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ADRENALINE, ANTI-ADRENALINE DRUGS AND POTASSIUM MOVEMENTS IN RABBIT AURICLES

BY

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Adrenaline (2×10^{-6} M) or isoprenaline (7.5×10^{-8} M) increased the rate of ^{42}K uptake and the potassium content of right (spontaneously beating) auricles, but had no effect on potassium movements in quiescent left auricles. Although faster beating induced by electrical stimulation increased the rate of ^{42}K uptake, the actions of adrenaline were also apparent in auricles which were electrically stimulated so that they beat at a constant rate. The increase in ^{42}K uptake produced by adrenaline accounted entirely for the increase in potassium content of the tissue. Adrenaline, in concentrations ranging from 2×10^{-6} M to 2×10^{-4} M, had no effect on ^{42}K loss from electrically stimulated auricles. The action of adrenaline on ^{42}K uptake was blocked by dichloroisoprenaline (4×10^{-6} M) but not by phenoxybenzamine (1.6×10^{-6} M).

The response of a muscle to adrenaline is accompanied by changes in the distribution of potassium between the cells and their environment. Ellis (1959) has reviewed evidence for increased loss of potassium, reduction in the membrane potential and increase in the frequency of spike potentials in smooth muscles during contraction in response to adrenaline. On the other hand, in smooth muscle relaxed by adrenaline, there is a gain of potassium, hyperpolarization of the membrane and a decrease in frequency of spike potentials (Bülbring, 1960). In skeletal muscle, adrenaline increases the force of contractions, and there is hyperpolarization and a decreased potassium loss (Ellis, 1959). The generalizations of Ellis (1959) about the ways in which adrenaline alters tissue potassium concentrations correspond with Ahlquist's classification of adrenaline receptors (Ahlquist, 1948; Levy & Ahlquist, 1961). Contractions of smooth muscle follow occupation of alpha receptors, while relaxation of smooth muscle and increase in force of contractions of skeletal muscle can be attributed to beta receptor occupation. It appears, therefore, that occupation of alpha receptors is associated with an increased rate of loss of potassium while occupation of beta receptors is associated with an increase in the potassium content of a tissue. There are some indications that these generalizations may apply also to cardiac muscle. For instance, the increases in rate and force of contractions of the heart produced by adrenaline are classified with occupation of beta receptors (Moran & Perkins, 1958), and adrenaline increases the ^{42}K uptake and the potassium content of rabbit auricles (Waddell, 1961). In intact animals, adrenaline produces cardiac arrhythmias which can be prevented by drugs blocking alpha receptors (Green, 1958), although these drugs may be acting by preventing the rise in blood

pressure. Arrhythmias in isolated, perfused rabbit hearts caused by adrenaline are associated with an increased rate of loss of potassium into the perfusion fluid (Melville, Mazurkiewicz & Korol, 1955).

This paper reports the effects of adrenaline on movements of ^{42}K into and out of rabbit auricles. Dichloroisoprenaline (1-(3,4 dichlorophenyl)-2 isopropyl-amino-ethanol hydrochloride), which blocks beta receptors, and phenoxybenzamine, which blocks alpha receptors, were used to localize the site of action of adrenaline on potassium movements. Increased potassium uptake induced by adrenaline was blocked by dichloroisoprenaline, suggesting that it is linked with occupation of beta receptors. Surprisingly, it proved impossible to elicit arrhythmias in isolated rabbit auricles, even with massive doses of adrenaline, so that the potassium movements associated with activation of alpha receptors in the heart, if any, will require investigation in a different way.

METHODS

Rabbit auricles were used because much is known about their normal potassium exchanges and the effects of drugs upon them (Rayner & Weatherall, 1957, 1959; Persoff, 1960; Waddell, 1961; Weatherall, 1962). Small rabbits (<1.5 kg) were killed by a blow on the head and the heart removed rapidly. The auricles were dissected at room temperature in a sintered glass funnel containing Krebs solution through which a mixture of 5% CO_2 in O_2 was bubbled. The composition (mM) of the Krebs solution was: Na^+ 145, K^+ 5.8, Ca^{++} 1.7, Mg^{++} 1.2, Cl^- 128, HCO_3^- 25, SO_4^{--} 1.2, $H_2PO_4^-$ 1.2, dextrose 11; gas phase 5% CO_2 in O_2. All experiments were carried out at 30° C.

Measurement of ^{42}K uptake. Measurements of ^{42}K uptake were made on spontaneously beating right auricles, quiescent left auricles and left auricles stimulated electrically. For 1 hr after dissection, auricles were immersed in tubes which contained Krebs solution at 30° C. Right auricles always beat spontaneously. Left auricles sometimes began to beat while warming, but stopped after a few minutes. Some left auricles were impaled on platinum electrodes, and driven by rectangular pulses of 1 msec duration at 125/min. In some experiments, either dichloroisoprenaline or phenoxybenzamine was added to the Krebs solution, and left in contact with the auricles for 1 hr. Then the auricles were transferred to a Krebs solution containing part of its potassium as ^{42}K, and were allowed to take up ^{42}K for 15 min. Adrenaline or isoprenaline was added to some of the tubes containing ^{42}K labelled Krebs solution immediately before the auricles were placed in them. The left auricles attached to stimulating electrodes were driven at 190/min during the 15 min period of exposure to ^{42}K labelled Krebs solution. After removal from radioactive Krebs solution, the auricles were washed with isotonic choline chloride, blotted on filter paper and weighed. They were then ashed and their ^{42}K and total K content determined by the method of Rayner & Weatherall (1959).

Stability of adrenaline. Samples of a solution of adrenaline (2×10^{-6} M) in Krebs solution at 30° C gassed with 5% CO_2 in O_2 were assayed at intervals on the blood pressure of a pithed rat (Shipley & Tilden, 1947).

Measurement of ^{42}K loss. The method was similar to that of Persoff (1960). Left auricles, stimulated at 125/min, were placed in ^{42}K labelled Krebs solution immediately after dissection, and left to take up ^{42}K for 80 to 90 min. They were then stretched above the end window of a Geiger-Müller tube. The rate of stimulation was increased to 190/min. A stream of Krebs solution flowed over the auricle (25 to 30 ml./min) and carried away the ^{42}K as it was released from the tissue. The effluent was collected for each 90 sec period and its ^{42}K content estimated in a liquid counter. Measurement of loss of ^{42}K was begun 15 min

after removal of the auricle from radioactive Krebs solution. Adrenaline was injected with a motor-driven syringe into the stream of Krebs solution flowing to the auricle at rates ranging from 0.1 to 0.5% of the flow rate of the Krebs solution.

Contractions of auricles. In preliminary experiments, isolated rabbit auricles were attached to a spring lever writing on smoked paper. Rate of beating was counted over 30 sec periods. Contractions of auricles were not recorded during measurement of ^{42}K uptake, but rate of beating was counted. During measurement of ^{42}K loss, isometric contractions of the auricles were detected with a mechano-electronic transducer (RCA 5734) and displayed on an oscilloscope.

Inulin space and intracellular Na and K concentrations. Undivided pairs of auricles were soaked in Krebs solution containing 1% inulin for 1 hr; some solutions also contained adrenaline. Adrenaline was added either for the last 20 min only, or at 20 min intervals for the whole period. The auricles were then rinsed in isotonic choline chloride, blotted on filter paper, weighed and placed in 20 ml. of distilled water overnight at 6° C. Inulin was estimated in this extract by the method of Bacon & Bell (1948), and Na and K with a flame photometer. After extraction with water, 4 to 5 auricles were ashed together to determine if any Na or K remained in them. It was found that 2% of the total Na and K remained in the auricles, and this represents the amount that is still in the tissue in equilibrium with the extraction fluid. The total water content was not measured on the same auricles, but mean values from similarly treated auricles dried overnight at 110° C were used in calculation of intracellular water content.

Drugs. Adrenaline (B.D.H.) was dissolved in 5 mM hydrochloric acid. Dichloroisoprenaline hydrochloride was given to me by Dr M. J. Rand, who had obtained it from Dr I. H. Slater, of Eli Lilly. Phenoxybenzamine from S.K.F. and inulin from two sources (B.D.H. and T. Kerfoot) were used.

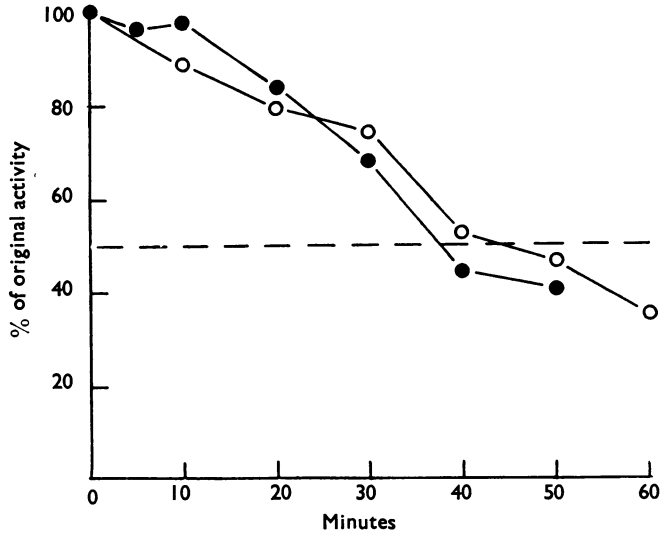

Fig. 1. Loss of activity of 2×10^{-6} M adrenaline in Krebs solution gassed with 5% CO_2 and 95% O_2 at 30° in two experiments. Pharmacological activity was assayed on the blood pressure of pithed rats.

RESULTS

Stability of adrenaline

Fig. 1 illustrates two experiments measuring the loss of activity of 2×10^{-6} M adrenaline in Krebs solution. The half-life of adrenaline was about 40 min, and 80 to 90% of the original activity remained after 15 min. It is unlikely that such a loss in activity would influence the results. Concentrations of adrenaline given in this paper are those originally added, although, at the end of a 15-min period of treatment, this concentration might have been reduced by as much as 20%.

Mechanical responses of rabbit auricles to adrenaline, isoprenaline, dichloroisoprenaline and phenoxybenzamine

Adrenaline (2×10^{-6} M) and isoprenaline (7.5×10^{-8} M) produced a sustained increase in the rate and force of contractions of isolated rabbit auricles, and these concentrations were used in all experiments measuring ^{42}K uptake. Treatment of the auricles for 1 hr with dichloroisoprenaline (4×10^{-6} M) produced a 10% increase in the rate and force of contractions, but blocked the action of adrenaline and isoprenaline. This block persisted for at least 1 hr after repeated washing with fresh Krebs solution, which confirms the findings of Moran & Perkins (1958). Phenoxybenzamine (1.6×10^{-6} M) had no effect on the contractions of the auricles, or on the responses to adrenaline (2×10^{-6} M) or isoprenaline (7.5×10^{-8} M).

When exposed to higher concentrations of adrenaline, isoprenaline or noradrenaline (5×10^{-4} M) for up to 30 min, isolated rabbit auricles developed no arrhythmias. In 5 experiments with adrenaline (5×10^{-4} to 10^{-2} M), the initial increase in heart rate up to about 200/min was sustained, though the increase in amplitude of contraction was not, but not even 10^{-2} M adrenaline induced arrhythmias.

Actions of adrenaline, isoprenaline and anti-adrenaline drugs on ^{42}K uptake by rabbit auricles

Right auricles. Table 1 shows that adrenaline (2×10^{-6} M) and isoprenaline (7.5×10^{-8} M) increased the uptake of ^{42}K by spontaneously beating right auricles ($P<0.001$; $0.01<P<0.02$ respectively) and also increased their potassium content ($0.001<P<0.01$). Dichloroisoprenaline (4×10^{-6} M) produced only a slight, but not significant ($P>0.1$), increase in ^{42}K uptake, and in the potassium content of the tissue. Pretreatment of the auricles with dichloroisoprenaline abolished the actions of adrenaline and isoprenaline on ^{42}K uptake. The mean uptake of ^{42}K and the mean potassium content were lower (but not significantly, $P>0.1$) in auricles treated with dichloroisoprenaline and adrenaline or isoprenaline than in auricles treated with dichloroisoprenaline alone (Table 1).

Left auricles. Potassium uptake by quiescent left auricles (Table 1) was very much less than in beating right auricles, confirming the report of Rayner & Weatherall (1957). Dichloroisoprenaline produced no significant change ($P>0.1$) in either the ^{42}K uptake or the potassium content of left auricles. The effects of adrenaline and isoprenaline on ^{42}K uptake by left auricles depended upon whether the auricles began to beat in the 15-min period during which uptake was measured.

TABLE 1

^{42}K UPTAKE BY RIGHT AND LEFT RABBIT AURICLES (MEAN±S.E. OF MEAN)

Pretreatment for 60 min in normal Krebs solution	Treatment during 15 min in radioactive Krebs solution	No. of expts.	Minimum ^{42}K uptake μmoles/g wet weight/15 min	Final K content μmoles/g wet weight
Right auricles (beating spontaneously)				
Control	Control	7	14·2±0·41	58·0±1·4
Dichloroisoprenaline 4×10^{-6} M	Control	7	15·7±0·76	61·8±1·6
Control	Adrenaline 2×10^{-6} M	7	18·1±0·64	64·3±1·3
Dichloroisoprenaline 4×10^{-6} M	Adrenaline 2×10^{-6} M	7	15·3±0·73	58·9±3·4
Control	Isoprenaline $7·5\times10^{-8}$ M	3	17·5±0·30	67·4±1·8
Dichloroisoprenaline 4×10^{-6} M	Isoprenaline $7·5\times10^{-8}$ M	3	13·6±1·9	54·9±8·6
Left auricles (quiescent except for adrenaline or isoprenaline treated auricles marked with asterisk)				
Control	Control	7	8·6±0·62	61·7±2·5
Dichloroisoprenaline 4×10^{-6} M	Control	7	9·1±0·69	60·1±0·71
Control	Adrenaline 2×10^{-6} M	7	13·3±2·3*	64·0±1·5
Dichloroisoprenaline 4×10^{-6} M	Adrenaline 2×10^{-6} M	7	9·1±0·68	61·6±2·0
Control	Isoprenaline $7·5\times10^{-8}$ M	3	16·0±2·6*	64·8±1·5
Dichloroisoprenaline 4×10^{-6} M	Isoprenaline $7·5\times10^{-8}$ M	3	7·8±2·2	61·7±4·4

About half the left auricles treated with adrenaline or isoprenaline began beating at some time during measurement of ^{42}K uptake. The ^{42}K uptake of these beating left auricles was as great as that of spontaneously beating right auricles.

Some additional experiments (not included in Table 1) were done on ^{42}K uptake in left auricles with concentrations of adrenaline between 10^{-5} and 10^{-6} M. The ^{42}K uptake in 11 control left auricles (9.5±0.54 μmoles/g wet weight/15 min) was not significantly different ($P>0.1$) from that in 7 out of 11 adrenaline treated auricles that did not begin to beat (10.2±0.77). There was also no significant change in the potassium content of these left auricles (controls: 60.7±1.7 μmoles/g wet weight; adrenaline treated: 61.3±1.0 μmoles/g wet weight; $P>0.1$). This suggests that there is no, or very little, change produced by these concentrations of adrenaline on the entry of potassium through the resting membrane.

The only effect of dichloroisoprenaline on left auricles, therefore, in the experiments summarized in Table 1 was to prevent the onset of beating in the left auricles treated with adrenaline or isoprenaline. None of the dichloroisoprenaline-treated left auricles began to beat when placed in Krebs solution containing adrenaline or isoprenaline. Similarly, Dresel & Duncan (1961) found that dichloroisoprenaline prevented adrenaline from initiating rhythmic contractions in cat papillary muscles.

Electrically stimulated left auricles. As the loss of ^{42}K from rabbit auricles was increased when the auricles beat faster (Rayner & Weatherall, 1959), it is probable

that ^{42}K entry would also increase under these circumstances. The experiments described so far did not exclude the possibility that the increase in ^{42}K uptake produced by adrenaline was due only to the increased rate of beating. Fig. 2 shows that the ^{42}K uptake by left auricles, stimulated electrically at various rates, increased with increasing rates of stimulation up to 190/min. This effect of rate is large

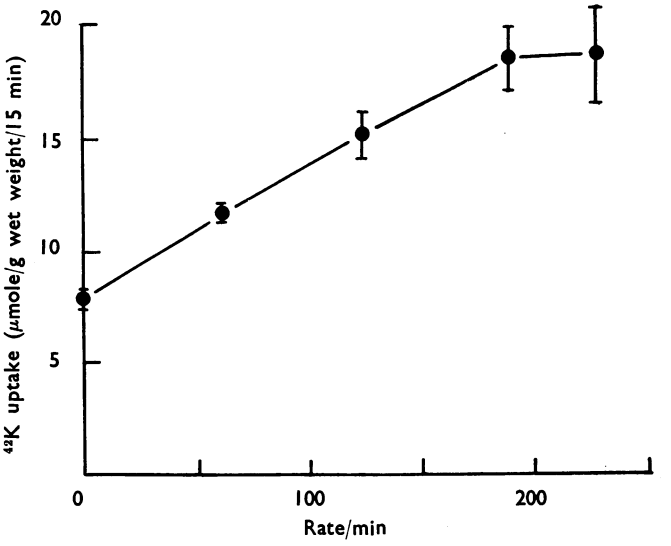

Fig. 2. The effect of rate of stimulation of left auricles on ^{42}K uptake. Each point is the mean of seven observations and the vertical lines indicate the standard errors.

TABLE 2

^{42}K UPTAKE BY LEFT AURICLES STIMULATED ELECTRICALLY
(Mean±s.e. of mean)

Pretreatment for 60 min in normal Krebs solution, stimulated 125/min	Treatment during 15 min in radioactive Krebs solution, stimulated 190/min	No. of expts.	Minimum ^{42}K uptake μmole/g wet weight/ 15 min	Final K content μmole/g wet weight
Control	Control	12	16·5±0·52	68·0±0·66
Control	Adrenaline 2×10^{-6} M	12	19·7±0·39	71·8±0·94
Dichloroisoprenaline 4×10^{-6} M	Control	7	16·0±0·97	67·3±1·1
Phenoxybenzamine $1·6\times10^{-6}$ M	Control	5	17·4±1·1	68·7±1·1
Dichloroisoprenaline 4×10^{-6} M	Adrenaline 2×10^{-6} M	7	17·2±0·84	68·3±1·7
Phenoxybenzamine $1·6\times10^{-6}$ M	Adrenaline 2×10^{-6} M	5	21·8±0·45	72·6±1·3

enough to suggest that adrenaline-treated auricles take up more ^{42}K simply because they are beating faster. However, this is not the explanation. In left auricles stimulated at 190/min, adrenaline still increased the uptake of potassium from 16.5 to 19.7 μmoles/g wet weight/15 min (Table 2); this difference is highly significant ($P<0.001$). Also adrenaline increased the mean potassium content of the

auricles from 68.0 to 71.8 μmoles/g wet weight ($0.001<P<0.01$). Thus the effect of adrenaline on potassium uptake is not attributable only to the increased rate of beating.

In some experiments, either dichloroisoprenaline (4×10^{-6} M) or phenoxybenzamine (1.6×10^{-6} M) was added to the Krebs solution 1 hr before the auricles were moved to the ^{42}K labelled Krebs solution. Dichloroisoprenaline or phenoxybenzamine (Table 2) did not change significantly the rate of ^{42}K uptake or the potassium content of the auricles ($P>0.1$ for each comparison). Pretreatment of the auricles with dichloroisoprenaline blocked the action of adrenaline on potassium uptake, but after treatment with phenoxybenzamine, adrenaline still accelerated the rate of ^{42}K uptake.

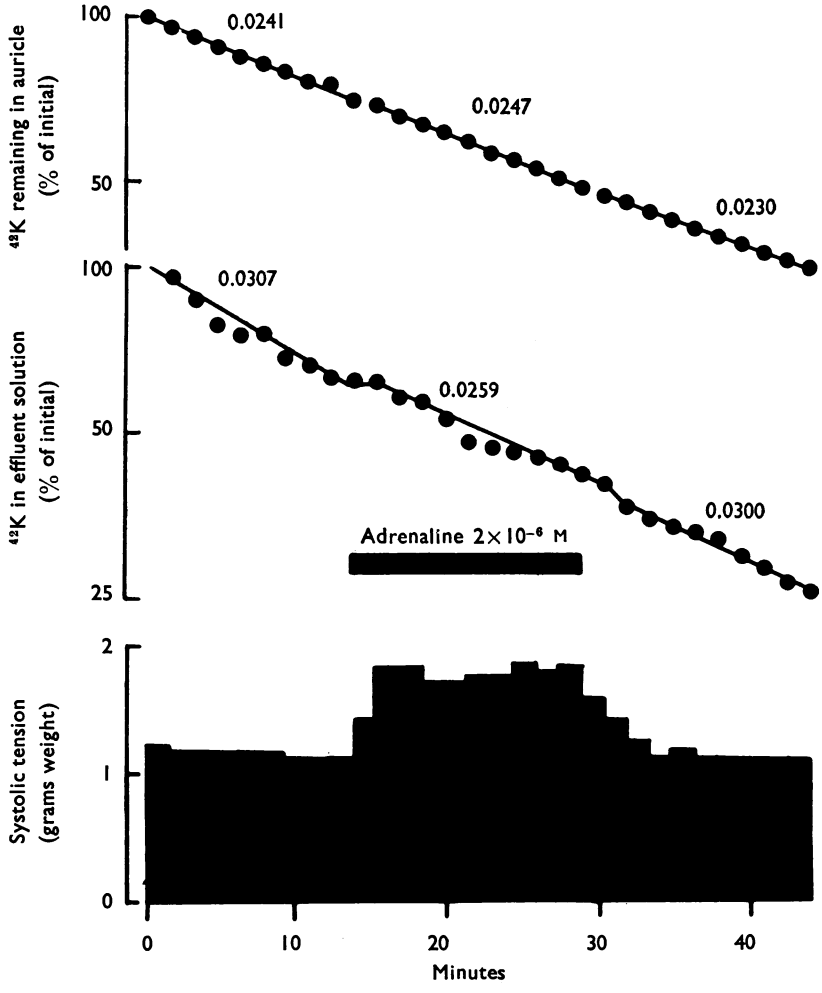

Fig. 3. The effect of adrenaline on the rate of loss of ^{42}K from left auricles stimulated at 190/min (mean of four experiments). The upper line shows ^{42}K remaining in tissue and the lower line shows ^{42}K appearing in the effluent solution; the numerals above the two lines are the rate constants calculated for each 15-min period (in min^{-1}). The histogram shows the force of contraction.

Action of adrenaline on ^{42}K loss

Adrenaline (2×10^{-6} M) had no effect on the rate of loss of ^{42}K from auricles stimulated electrically at 190/min. The mean results from 4 experiments are shown in Fig. 3. The rate constant for loss of ^{42}K was higher for effluent counting than for direct counting, confirming the findings of Persoff (1960). This indicated non-uniformity of labelling of the potassium in the auricle (Keynes & Swan, 1959).

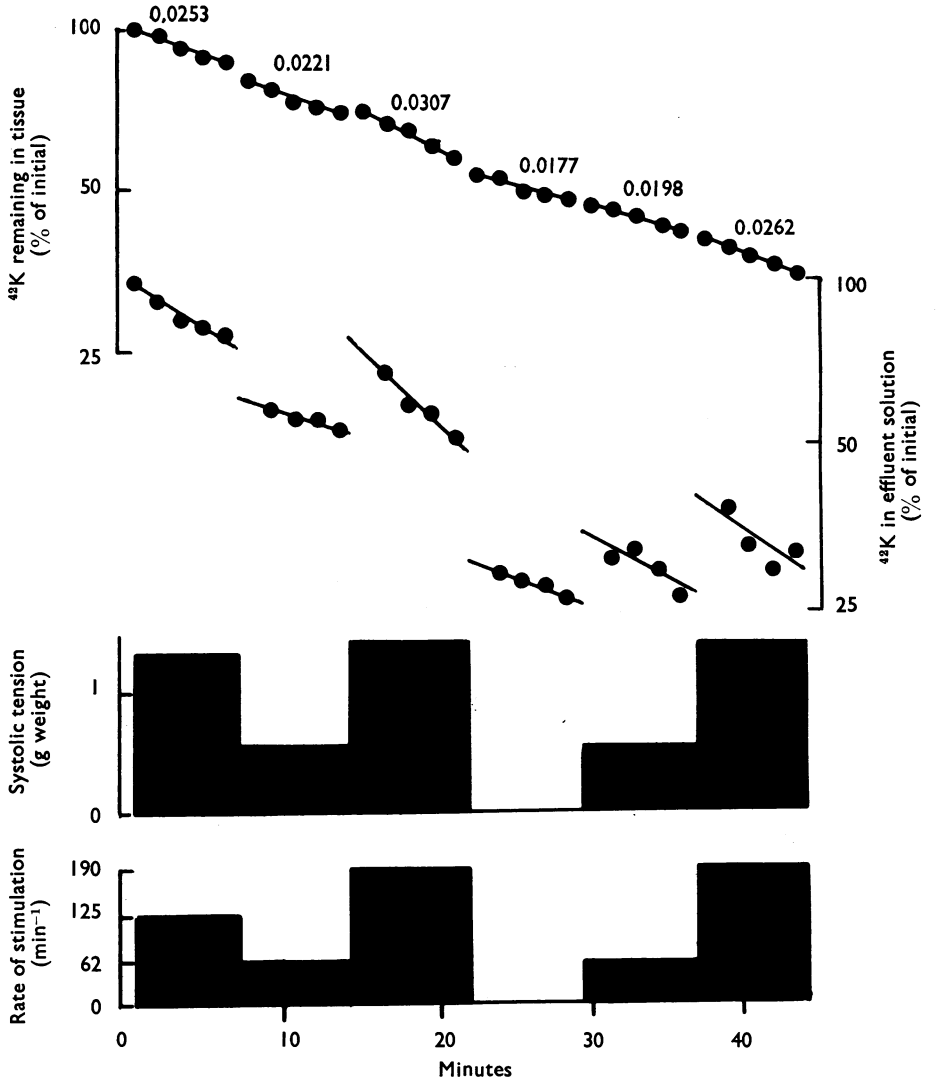

Fig. 4. The effect of rate of stimulation on ^{42}K loss from a left auricle. The figure shows, from top to bottom: ^{42}K remaining in auricle, ^{42}K in the effluent solution, force of contraction of auricle, and rate of stimulation. The numerals above the top line are the rate constants (min^{-1}) calculated for each period. A change in rate of ^{42}K loss shows as a change of slope in the direct counting (upper) graph, and as a displacement of the line as well as a change in slope for the (lower) graph of ^{42}K in the effluent. Rate of loss of ^{42}K from the auricle increases with increasing rates of stimulation.

Higher concentrations of adrenaline (2×10^{-5} M and 2×10^{-4} M) were tested on 5 auricles and did not affect the rate of loss of ^{42}K.

Fig. 4 shows the effect of changing the rate of stimulation on the rate of loss of ^{42}K. With faster rates of stimulation, the rate of ^{42}K loss was increased.

Intracellular sodium and potassium concentrations

Undivided pairs of rabbit auricles were placed in Krebs solution containing 1% inulin for 1 hr. In the first experiment, adrenaline (2×10^{-6} M) was present for the last 20 min; in the second experiment, adrenaline was present for 1 hr. Treatment with adrenaline for 20 min increased the total potassium content of the tissue. However, the total potassium content of the auricles treated with adrenaline for 1 hr was not significantly higher than that of the control auricles, even though the rate of beating of the adrenaline-treated auricles remained faster for the entire period. Apparently the increase in total potassium content which adrenaline produced after 15 or 20 min treatment was not maintained (Table 3). In both experiments, the inulin (extracellular) space was slightly lower in the adrenaline-treated

TABLE 3
ADRENALINE ON EXTRACELLULAR WATER AND INTRACELLULAR K AND Na
(Mean±s.e.)

	No. of expts.	Inulin space ml./g wet weight	Total K μmoles/g wet weight	Total Na μmoles/g wet weight	Intracellular K mM	Intracellular Na mM
Experiment 1						
Control	8	0·273±0·013	60·0±0·8	54·2±1·5	103±2·0	25·4±2·8
20′ Adrenaline (2×10^{-6} M)	8	0·249±0·013	64·6±1·2	51·3±1·4	106±2·0	26·1±2·1
Experiment 2						
Control	4	0·273±0·011	62·2±1·0	53·8±1·0	106±1·4	24·8±1·3
60′ Adrenaline (2×10^{-6} M)	4	0·254±0·005	62·6±0·6	52·7±1·9	104±1·0	26·9±2·6

auricles, but this decrease was not statistically significant even when the results of the 2 experiments were combined ($0.05<P<0.1$). Control auricles had a water content of 84.44±0.13%, which was slightly but significantly higher than that of auricles treated with adrenaline for 20 min, 83.86±0.13% ($0.01<P<0.02$). After 1 hr in adrenaline, the water content was 84.18±0.31%, and was not significantly different from the controls. Although adrenaline increased the total potassium content of the auricles, there was no significant change in the concentration of potassium in the intracellular water. Adrenaline did not change significantly ($P>0.1$) the total sodium content or the intracellular sodium concentration (Table 3).

DISCUSSION

In electrically-driven left auricles, in which there was no change in rate of beating throughout the experiment, adrenaline (2×10^{-6} M) produced a 20% increase in the rate of uptake of ^{42}K without altering the rate of loss; there was consequently an increase in the potassium content of the tissue. This increase in potassium uptake was blocked by dichloroisoprenaline, in concentrations which blocked the increase

in force of contraction produced by adrenaline, and this increase was not blocked by phenoxybenzamine, which did not block the increase in force of contraction produced by adrenaline. Isoprenaline also produced a similar increase in potassium uptake and an increase in potassium content, but at lower concentrations than did adrenaline. These observations indicate that the increase in potassium uptake was, like the increase in rate and force of contraction and the activation of phosphorylase *b*, a response due to beta receptor occupation. They provide no further information about which, if any, of these responses is the first step, but it seems unlikely that they are all independent effects. Even in much higher concentrations, adrenaline did not produce arrhythmias in isolated rabbit auricles, and had no effect on the rate of loss of potassium. It appears therefore that the action of adrenaline on rabbit auricles, irrespective of concentration, was monophasic and due entirely to beta receptor occupation. There was no indication of an increased permeability to potassium. This suggests that there is a qualitative difference between the actions of high concentrations of adrenaline on rabbit auricles and rabbit ventricles, in which arrhythmias induced by adrenaline are associated with an increased loss of potassium (Melville *et al.*, 1955).

Agreement between measurements of ^{42}K uptake, ^{42}K loss and changes in potassium content. As adrenaline had no effect on the rate of loss of potassium from left auricles beating at constant rate, it follows that the increase in potassium uptake produced by adrenaline should account entirely for the increase in potassium content of the tissue. It appears from Table 2 that the mean increase in potassium uptake produced by adrenaline (3.2 μmoles/g wet weight/15 min) is insufficient to account for the increase in content of potassium (3.8 μmoles/g wet weight), and the discrepancy between increase in uptake and increase in content in spontaneously beating auricles (Table 1) is even greater. However, the values given in Tables 1 and 2 are *minimum* potassium uptake based on the final content of ^{42}K in the auricles. But, as well as taking up ^{42}K, the auricles were also losing ^{42}K, at a rate which was initially slow, but which increased as the percentage of labelled potassium in the auricle increased. A correction factor which compensates for this loss is $k\mathrm{T}/1\text{–}e^{-k\mathrm{T}}$ (see Keynes, 1951), where T is the time of uptake (here 15 min) and k is the rate constant calculated from efflux experiments. Because potassium exchanges in beating auricles differ considerably from a single exponential process, it is not strictly correct to apply this adjustment (Weatherall, 1962). However, it probably gives a better estimate of *total* potassium uptake than the uncorrected data. The value of k, the efflux rate constant, depended upon whether the auricles were quiescent or beating and the rate at which they were beating (Fig. 4). For a rate of beating of 190/min, $k=0.0244$ (mean value from Fig. 3), and $k\mathrm{T}/1\text{–}e^{-k\mathrm{T}}=1.16$. Therefore *total* potassium uptake exceeds *minimum* potassium uptake by 16%. The increase in *total* potassium uptake (from Table 2) now becomes $3.2\times1.16=3.7$ μmoles/g wet weight/15 min. This is in close agreement with the observed increase in content of 3.8 μmoles/g wet weight, and confirms the experiments showing that adrenaline does not change the rate of loss of potassium from electrically stimulated left auricles. In spontaneously beating auricles, the increase in *total* potassium uptake did not account for the observed increase in potassium content of the tissue, suggesting that part of the increase in content might be due to a decreased rate

of potassium. The effect of adrenaline on the rate of loss of potassium from spontaneously beating auricles was not measured.

There are some differences between my results and those of Waddell (1961), who found that adrenaline increased influx and efflux of ^{42}K and potassium content in left auricles whether or not they began to beat under the influence of adrenaline. My results show that adrenaline had no effect on ^{42}K uptake or content of potassium in left auricles unless they began to beat. Waddell (1961) described an increased efflux of ^{42}K in beating auricles in the presence of adrenaline, which has not been confirmed in this paper. This increased efflux is probably entirely due to an increase in the rate of spontaneous beating produced by adrenaline, for in electrically stimulated left auricles no such increase in potassium efflux occurred. Waddell (1961) concluded that " there is no evidence that more than normal amounts of potassium are exchanged at each beat under the influence of either amine " (adrenaline or noradrenaline). However, as adrenaline increased the potassium uptake in left auricles beating at constant rate, and did not alter uptake in quiescent left auricles, the inward flux per beat must have been increased by adrenaline.

Correlation with electrical changes. Adrenaline produces little change in the resting potential or action potential of auricular muscle fibres measured with intracellular electrodes, in contrast to its effects on sino-auricular nodal tissue (Hoffman & Cranefield, 1960). In rat, guinea-pig and rabbit auricles, stimulated to beat at constant rate, adrenaline prolongs the action potential slightly (Webb & Hollander, 1956 ; Furchgott, Sleator & de Gubareff, 1960 ; reviewed by Hoffman & Cranefield, 1960). Vaughan Williams (1958) described no change in the resting potential, and a slight increase in the height of the action potential in rabbit auricles beating at 175/min in the presence of 1.3×10^{-6} adrenaline. With lower concentrations of adrenaline (3×10^{-7}, approximately equal to 2×10^{-6} M which was used here in ^{42}K uptake experiments), Vaughan Williams (1958) found no change in electrical activity associated with a 60% increase in the force of contraction. Dudel & Trautwein (1955) found that adrenaline hyperpolarized cat auricular cells, but the effect was more marked when their resting potential was low.

As adrenaline increased the total potassium content of auricles without any appreciable effect on the intracellular potassium concentration, there is no reason to expect a change in the resting potential. The increased entry of potassium and water into the cell may be associated with the accelerated synthesis of indiffusible anions—the organic phosphates—from glycogen. Increased glycogenolysis has been described in many tissues under the influence of adrenaline (Ellis, 1959) and may lead to a retention of potassium (Shanes, 1958). The present results do not suggest that the increased potassium content is due to an increased rate of sodium extrusion, but, because of the large extracellular space in rabbit auricles, estimates of intracellular sodium concentrations are unreliable. Measurements of ^{24}Na movements in rabbit auricles probably indicate mainly exchange between the medium and the extracellular space, as there is no observable difference in exchange rates in beating and quiescent auricles (Carslake & Weatherall, 1962); a direct action of adrenaline on the movement of sodium in this tissue would be difficult to measure.

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