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THE EFFECT OF MEPHENTERMINE ON ISOLATED DOG HEARTS, NORMAL AND PRETREATED WITH RESERPINE

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The inotropic activity of the non-catechol sympathomimetic amine, mephentermine sulphate, on the failing dog heart-lung preparation, was 1/10 to 1/20 that of adrenaline. Mephentermine showed no inotropic effect on preparations from animals pretreated with reserpine. The chronotropic and "calorigenic" actions of mephentermine were tested on modified heart-lung preparations to permit a more accurate measurement of coronary flow, and were found to be greater than its inotropic effect relative to adrenaline. Furthermore, the action of mephentermine was longer-lasting than that of adrenaline. If adrenaline was infused 15 min after the termination of mephentermine administration and when the action of the latter was still at a maximum, a further increase in heart rate and especially oxygen consumption was observed. In preparations from dogs treated with enough reserpine to deplete the heart of noradrenaline, mephentermine had only slight chronotropic and calorigenic actions. However, further addition of adrenaline after a 15 min pause caused a rise in heart rate, oxygen consumption, and coronary flow which almost duplicated the additive effects of both amines on the preparations not treated with reserpine. It would appear that adrenaline acted on its own and in addition "restored" the action of mephentermine on the reserpinized preparations. The action of adrenaline alone on reserpinized preparations was not increased compared with that on normal preparations. These observations are relevant to a consideration of the mechanism of action of non-catechol sympathomimetic amines on the heart, and are in harmony with the concept that mephentermine, a non-catechol amine, requires the presence of added or stored catechol amines for its action. Reserpine treatment did not alter the mechanical efficiency of the heart despite its depletion of noradrenaline.

Mephentermine is N,α,α-trimethylphenethylamine, and its sulphate has found use as a pressor agent in hypotensive states resulting from myocardial infarction and general or spinal anaesthesia (*New and Non-official Drugs*, 1960). It has also been reported to act on the heart. Goldberg, Cotten, Darby & Howell (1953), using intact open-chest, vagotomized dogs, found that mephentermine was about 1/1,000 as active as adrenaline in its inotropic effect, whereas Kukovetz, Hess, Shanfeld & Haugaard (1959) found that mephentermine had no action on the contractile force of the Langendorff perfused heart. In view of these findings and in the hope of contributing to the mechanism of action of non-catechol sympathomimetic amines, experiments were performed to study the effects of mephentermine on isolated dog hearts under the same conditions previously used for comparative studies of adrenaline and noradrenaline (Fawaz & Tutunji, 1960).

METHODS

The inotropic action of mephentermine was tested on the classical Starling heart-lung preparation. Failure was induced within 15 min by repeated additions of pentobarbitone until the systemic output, originally 800 to 900 ml./min, fell to about half this level with a corresponding rise in right auricular pressure. Mephentermine, 100 μg, or adrenaline in doses of 5 or 10 μg was then injected into the venous inflow tube near the right heart or added to the reservoir. Experiments were also carried out on heart-lung preparations made from dogs pretreated with reserpine to see if depletion of catechol amines by reserpine affected the inotropic action of mephentermine. Reserpine was administered intraperitoneally in two consecutive doses of 0.5 mg/kg at intervals of 24 hr, the second dose being given 24 hr before the experiment.

The chronotropic, calorigenic and coronary-vasodilating actions of either mephentermine or adrenaline alone were studied on heart-lung preparations as described previously (Fawaz & Tutunji, 1960). The "calorigenic" action of a sympathomimetic amine is defined as the increase in oxygen consumption which, in the absence of a change in work performed, cannot be explained solely by a rise in heart rate. In these experiments, reserpine was given intraperitoneally in two or three doses of 0.1 mg/kg each at 48 hr intervals, the last dose being given 24 hr before the experiment. We chose this dose because larger doses made the animals very ill and they abstained from eating. Furthermore, Waud, Kottegoda & Krayer (1958) have shown that one dose of 0.1 mg/kg of reserpine was sufficient to deplete the heart of noradrenaline in 24 hr.

The mechanical efficiency of the heart was calculated on the basis that 1 ml. of oxygen consumed/2 kg-m of work performed constituted 100% efficiency.

Mephentermine sulphate, L-adrenaline bitartrate, and reserpine ascorbate (kindly supplied by Wyeth, Sterling-Winthrop and Ciba respectively) were used in these experiments, but the dosages always refer to the base.

RESULTS

The inotropic actions of mephentermine and adrenaline

The relative inotropic actions of mephentermine and adrenaline were assessed by their effects in increasing the output and in reducing right auricular pressure in the failing heart. In 4 experiments adrenaline was given first, and after its action had subsided mephentermine was given. In another 4 experiments mephentermine was given first, and then adrenaline. On the basis of these observations it was concluded that 100 μg of mephentermine was roughly equivalent in its maximum effect to 5 to 10 μg of adrenaline, although the action of mephentermine was longer-lasting than that of adrenaline. These doses of mephentermine and adrenaline restored the output of the failing heart to 80 to 100% of its original value and reduced the right auricular pressure correspondingly.

The comparison between mephentermine and adrenaline was difficult because a second injection of one amine was rarely as effective as the first injection, and because there was considerable variation between preparations in the ease with which failure was produced. Despite these inherent sources of inaccuracy it is reasonable to assess the inotropic activity of mephentermine as 1/10 to 1/20 of that of adrenaline in the failing dog heart-lung preparation.

In 4 experiments on heart-lung preparations from reserpine-treated dogs mephentermine was almost entirely without an inotropic action.

TABLE 1

EFFECT OF MEPHENTERMINE ON NORMAL AND RESERPINE-TREATED ISOLATED DOG HEARTS

Mephentermine sulphate was added to the reservoir at a rate of 50 μg of base/min for 15 min, followed by a 15 min interval, then a 15 min infusion of 4 μg adrenaline base/min. The numeral (1) indicates at the start of an experiment, (2) after 15 min, (3) after 30 min, (4) after 45 min. All % changes refer to (1) as a standard. The figures in columns 5(a) and 5(b) refer to the effects of adrenaline given at the start of an experiment at the rate of 4 μg adrenaline base/min for 15 min. The figures in 5(a) were reported by Fawaz and Tutunji (1960)

	Normal hearts (8 experiments)					Reserpine-treated hearts (8 experiments)				
	1	2	3	4	5(a)	1	2	3	4	5(b)
Heart rate Mean±s.e.	141 (±5)	250 (±17)			195 (±11)	131 (±6)				
% change in heart rate Mean±s.e.		78 (±7)	68 (±5)	83 (±5)	48 (±5)		18 (±5)	17 (±4)	92 (±8)	68 (±7·2)
Oxygen consumption (ml./100 g/min)	7·1 (±0·35)					6·3 (±0·28)				
Mechanical efficiency Mean±s.e.	10·9 (±0·6)					11·1 (±0·6)				
% change in oxygen consumption Mean±s.e.		74 (±17)	75 (±12)	143 (±18)	54 (±10)		12 (±6)	20 (±6)	140 (±22)	61 (±10·3)
Mean % change in work performed		−5·0	−3·0	+8·0			0	+1·5	+1·0	
Coronary flow (ml./min) Mean±s.e.	59 (±6)					57 (±6)				
% Change in coronary flow Mean±s.e.		93 (±20)	120 (±17)	320 (±32)	113 (±12)		27 (±10)	75 (±25)	322 (±47)	75 (±10·6)

The chronotropic, calorigenic and coronary-dilator actions of mephentermine

Normal animals. Since the inotropic action of mephentermine was found to be 1/20 to 1/10 that of adrenaline, an amount of mephentermine was infused in the course of 15 min which was 12.5 times the quantity of adrenaline used in a previous publication that dealt with the relative potencies of adrenaline and noradrenaline on the isolated heart (Fawaz & Tutunji, 1960). The results obtained in the previous publication may be used for comparison, because in both studies the initial values for heart rate (138 ± 4.8 and 141 ± 5.2), oxygen consumption (6.7 ± 0.38 and 7.1 ± 0.35) and coronary flow (55 ± 6 and 59 ± 5.8) were very similar. Furthermore, the experimental conditions were similar.

It can be seen from Table 1 that the chronotropic action of mephentermine is greater than its inotropic action, if adrenaline is used as a standard. The average maximum heart rate obtained after the first infusion of 60 μg adrenaline was 195, whereas the figure for 750 μg mephentermine was 250. Furthermore, the action of mephentermine lasted much longer than that of adrenaline, for, while the action of adrenaline subsided within 30 min after the end of the infusion, that of mephentermine continued for at least 1 hr, and there was only a slight decrease in heart rate 15 min after the end of the infusion. If at this stage 60 μg adrenaline was infused in the course of 15 min, there was a further, although small, rise in heart rate over and above the maximum rate obtained at the end of the 15 min infusion period with mephentermine.

What has been said of the chronotropic action of mephentermine applies also to its calorigenic action, which is greater than its inotropic action if adrenaline is taken as a standard. Here, however, the addition of 60 μg adrenaline after the 15 min pause following the mephentermine infusion resulted in a significant increase in oxygen consumption in every experiment over and above the maximum value obtained with mephentermine. The relative increase in oxygen consumption after the additional adrenaline infusion was much greater than the corresponding increase in heart rate. However, no special significance should be attached to this latter finding, since with ventricular rates between 250 and 260 the maximum chronotropic effect that can be attained by the use of drugs is reached.

The increased coronary flow after mephentermine is to be expected in view of the increase in oxygen consumption. Again, our experiments do not answer the question as to whether the sympathomimetic amines studied dilate the coronary vessels by a direct action or as a result of increased cardiac oxygen consumption. In the previous experiments (Fawaz & Tutunji, 1960) a $54 \pm 10\%$ increase in oxygen consumption due to adrenaline was accompanied by a $113 \pm 12\%$ increase in coronary flow. In the present experiments, starting with almost identical values for coronary flow and oxygen consumption, mephentermine caused a $74 \pm 17\%$ increase in oxygen consumption with $93 \pm 20.4\%$ increase in coronary flow. It would appear from this that adrenaline had a direct coronary vasodilator action. However, in view of the magnitude of the standard errors, the author is reluctant to draw such a conclusion.

Reserpine-pretreated animals. Mephentermine had only slight chronotropic and calorigenic effects on the reserpine-pretreated animals. However, the administration

of adrenaline after the termination of a mephentermine infusion resulted in an increase in heart rate, oxygen consumption and coronary flow which was almost identical with that obtained when adrenaline was added on top of mephentermine in preparations from animals not pretreated with reserpine. The response of reserpinized hearts to adrenaline alone is shown in column 5(b) of Table 1, where only the chronotropic action was increased as compared with that on normal hearts, but the calorigenic and coronary dilating actions were even less than in normal hearts. The calorigenic and chronotropic actions of adrenaline on reserpinized hearts subsided after 30 min just as in the case of normal hearts. Table 1 also shows that a dose of reserpine which depleted the heart of noradrenaline had no influence on the mechanical efficiency of the isolated heart.

DISCUSSION

The inotropic action of mephentermine on the isolated heart is 1/10 to 1/20 that of adrenaline, and the ratio is even more in favour of mephentermine when the chronotropic and calorigenic actions are considered. Furthermore, the actions of mephentermine are longer-lasting than those of adrenaline. These findings are in marked contrast with those of Goldberg *et al.* (1953), who reported a ratio of 1 : 1,000 for the inotropic action of mephentermine as compared to adrenaline. Goldberg *et al.*, however, did not use failing isolated hearts but intact open-chest dogs, and assessed the inotropic action by measuring the contractile force by means of levers attached to the right ventricle. We have no explanation to offer for this marked difference in response between the intact animal and the isolated heart.

The ineffectiveness of mephentermine when tested on reserpinized hearts is not surprising in view of observations made by various authors (Burn & Rand, 1958) that non-catechol sympathomimetic amines, such as tyramine and phenylethylamine, lose most of their pressor activity in animals pretreated with reserpine. What was not expected in our experiments was the effect of administering adrenaline after the termination of the mephentermine infusion. The result was an additive effect of both amines similar to and almost identical with that obtained on the preparations not treated with reserpine. One may regard this as a " reactivation " by adrenaline of the effects of mephentermine. It does not support the concept that non-catechol sympathomimetic amines, of which mephentermine is a representative, have no action of their own but only act indirectly either by protecting catechol amines from enzymatic inactivation, or by releasing " stored " catechol amines. In a reserpinized heart with little or no catechol amine content, mephentermine was inactive. Addition of adrenaline restored the action of mephentermine and in addition exerted its own independent action. One conclusion that may be drawn from these experiments is that mephentermine requires the presence of added or " stored " catechol amines for its action.

The observation that the mechanical efficiency of a reserpinized heart is not altered is important in connexion with the question as to whether stored cardiac noradrenaline is " available " for metabolic purposes, and with the extent to which adrenergic and cholinergic substances normally influence the mechanical efficiency of the heart.

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