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THE ACTION OF HISTAMINE ON THE ISOLATED HEART

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A method is described for recording the coronary flow and the rate and the amplitude of contraction of an isolated heart maintained at constant temperature. Both histamine and noradrenaline increased the contractility of the guinea-pig heart. Pronethalol antagonized noradrenaline but not histamine. Mepyramine, 10-(2-pyrrolidin-1′-ylethyl)phenothiazine hydrochloride (pyrathiazine) and diphenhydramine reduced the contractility of the guinea-pig heart but did not antagonize the action of histamine. The influence of histamine and noradrenaline on coronary flow was variable but when the contractility of the heart increased there was a concomitant increase in coronary flow. Histamine decreased the contractility of the rat heart and the domestic fowl heart.

In 1910, Dale & Laidlaw showed that histamine increased the contractility of the isolated heart of the cat and the rabbit. A similar effect has been shown on the heart of the guinea-pig (Went & Lissak, 1935), the frog (Tiffeneau, 1941) and the rat (Went, Varga, Szücs & Fehér, 1952).

Went, Varga, Szücs & Fehér (1952, 1954) have described experiments in which histamine released an adrenaline-like substance from the heart of the rat, the rabbit, the cat and the guinea-pig, which they considered to be sympathin. However, according to Mannaioni (1960), histamine combines with receptors in the myocardium which are specific for this compound, since in experiments with guinea-pig isolated auricles diphenhydramine antagonized histamine but not noradrenaline, and dichlorisoprenaline antagonized noradrenaline but not histamine. In contrast, Trendelenburg (1960) found that the antihistamine drugs, mepyramine and tripelennamine, did not specifically antagonize histamine acting on isolated auricles. He was also unable to detect any change in the action of histamine when the tests were made with auricles depleted of catechol amines and obtained from animals treated with reserpine.

The experiments described in the present paper show that, although histamine increased the contractility of the guinea-pig heart, it depressed the heart of the rat and of the domestic fowl. The action of histamine was not sympathomimetic since it was dissimilar to the action of noradrenaline on the rat heart and the domestic fowl heart, and pronethalol discriminated between the action of histamine and that of noradrenaline on the guinea-pig heart. The antihistamine compounds, mepyramine maleate, 10-(2-pyrrolidin-1′-ylethyl)phenothiazine hydrochloride (pyrathiazine hydrochloride) and diphenhydramine hydrochloride did not antagonize histamine acting on the guinea-pig heart.

METHODS

Heart organ-bath. The organ-bath is depicted in Fig. 1. It was made of Perspex and consisted essentially of a glass cannula fixed into the side of the bath with a rubber bung, a gas distributor tube, a light Perspex pulley which transmitted movements of the heart to a spring-loaded lever, a baffle, a wide overflow tube just below the rim of the bath and inflow and outflow tubes placed at the bottom of the bath. The tube underneath the heart was used as the inflow as it became blocked by the heart when used as the outflow.

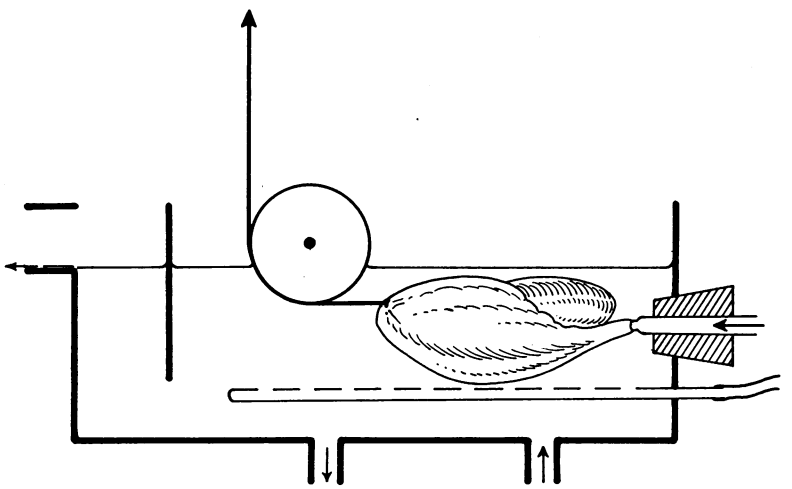

Fig. 1. Organ-bath for the isolated heart.

Perfusion. The perfusion fluid was Krebs saline-bicarbonate solution (Krebs & Henseleit, 1932) in which the concentration of calcium had been halved so that it approximated to the concentration of ionized calcium in plasma. The perfusion pressure was 70 cm of water. Fine particles were removed from the perfusion fluid by filtration, as recommended by Bleehen & Fisher (1954). The Krebs solution was gassed with 5% carbon dioxide in oxygen and was filtered through a sintered glass disc before it perfused the coronary vessels. The sintered glass had an average pore size of 20 to 30 μ and the diameter of the filter was 5 cm. 5% carbon dioxide in oxygen was also passed through the gas distributor in the organ-bath. The filter, glass warming-coils and the heart organ-bath were surrounded by a water bath kept at 32° C by a toluene-mercury thermostat and heating element.

Dissection. Birds and rodents were killed by dislocation of the neck. The heart was rapidly excised from the thorax and cleaned under Krebs solution at room temperature. No heparin was used. The right and left brachiocephalic arteries of the domestic fowl were ligated close to the aorta. The cannula was tied into the aorta and perfusion commenced. The time from incising the thorax to starting perfusion did not normally exceed 5 min.

Recording. A thread was tied to the left ventricle and passed round the pulley to a spring-loaded lever, which recorded the amplitude of contraction of the heart. Each excursion of the lever made an electrical contact between a wire attached to the lever support and a second wire attached to its fulcrum, a current being relayed to a Thorpe counter which recorded the heart rate. The coronary flow was recorded by passing the overflow from the organ-bath through a photoelectric drop recorder connected to a second Thorpe impulse counter.

Drugs. Histamine acid phosphate, (−)-noradrenaline bitartrate, diphenhydramine, 10-(2-pyrrolidin-1′-ylethyl)phenothiazine hydrochloride (pyrathiazine hydrochloride), mepyramine

maleatae, and pronethalol [2-isopropylamino-1-(2-naphthyl)ethanol] hydrochloride were used. Values given for histamine and noradrenaline refer to the base but concentrations of other drugs refer to the corresponding salts.

All solutions of drugs were filtered through paper before use. In some experiments drugs were injected into the perfusion fluid, either through the rubber cap of an injection chamber attached to the perfusion cannula (Gaddum & Kwiatkowski, 1938), or from a micrometer syringe when the volume injected did not exceed 0.02 ml. In other experiments a drug was added to the Krebs solution which perfused the coronary vessels.

In the experiments described in the present paper the organ-bath was not emptied through the outflow but the compounds tested were washed from the organ-bath via the overflow. This allowed a continuous record of the coronary flow to be made during a test, the action of a drug persisting until its concentration in the organ-bath became ineffective. The removal of a drug from the organ-bath by overflow proved satisfactory in these experiments but when a large dose of a substance is injected into the perfusion fluid it is sometimes advisable to change the fluid in the organ-bath to hasten the recovery of the heart.

Where three or more observations were made the values given in text and Tables are means with standard errors and number of observations in parentheses, but where only two observations were made each value has been given. The significance of differences between means was estimated by the "t" test and probability (P) values are given. A value for P of less than 0.05 is reported as not significant. Regression lines were calculated by the method of least squares and the probability (P) of significant regression was computed by analysis of variance.

RESULTS

Rat heart

In three experiments with the rat heart, histamine (5 μg to 2.5 mg) was injected into the perfusion fluid. Small doses had no action on the heart but larger doses transiently depressed the amplitude of contraction. In two experiments 1 mg of histamine depressed the amplitude of contraction of the heart but 500 μg was inactive. In a third experiment the amplitude of contraction of the heart was decreased considerably by 500 μg of histamine and slightly by 250 μg, but was unaffected by 100 μg (Fig. 2). In the first two experiments histamine had no effect on the coronary flow, but in the third experiment 500 μg of histamine increased it slightly. Large doses of histamine, which depressed the amplitude of contraction of the heart, sometimes produced a small decrease in the heart rate (see second response to 500 μg of histamine, Fig. 2). Sometimes, however, the heart rate could not be recorded as the movements of the lever were too small to complete the circuit which recorded the heart rate (see first response to 500 μg of histamine, Fig. 2). In each of these three experiments the rate and the amplitude of contraction of the heart increased in response to 0.1 μg of noradrenaline.

The changes in contractility and coronary flow which occurred when histamine or noradrenaline was perfused through the heart for 15 min are shown in Table 1. Perfusion with histamine in concentrations of 1, 10 and 100 mg/l. decreased the coronary flow and the amplitude of contraction of the heart, but the heart rate was decreased by histamine only in a concentration of 100 mg/l. The response of two rat hearts to a perfusion of noradrenaline (1 μg/l.) was similar to that of the guinea-pig heart (Tables 1 and 2); in both species the amplitude of contraction of the heart was increased but the coronary flow and heart rate remained unchanged.

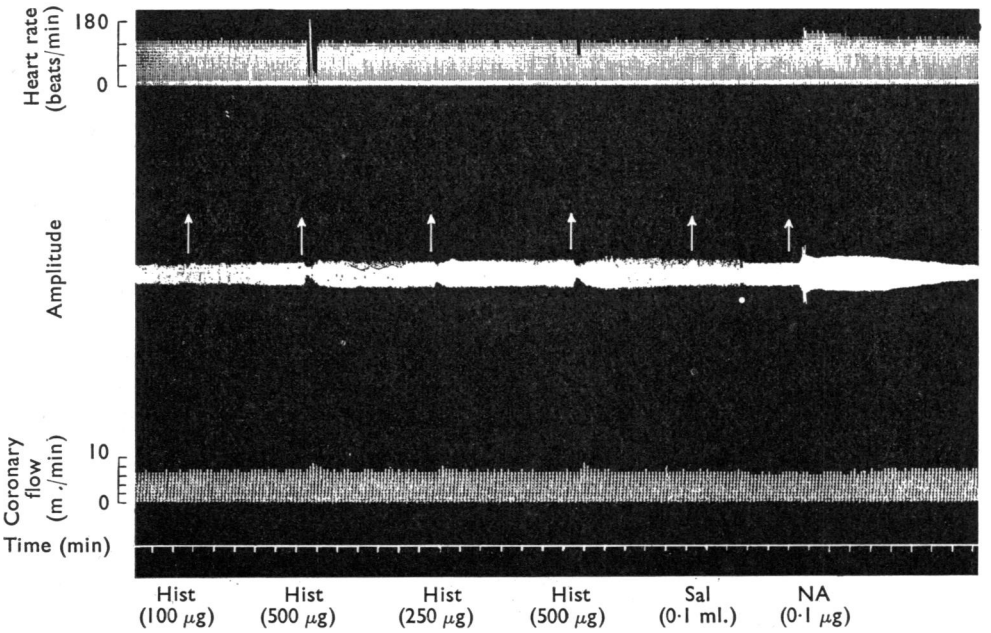

Fig. 2. Rat heart. From above down: rate (beats/min); amplitude of contraction; coronary flow (ml./min); and time (min). Numerals depict μg of noradrenaline (NA) and of histamine (Hist), and ml. of saline (Sal) injected into the perfusion fluid at the arrows. At the dot the writing point was brought nearer to the kymograph.

TABLE 1

THE RESPONSE OF RAT HEARTS TO PERFUSIONS OF HISTAMINE AND NORADRENALINE

Drug	Concentration in perfusion fluid (μg/l.)	Percentage change in Coronary flow	Heart rate	Amplitude of contraction
Noradrenaline	1	0, −20	0, −6	+46, +69
Histamine	1,000	−10	0	−10
Histamine	10,000	−17	+3	−46
Histamine	100,000	−41, −14	−13, −14	−64, −69

TABLE 2

THE RESPONSE OF GUINEA-PIG HEARTS TO PERFUSIONS OF HISTAMINE AND NORADRENALINE

Values are means with standard errors and numbers of experiments in parentheses. † Significant at $P<0.05$; * significant at $P<0.1$

Drug	Concentration in perfusion fluid (μg/l.)	Percentage change in Coronary flow	Heart rate	Amplitude of contraction
Histamine	10	+22±13 (4)	+12± 8 (4)	+31± 7 (4)†
Histamine	100	+60±24 (4)*	+67±23 (4)*	+199± 40 (4)†
Histamine	1,000	+46± 9 (4)†	+69±10 (4)†	+406± 28 (4)†
Noradrenaline	1	+8±11 (4)	+2± 3 (4)	+43± 11 (4)†
Noradrenaline	10	+8± 8 (4)	+50±16 (4)†	+233±112 (4)
Noradrenaline	100	+20±17 (4)	+68±10 (4)†	+299±104 (4)*

Domestic fowl heart

Injections of histamine depressed the amplitude of contraction of three domestic fowl hearts, usually in smaller doses than those required to inhibit the rat heart. In one experiment 500 μg of histamine were required to reduce the amplitude of contraction of the heart, but in another experiment 50 μg of histamine inhibited the heart although a second injection of this dose of histamine failed to do so (Fig. 3).

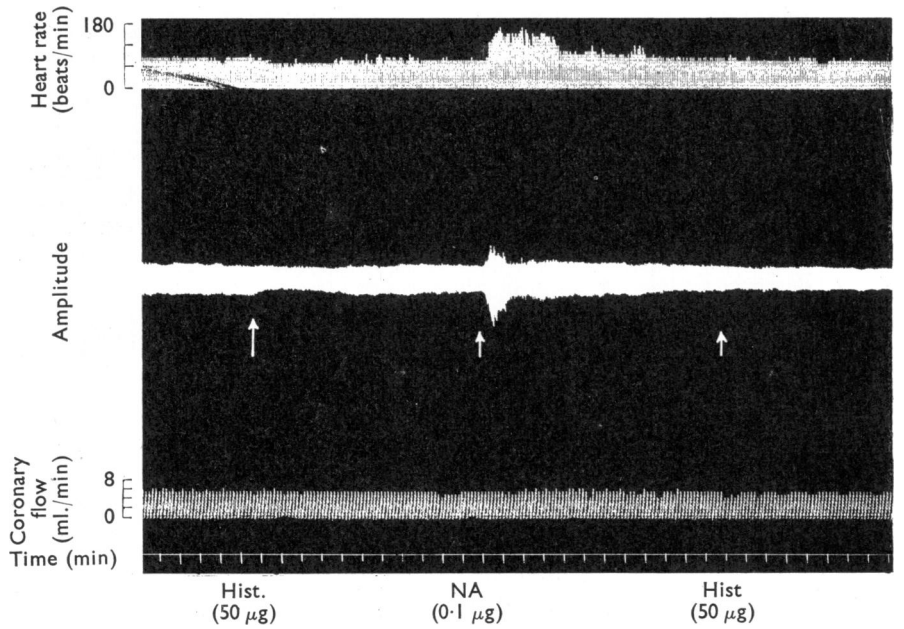

Fig. 3. Domestic fowl heart. From above down: rate (beats/min); amplitude of contraction; coronary flow (ml./min); and time (min). Numerals depict μg of noradrenaline (NA) and of histamine (Hist) injected into the perfusion fluid at the arrow.

Tachyphylaxis to histamine was also observed in the third experiment in which a first injection of 20 μg of histamine reduced the amplitude of contraction of the heart but a second injection of the same dose was inactive; when the dose of histamine was increased to 50 μg the drug again inhibited the heart but a second injection of 50 μg was without effect. Injections of histamine which reduced the amplitude of contraction of the domestic fowl heart did not change the heart rate or the coronary flow. Noradrenaline (0.1 μg) increased the rate and the amplitude of contraction of the heart in each experiment.

Guinea-pig heart

The stimulant action of histamine on the guinea-pig heart was confirmed and an attempt was made to find out how closely it resembled the action of noradrenaline on this preparation. Two series of experiments were made with this purpose in mind. First, various concentrations of histamine and noradrenaline were perfused through the heart and their actions compared, and secondly, the influence of some

antagonists on the response of the heart to histamine and noradrenaline was examined.

Effect of perfusions of histamine and noradrenaline. When the coronary flow, the rate and the amplitude of contraction of a heart had become nearly constant, histamine or noradenaline was added to the perfusion fluid and the perfusion continued for 15 min. Noradrenaline was about ten-times as active by weight as histamine in stimulating the guinea-pig heart, so the effect of perfusing noradrenaline in concentrations of 1, 10 and 100 μg/l. was compared with that of perfusing histamine in concentrations of 10, 100 and 1,000 μg/l. A single concentration of histamine or noradrenaline was perfused through each heart, but each concentration of each amine was tested on four hearts. The maximum change in the coronary flow, the rate and the amplitude of contraction of the heart during perfusion of amines was measured and expressed as a percentage of the corresponding function of the nonstimulated heart. The results are shown in Table 2.

Both histamine and noradrenaline increased the amplitude of contraction of the heart. The regression of the increase in the amplitude of contraction of the heart on the logs of the concentrations of histamine and noradrenaline was significantly greater than the error variance ($P<0.001$), but the difference between histamine and noradrenaline was not significant ($P>0.2$). Departures from linearity and parallelism were very small ($P>0.2$).

The threshold concentrations of histamine and noradrenaline for increase of the heart rate were greater than the threshold concentrations for increase of the amplitude of contraction of the heart, since both histamine (10 μg/l.) and noradrenaline (1 μg/l.) increased the amplitude of contraction of the heart but had no significant action on the heart rate. When the concentrations of histamine and noradrenaline were increased by a factor of 10, both drugs increased the heart rate, histamine by $67 \pm 23\%$ (4) and noradrenaline by $50 \pm 16\%$ (4). A further tenfold increase in the concentration of histamine or noradrenaline did not result in any further significant increase in the action of the amines on heart rate.

In Fig. 4, the effect of each perfusion of histamine or noradrenaline on heart rate is plotted against the log of its effect on the amplitude of contraction of the heart, with the regression line calculated from the combined results. The results for histamine and noradrenaline are both evenly distributed about the regression line, which shows that increases in rate and increases in amplitude of contraction are interrelated in much the same way both in the response to histamine and to noradrenaline.

The effects of histamine and noradrenaline on coronary flow were variable. Histamine increased coronary flow in eleven experiments but reduced it in another ; noradrenaline increased coronary flow in seven experiments but had no effect in two experiments and reduced it in three others. Histamine (1 mg/l.) was the only drug to increase the mean coronary flow significantly at the 5% level (Table 2).

It was thought that the effect of these compounds on coronary flow might be related to their action on the contractility of the heart, so the effect of the perfusions

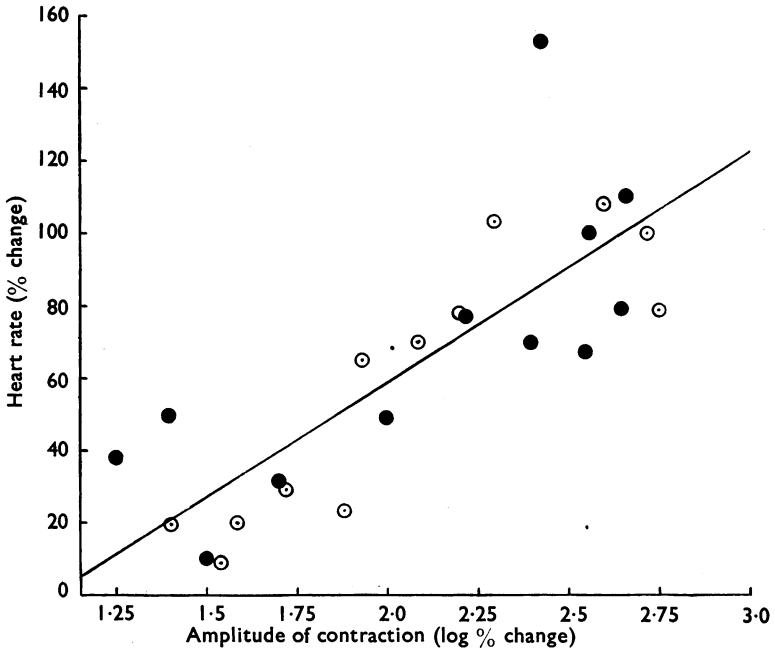

Fig. 4. The relation between percentage change in rate and the log of percentage change in amplitude of contraction of guinea-pig hearts produced by histamine (●), and by noradrenaline (○). The calculated regression line is significant at the 0.1% level.

of amines on the rate and the amplitude of contraction of the heart were summed and plotted against the coresponding changes in coronary flow (Fig. 5). This revealed that there was a significant positive regression of increase in coronary flow on the sum of the increases in rate and amplitude of contraction of the heart ($P<0.01$).

Effect of antagonists. In these experiments histamine (2 μg) and noradrenaline (0.2 μg) were injected alternately into the perfusion fluid at intervals of 15 min. These doses of the amines increased the amplitude of contraction of the heart but were sometimes too small to increase the heart rate. The response, the percentage increase in the amplitude of contraction of the heart, was measured after each injection of histamine or noradrenaline.

When the responses to histamine and to noradrenaline became nearly constant an antihistamine or a "β-antagonist" of adrenaline was added to the perfusion fluid and each amine was tested twice again. A change in the response to an amine in the presence of an antagonist did not always mean that the action of the amine had been specifically antagonized or potentiated, since some antagonists altered the contractility of the heart (Table 3). The relative effect of an antagonist on the actions of histamine and noradrenaline was found by comparing the changes in response to the two amines that occurred in the presence of the antagonist; these changes differed significantly from one another when the antagonist discriminated between the actions of histamine and noradrenaline.

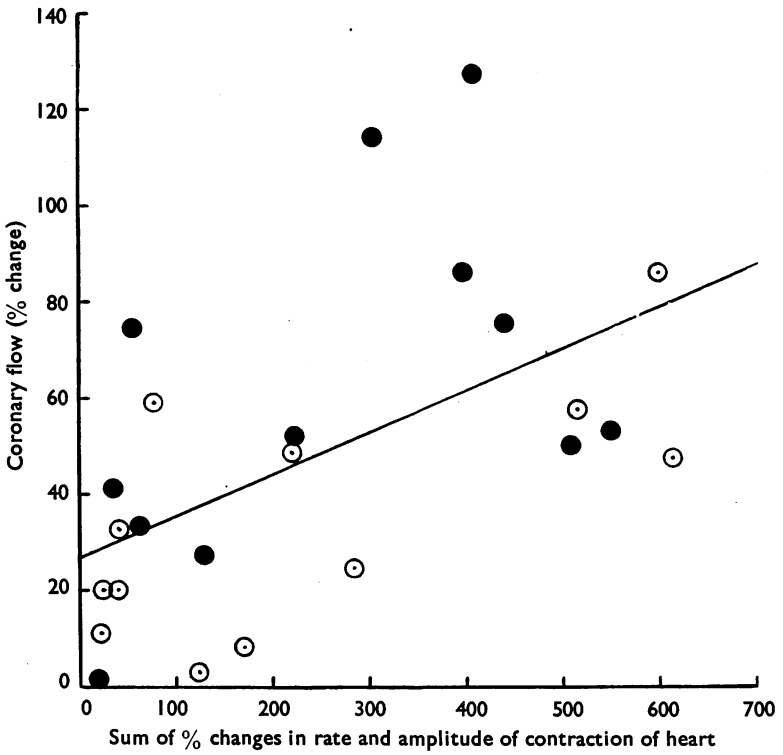

Fig. 5. The relation between percentage change in coronary flow and the sum of percentage changes in rate and amplitude of contraction of guinea-pig hearts produced by histamine (●), and by noradrenaline (○). The calculated regression line is significant at the 1% level.

TABLE 3

THE INFLUENCE OF SOME ANTAGONISTS ON THE CORONARY FLOW, THE RATE AND THE AMPLITUDE OF CONTRACTION OF THE GUINEA-PIG HEART

Values are means with standard errors and numbers of experiments in parentheses. † Significant at $P<0{\cdot}05$

Antagonist	Concentration in perfusion fluid (μg/l.)	Percentage change in		
		Coronary flow	Heart rate	Amplitude of contraction
Pronethalol	500	−11±11 (3)	0	−10± 5 (3)
Pronethalol	1,000	−22± 7 (3)	0	− 2± 2 (3)
Mepyramine	1,000	+16± 8 (3)	+6±6 (3)	−47±20 (3)
Pyrathiazine	1,000	+13±10 (3)	0	−38±20 (3)
Diphenhydramine	1,000	0	0	−56±13 (3)†

In the presence of pronethalol (0.5 or 1 mg/l.) the action of noradrenaline on the heart was abolished but the action of histamine was not significantly changed (Table 4). On the other hand, mepyramine, diphenhydramine and pyrathiazine, in concentrations of 1 mg/l., all failed to discriminate between histamine and noradrenaline when they were added to the perfusion fluid.

TABLE 4

THE INFLUENCE OF SOME ANTAGONISTS ON THE ACTION OF HISTAMINE AND NORADRENALINE ON THE AMPLITUDE OF CONTRACTION OF THE GUINEA-PIG HEART

The actions of histamine and of noradrenaline in the presence of an antagonist are expressed as percentages of their actions in the absence of an antagonist. Values are means with standard errors and numbers of experiments in parentheses

Antagonist	Concentration in perfusion fluid (μg/l.)	Action of: Histamine, 2 μg	Action of: Noradrenaline, 0·2 μg	Discrimination between histamine and noradrenaline P
Pronethalol	500	91±30 (3)	6± 5 (3)	<0·05
Pronethalol	1,000	101±20 (3)	7± 7 (3)	<0·02
Mepyramine	1,000	153±81 (3)	127± 57 (3)	>0·8
Pyrathiazine	1,000	170±68 (3)	193±108 (3)	>0·8
Diphenhydramine	1,000	127±42 (3)	153± 30 (3)	>0·7

In Table 4, the antihistamine compounds appear to have potentiated histamine and noradrenaline acting on the heart, but this is the result of expressing the response as a percentage increase in the amplitude of contraction of the heart, as the antihistamine compounds did not increase the action of the amines but reduced the amplitude of contraction of the nonstimulated heart (Table 3). For example, in one experiment the amplitude of contraction of the heart increased from 34 to 78 mm (on the kymograph) in response to noradrenaline and from 41 to 87 mm in response to histamine, but when pyrathiazine was added to the perfusion fluid the amplitude of contraction of the heart was reduced to 6 mm and increased to 34 mm in response to noradrenaline and to 31 mm in response to histamine; in this experiment histamine and noradrenaline increased the amplitude of contraction of the heart by 112 and 129% in the absence of pyrathiazine and by 417 and 467% in the presence of the antagonist, respectively.

Some further experiments were made using mepyramine, diphenhydramine and pyrathiazine in a concentration of 10 mg/l. In this concentration the antihistamine compounds depressed the amplitude of contraction of the guinea-pig heart to such a degree that the heart no longer moved the recording lever, so that neither the rate nor the amplitude of contraction of the nonstimulated heart was recorded. The heart was not completely arrested by the antihistamine compounds, however, as very small contractions of the heart could still be seen, and when histamine or noradrenaline was injected into the perfusion fluid their stimulant actions on the heart were still recorded. In a typical experiment, succeeding injections of noradrenaline increased the amplitude of contraction of the heart from 20 to 69 mm, from 17 to 57 mm and from 13 to 39 mm, and, in the presence of mepyramine when the contractions of the nonstimulated heart were too small to be recorded, noradrenaline produced a small response measuring 5 mm on the kymograph: the alternate injections of histamine increased the amplitude of contraction of the heart from 22 to 69 mm, from 14 to 45 mm and from 12 to 37 mm, and, in the presence of the antagonist, histamine produced a response measuring 5 mm. Part of the kymograph record from another experiment in which pyrathiazine (10 mg/l.) was tested is shown in Fig. 6. Two experiments with mepyramine, one with diphenhydramine and two with pyrathiazine were made, but none of these drugs in a

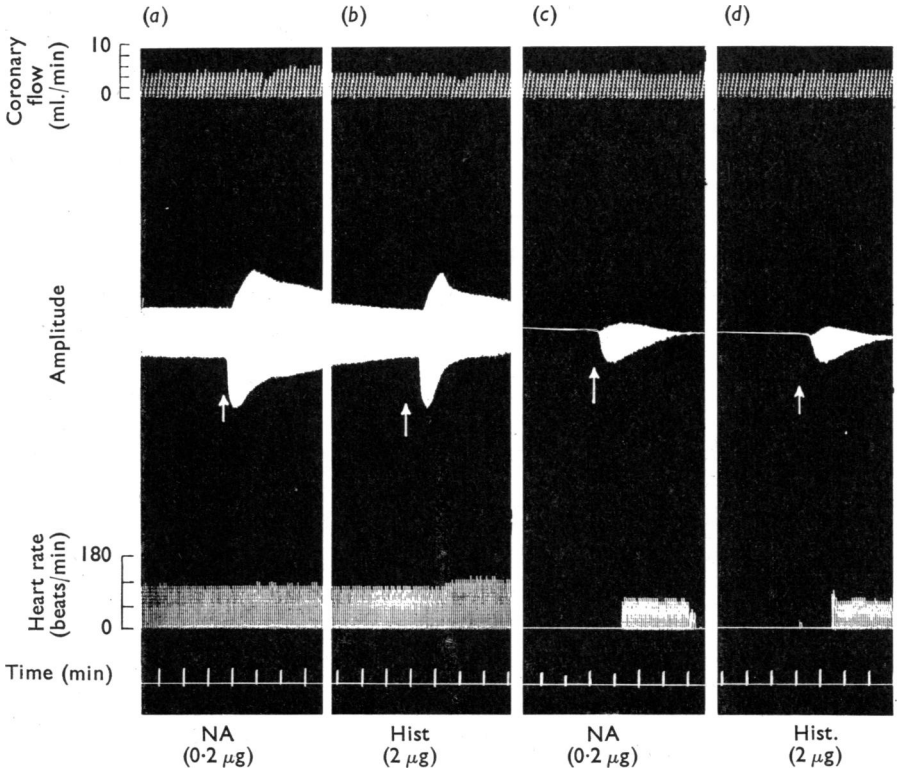

Fig. 6. Guinea-pig heart. From above down: coronary flow (ml./min); amplitude of contraction; rate (beats/min); and time (min). Numerals depict μg of noradrenaline (NA) and histamine (Hist) injected into the perfusion fluid at the arrows. Pyrathiazine (10 mg/l.) was included in the perfusion fluid in (*c*) and in (*d*).

concentration of 10 mg/l. discriminated between the actions of histamine and noradrenaline, since doses of histamine and noradrenaline which were equiactive in the absence of antagonist were still equiactive when an antagonist had been added to the perfusion fluid.

DISCUSSION

In Langendorff's (1895) method for perfusion of the heart a warm oxygenated Ringer solution is perfused through the coronary vessels and the heart allowed to beat in air. A disadvantage of this method is that changes in the rate of coronary flow cause fluctuations in the temperature of the solution in the coronary vessels. The action of drugs which alter coronary flow is thus to some extent obscured by the effect of temperature changes with this preparation. The present paper describes an organ-bath with an open perfusion circuit, in which the heart was immersed in perfusate maintained at the temperature of the fluid perfusing the coronary vessels. The temperature of the organ-bath remained constant during fluctuations in coronary flow. The heart perfusate frothed when it was gassed and this interfered with the

overflow from the bath, but the baffle overcame this problem as the gas distributor did not gas the perfusate on the overflow side of the baffle.

According to Went, Varga, Szücs & Fehér (1954), histamine first decreases and subsequently increases the amplitude of contraction of the rat heart. The second component of this response was not observed in any of the present experiments with the rat heart, even when histamine was perfused through the heart for 15 min. The effect of histamine on the heart of the rat and the domestic fowl was clearly not the result of a sympathomimetic action since histamine decreased the contractility of these preparations whereas noradrenaline increased it.

One might postulate, however, that specific receptors were involved in the release of a sympathomimetic substance from the heart by histamine, and if this was so it was not surprising to find that histamine failed to stimulate the rat and the domestic fowl hearts which were comparatively insensitive to histamine. This possibility seems improbable, however, as the action of histamine on the more sensitive guinea-pig heart was not antagonized by pronethalol (Black & Stephenson, 1962) in a concentration which abolished the action of noradrenaline. Nevertheless histamine produced changes in the coronary flow and in the rate and amplitude of contraction of the guinea-pig heart which were remarkably like those produced by noradrenaline.

The antihistamine compounds did not antagonize the action of histamine on the guinea-pig heart, even though mepyramine and diphenhydramine were tested in concentrations which were 200- and 2,000-times greater respectively than those which antagonized the action of histamine on the guinea-pig ileum (Lockett & Bartlet, 1956). A similar observation was made by Trendelenburg (1960) and, although Mannaioni (1960) reported that diphenhydramine antagonized histamine acting on the heart, this could not be confirmed. The present experiments show that, in the heart, histamine did not combine with receptors which react with the well-known antihistamine compounds. The question of the possible presence of specific receptors for histamine in the myocardium remains unanswered, however, as these may exist even though no specific antagonist of the cardiac stimulant action of histamine has been found.

Pyrathiazine was used as it had been reported to be less potent than other antihistamine compounds in reducing the rate and the amplitude of contraction of rabbit isolated auricles (Wanebo, Katsh & Bromberger-Barnea, 1962), but in the present experiments pyrathiazine, mepyramine and diphenhydramine were nearly equiactive in reducing the amplitude of contraction of the guinea-pig heart.

In the experiments with the guinea-pig heart perfusions of histamine and noradrenaline increased coronary flow when the rate and the amplitude of contraction of the heart increased. On the other hand, in the rat, where histamine reduced the rate and the amplitude of contraction of the heart, the coronary flow was also reduced. There are at least two possible explanations of this phenomenon. In the first place, fluid may be propelled through the coronary vessels by the contractions of the heart so that a stimulation of contractility might increase the coronary flow. Secondly, there may be a concomitant dilatation of the coronary vessels when the contractility of the heart increases.

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REFERENCES

BLACK, J. W. & STEPHENSON, J. S. (1962). Pharmacology of a new adrenergic beta-receptor-blocking compound (nethalide). *Lancet, ii*, 311–314.

BLEEHEN, N. M. & FISHER, R. B. (1954). The action of insulin on the isolated rat heart. *J. Physiol. (Lond.)*, **123**, 260–276.

DALE, H. H. & LAIDLAW, P. P. (1910). The physiological action of β-iminazolylethylamine. *J. Physiol. (Lond.)*, **41**, 318–344.

GADDUM, J. H. & KWIATKOWSKI, H. (1938). The action of ephedrine. *J. Physiol. (Lond.)*, **94**, 87–100.

KREBS, H. A. & HENSELEIT, K. (1932). Untersuchungen über die Harnstoffbildung im Tierkörper. *Hoppe-Seylers Z. physiol. Chem.*, **210**, 33–66.

LANGENDORFF, O. (1895). Untersuchungen am überlebenden Säugethierherzen. *Pflügers Arch. ges. Physiol.*, **61**, 291–332.

LOCKETT, M. F. & BARTLET, A. L. (1956). A method for the determination of $p.A._2$ at two minutes. *J. Pharm. Pharmacol.*, **8**, 18–26.

MANNAIONI, P. F. (1960). Interaction between histamine and dichlorisoproterenol, hexamethonium, pempidine and diphenhydramine in normal and reserpine-treated heart preparations. *Brit. J. Pharmacol.*, **15**, 500–505.

TIFFENEAU, R. (1941). Action inotrope négative de l'histamine sur le coeur de grenouille. Effet secondaire inotrope positif, dû à la formation d'une substance antagoniste. *C.R. Soc. Biol. (Paris)*, **135**, 1031–1034.

TRENDELENBURG, U. (1960). The action of histamine and 5-hydroxytryptamine on isolated mammalian atria. *J. Pharmacol. exp. Ther.*, **130**, 450–460.

WANEBO, H., KATSH, S. & BROMBERGER-BARNEA, B. (1962). Comparative activities of certain antihistamines on inhibition of isolated rabbit auricles. *Arch. int. Pharmacodyn.*, **137**, 116–120.

WENT, S. & LISSAK, K. (1935). Histamin-und Proteinwirkung am normalen und sensibilisierten Meerschweinchenherz. *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmakol.*, **179**, 609–615.

WENT, S., VARGA, E., SZÜCS, E. & FEHÉR, O. (1952). Übereine "sympathomimetische" Wirkung des Histamins. *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmakol.*, **215**, 129–132.

WENT, S., VARGA, E., SZÜCS, E. & FEHÉR, O. (1954). Eine Analyse der "sympathomimetischen" Wirkung des Histamins an isolierten Säugetierherzpräparaten. *Acta physiol. Acad. Sci. hung.*, **5**, 121–130.