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THE MOVEMENT OF POTASSIUM BETWEEN SMOOTH MUSCLE AND THE SURROUNDING FLUID

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Previous work on ionic fluxes in excitable tissues has been mainly concerned with nerve and striated muscle; it has provided a basis for the interpretation of electrical phenomena in these tissues. From recent study it has become evident that in smooth muscle a close correlation exists between membrane potential, discharge of spike potentials and tension (Bülbring, 1955); but no information is available about ionic exchange in this tissue.

The work here described was undertaken to find out whether it was possible to establish a correlation between changes in tension and the movement of potassium in smooth muscle. The results showed that during changes in tension occurring spontaneously or in response to mechanical and chemical stimuli the rates of uptake and loss of ^{42}K were correspondingly altered.

METHODS

Radioactive potassium was obtained from the Atomic Energy Research Establishment, Harwell, as irradiated K_2CO_3 (Johnson, Matthey, 'Specpure'). The salt was dissolved in a volume of 1·0 N-HCl to neutralize the solution. The requisite amount of this radioactive solution was added to a modified Krebs's solution to give a KCl concentration of 0·35 g/l. The composition of the bathing solution used throughout was as follows (mM): 133 NaCl, 4·7 KCl, 1·38 NaH_2PO_4, 16·3 $NaHCO_3$, and after equilibration with 95% O_2 and 5% CO_2, 2·5 $CaCl_2$, 0·105 $MgCl_2$ and 7·8 dextrose were added.

The isolated taenia coli of the guinea-pig was the smooth muscle preparation used. For most experiments it was placed in a small chamber through which bathing solution flowed.

The muscle chamber was made of a block of Perspex. A channel 3·2 cm long and 0·16 cm in diameter was drilled 0·1 cm below and parallel to the upper surface. One end of the channel was closed by a stopper with a centre hole to admit bathing fluid. The other end of the channel opened on to a Perspex lip from which the effluent could be collected. The muscle was attached at one end to a hook on the stopper, and at the other end by a thread leading out of the channel to a mechano-electronic transducer valve (RCA 5734) to record the tension. Warm water was circulated through channels drilled alongside the muscle chamber which kept the preparation at 37° C. A Geiger counter tube (G.E.C. Type GM 4) was mounted with its window downwards on top of the muscle chamber, separated from the preparation by a distance of 0·2 cm. Of this, 0·1 cm was Perspex wall, and 0·1 cm was the thickness of a lead shield. This shield had a central slot

0·16 × 1·0 cm. Thus the central part of the channel containing 1 cm of the total muscle length was exposed to the Geiger tube.

The rate of uptake of ^{42}K by smooth muscle was measured in different ways. One method allowed a simultaneous comparison of the rate of ^{42}K uptake by several pieces of muscle. Up to eight pieces of taenia of the same *in situ* length were taken from a freshly killed guinea-pig, weighed and incubated at 30–37° C. They were placed in radioactive solution, either unweighted or with a load of 5 g. In other experiments they were suspended in isolated organ baths filled with inactive solution and attached to isometric or to isotonic levers; the tension or the contractions were recorded on a kymograph, and after 1 hr, during which the muscles developed a constant rhythm of spontaneous activity, the baths were filled with radioactive solution. At the end of each experiment the active solution was replaced by inactive solution which was changed three times in 5 min. Then each taenia was rapidly taken out and dissolved in 1 ml. of concentrated nitric acid. 4 ml. of water were added and small duplicate samples of this solution were dried on planchets and their radioactivity was determined. The activity was expressed as counts/min per mg wet weight of tissue.

In another method a length of taenia was placed in the muscle chamber and bathed with inactive solution until the mean tension had become constant. The muscle was then bathed with radioactive solution for 5 min, and with inactive solution for the next 5 min. The radioactivity of the muscle was measured during the last minute of the total 10 min period by means of the Geiger tube which was fixed above the muscle channel. The cycle was then repeated, so that the uptake was measured every 10 min, during only half of which it had been exposed to radioactive solution. In other experiments the radioactive solution flowed for 25 min, and the radioactivity of the muscle was determined after 5 min washing, i.e. every 30 min.

The rate of loss of ^{42}K from smooth muscle was measured as follows. A piece of taenia of about 2 cm *in situ* length was soaked in radioactive solution at room temperature for periods varying from 1 to 6 hr. It was then placed in the Perspex chamber and washed with inactive solution, which flowed at a constant rate varying from 2 to 5 ml. per min in different experiments. The radioactivity of the muscle was measured using the Geiger tube mounted on top of the muscle chamber, either at intervals with a scaler or continuously with a ratemeter with a maximal paralysis time of 400 μsec.

For higher resolution the effluent was collected in many successive samples of constant volume (0·4–0·5 ml.) on aluminium planchets. The samples were evaporated to dryness and their radioactivity was determined. The counting of each sample was continued until the S.E. of the count was less than 7%. All results were corrected for decay of ^{42}K, and (where appropriate) for the dead time of the Geiger tube and scaler.

RESULTS

The rate of uptake of ^{42}*K by taenia coli*

The taeniae coli from one guinea-pig were divided into pieces of similar *in situ* length (about 2 cm) and weight (about 20 mg). They were immersed in radioactive solutions and removed after periods varying from 10 min to 7 hr, and their radioactivity was determined. The results of six such experiments are shown in Table 1. The rate of uptake of ^{42}K was rapid at first and then became progressively slower. After about 3 hr the radioactivity increased no more. In order to observe the rate of uptake in one single piece of taenia it was inserted into the muscle chamber and exposed to radioactive solution. At intervals of 10 min in one experiment, and of 30 min in another, the tissue was washed with inactive solution and its radioactivity was measured. Every

fourth reading of the first experiment is tabulated in Table 1 (Expt. 7). The results of the other experiment are shown in Fig. 1. The half-time of uptake was 55 min.

TABLE 1. Uptake of ^{42}K by taenia coli

No. and conditions of experiment	Period of soaking (min)	counts/min per mg
No. 1, 36° C, unweighted	20	408
	40	964
	80	1334
No. 2, 36° C, unweighted	15	108
	30	141
	60	316
	120	417
No. 3, 35° C, unweighted	30	403
	60	480
	90	684
	120	589
	150	858
	180	872
No. 4, 35° C, unweighted	30	307
	60	360
	90	590
	120	716
	150	876
	180	801
No. 5, 37° C, unweighted	120	357
	240	920
	360	966
	420	954
No. 6, 30° C, 5 g load	10	77
	20	242
	40	346
	80	470
No. 7, 37° C, intermittent soaking in muscle chamber, tension fluctuating from 2 to 5 g	40	*2727
	80	4249
	120	5062
	160	5866
	200	6470
	240	6481

* Direct muscle counts, not per mg weight.

The rate of loss of ^{42}K from taenia coli

A piece of taenia, which had previously been soaked in radioactive solution, was transferred to the muscle chamber and its radioactivity was measured at intervals while it was washed continuously by a steady stream of inactive solution. It was found that the rate of loss of ^{42}K decreased exponentially. In two such experiments the half time of loss was approximately 75 min (see inset of Fig. 2). However, the first count was too high to fall on the straight line shown. This suggested that in the first few minutes the rate of loss decreased more rapidly than later. Therefore the rate at which ^{42}K was lost from the taenia during the first 30 min was determined. The taenia in the chamber was bathed with radioactive solution for 5 min, and then with inactive solution. The radioactivity of the muscle was measured twice a minute for the first

10 min and then once every 2 min for the next 15 min. The result of such an experiment, plotted semilogarithmically, is shown in Fig. 2. During the first 2 min the decrease of radioactivity was very rapid. After the third min the decrease became much slower and exponential. This suggests that the radioactivity was lost from more than one source. The initial rapid loss was pre-

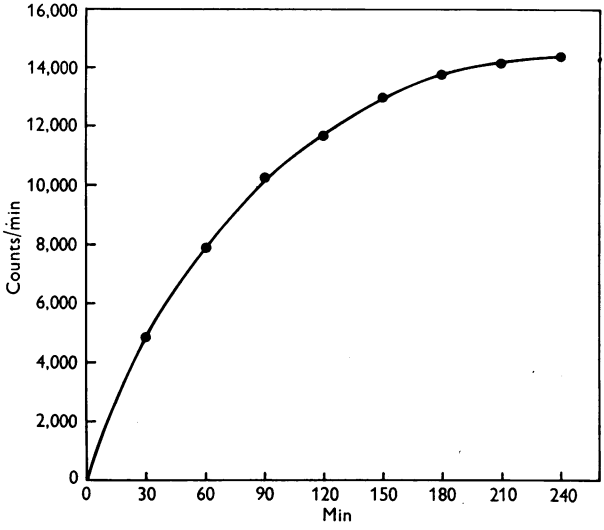

Fig. 1. Uptake of ^{42}K by taenia coli.

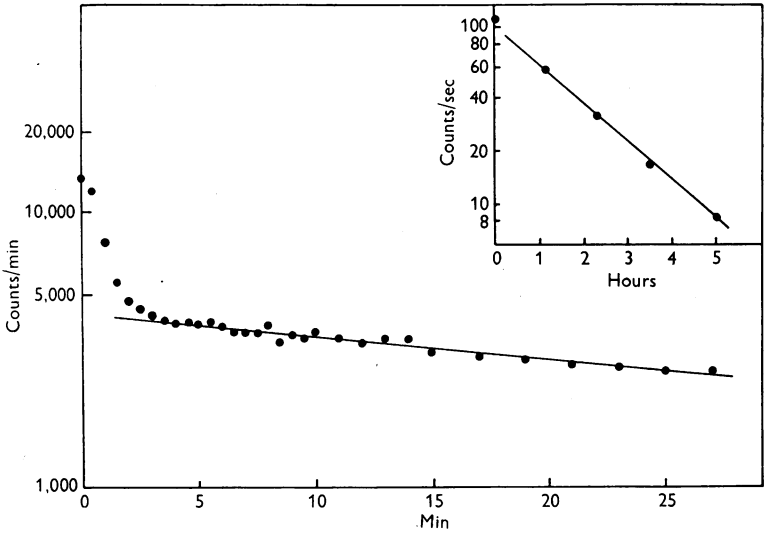

Fig. 2. Decrease in radioactivity of taenia, previously loaded with ^{42}K, during washing with inactive solution. Constant for rate of loss, $K = 1{\cdot}14$ hr.$^{-1}$. Inset: decrease in radioactivity in 5 hr. Period of soaking: main figure 5 min, inset 2 hr.

sumably from the channel and from the extracellular space. Control experiments showed that within 2 min after switching from radioactive to inactive solution, over 90% of the radioactivity was lost from the chamber when no muscle was present. The initial high count and the first part of the rapid loss was thus due to the contribution from the channel which was relatively great when the muscle had only been soaked for a short time, e.g. 5 min. The later, less rapid exponential loss represented ^{42}K coming from the muscle cells (Harris & Burn, 1949; Keynes, 1954). A period of 5 min washing with inactive solution was adopted throughout to remove extracellular potassium before measurements of radioactivity of the muscle were made.

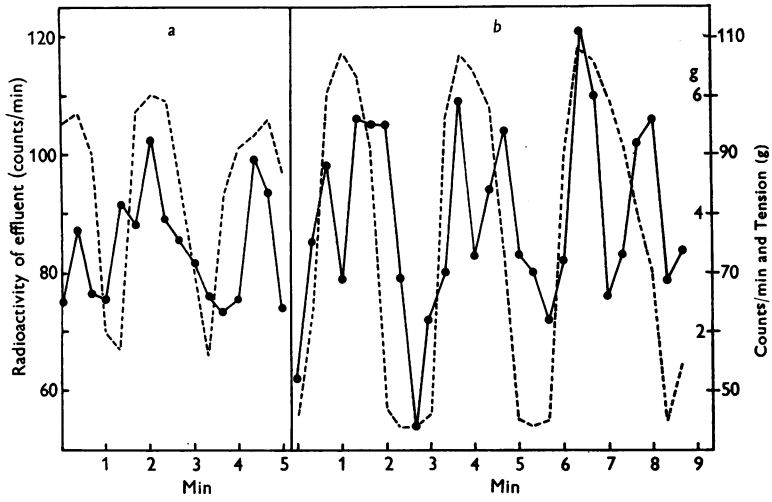

Fig. 3. Fluctuations of tension (broken line) and of radioactivity appearing in the washing solution (continuous line) of taenia coli during spontaneous activity: (*a*) before, (*b*) in the presence of atropine 2×10^{-6}.

The rate of loss of ^{42}K from taenia during spontaneous activity

In order to study changes in the loss of potassium in relation to changes in tension the radioactivity appearing in the washing solution was measured. A piece of taenia was inserted into the muscle chamber and bathed with radioactive solution. When the muscle had developed a vigorous spontaneous rhythm the radioactive solution was replaced by inactive solution and after 10 min washing the effluent was collected in equal consecutive samples every 20 sec. At the end of each collection the tension was noted. The duration of a full cycle of the spontaneous pendular rhythm was about 2 min. Thus a high resolution in the measurement of radioactivity was required over a short period. However, the rate of loss of K from the smooth muscle was such that small samples of washing fluid were sufficiently active to provide statistically significant results, when counted over long periods. In Fig. 3*a* the tension and

the radioactivity measured in the effluent have been plotted against time. The rate of loss of ^{42}K showed fluctuations which were synchronous with the fluctuations in tension which varied over a range of 4–6 g. The loss of ^{42}K was rapid during each rise in tension and slowed during relaxation. Four hours later the experiment was repeated with the same preparation in the presence of atropine in a concentration of 2×10^{-6} g/ml. which would eliminate the participation of parasympathetic nerves in causing the changes in tension. Fig. 3*b* shows that the variations in the loss of ^{42}K bore the same relation to the changes in tension as before.

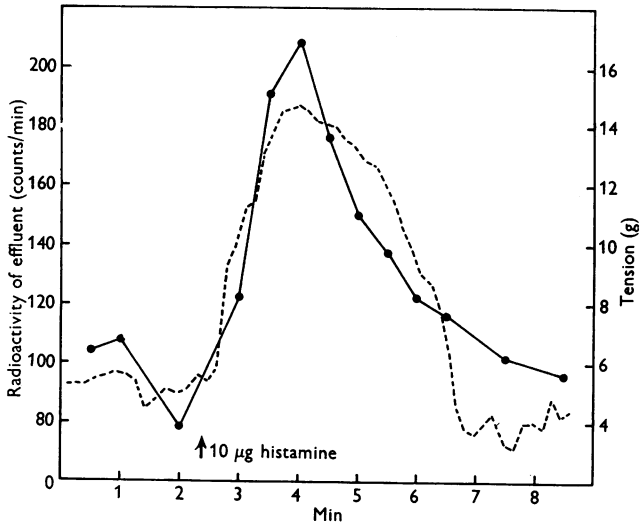

Fig. 4. Effect of histamine on tension (broken line) and on the loss of ^{42}K from taenia (continuous line).

The effect of histamine and acetylcholine on the rate of loss of ^{42}K from taenia

Both substances stimulate the taenia coli, and their effect on the rate of loss of potassium was studied by measuring the radioactivity appearing in the washing fluid. A piece of taenia previously soaked in radioactive solution was inserted into the muscle chamber and bathed with inactive solution. Equal samples of effluent were collected at frequent intervals. Histamine was slowly injected into the bathing fluid and the collection of samples was continued while its effect took place. The changes in the radioactivity of the effluent and the changes in tension produced by 10 μg histamine are shown in Fig. 4. As during spontaneous activity, the rate of loss of ^{42}K increased at the same time as the tension increased, and returned to the initial rate when the muscle relaxed.

The effect of acetylcholine was studied in the same way. It was found that the rate of loss of potassium from the muscle increased with the increasing

tension and returned with the falling tension to the initial rate. Fig. 5 shows the effect of three different doses, observed in the course of 40 min. The muscle exhibited no spontaneous activity in the beginning of the experiment but became active at the end. The areas beneath the records of the effects of acetylcholine on the tension and on the radioactivity were measured, and the inset shows the percentage changes as a function of the logarithm of the dose. Both responses increased with the dose.

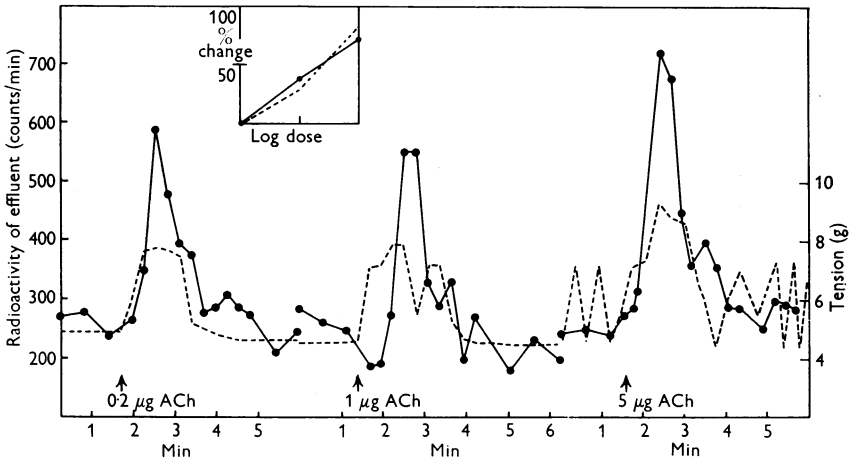

Fig. 5. Effect of three doses of acetylcholine on the tension (broken line) and on the loss of ^{42}K from taenia (radioactivity of effluent = continuous line). Inset shows percentage increase in area of both effects plotted in relation to the log of the dose.

The effect of adrenaline on the movement of ^{42}K

Since the rate of loss of potassium from the muscle was closely associated with increase in tension, it was surprising to find that relaxation in response to adrenaline was not accompanied by a diminution in the rate of loss. There was usually no change in the rate of loss of ^{42}K (Fig. 6*a*) and rarely a slight increase; the greatest observed is shown in Fig. 6*b*.

We then studied the effect of adrenaline on the uptake of ^{42}K. Pieces of taenia were suspended in radioactive solution with or without adrenaline. After incubation the muscles were washed, dissolved in nitric acid and their radioactivity was measured. The effect of adrenaline could thus be expressed as percentage of a control treated for the same length of time without adrenaline. The results of these experiments, set out in Table 2, show the following points:

(1) In thirteen out of twenty-four muscles adrenaline increased the uptake of ^{42}K. The maximum increase was 54%. In the other muscles adrenaline produced no statistically significant change.

(2) There appeared to be no correlation between the increase in uptake of ^{42}K and the concentration of adrenaline.

(3) The greatest increases were seen with short periods of incubation.

This last observation suggested that any immediate effect on the uptake which adrenaline had might have been masked by processes taking place afterwards. For instance, in vigorously oxygenated solution at 37° C adrenaline is oxidized and its effect on the muscle might have passed off.

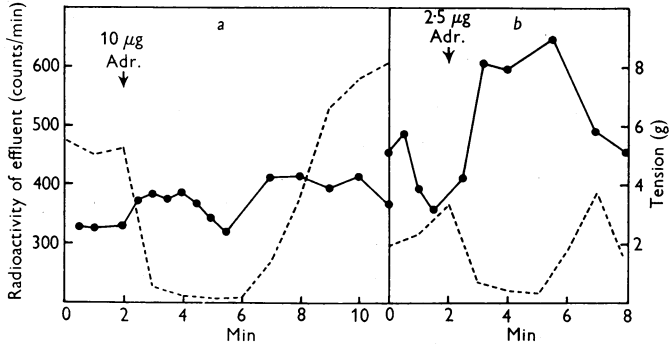

Fig. 6. Effect of adrenaline on tension (broken line) recorded from taenia, and on the loss of ^{42}K measured in the effluent (continuous line).

TABLE 2. The effect of adrenaline on the uptake of ^{42}K

No. of expt.	Conditions	Concentration of adrenaline	Time of incubation (min)	Radioactivity (% of control)
1	No load	1×10^{-5}	20	142
			40	95
			80	112
2	No load	2×10^{-5}	15	154
			30	126
			60	107
			120	99
3	Isometric, 5 g	2×10^{-6}	10	147
		4×10^{-6}	10	100
	Isotonic, 5 g	1×10^{-6}	10	134
		2×10^{-6}	10	117
		4×10^{-6}	10	102
4	Isometric, 5 g	1×10^{-7}	10	107
		5×10^{-7}	10	99
		$2{\cdot}5 \times 10^{-6}$	10	109
		5×10^{-6}	10	109
		1×10^{-5}	10	113
		2×10^{-5}	10	96
	Isotonic, 5 g	1×10^{-7}	10	102
		5×10^{-7}	10	107
		$2{\cdot}5 \times 10^{-6}$	10	104
		5×10^{-6}	10	123
		1×10^{-5}	10	123
		2×10^{-5}	10	127

Therefore another method was used. The taenia was placed in the muscle chamber and was loaded with ^{42}K until its radioactivity changed no further. Then the following cycle was adopted. The muscle was bathed for 5 min in radioactive solution alternating with 5 min in inactive solution to allow counting. Adrenaline was infused at a slow constant rate, starting simultaneously with the admission of radioactive solution. The adrenaline infusion was continued while the muscle was washed with inactive solution, and the radioactivity of the muscle was thus measured while it was still relaxed. Using this method the effect of adrenaline in enhancing the uptake of ^{42}K could be demonstrated regularly. If conditions had not been strictly isometric and the muscle had been allowed to lengthen, less tissue would have been exposed to the Geiger tube resulting in lower counts. The opposite was observed.

The changes in the radioactivity and the tension of the muscle are shown in Fig. 7*a*. During successive periods of bathing in radioactive solution the radioactivity increased steadily. When adrenaline was infused at the same time as the radioactive solution flowed, the muscle relaxed and the increase in radioactivity was greater. After the adrenaline inhibition, when the tension increased again, radioactivity was lost. Fig. 7*b* shows an experiment in which the radioactivity of the muscle had reached a steady state and changed very little during the control periods of soaking in radioactive solution. However, when, at the time of soaking, an adrenaline relaxation took place, the muscle took up more ^{42}K. The figure shows this effect three times.

The effects of histamine and acetylcholine on the uptake of ^{42}K

Using the same technique as that described in the preceding section the muscle was exposed to the radioactive solution in the absence and presence of histamine or acetylcholine. It was found that during the rise in tension there was a decrease in the radioactivity of the muscle; but when the muscle relaxed again the rate of uptake was increased above the initial rate. In the first experiment shown in Table 3 the muscle was repeatedly stimulated by histamine during the time in which it was bathed in radioactive solution. The muscle lost radioactivity each time, but during the recovery periods it gained more than it had lost. In the second experiment acetylcholine was used to stimulate the muscle. Two control periods were allowed between each activation, and it was found that the loss was balanced by the subsequent gain.

The balance of inward and outward movement

When a muscle, which was in a steady state of activity as well as in a steady state of potassium exchange, was relaxed by adrenaline its uptake of potassium increased. Since the earlier experiments had shown that the rate of loss usually remained unchanged, adrenaline appeared to produce a net gain of potassium. A similar net gain was observed when a muscle in a steady state was so

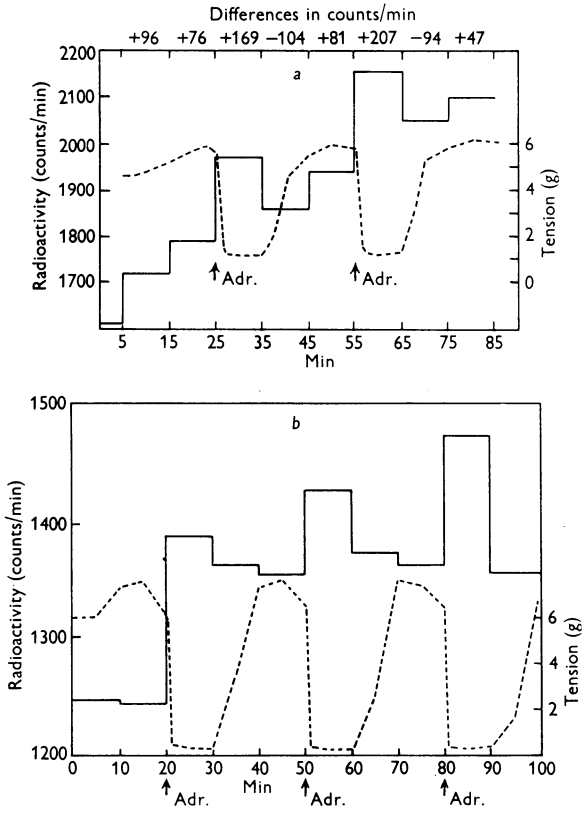

Fig. 7. Two experiments showing the effect of adrenaline 2×10^{-6} on the rate of uptake of ^{42}K by taenia coli. (*a*) Shows stepwise increase of radioactivity of muscle (continuous line) during successive periods of 5 min bathing in radioactive solution. During relaxation (tension = broken line) in response to adrenaline the uptake was greater. Actual differences in counting rate recorded on top. (*b*) Shows constant level of radioactivity during control periods and three increases in radioactivity brought about by adrenaline.

TABLE 3

Changes in radioactivity of the muscle (in counts per min, measured every 10 min) when it was soaked while it was repeatedly activated by

Histamine			Acetylcholine		
Concentration	Activated	At rest	Concentration	Activated	At rest
2×10^{-7}	−88		$1{\cdot}6 \times 10^{-6}$	−445	
		+286			+132
4×10^{-7}	−135				+305
		+296	4×10^{-7}	−270	
4×10^{-7}	−106				+287
		+308			+ 36
4×10^{-7}	−295				
		+238			
2×10^{-7}	−99				
		+208			
Total change	−723	+1336	Total change	−715	+760

frequently activated (e.g. by histamine, Table 3) that the gain during the relatively short period of recovery exceeded the loss. If, however, the interval between activation was longer, the imbalance disappeared; the greater loss of potassium during the period of activity was then about equal to the greater uptake during recovery, and thus the net result was a faster rate of exchange.

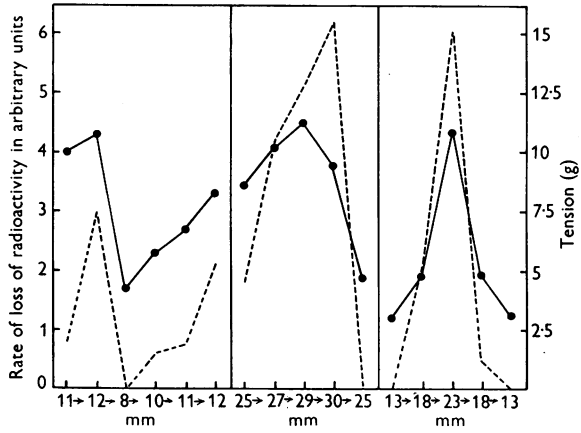

Fig. 8. The effect of stretching the taenia on tension (broken line) and on the rate of loss of ^{42}K (continuous line) as measured in the effluent. The abscissa shows the order and extent to which the length of the preparation was altered.

The effect of stretch upon the rate of loss of ^{42}K from taenia

It had previously been found (Bülbring, 1954, 1955) that stretching the taenia caused a fall in membrane potential, an increase in spike frequency and an increase of tension. To study the effect of stretch on the outward movement of potassium a piece of taenia previously loaded with ^{42}K was placed in the flow chamber and washed with inactive solution. The rate of loss of ^{42}K was determined by measuring the radioactivity of the effluent. In the experiments illustrated in Fig. 8 the length of the muscle was changed at 2 min intervals in (*a*) and at 1 min intervals in (*b*) and (*c*). The tension and the rate of loss of ^{42}K both increased together when the muscle was stretched. When it was allowed to resume its initial length and the tension decreased, the rate of loss of radioactive potassium also diminished.

DISCUSSION

The observations here recorded on the movements of potassium in the smooth muscle of the taenia coli of the guinea-pig are entirely qualitative. As far as the results can be compared, they are analogous to those obtained in the extensive studies on nerve and on striated muscle (for reviews see Hodgkin, 1951; Fleckenstein, 1955). The uptake of ^{42}K proceeds in a similar way to that which Creese (1954) found in the rat's diaphragm. When the taenia is exposed

to radioactive solution its radioactivity, like that of the diaphragm, increases rapidly at first, but becomes constant within 3–4 hr. When striated muscle is transferred from radioactive to non-radioactive solution, the rate of loss of ^{42}K shows an exponential decline (for frog muscle see Keynes, 1954). Smooth muscle under similar conditions also loses ^{42}K with an exponential decline, but the rate of loss fluctuates over short periods of time. In striated muscle there is a clear distinction between rest and activity, but in our experimental conditions the smooth muscle was in its physiological state of continuous spontaneous activity which fluctuated in degree. The periodic fluctuations in the rate of loss of potassium were found to be associated with the spontaneous pendular rhythm. There appeared to be a rapid succession of changes in the permeability of the membrane to potassium, periods of increased loss alternating with periods of increased uptake. This view is supported by the observation that the membrane potential and the frequency of discharge of spike potentials also undergo rapid fluctuations (Bülbring, 1955). The spontaneous activity of smooth muscle can be regarded as a steady state with brief, regular fluctuations in tension and in the movement of potassium. The rate of exchange is accelerated by stimulating the muscle to more activity. Fenn (1940) came to the conclusion that rhythmical activity assists the liberation of potassium, since incomplete tetanus liberates more potassium from striated muscle than a complete tetanus. He assumed that in heart muscle a steady state is reached in which the loss during contraction is just equal to the gain during recovery. In the turtle heart (O'Brien & Wilde, 1952) fluctuations in the rate of loss of potassium have been shown to coincide with the heart rhythm. During each systole there was a greater loss of potassium from the heart muscle than during diastole. Similarly, in smooth muscle there was a greater loss of potassium each time the tension increased during a cycle of spontaneous activity. The outward movement of potassium was also increased when the smooth muscle produced an increase in tension in response to histamine or to acetylcholine. Recently Lembeck & Strobach (1955) found that in pieces of the cat's small intestine, suspended in potassium-free solution, the loss of potassium was increased by acetylcholine (which caused contraction) but not by histamine (which in this tissue caused no contraction).

Evidence exists that in striated muscle during activity not only the efflux but also the influx of potassium is increased. In rat muscle Hahn & Hevesy (1941) and Noonan, Feng & Haege (1941) found a four- to five-fold increase in the rate of uptake of ^{42}K during exercise. This increased rate of exchange observed in striated muscle during intermittent activity may be compared with the increased rate of exchange occurring in smooth muscle when it is repeatedly activated by successive doses of histamine or acetylcholine.

The relaxation brought about by adrenaline was not associated with a detectable reduction in the rate of loss which remained either unchanged or

was slightly increased. This was surprising in view of the observation of Goffart & Perry (1951) that in mammalian striated muscle adrenaline caused first a decrease and then an increase in the rate of loss of ^{42}K. These authors did not study the action of adrenaline on the uptake. Fenn (1940) quotes the work of Sugimoto (1932), who showed that adrenaline increased the potassium content of the quadriceps muscle. Dresel & Wollheim (1924) found that in isolated loops of guinea-pig intestine adrenaline decreased the potassium content of the bath and increased that of the piece of intestine. However, their results were variable. We found that in the smooth muscle of the taenia the relaxation in response to adrenaline was accompanied by a greatly increased inward movement of potassium.

The demonstration of the effect of adrenaline presented a practical problem for the following reasons: on the one hand, when the muscle was soaked in radioactive solution the uptake at the beginning was very fast, and during this time increased inward movement of ^{42}K brought about by adrenaline was not clearly demonstrable. On the other hand, when the exchange of ^{42}K had reached a steady state the radioactivity of the muscle was high. Consequently, any changes brought about by adrenaline were necessarily small in proportion. Despite this the uptake of ^{42}K during a relaxation in the presence of adrenaline was clearly increased. It was followed by some loss of radioactivity when the muscle resumed its initial tension. Moreover, the relaxation which followed a rise in tension produced by histamine or acetylcholine was similarly associated with an increased inward movement of ^{42}K.

Our results suggest that adrenaline increases the rate of an active process (Hodgkin & Keynes, 1955) which pumps potassium back into muscle, thus accelerating a process which normally takes place during recovery from activity.

SUMMARY

1. The inward and outward movement of radioactive potassium (^{42}K) was studied in isolated intestinal smooth muscle preparations (taenia coli) of the guinea-pig.

2. The rate of uptake of ^{42}K decreased with time, half the final radioactivity being taken up within the first hour. After 3–4 hr a steady state was reached.

3. The rate of loss of ^{42}K was exponential with a half-time of 75 min.

4. During spontaneous rhythmic activity each increase in tension was associated with increased outward movement of ^{42}K.

5. Histamine and acetylcholine caused an increased rate of outward movement of ^{42}K, closely related to the increased tension. Stretching the muscle had the same effect.

6. Adrenaline did not reduce the outward movement, but increased the rate of inward movement of ^{42}K.

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