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Research Article

THE EFFECT OF CAFFEIN SODIO-BENZOATE, THEOBROMIN SODIO-SALICYLATE, THEOPHYLLIN AND EUPHYLLIN ON THE CORONARY FLOW AND CARDIAC ACTION OF THE RABBIT[1]

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INTRODUCTION

The results of the investigation of the action of caffein, theobromin and theophyllin on the coronary arteries vary considerably with the different observers. Hedbom (1), employing the Langendorf method, produced an increase in coronary flow which, in some instances, was said to be great with caffein in concentrations of 1–20,000. Loeb (2), on the other hand, observed very little increase in the coronary output following the administration of caffein, whereas theobromin greatly augmented the rate of perfusion. Heathcote, (3) working with solutions of caffein, theobromin and theophyllin, in concentrations ranging from 1–2,000 to 1–40,000, obtained a marked increase in rate of coronary flow with the higher concentrations, whereas in dilutions of 1–20,000 and 1–40,000 caffein produced no change; theobromin very slight and theophyllin 20 to 30 per cent increase. Sakai and Saneyoshi (4), from experiments on the intact heart of the cat in which they employed the Morovitz-Zahn cannula, concluded that the increase in the coronary output which they observed following the injection of caffein sodio-benzoate could satisfactorily be explained on the basis of the elevation in blood pressure. These investigators reported a slight decrease in the coronary flow with small doses of theobromin sodio-salicylate, whereas, when large doses of the drug were

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introduced, there was a drop in blood pressure associated with a marked augmentation of the flow through the coronary arteries.

Guggenheimer and Sassa (5) have more recently checked the action of caffein, theophyllin and euphyllin on the coronary arteries of the isolated heart of the cat. Caffein in a dilution of 1–25,000 increased the rate of coronary flow 41 per cent. Theophyllin and euphyllin, in similar concentrations, produced a 40 and 80 per cent increase, respectively. They attributed the change in the rate of the flow of the perfusate after caffein and theophyllin to the acceleration of cardiac rate and pointed out that euphyllin did not elevate heart rate more than 10 per cent. The latter drug, which is a combination—80 per cent theophyllin and 20 per cent ethylenediamine, was recommended therapeutically in coronary artery disease because of its marked dilating action.

The object of the present investigation was to substantiate, if possible, the claims made by Guggenheimer and Sassa (5) for euphyllin and to compare the action of this drug with that of caffein sodiobenzoate, theobromin sodio-salicylate and theophyllin in experiments in which the cardiac rate was controlled.

METHODS

The isolated heart of the rabbit was employed. The rabbit was killed in the usual manner, the chest quickly opened, the heart removed and placed in a basin containing Locke-Ringer solution. The blood was carefully washed from the left ventricular cavity in order that it might not coagulate, and bits of coagulum later be thrown into the coronary circulation. A cannula was then introduced into the aorta, and the heart perfused at a pressure of 55 mm. Hg with a Locke-Ringer solution saturated with oxygen. The temperature of the perfusate was maintained at a constant level of 100° by a series of coils passing through a water bath. The control temperature was registered by a thermometer introduced into the cannula connecting directly with the aorta.

The rate of the coronary flow was determined by allowing the fluid which escaped from the heart to pass through a small funnel into a tipping bucket, the emptying of which was automatically registered on a kymograph. It is recognized that this method of measuring the coronary flow does not take into consideration the possibility of leakage through the aortic valves. This feature was, however, carefully investigated in a series of experiments[2] and found to be negligible.

[2] In a series of experiments a cannula was placed in the pulmonary artery. The return of the perfusate to the right heart was thus separated from any that might

The cardiac rate and amplitude were registered by means of a lever connected to the apex. In the records, the upstroke represents the cardiac contraction and the down stroke relaxation.

The concentration of the drug employed varied from 1–25,000 to 1–50,000[3] which was estimated to be within the range of the concentration obtained in the blood in man following the administration of a therapeutic dose. The drug was not administered until the cardiac rate, amplitude of contraction and the coronary flow assumed a uniform level. In each instance the condition of the heart remained satisfactory throughout the experiment. The results were discarded in those experiments in which the heart failed to return to a satisfactory condition from the standpoint of amplitude of contraction and rate of coronary flow following the discontinuation of the drug.

In those instances in which there was an increase in heart rate from the action of the drug, the cause of the increased coronary flow was verified by experiments in which a uniform cardiac rate was maintained by rhythmically induced break shocks. The rhythmical stimulation of the heart was produced by an oscillating contact maker, employing the principle of the tuning fork, which was connected with an ordinary induction coil. The rate of stimulation used was always well above that produced by the action of the drug on the heart with normal mechanism. In most instances the rate employed was 224 per minute.

RESULTS

Caffein sodio-benzoate in concentration of 1–25,000 solution had little or no effect on the cardiac rate, amplitude of contraction and coronary flow (fig. 1).

Theobromin sodio-salicylate in dilution of 1–25,000 in most instances produced no change, or even decreased the coronary flow (fig. 2). In one instance in which 1–12,500 concentration was employed there was 17.6 per cent reduction in the rate of perfusion. When, however, the concentration of 1–50,000 was used, the rate of flow was slightly accelerated. In two instances the percentage of increase was 25 and 28 per cent, respectively. Theobromin sodio-salicylate in either of the above concentrations apparently had no

leak past the aortic valves or return directly into the left ventricle from the coronary circulation. The same feature was investigated by ligating the pulmonary veins and inserting a cannula in the tip of the left auricle. In both instances the amount of perfusate which passed from the left heart was negligible.

[3] A dilution of 1–50,000 was estimated to correspond to a dose in man of 1.5–2.5 grains, depending on the size of the individual; a dilution of 1–25,000 to a dose 3–5 grains and a dilution of 1–12,500 to a dose of 6–10 grains.

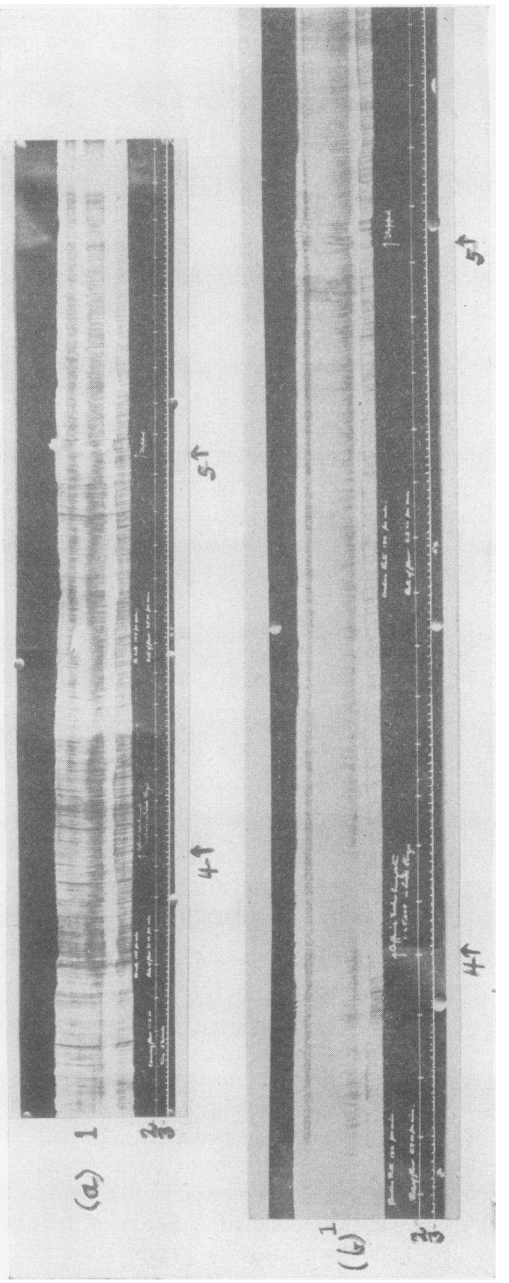

FIG. 1. CAFFEIN SODIO-BENZOATE

a, dilution 1–50,000. Increase in coronary flow 5 per cent. *b*, dilution 1–25,000. Increase in coronary flow 5 per cent.

In all of the figures: *1*, represents cardiac contractions; *2*, coronary flow in which each registration equals 2 cc.; *3*, time—3-second intervals; *4*, administration of drug; *5*, the drug discontinued.

effect on the cardiac rate. In some instances the amplitude of cardiac contraction was diminished by the drug, associated with some increase in tone (fig. 2, *b*).

Theophyllin, in concentration of 1–25,000 and 1–50,000 increased the rate of coronary flow from 20 to 45 per cent (fig. 3). In some of the experiments there was an acceleration in cardiac rate of approximately 20 beats to the minute. In one instance in which a 44 per cent increase in the rate of the flow of the perfusate was observed, there was

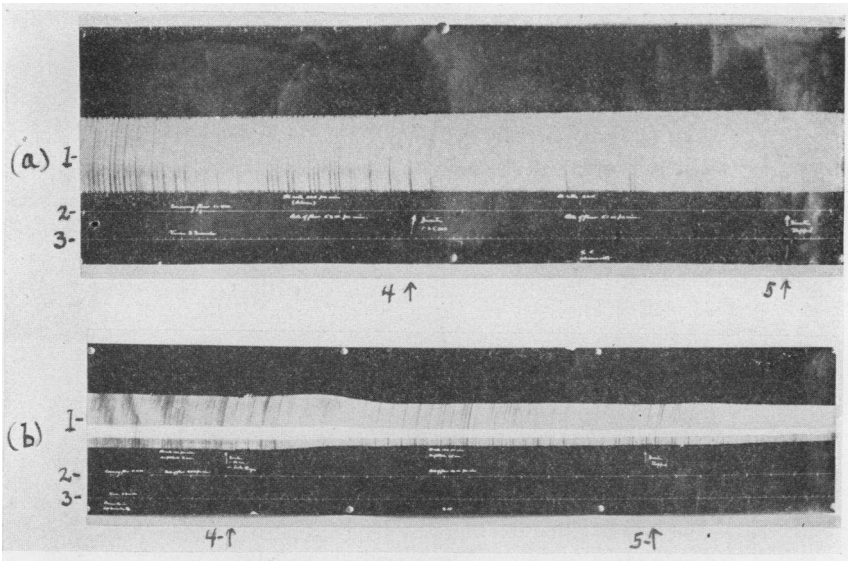

FIG. 2. THEOBROMIN SODIO-SALICYLATE

a, dilution 1–25,000. Increase in coronary flow 4 per cent. *b*, dilution 1–50,000. Increase in flow 15 per cent.

no acceleration of cardiac rate and no increase whatever in amplitude of contraction. In a few experiments an increase in amplitude of the contraction was observed shortly following the introduction of the drug (fig. 3, *c*). This feature was negligible in those instances in which the heart was driven by rhythmically induced break shocks (fig. 3, *a*). In these experiments in which a constant heart rate was maintained, the influence of the drug on the rate of coronary flow was approximately the same as in those in which a normal cardiac mechanism prevailed (fig. 3, *a* and *c*).

Euphyllin in dilutions of 1–25,000 and 1–50,000 increased the rate of coronary flow from 40 to 90 per cent. The drug, in addition, produced a distinct increase in amplitude of the cardiac contractions for a short time following the administration and accelerated the rate from 20 to 30 beats per minute (fig. 4, *b* and *c*). The increase in the rate of

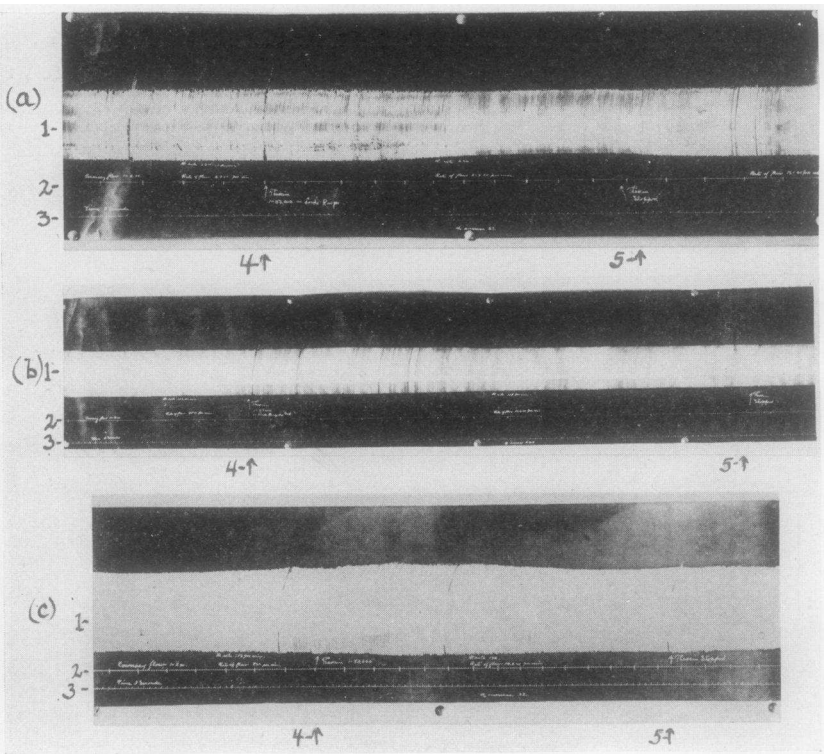

FIG. 3. THEOPHYLLIN

a, dilution 1–50,000. Increase in coronary flow 27 per cent. (Driven heart.)
b, dilution 1–25,000. Increase in coronary flow 42 per cent.
c, dilution 1–50,000. Increase in coronary flow 28 per cent.

the flow of the perfusate was, however, independent of the acceleration in cardiac rate, for practically the same degree of dilating action was observed in those experiments in which the cardiac rate was controlled by electrical stimulation (fig. 4, *a*).

In this series of experiments an attempt was made to control, as

far as possible, those factors which might influence the rate of coronary flow. It is felt that the changes observed in the flow of the perfusate may in a large measure be attributed to the action of the drug on the coronary vessels.

The action of theophyllin and euphyllin was very striking, whereas that of caffein sodio-benzoate and theobromin sodio-salicylate was

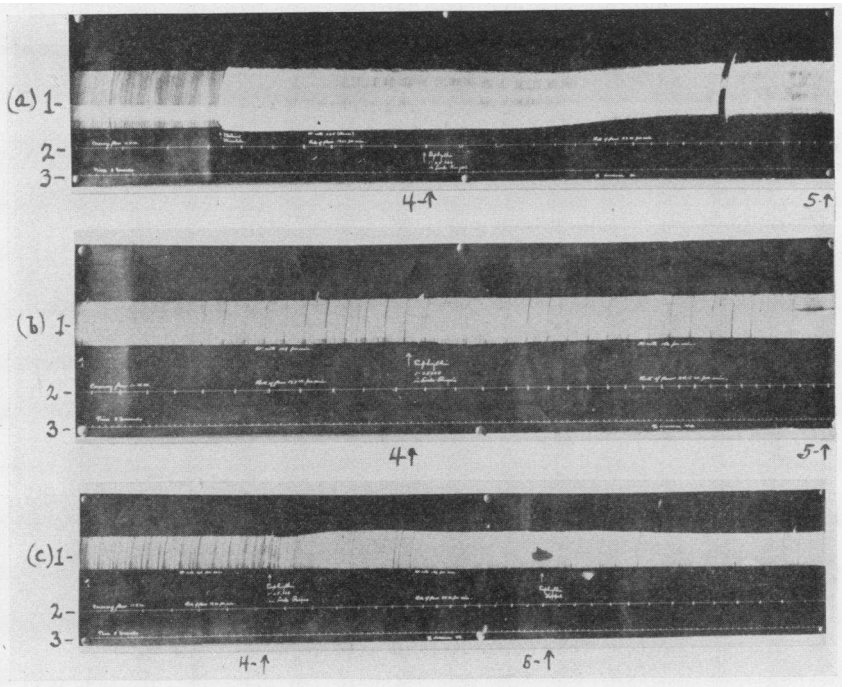

FIG. 4. EUPHYLLIN

a, dilution 1–25,000. Increase coronary flow 60 per cent. (Driven heart.) *b*, dilution 1–25,000. Increase in coronary flow 40 per cent. *c*, dilution 1–25,000. Increase in coronary flow 46 per cent.

negligible. The effect of euphyllin was definitely greater than that of theophyllin. These two drugs, in addition to their effect on the flow of the perfusate, exerted a beneficial action on the heart. This feature was not observed following the administration of caffein sodio-benzoate or theobromin sodio-salicylate. It is to be recalled that the latter drugs, in concentrations of 1–25,000 and even more marked in concentration of 1–12,500, definitely depressed the action of the heart.

The results obtained in this series of experiments from the standpoint of the action of theophyllin and euphyllin on the rate of coronary flow compare very favorably with those reported by Guggenheimer and Sassa. It is to be recalled that they employed similar concentrations of the drug and observed 40 per cent increase in the rate of perfusion with theophyllin and 80 per cent with euphyllin. These authors attributed the augmentation of the rate of the perfusion following the

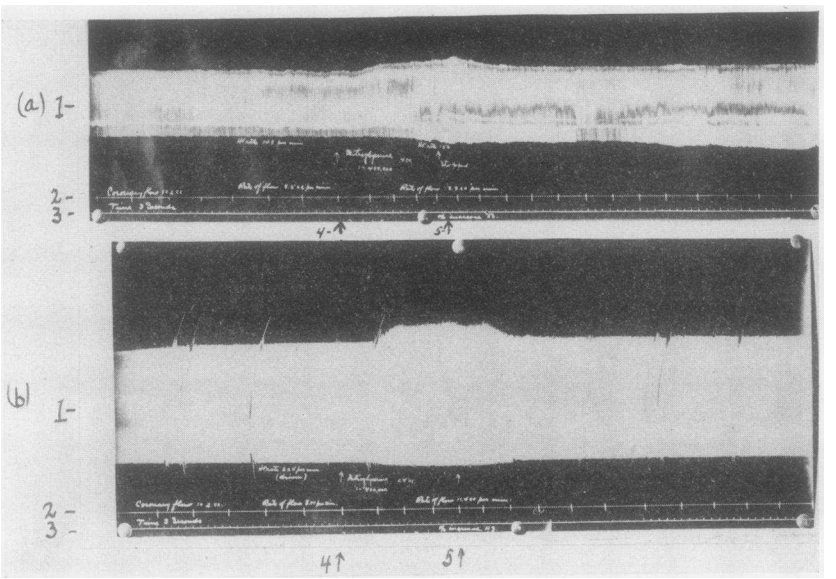

FIG. 5. NITROGLYCERIN

Dilution 1–400,000 injected at rate estimated to give concentration of 1–4,000,000 in coronary artery. This calculated to approximate therapeutic dose in man of $\frac{1}{100}$ grain.

a, increase coronary flow 56 per cent. *b*, increase coronary flow 43 per cent.

administration of theophyllin to the acceleration of the heart rate and the increase in the amplitude of the cardiac contraction. In the present experiments the acceleration of the heart rate by theophyllin was not a prominent feature. It will be recalled that in one instance in which a 44 per cent increase in the rate of coronary flow was observed, the heart rate and amplitude of contraction remained constant. Furthermore, in those experiments in which the heart rate was controlled, practically the same degree of augmentation of the rate of

perfusion was obtained after the introduction of theophyllin. Euphyllin had a somewhat greater tendency to accelerate the cardiac rate. The increase in the rate of perfusion was, however, for the most part independent of this feature as shown in those experiments in which a constant heart rate was maintained by electrical stimulation.

In a few experiments, the spirit of nitroglycerin in dilutions of 1–400,000 and 1–800,000[4] was employed in order that the action of this drug on the coronary arteries might be compared with that of euphyllin. Nitrogelycerin in the above dilutions augmented the rate of perfusion from 40 to 80 per cent, which, as will be recalled, corresponds favorably with that produced by euphyllin. The two drugs produced about the same acceleration in cardiac rate. Nitroglycerin, however, caused a more striking increase in amplitude of cardiac contraction which was maintained for some time after the action of the drug on the rate of perfusion had subsided.

The action of theobromin and theophyllin on the coronary vessels observed in the present investigation was similar to that reported by Heathcote in those instances in which corresponding concentrations of the drugs were employed. A much greater increase in the coronary output was, however, noted by Heathcote when higher concentrations of these drugs were used. In some instances the concentrations of the drugs introduced were as great as 1–2000. In these experiments the great increase in rate of perfusion was probably due to toxic action of the drug on the heart. Furthermore, it is possible that the change in hydrogen-ion concentration produced by high concentrations of the drug might have been a definite factor in producing the marked increase in coronary flow.[5]

CONCLUSIONS

Caffein sodio-benzoate in concentrations of 1–25,000 has little or no effect on the cardiac rate, amplitude of contraction and coronary flow in the perfused heart of the rabbit.

[4] This concentration was calculated to be comparable to a therapeutic dose of $\frac{1}{100}$ grain in man.

[5] In an experiment in which the influence of change in the hydrogen-ion concentration on rate of coronary flow was investigated, a decrease in pH from 7.68 to 7.38 increased the coronary flow 7 per cent. When the pH was reduced from 7.68 to 7 the coronary flow was augmented 80 per cent.

Theobromin sodio-salicylate in concentrations of 1–25,000 produces no change in rate of coronary flow. In higher concentrations, as 1–12,500, the rate of perfusion was decreased. The drug apparently had no effect on cardiac rate. In some instances the amplitude of contraction was diminished.

Theophyllin in concentrations of 1–25,000 and 1–50,000 augments the coronary flow from 20 to 45 per cent. The acceleration of the cardiac rate by the drug is not a prominent feature. The greatest increase in coronary flow was produced by the drug when there was no change in cardiac rate.

Euphyllin in above concentrations increased the rate of perfusion from 40 to 90 per cent. Euphyllin has a somewhat greater tendency to accelerate cardiac rate than theophyllin. With both drugs, however, the increase in coronary output was independent o f the accelerating action on the heart, as was indicated by experiments in which a uniform cardiac rate was maintained by rhythmical stimulation.

The action of euphyllin on the coronary flow compares favorably with that of nitroglycerin when comparable concentrations of the drugs are introduced into the perfusate.

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