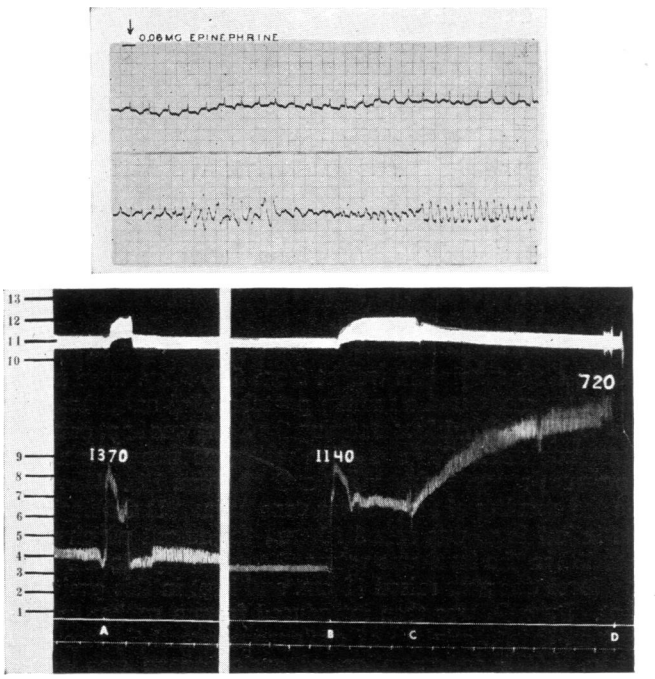

FIG. 1.—Effect of cyclopropane-adrenaline on an isolated heart. Dog 5.2 kg. Heart-lung preparation. *Top:* E.C.G. tracings (lead II) from the time the adrenaline injection was completed. Fibrillation occurred after 15 sec. *Bottom:* Tracings from top to bottom: arterial pressure in cm. Hg; right auricular pressure in cm. H_2O; time signal in minutes. At A venous inflow level raised 10 cm.; output at higher level 1,370 c.c. per minute. At B, 30 min. after A, inflow level again raised 10 cm. and kept at high level. At C, cyclopropane-O_2 introduced. Output at higher level just before D, 720 c.c. per min. At D, 0.06 mg. adrenaline injected.

simultaneous decrease in output after the introduction of cyclopropane are significant, and are in harmony with the findings of Moe *et al.* (1949). Dibenamine did not prevent the production of arrhythmias under the prevailing experimental conditions, whether it was introduced into the venous reservoir or injected into the animal several hours before the operation.

TABLE I

PRODUCTION OF ARRHYTHMIAS IN HEART-LUNG PREPARATION WITH CYCLOPROPANE-EPINEPHRINE. EFFECT OF DIBENAMINE

F = ventricular fibrillation. v.T. = ventricular tachycardia. Room temperature, 14°–18° C.

Dog No.	Initial output (with venous inflow level 17 cm.) in c.c /min.	Output after 30 min. in c.c /min.	Output after 10 min. cyclopropane-O_2 in c.c./min.	Dibenamine	Arrhythmia	Remarks
1	—	1,100	770	None	F	
2	890	—	—	,,	F	
3	—	1,050	—	,,	F	
4	—	1,090	—	,,	F	
5	—	620	620	,,	F	
6	1,510	960	510	,,	F	
7	1,240	1,080	330	,,	v.T.	
8	1,300	1,230	1,050	,,	F	
9	1,270	1,270	1,060	,,	F	
10	1,580	1,300	1,080	,,	v.T.	
1	—	940	—	45 mg.	v.T.	Dibenamine added to venous reservoir during 30 min.
2	1,320	1,200	456	35 ,,	F	
3	1,340	1,190	1,020	70 mg./kg.	F	Dibenamine injected 5–17 hr. before operation
4	1,270	1,170	1,030	30 ,,	F	
5	624	624	200	30 ,,	v.T.	
6	1,380	1,180	1,170	30 ,,	F	
7	900	840	320	30 ,,	F	
8	1,010	900	460	30 ,,	v.T.	
9	1,560	1,250	840	30 ,,	F	Both donor and "heart-lung dogs" injected with dibenamine
10	1,390	1,200	—	30 ,,	F	

In three control experiments performed during the same period, heart-lung preparations were equilibrated with a mixture of 40 per cent N_2 and 60 per cent O_2. Injection of adrenaline produced only sinus tachycardia.

The experiments reported in Table I were performed in an unheated laboratory in the winter of 1949–50. Those in Table II were performed in July, 1950. It can be seen that at a room temperature of 29–30° the severity of the arrhythmias was not as great as in winter. Eight experiments performed in the cold room gave evidence of this effect of temperature, the nature of which is not clear. Nickerson and Smith (1949) reported a "seasonal variation in the severity of cyclopropane-epinephrine arrhythmias." Other investigators have also stressed the importance of temperature in influencing ventricular conduction (de Boer, 1923).

Experiments with chloroform.—It is also possible to produce arrhythmias in heart-lung preparations with chloroform and adrenaline (0.02 mg./kg.). The

TABLE II

EFFECT OF TEMPERATURE ON THE PRODUCTION OF ARRHYTHMIAS IN HEART-LUNG PREPARATIONS BY CYCLOPROPANE-EPINEPHRINE

F = ventricular fibrillation. v.T. = ventricular tachycardia. v.P.S. = ventricular premature systole. v.Fl. = ventricular flutter

Dog No.	Initial output (with venous inflow level 17 cm.) in c.c./min.	Output after 30 min. in c.c./min.	Output after 10 min. cyclopropane-O_2 in c.c./min.	Arrhythmia	Room temp. °C.
1	1,340	1,320	1,030	v.T.	29–30
2	1,200	960	540	Few v.P.S.	29–30
3	1,100	1,080	960	Few v.P.S.	29–30
4	1,080	960	720	Many v.P.S.	29–30
5	980	820	480	F	29–30
6	1,400	1,320	820	Few v.P.S.	29–30
7	1,080	1,100	180	F	29–30
8	810	910	310	Few v.P.S.	29–30
9	840	800	620	Many v.P.S.	24
10	1,370	1,140	720	F	24
1	1,200	1,080	170	F	14–16
2	1,370	1,180	540	F	14–16
3	780	1,066	744	v.T.	14–16
4	1,340	1,320	720	v.T.	14–16
5	960	—	670	v.T.	14–16
6	912	1,200	840	F	14–16
7	600	480	216	v.Fl.	14–16
8	1,152	1,056	840	F	14–16

arrhythmias noted were premature systoles (4 out of 10 preparations) and ventricular fibrillation (5 out of 10 preparations). However, no sustained ventricular tachycardia was obtained. The same was true of experiments with intact animals to be described below. Here again in five control experiments where adrenaline was injected without chloroform, only sinus tachycardia was produced.

N-*Iso*propyl*nor*adrenaline (isoprenaline), a substance causing vasodepression in intact animals but producing positive chronotropic and inotropic actions on the isolated heart (Konzett, 1940), also caused ventricular fibrillation in three out of six isolated hearts.

Ephedrine in a dose of 2 mg./kg. produced no arrhythmias, not even a single ventricular premature systole in all six isolated hearts. This finding is in harmony with those of Meek (1940–1) on intact animals using cyclopropane.

Intact animals

The infusion of dibenamine at the rate of 1 mg./kg./min. five hours before the experiment (total dose, 30 mg./kg.) protected dogs against arrhythmias produced by chloroform-adrenaline in four out of five animals. The blood pressure before adrenaline administration was low as compared with the controls. Adrenaline here caused no rise in blood pressure.

*l-Nor*adrenaline (0.02 mg./kg.) can also produce severe arrhythmias, like those obtained with adrenaline, under comparable conditions. Dibenamine here affords

protection (7 out of 10 dogs) although it only diminishes the pressor action of *nor*-adrenaline and does not reverse it. Here again the effect of dibenamine in reducing the blood pressure of dogs, before the injection of *nor*adrenaline, was clearly seen.

A slightly higher dose of *nor*adrenaline (0.03 mg./kg.) produced ventricular fibrillation in 11 out of 13 dogs and many ventricular premature systoles in the other two. When dibenamine (20 mg./kg.) was infused at the rate of 1 mg./kg./min. 30 minutes before the injection of *nor*adrenaline (0.03 mg./kg.) ventricular fibrillation occurred in only two out of twelve dogs; no arrhythmia was observed in six dogs, and in only one of the remaining four were frequent ventricular premature systoles obtained. The average blood pressure of dogs which had received dibenamine (92 mm.) was less than that of the controls (130 mm.), and the rise in blood pressure produced by *nor*adrenaline was also less (40 mm. against 63 mm. in the controls).

Isoprenaline in combination with chloroform produced no arrhythmias whatsoever in a series of 12 experiments. The doses ranged from 0.02 to 0.07 mg./kg. The blood pressure fall was marked in all experiments, reaching as low a level as 25 mm. Hg in some.

Discussion

There is no reason to believe that the arrhythmias produced in isolated hearts as reported in this work or those reported by Moe *et al.* (1948) are qualitatively different from those produced in the intact animals. In the first place, adrenaline alone produces only a sinus tachycardia. For the production of arrhythmias, cyclopropane or chloroform are required. In the second place, adrenaline and isoprenaline, but not ephedrine, can produce arrhythmias, a finding in harmony with the results obtained by Meek (1941), who found that only sympathomimetic amines containing a catechol nucleus produced arrhythmias in intact animals. Furthermore, the dosage of adrenaline chosen, which was equivalent to that used for an intact animal, was not excessive, since in our experiments ventricular fibrillation, when it occurred, did so less than 30 seconds after the injection of adrenaline. Since in our system it takes about one minute for the blood to make one complete circuit, the adrenaline must have produced the arrhythmia by one passage through the heart. This finding is in agreement with the interpretation of Nickerson and Nomaguchi (1949). It may perhaps be appropriate to say that it is more difficult to elicit arrhythmias in an isolated heart than in an intact animal.

Nickerson (1949) maintains that dibenamine exerts a direct protective action on the myocardium. He states further that this effect appears to be correlated with its adrenergic blocking action since it is irreversible and non-competitive. Now, if dibenamine acted on the myocardium directly and irreversibly it should have a protective action on the isolated heart whether it was added directly to the venous reservoir or administered several hours before the operation. Furthermore, Acheson, Farah, and French (1949) found that none of the known cardiac actions of adrenaline (viz., positive chronotropic, inotropic, bathmotropic, and dromotropic actions) is influenced by dibenamine.

In view of all this, it is difficult to attribute the protective action of dibenamine in the intact animal to a direct effect on the myocardium. The peripheral actions of dibenamine are probably responsible for its protective action.

In the experiments with chloroform, isoprenaline, which is a vasodepressor, produced no arrhythmias in the intact animal. In the heart-lung preparation, however, where isoprenaline exerts no depressor activity but positive chronotropic and inotropic actions, arrhythmias were produced. On the other hand, dibenamine protected the animal against *nor*adrenaline-chloroform arrhythmia although it only diminished the pressor action of *l-nor*adrenaline.

SUMMARY

1. Arrhythmias can be produced in dog heart-lung preparations by certain sympathomimetic amines when cyclopropane or chloroform is used as anaesthetic.

2. N : N-dibenzyl-β-chloroethylamine (Dibenamine) protects the intact animal against cyclopropane-adrenaline arrhythmias, but it does not protect the isolated heart.

3. N-*Iso*propyl*nor*adrenaline (isoprenaline) does not produce arrhythmias in the intact dog under chloroform, but it does so in the isolated heart.

4. Dibenamine protects the intact dog against *l-nor*adrenaline-chloroform arrhythmias, although it only diminishes the pressor action of *nor*adrenaline and does not reverse it.

5. Forty per cent cyclopropane in oxygen decreases the work capacity of the isolated dog heart.

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