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ADRENALINE, NORADRENALINE AND POTASSIUM FLUXES IN RABBIT AURICLES

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The rate and force of rhythmic contraction in the heart are increased by adrenaline (Oliver & Schäfer, 1895; Elliott, 1905) and noradrenaline (Ahlquist, 1948). Adrenaline increases the slope of the diastolic pre-potential in pace-maker cells of spontaneously beating auricles (West, Falk & Cervoni, 1956), and both drugs increase the rate of repolarization after an action potential in all auricular cells (Brooks, Hoffman, Suckling & Orias, 1955). As repolarization after an action potential is generally assumed to be due to the passive efflux of potassium from the tissue, it would be expected that adrenaline and noradrenaline would accelerate this flux. There appears to be little published information about the effect of these amines on the resting membrane potential in quiescent left auricles, so it is difficult to predict what changes in potassium fluxes might be expected. The present paper describes observations on the potassium fluxes of left (quiescent) and right (spontaneously beating) rabbit auricles under the influence of noradrenaline and adrenaline, and enables a distinction to be made between effects on the fluxes through the resting membrane, and on fluxes in spontaneously contracting tissue.

METHODS

Potassium influx was measured over periods of 20 min as described by Rayner & Weatherall (1957), except that a temperature of 29° C was used instead of 37° C. Unstretched divided auricles were immersed for 1 hr in inactive saline medium, containing (mM): 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, and were then transferred to a similar medium containing some of the potassium as the isotope ^{42}K and sometimes either noradrenaline bitartrate (4×10^{-5} M) or adrenaline hydrochloride (4×10^{-5} M) for 20 min. The solutions were equilibrated throughout with 95 % O_2 + 5 % CO_2. To minimize the risk of oxidation, the amines were added to the previously warmed and gassed radioactive medium immediately before they were used experimentally.

After immersion in radioactive medium the tissues were rinsed in 0·15 M choline chloride, blotted, dried at 110° C for more than 2 hr, and were ashed and estimated for ^{42}K and total K (Rayner & Weatherall, 1959).

Potassium efflux was estimated at 29° C, but otherwise as described by Rayner & Weatherall (1959). Auricles were placed in medium containing ^{42}K immediately after dissection or

after a period of 50–310 min in inactive medium, and allowed to take up ^{42}K for 50–160 min before being transferred to a bath in which they were surrounded by flowing inactive medium over the end window of a Geiger–Müller counter. The amines, dissolved in saline medium, were administered from a syringe through a polythene cannula placed upstream to the tissue, at a measured rate which was approximately 1/100 of the rate at which medium passed through the bath, and the final concentrations were calculated from the ratio of the two rates. To retard oxidation the solution of amines placed in the syringe was acidified slightly with 0·3 ml. 2N-HCl/100 ml. solution. Contractions of the auricles were recorded with a suitable transducer and oscilloscope, and photographed as required.

RESULTS

Mechanical activity of the auricles

In these experiments right auricles always contracted spontaneously throughout the period of study. The rate of contraction was recorded in experiments on ^{42}K efflux but not in experiments on uptake; it was increased when the medium contained noradrenaline or adrenaline. Left auricles did not beat spontaneously except sometimes after treatment with noradrenaline or adrenaline. Such beating started at any time after 3 min exposure of unstretched left auricles to medium containing 4×10^{-5}M noradrenaline or adrenaline; the experiments in this concentration were not continued for longer than 20 min, within which time about half the left auricles had begun to beat. In efflux experiments, with 3×10^{-6}M–$7{\cdot}5 \times 10^{-5}$M noradrenaline or adrenaline, beating never started in less than 20 min, but occasionally began later than this, although the tissues had been returned to a control medium. Reference is made to the occurrence of beating in the text and tables where appropriate.

Final potassium concentrations

The quantity of potassium inside the cells was estimated from the total amount of potassium in the tissue less the amount which was expected to be in the extracellular fluid. The volume of extracellular fluid was taken as 44·1 ml./100 g wet weight of tissue (Rayner & Weatherall, 1957). The concentration of potassium in the extracellular fluid was assumed to be the same as that in the medium. The quantity of water in the cells was estimated from the total tissue water (wet weight minus dry weight) less the extracellular water. Intracellular potassium concentrations were calculated from the quantities of potassium and of water in the cells. Untreated auricles had mean potassium concentrations of $142{\cdot}3 \pm 3{\cdot}2$ m-mole/l. cell water (S.E. of 16 observations) in the shorter (80 min) and $136{\cdot}6 \pm 3{\cdot}8$ m-mole/l. (S.E. of 5 observations) in the longer (190–420 min) experiments. These figures agree closely with those previously reported by Rayner & Weatherall (1957, 1959) at 37° C and by Goodford (1959) at 35° C.

Unstretched auricles which had been treated with noradrenaline and adrenaline contained 6–10% more potassium than untreated controls (Table 1). The experiments were not all carried out on the same day, and part of the variation within each group is due to day-to-day variation of unknown origin. When comparisons were made between auricles run at the same time, the control auricles contained more potassium than those treated with noradrenaline or adrenaline in only 4 out of 23 comparisons. The means of the differences between the control and the corresponding treated values were significant in each group ($0{\cdot}05 > P > 0{\cdot}02$) except in right auricles treated with noradrenaline, for which $P < 0{\cdot}4$. The cause of the day-to-day variation in the potassium content of auricles has not been examined; it is in any case not large, and its practical importance in

TABLE 1. Uptake of ^{42}K by unstretched auricles (means ± S.E. of means)

Treatment during uptake of ^{42}K	No. of expts.	Dry wt. (mg)	Final $[K]_i$ (m-mole/l. cell water)	Exchange at end of influx (%)	Rate of uptake (m-mole K/l. cell water/min)
Left auricles					
Control	8	19·7 ± 1·9	136·8 ± 4·4	17·5 ± 0·8	1·34 ± 0·05
Noradrenaline 4×10^{-5} M	7	21·6 ± 2·0	150·7 ± 4·8	27·4 ± 3·5	2·41 ± 0·37
Adrenaline 4×10^{-5} M	5	23·7 ± 2·3	145·6 ± 3·6	25·1 ± 1·9	2·08 ± 0·19
Right auricles					
Control	8	13·7 ± 0·8	147·8 ± 4·1	30·2 ± 0·9	2·84 ± 0·14
Noradrenaline 4×10^{-5} M	6	17·4 ± 1·7	156·0 ± 2·7	37·1 ± 1·5	3·88 ± 0·17
Adrenaline 4×10^{-5} M	5	13·4 ± 1·1	157·8 ± 5·1	37·6 ± 1·6	3·71 ± 0·25

the present experiments lies in its relevance to the significance of differences observed in individual experiments. Differences in the final potassium concentrations of treated and untreated auricles after efflux measurements (Tables 2 and 3) were not statistically significant, but most of these auricles had been restored to the control medium for at least 20 min after exposure to the drugs.

Inward movement of ^{42}K

Table 1 shows the results of experiments in which the rates of uptake of ^{42}K were measured in left and right auricles. The influx rate constant is known to depend in part on the weight of the tissue (Rayner & Weatherall, 1959), but these experiments were performed with auricles which did not vary greatly in size, apart from the difference between left and right auricles. It will be seen that in addition to the net gain in potassium, the auricles treated with noradrenaline or adrenaline have exchanged a larger fraction of their potassium. The total influx has been estimated from the

proportion exchanged by the adjustment (Keynes, 1951; Hodgkin & Horowicz, 1959),

$$(dY/dT)_{t=0} = Y.kT/T(1-\exp(-kT)),$$

where Y = ^{42}K (m-mole/l.) taken up by auricles in time T;
T = time (min) during which influx took place (here, 20 min);
t = zero time, time when ^{42}K starts to enter tissue; and
k = rate constants obtained in efflux experiments described later in this paper.

In view of the considerable departure from a single exponential process of the potassium exchange of right auricles (Rayner & Weatherall, 1957; Persoff, 1960), this adjustment is unlikely to be quite correct, but probably gives a better estimate of the total influx than the unadjusted figures. The adjustment enlarges the difference between control and treated auricles because, as is shown below, the efflux rate constants are increased by noradrenaline and adrenaline and so $k/(1-\exp(-kT))$ is also greater. When allowance was made for the different intracellular potassium concentrations and the accelerated efflux rate constants, the mean rates of uptake of ^{42}K in noradrenaline-treated left auricles were 80% higher, and in adrenaline-treated left auricles 55% higher, than in the controls. Both increments are significant ($P < 0.05$). The increased influx was greatest in the auricles which had started to beat, but it occurred also in those which remained quiescent. In right auricles the corresponding mean increases in the rate of uptake of ^{42}K were 37 and 31% in noradrenaline- and adrenaline-treated auricles respectively, and again were significant ($P < 0.01$ in each case).

Differences between the rates of uptake of ^{42}K in auricles treated with the two amines did not suggest any appreciable difference in potency, but the number of experiments in which direct comparison was made was small ($n = 3$).

Outward movements of ^{42}K

Tables 2 and 3 show results of individual experiments during which measurements were made of the rate of loss of ^{42}K from left and right auricles respectively. As Fig. 1 shows, irregular departures from linearity were small and lines through the points were fitted by eye. It has been shown by Rayner & Weatherall (1957, 1959), Klein & Holland (1958) and Persoff (1958, 1960) that whereas the early efflux of ^{42}K from untreated left auricles follows an approximately linear course when plotted semi-logarithmically, the rate of loss of ^{42}K from untreated right auricles declines rather rapidly. The efflux rate constants of the control auricles in Tables 2 and 3 illustrate this point, as does Fig. 1, which shows the effect of 10^{-5}M

TABLE 2. Rate of loss of ^{42}K from left auricles

Expt. no.	Duration of uptake of radioactivity (min)	Treatment during loss of ^{42}K and period in which treatment was applied	Dry weight (mg)	Final $[K]_i$ (mM)	Efflux rate constant (min^{-1}) Period (1)	Period (2)	Period (3)	Period (4)	Period (5)
3L	82	Control	14·2	147	0·011	0·011	0·011	0·011	0·011
4L	98	Control	16·3	132	—	0·009	0·009	0·008	—
10L	35	Control	12·8	125	—	0·011	0·009	0·009	—
Mean				134·7	—	0·010	0·010	0·009	—
S.E.				±6·49	—	±0·0007	±0·0005	±0·0007	—
12L*†	81	(2), (4), (5) Noradrenaline 5×10^{-6} M	15·6	126	0·009	**0·014**	0·012	**0·020**	**0·020**
14L	60	(2) Noradrenaline $5·5 \times 10^{-6}$ M	12·8	155	0·013	**0·017**	0·013	—	—
15L*	91	(2) Noradrenaline 10^{-5} M	11·9	120	0·010	**0·019**	—	—	—
16L	45	(2) Noradrenaline 10^{-5} M	13·2	141	0·013	**0·018**	0·013	0·013	—
17L	50	(2), (4) Noradrenaline 10^{-5} M	16·8	154	0·012	**0·012**	0·007	**0·015**	—
Mean				139·2	0·011	0·016	0·011	—	—
S.E.				±7·12	±0·0009	±0·0004	±0·0014	—	—
8L†	90	(2), (5) Adrenaline 10^{-5} M, (4), (5) stimulated 2/sec	11·2	132	0·011	**0·016**	0·012	0·012	**0·026**
9L	63	(2), (5) Adrenaline 10^{-5} M, (4), (5), (6) stimulated 2/sec	13·5	146	0·012	**0·013**	0·013	0·019	**0·024**
18L*	63	(2) Adrenaline 10^{-5} M	16·0	140	0·010	**0·011**	0·011	—	—
6L	88	(2) Adrenaline $7·5 \times 10^{-5}$ M	10·0	143	0·010	**0·014**	0·013	—	—
Mean				140·3	0·011	0·013	0·012	0·016	0·025
S.E.				±3·01	±0·0006	±0·0011	±0·0004	—	—

The uptake of radioactivity took place in control medium throughout.

The periods were all of 20 min duration, but in period (1) the first 5 min were ignored when the estimate of the rate constant was made. Figures in heavy type refer to periods in which auricles were treated with drugs. Auricle 9L had a rate constant of 0·021 in period (6).

* Auricles which beat spontaneously during all or part of period (3). † Auricles removed for ashing during infusion of amine.

TABLE 3. Rate of loss of ^{42}K from right auricles

Expt. no.	Duration of uptake of radio-activity (min)	Treatment during loss of ^{42}K and period in which treatment was applied	Dry weight (mg)	Final $[K]_i$ (mM)	Efflux rate constant (min^{-1}) Period (1)	Period (2)	Period (3)	Period (4)	Period (5)
2R	70	Control	9·8	142	0·023	0·020	0·018	0·016	0·016
3R	100	Control	8·1	137	0·024	0·022	0·018	0·018	0·018
Mean				139·5	0·024	0·021	0·018	0·017	0·017
S.E.				±2·45	±0·0005	±0·0008	±0·0001	—	—
13R	50	(2) Noradrenaline 5×10^{-6} M	10·5	140	0·022	**0·031**	0·014	—	—
14R	112	(2) Noradrenaline 6×10^{-6} M	12·3	148	0·026	**0·028**	0·022	0·016	—
15R	40	(2) Noradrenaline 10^{-5} M	12·9	97	0·034	**0·034**	0·025	0·025	—
16R	33	(2) Noradrenaline 10^{-5} M	10·6	143	0·033	**0·033**	0·027	—	—
Mean				132·0	0·029	0·031	0·022	0·021	—
S.E.				±11·78	±0·0029	±0·0012	±0·0029	—	—
5R	113	(2) Adrenaline 3×10^{-6} M	10·3	134	0·022	**0·022**	0·018	0·016	0·016
8R	162	(2), (4) Adrenaline 10^{-5} M	9·5	115	0·020	**0·019**	0·016	**0·018**	—
18R	63	(2) Adrenaline 10^{-5} M	12·0	135	0·021	**0·019**	—	—	—
7R	73	(2), (4) Adrenaline 6×10^{-5} M	10·2	152	0·024	**0·025**	0·020	**0·017**	0·017
6R†	65	(2), (4) Adrenaline 7×10^{-5} M	8·0	132	0·033	**0·031**	0·025	**0·020**	—
Mean				133·6	0·024	0·023	0·020	—	0·017
S.E.				±5·87	±0·0024	±0·0022	±0·0019	—	—

The uptake of radioactivity took place in control medium throughout. Duration of periods and figures in heavy type as in Table 2. † Auricle removed for ashing during infusion of amine.

noradrenaline on the rate of outward movement of ^{42}K in a left and a right auricle. It is therefore appropriate to compare the rate constants of treated auricles with those of controls in the same period as well as with those of the auricles themselves in the period before treatment. In left auricles there is anyway a clear acceleration of efflux of ^{42}K by noradrenaline, by about 55% ($P < 0.01$), and to a less extent by adrenaline

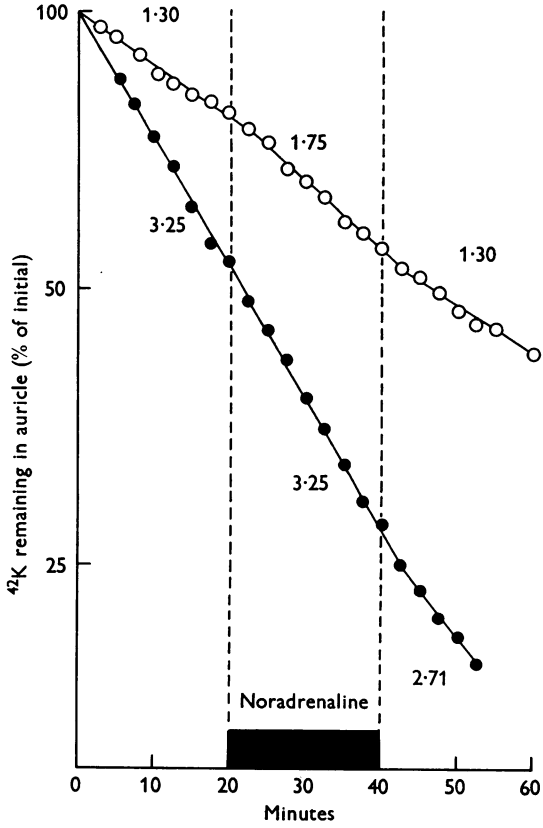

Fig. 1. Influence of noradrenaline on efflux of ^{42}K in left (○) and right (●) auricles. Noradrenaline was infused to give a final concentration of 10 μM during the middle 20 min period. The numerals above and below the two lines give the appropriate rate constants (in 10^{-2} min^{-1}). Expts. 16L and 16R.

(31%, $P \approx 0.05$). This effect occurred whether or not spontaneous beating started, and persisted slightly after the end of treatment, as is shown by the higher values for treated than for control auricles in period (3). The acceleration of ^{42}K efflux recurred in those experiments in which treatment was repeated (Table 2, last col.), and it was also observable in two auricles (8L, 9L) in which beating was maintained by electrical stimulation before and during administration of adrenaline. In right auricles, with the rapid

decline in the rate of ^{42}K efflux in control tissues (Table 3, Expts. 2R and 3R), less increase might be expected from treatment, and in fact the mean rate (0·023 min^{-1}) during period (2) for adrenaline-treated auricles was lower than in the preceding period, though higher than in control auricles (0·021 min^{-1}): the difference is not significant but probably real in view of other findings. With noradrenaline a more definite acceleration of efflux was observed, with an efflux rate during treatment appreciably higher than before, and as before some persistence of the effect in the period after treatment.

Estimation of potassium fluxes

Estimations of potassium fluxes, both inwards and outwards, are given in Table 4 for left and right auricles. In order to convert rate constants into fluxes it is necessary to obtain an estimate of the total surface area of the cells. This has been derived from the tissue dimensions by the method described by Rayner & Weatherall (1957). A correction for delays due to diffusion (Keynes, 1954) is desirable, but this introduces some uncertainties, particularly as diffusion effects may not be the same in quiescent and beating auricles. For this reason, the flux values given in the table and text have not been corrected for diffusion, and they are probably underestimates. To obtain values corrected according to Keynes from these apparent fluxes they must be multiplied by factors varying in different instances from 1·1 to 2·2, depending on the size of the tissues and on the magnitude of the rate constants observed.

Final potassium concentrations in the untreated auricles were within the range observed by Rayner & Weatherall (1957) for fresh auricles. Because of this, and because the efflux of ^{42}K from quiescent left auricles hardly deviates from a single exponential course, the conventional method of estimating potassium fluxes in these auricles is justifiable. In contracting right auricles, where the efflux of ^{42}K does not follow a single exponential course, and in noradrenaline- and adrenaline-treated auricles which have gained potassium, it is possible that a larger error is introduced into estimates of the fluxes made in this way. In untreated left auricles the mean inward flux was estimated to be 3·8 pmole/cm^2.sec, while the mean outward flux in the first 20 min of efflux was estimated to be 4·7 pmole/cm^2.sec. These fluxes are slightly smaller than the uncorrected fluxes obtained by Rayner & Weatherall (1959) under identical conditions, except at a temperature of 37° C. Rate constants at 29° C are consistently lower than those at 37° C, which would account for the smaller fluxes obtained at the lower temperature. The corresponding values for untreated contracting right auricles were 7·9 pmole/cm^2.sec (inwards) and 10·3 pmole/cm^2.sec (outwards, based on the rate constant obtained in the first 20 min

of efflux). In view of the curvature of the semilogarithmic plot of the efflux in right auricles, these figures are based on a somewhat uncertain foundation and as there is no evidence of net changes in the potassium content of the right auricles, the true values for influx and efflux probably do not differ as much as these figures suggest.

It may be provisionally assumed that part of the flux in right auricles takes place through the resting membrane, and that this proportion of the total flux occurs at the same rate as the flux in left auricles. If the resting flux, i.e. the flux in left auricles, is subtracted from the total flux in right auricles, the remaining flux may be attributed to the movement through

TABLE 4. Estimated K fluxes in left and right auricles

Treatment		Influx No. of expts.	Influx (pmole/cm².sec; mean ± S.E.)	Efflux No. of expts.	Efflux (pmole/cm².sec; mean ± S.E.)
Left auricles					
Control	(*a*)	8	3·8 ± 0·2	9	4·7 ± 0·3
Control	(*b*)			4	4·2 ± 0·3
Noradrenaline	(*b*)	7	7·3 ± 1·4	5	7·0 ± 0·5
Adrenaline	(*b*)	5	6·2 ± 0·7	4	5·4 ± 0·4
Right auricles					
Control	(*a*)	8	7·9 ± 0·4	9	10·3 ± 0·7
Control	(*b*)			2	8·4 ± 0·2
Noradrenaline	(*b*)	6	10·6 ± 0·5	4	11·9 ± 0·9
Adrenaline	(*b*)	5	10·9 ± 0·9	5	9·2 ± 1·0

These estimates of influx are based on the rate constants for the first 20 min uptake of tracer, either in control conditions or using 4×10^{-5} M noradrenaline or adrenaline. The estimates of efflux are based (*a*) on the rate constants for the period 5–20 min of loss of tracer, in control conditions or (*b*) on the rate constants for the period 20–40 min of loss of tracer either in control conditions or with from 3×10^{-6} to $7{\cdot}5 \times 10^{-5}$ M noradrenaline and adrenaline.

the active membrane. From influx determinations this value was estimated to be 4·1 pmole/cm².sec; from efflux determinations it was 5·6 pmole/cm².sec. As the rate of beating averaged 1·82 beats/sec in the experiments considered here, the extra flux per beat was estimated to be 2·25 pmole/cm².beat using influx, or 3·07 pmole/cm².beat using efflux determinations.

The effect of treatment of left and right auricles with noradrenaline and adrenaline was to increase both inward and outward potassium fluxes (Table 4). The drugs were generally applied during the second 20 min period of efflux when the control rate constants were declining from their initial values, especially in right auricles. Estimates of fluxes for control tissues derived from the rate constant in the second 20 min period are therefore included in the table for comparison. As Table 4 shows, both amines increased inward and outward fluxes. On the whole, the influx rates were increased more than the efflux rates, as would be expected from the observed net gain of potassium in tissues treated with adrenaline

or noradrenaline. As the estimates involve various approximations and in the control auricles do not give as close agreement between influx and efflux as is indicated by the observations on the total potassium content of the tissue, exact agreement between flux difference and net gain is not to be expected in the treated tissues, but the general trend of the results does not suggest inconsistency between the various estimates made.

If it is assumed, as before, that the difference between the outward fluxes in left and right auricles during treatment gives an estimate of the flux through the active membrane in right auricles, then an estimate of the extra flux can be obtained in noradrenaline- and adrenaline-treated right auricles. These differences were 4·9 and 3·8 pmole/cm^2. sec respectively for noradrenaline- and adrenaline-treated auricles. The mean rates of contraction of noradrenaline- and adrenaline-treated right auricles were, respectively, 2·09 and 2·30 beats/sec, so that the estimated extra outward fluxes per beat were 2·34 and 1·65 pmole/cm^2. beat respectively. These figures are somewhat smaller than the estimated extra outward flux per beat in untreated auricles, but the difference is probably not larger than might be due to approximations used in making the estimates. It can reasonably be inferred that the extra outward flux of potassium found in treated right auricles is partly accounted for by the faster rate of contraction during treatment (14–20 %), since there is little indication that the flux per beat is altered by treatment with the amines. However, much of the increase in rate of loss of potassium is shared by left and right auricles, and may be caused by an increase in permeability of the resting cell membrane to potassium ions.

DISCUSSION

Evidence has been presented that adrenaline and noradrenaline accelerate both inward and outward potassium movements from left and right auricles, and that these changes are accompanied by a small gain in potassium by the treated auricles. The mean potassium content of the treated auricles was increased, but only by 6–10 %; and this increment was not sufficient to account for the 30–55 % acceleration of outward movement.

Any alteration in permeability would be expected to produce effects on the electrical behaviour of the cell membrane. Adrenaline increases the slope of the diastolic prepotential in pace-maker cells (which may partly account for its acceleration of contractions in right auricles), and is capable of making cells adjacent to the pace-maker region develop diastolic prepotentials (West *et al.* 1956). It is possible that the quiescent left auricles which showed increased potassium movements after treatment possessed some cells which developed these subthreshold depolarizations and that in the auricles which started to contract these prepotentials were

large enough to fire off action potentials: but it is not known at present how far subthreshold changes in potential are associated with measurable effects on potassium movements.

As in smooth muscle (Born & Bülbring, 1956), inward potassium movements were increased more than outward movements by the catecholamines, indicating that the mechanisms for the active, inward transport of potassium must be stimulated either directly or indirectly by these agents. Adrenaline has been demonstrated to promote glycogenolysis both in cardiac slices (Ellis, McGill & Anderson, 1957) and in isolated perfused rat hearts (Hess & Haugaard, 1958). It has now been demonstrated that adrenaline stimulates the formation from adenosine triphosphate of a cyclic mononucleotide, adenosine-3′,5′-phosphoric acid, which appears to catalyse the formation of phosphorlyase-a, the active form of the enzyme, from the inactive form, phosphorylase-b (Rall & Sutherland, 1958). No relationship has been established between this sequence of events and other effects of adrenaline, but it would be unlikely that this stimulation of metabolism would not affect other processes going on in cardiac tissues.

SUMMARY

1. The effect of adrenaline and noradrenaline on potassium movements in isolated rabbit auricles has been determined.

2. The influx and efflux of potassium were increased by adrenaline and noradrenaline (3×10^{-6}–$7{\cdot}5 \times 10^{-5}$M) in beating right auricles and in quiescent left auricles. The effect on influx was slightly greater than that on efflux, and net gains of potassium were observed in treated auricles.

3. Quiescent left auricles sometimes started to beat spontaneously during or after exposure to the amines, but increased potassium movements occurred without these mechanical effects, or before they appeared.

4. The total increase in the potassium fluxes is considered to be due to two factors, an increased flux through the resting membrane and a faster rate of beating. There is no evidence that more than normal amounts of potassium are exchanged at each beat under the influence of either amine.

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