PRELIMINARY INVESTIGATION ON THE ACTION OF BRETYLIUM ON FROG'S ISOLATED HEART

By

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(*Received October 1, 1962*).

The response of the frog's isolated heart to bretylium is investigated with different concentrations of bretylium. The minimal stimulant concentration is 1,600 times lower than the maximal stimulant concentration. The heart is stimulated by the drug in two ranges of concentrations separated by an intermediate zone. The intermediate zone is characterised by no stimulation or minimal stimulation or depression of the heart. Bradycardia is associated with both stimulant and depressant effects in the higher range of concentrations; but is not met with either in the lower range or in the intermediate zone.

It has been shown that an intravenous injection of bretylium in doses of 50 μg in rats elicits reproducible initial pressor action (Gillis and Nash, 1961). Gaffney (1961) has mentioned that positive inotropic and chronotropic effects are produced by bretylium in dog's heart. Gillis and Nash 1961) suggested that the rise of blood pressure in rats could be due to release of catecholamines from the heart and/or blood vessels. Gaffney (1961) has stated that at least part of the stimulant effect of bretylium on dog's heart is due to release of catecholamines. This suggests that there could be other mechanisms of action as well. McCoubrey (1962) described bretylium as a weak inhibitor of mono amine oxidase. The present paper describes the action of bretylium on the frog heart.

METHODS

The heart was isolated from the frog after ligating the great veins on either side of the heart and introducing a perfusion cannula into the sinus venosus. The heart was perfused with frog Ringer from a funnel reservoir. The level of the Ringer in the cannula was varied according to the response of the heart, in any case keeping the level not more than 1.5 cm above the heart. With any one heart the level was maintained constant during perfusion with plain Ringer or with Ringer containing the drug. The responses of the heart were recorded on a smoked paper.

Bretylium tosylate tablets were dissolved in frog Ringer and filtered. Different concentrations were employed using frog Ringer as the diluent. In the earlier experiments 150 ml of the solution were perfused through the

heart. In later experiments the volume of the perfusion fluid was gradually reduced to 20 ml because this volume was enough to demonstrate the effect of the drug. After the effect of the drug was noted the drug in the perfusion system was flushed out under the same pressure with plain Ringer till control responses were obtained.

As the pure drug solution used in 2 frogs showed results similar to those with tablet extracts, tablet extracts were used in all subsequent experiments on account of the easier availability of tablets.

Concentrations of the drug were used in geometrical ratios of 0.0005, 0.001, 0.002, 0.004, 0.008, 0.016, 0.032, and 0.064 per cent and again 0.1 0.2, 0.4, 0.8 and 1.6 per cent.

In some experiments the effect of atropine on bretylium responses was studied. In the present series of investigations the effect of atropine was studied with the higher concentrations of bretylium (0.1 per cent and above). In many of these experiments the solution of bretylium contained 0.0024 per cent of atropine so that both bretylium and atropine ran through the heart simultaneously. In other experiments atropine solution was perfused prior to perfusion with bretylium solution. Other strengths of atropine viz. 0,0025, 0.0048 and 0.005 per cent were also used in some experiments.

RESULTS AND DISCUSSION

Table I shows the responses of frog heart to various concentrations of bretylium. It is seen that from 0.0005 to 0.1 per cent effects are restricted to amplitude of contraction. From 0.2 per cent upwards there is a tendency for an association of positive inotropic and negative chronotropic effects.

In Fig. 1 the response of the frog hearts to bretylium is shown graphically. Along the ordinate zero level represents the control height of the heart beats. Difference in the height of contraction from the control height is expressed as percentage of the control height. Thus values below the zero level mean decrease and values above the zero level mean increase in the height of contraction over the control level. In this figure the individual responses of a few preparations are shown in order to give an idea of the variations in individual responses. Average values with standard errors are given in the same graph in bold continuous line. It is seen that the compound stimulates the heart in as low a concentration as 0.0005 per cent and again in as high a concentration as 0.8 per cent, the maximum stimulant concentration being 1,600 times the minimum stimulant concentration. There is a clear trough in the response of the heart between 0.008 and 0.1 per cent

TABLE I

Effect of perfusion of bretylium tosylate through frog's isolated heart

Frog No.	Conc. %	Vol. ml.	Ampl.	Rate
2.	0.0005 (Pure)	100	+	C
	0.001 (Pure)	100	+++	C
	0.0005	100	++	C
	0.001	100	++	C
	0.4	100	+++	— —
3.	0.1	100	+	C
	0.2	150	+	—
	0.4	150	+	—
	0.8	130	—S	—S
11.	0.1	150	+	C
	0.2	150	+	—
	0.4	150	—	—S
16.	0.1	100	+	C
	0·2	100	+	C
	0.8	100	+	—
	1.6	75	+—	— — —
18.	0.1	100	+	C
	0.2	100	+	C
	0.8	100	+	—
21	0 0005	100	+	C
	0.001	100	C	C
	0.002	100	++	C
	0.004	100	+	C
	0.008	100	— —	C
	0.1	100	C	C
	0.4	100	++	— —

C as with plain Ringer; + stimulation — depression; S stopped; Pure, pure drug solution.

concentrations of the drug. The stimulant action of the drug rises on either side of this trough. In a few preparations 1.6 per cent concentration was tried and was found to be depressant (Fig. 3 and Table I: frog 16). In the trough area some preparations showed a clear depressant response but others exhibited the minimum stimulant response or response equal to control level.

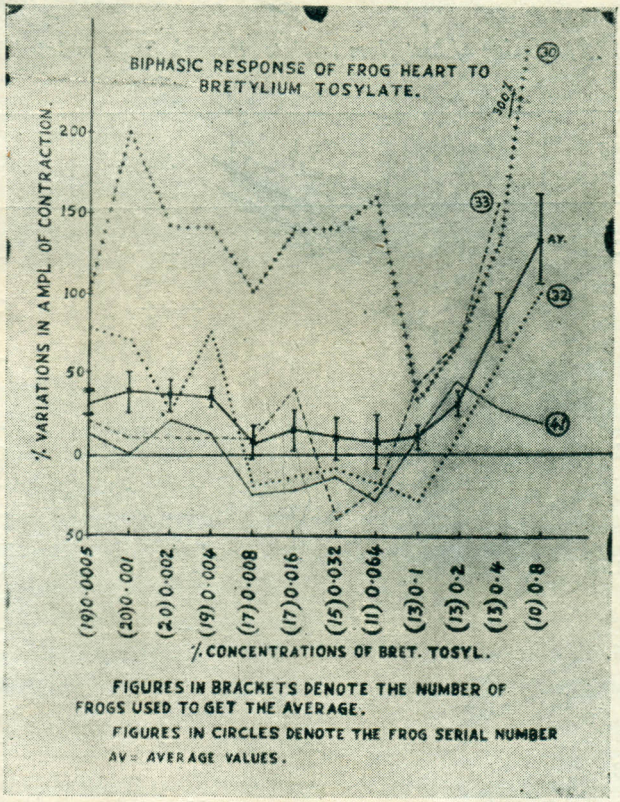

Fig. 1. Note the trough in the inotropic response of the hearts between 0.008% and 0.1% concentrations of bretylium and the rising of the stimulant response on either side of the trough, steeply on the right side and fluctuating on the left side.

Fig, 2 and 3 demonstrate the response of one preparation to bretylium. It is interesting to see that with 0.8 per cent concentration there was an appreciable increase in amplitude (Fig. 1) associated with bradycardia (Fig. 3). With 1.6 per cent concentration the bradycardia was very prominent although the amplitude of contraction was not so much depressed(Fig.3)

In table II the interaction of bretylium and atropine is shown. It is observed that atropine has neither accentuated the stimulant action of bretylium nor has it protected the heart from the depressant action of bretylium. This was the case with 14 of the 15 experiments done in 7 preparations. The only exception has been in respect of 0.2 per cent bretylium (frog 15). Fig. 4 illustrates the behaviour of one of the preparations in such an experiment. Two concentrations of bretylium with atropine were tried in this preparation.

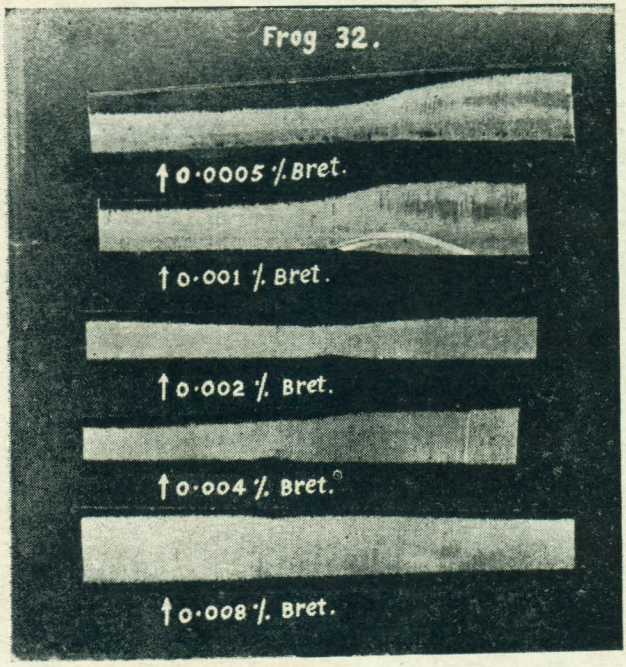

Fig. 2. Response of the frog's isolated heart to the lower range of concentrations of bretylium (0.0005 to 0.008 per cent).

TABLE II

Influence of atropine on the effect of bretylium tosylate on frog's isolated heart

Frog No.	Conc and Vol of solutions %	Method of perfusion	Without atropine		With atropine	
			Amp.	Rate	Amp.	Rate
0.	0.0024 Arrop. 100 ml 0.8 Bretyl. 100 ml	Successively	—	—	— —	— —
11.	0.0025 Atrop. 24 ml 0.8 Bretyl. 100 ml	Successively	—	—	— —	— —
15.	0.0024 Atrop. + 0.8 Bretyl. in 100 ml	Simultaneously	+ +	C	—	— —
16.	0·0024 Atrop. + 1.9 Bretyl. in 30 ml	Simultaneously	+ —	—	stopped.	
	0.0024 Atrop. + 0.1 Bretyl. in 100 ml	Simultaneously	+	C	C	—
18.	0.0024 Atrop. + 0.1 Bretyl. in 100 ml	Simultaneously	+	C	C	C
	0.0024 Atrop + 0.2 Bretyl. in 100 ml	Simultaneously	+	C	+	C

C as with plain Ringer; + stimulation; — depression

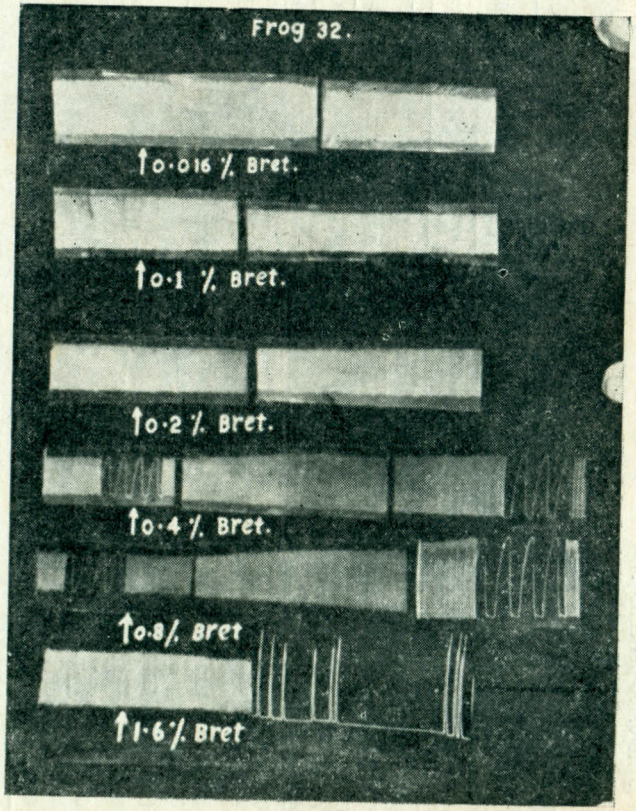

Fig. 3. Response of the frog's isolated heart to concentrations of bretylium (0.016 to 1.6 per cent).

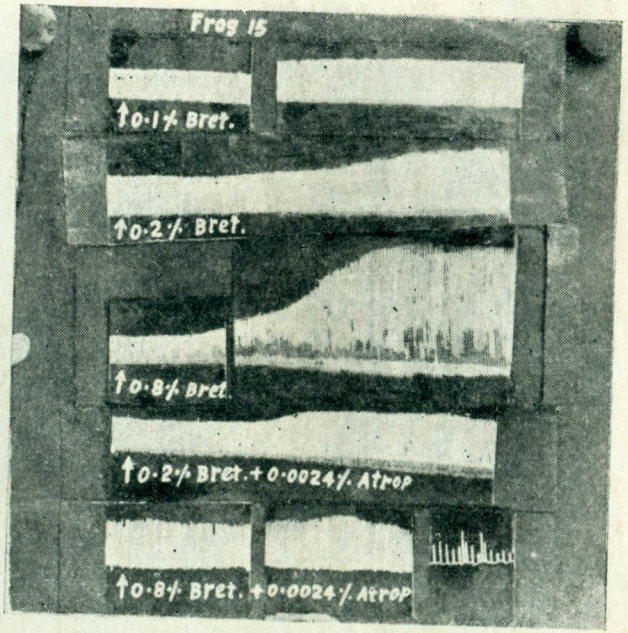

Fig. 4. Influence of atropine on the effect of bretylium on frog's heart. Note the profound positive inotropic effect with 0.8 per cent bretylium and the marked depression of both rate and force of contractions when atropine is combned with 0,8 per cent bretylium.

It is seen that 0.8 per cent bretylium has increased the amplitude of heart beats 5 times the control level ; but when 0.8 per cent bretylium was combined with 0.0024 per cent atropine there is a clear depression of both amplitude and rate of heart beats.

The association of positive inotropic effect with negative chronotropic effect with higher concentrations of bretylium seems interesting.

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