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OUABAIN-SENSITIVE THALLIUM FLUXES IN SMOOTH MUSCLE OF RABBIT UTERUS

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SUMMARY

1. Rabbit myometrium accumulates Tl in a time-dependent fashion and the majority of the uptake of Tl is ouabain-sensitive.

2. In normal chloride-containing media, the uptake of Tl, though ouabain-sensitive, is less than in chloride-free media and this difference is due to a greater ouabain-insensitive uptake.

3. The ouabain-insensitive uptake in normal chloride-containing media is reduced by furosemide and furosemide also reduces total uptake in this solution. In chloride-free media, however, furosemide is without effect on total or ouabain-sensitive uptake.

4. In chloride-free media, the uptake of Tl against Tl concentration is sigmoidal, suggesting that more than one Tl ion is being transported at a time.

5. Tl was capable of substituting for K in electrogenic Na pumping; it was approximately twice as effective as K and the inhibitory effect of Tl was blocked by ouabain.

6. Tl efflux can be explained by a simple two-compartment model in both normal and chloride-free solutions.

7. The uptake of Tl was inhibited by alkali cations with the order of potency being $Tl^+ > K^+ > Rb^+ > Cs^+$ at 10 mM and $Tl^+ > K^+ = Rb^+ > Cs^+$ at 5 mM ion concentrations.

8. It is concluded that Tl enters the smooth muscle of rabbit uterus by diffusion, active ouabain-sensitive transport and active chloride- and furosemide-sensitive transport.

INTRODUCTION

Thallous ions have been shown to be able to substitute for K ions in the activation of (Na^+–K^+) ATPase of rabbit kidney (Britten & Blank, 1968) and in K^+-activated phosphatase from brain (Inturrisi, 1969) as well as in other K^+ requiring enzymes. Rapid Tl fluxes have been reported in squid axon (Lansdowne, 1969), skeletal muscle (Mullins & Moore, 1960), mammalian red blood cells (Cavieres & Ellory, 1974) and in ascites cells (Bakker-Grunwald, 1979). In the squid axon, red blood cells and ascite cells, the uptake of Tl has been shown to be inhibited by ouabain at concentrations known to inhibit the Na–K pump. The affinity of the pump for Tl has

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been shown to be 3 times that for K in red blood cells and squid axon (Cavieres & Ellory, 1974; Lansdowne, 1975) and 9 times that of Rb in ascites cells (Bakker-Grunwald, 1979). Tl uptake has also been used as an indicator of membrane potential in bacteria (Bakker, 1978) although this method has been recently criticized (Damper, Epstein, Rossen & Sorensen, 1979). It was therefore decided to investigate the fluxes of Tl in the rabbit myometrium and the effect of Tl on electrogenic Na pumping in this tissue.

METHODS

Preparation of tissue

Oestrous female rabbits (3·5 kg average body weight) were killed by cervical dislocation. Their uteri were removed into either chloride-free or normal Krebs–Henseleit-type solution. Any connective tissue or fat was removed from the tissue by careful dissection and the tissues then cut into 10–30 mg portions. All tissues were then preincubated for 1 hr at 37 °C in either chloride-free or normal Krebs–Henseleit-type solution.

Uptake experiments

After the 1 hr preincubation at 37 °C, tissues were transferred to 5 ml. loading solution with or without ouabain for 15 min before $^{204}Tl_2SO_4$ (final concentration 1 μc/1·47 $\times$ 10^{-9} mole/ml.) was added. At the end of the appropriate time, tissues were removed, blotted lightly and weighed. Tissues were dissolved by adding 1 ml. Beckman Tissue Solubilizer (BTS 450) and heating to 37 °C overnight. The solubilized tissue was incorporated into 10 ml. of scintillation cocktail (Beckman Ready-Solv NA) and counted in a liquid scintillation counter (Beckman LS 330) with window settings of 3·0–8·0. Preliminary experiments showed that the size of the tissue did not affect the counting efficiency which was 94·6 $\pm$ 0·2% (n = 12). Samples of the loading solution (50 μl.) were treated in exactly the same way as the tissue samples so as to be sure the counting efficiency remained constant. In experiments where differing concentrations of Tl^+, K^+, Rb^+ and Cs^+ were used, the tissues were incubated in these solutions throughout the experiments. In experiments involving furosemide, the drug was present only during the 15 min period before loading and the loading period itself.

Efflux experiments

After the 1 hr pre-incubation in either normal or chloride-free Krebs, tissues were incubated in 5 ml. loading solution either with or without ouabain (10^{-4} M) for 15 min before $^{204}Tl_2SO_4$ was added (final concentration 1 μc/1·47 $\times$ 10^{-9} mole/ml.). Tissues were then loaded in this solution for 1 hr before being transferred sequentially through a total of twenty-three tubes containing 3 ml. solution of the same composition as the loading media for 1 hr. At the end of this time, tissues were removed, blotted, weighed, dissolved in tissue solubilizer (BTS 450), and incorporated into liquid scintillation fluid (Beckman Ready-Solv NA). The efflux solution (2 ml.) was incorporated into a second scintillation fluid (Beckman Ready-Solv HP) and counted. The 2 ml. fluid had no effect on the efficiency of counting, which in preliminary experiments was shown to be 94·6 $\pm$ 0·2% (n = 12).

Recording mechanical activity

After being removed from the animal, tissues (30–60 mg wet wt.) were set up vertically in isolated organ baths. The solution in the organ baths (chloride-free Krebs–Henseleit-type solution) was continuously changed by overflow at the rate of 2 ml./min. The tissues were set up at a resting tension of 1 g and the tension monitored by isometric force displacement transducers (Stathum type UC3) and displayed on a dynograph (Beckman type R611). After 1 hr the solution bathing the tissue was changed to a chloride- and K-free Krebs–Henseleit-type solution where the tissue remained for 1 hr. Responses to added K and $TlNO_3$ were then investigated in the presence and absence of ouabain (10^{-4} M) in each tissue. Tissues from six animals were investigated.

Solutions

The composition of the normal Krebs–Henseleit-type solution was (mM): NaCl, 116; KCl, 5·4; Na H_2PO_4, 1·2; $CaCl_2$, 2·5; Mg_2SO_4, 1·2; $NaHCO_3$, 22·0; D-glucose, 11·2. K-free Krebs was prepared by iso-osmotically replacing KCl with sucrose. High-K Krebs was prepared by replacing all the Na salts with an equivalent amount of the appropriate K salt. The composition of the chloride-free Krebs–Henseleit-type solution was (mM): $NaNO_3$, 116; KNO_3, 5·4; NaH_2PO_4, 1·2; $Ca(NO_3)_2$, 2·5; $Mg(NO_3)_2$, 1·2; $NaHCO_3$, 22·0, D-glucose, 11·2. Both these solutions, when equilibrated with 95% O_2:5% CO_2 gas mixture, had a pH of 7·4. K-free, chloride-free solution was prepared by replacing the K salt iso-osmotically with sucrose. In experiments where differing concentrations of Tl^+, K^+, Rb^+ and Cs^+ were used, the difference between normal (5·4 mM) and the concentrations used was compensated by removal or addition of $NaNO_3$.

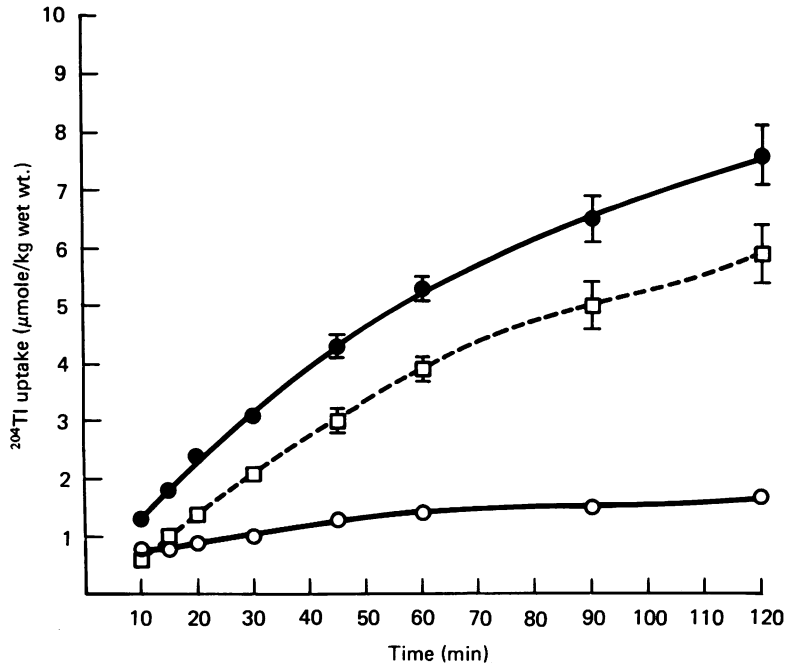

Fig. 1. The uptake of ^{204}Tl as a function of time in the rabbit myometrium in chloride-free Krebs in the presence (○—○) and absence (●—●) of 10^{-4} M-ouabain. Values shown are the mean of twelve experiments on six animals. The standard error is shown when larger than symbols. Also on this graph is shown the ouabain-sensitive uptake of ^{204}Tl (□—□). The vertical bars show the standard error of the mean difference.

Mathematical analysis of data

In the uptake experiments the thallium uptake was expressed as μmole uptake/kg wet wt. of tissue after compensation for quenching. The efflux curves were calculated by back addition of the amount left in the tissue at the end of the efflux period and the amount lost. The efflux coefficient was calculated by dividing the amount of ^{204}Tl lost per unit time by the average content of Tl in the tissue during that efflux period. All experiments were performed in duplicate and at least twelve values from six animals used. The values quoted are the mean ± S.E. of the mean of the indicated numbers of tissues from at least six animals. Statistical significance was determined by the Student's *t* test for direct comparison or the Student Neuman Kuells test for multiple comparisons; *P* values less than 0·05 were considered significantly different.

RESULTS

Uptake of Tl with time

Uptake of Tl at different times of incubation in chloride-free solutions is shown in Fig. 1. It can be seen that the total uptake curve is inhibited by 10^{-4} M-ouabain. In normal (chloride-containing solution), however, although the total ^{204}Tl uptake (Fig. 2) is similar to uptake in chloride-free solution, the ouabain-insensitive and ouabain-sensitive components of uptake are quite different. As can be seen, the ouabain-insensitive components of uptake are much greater than in chloride-free solution.

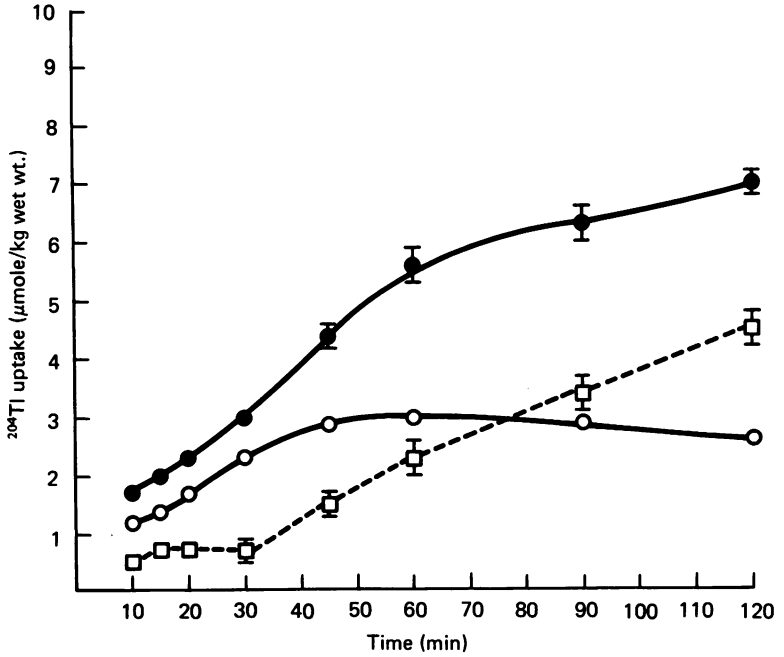

Fig. 2. The uptake of ^{204}Tl as a function of time in the rabbit myometrium in normal Krebs in the presence (○—○) and absence (●—●) of ouabain. Values shown are the mean of twenty-four experiments on twelve animals. The standard error is shown when larger than the symbol. Also on this Figure is shown the ouabain-sensitive uptake of ^{204}Tl (□—□). The vertical bar represents the standard error of the mean difference.

Effect of ouabain on Tl uptake

The effect of differing concentrations of ouabain on the 30 min uptake of ^{204}Tl is shown in Fig. 3. It can be seen that with concentrations of ouabain above 10^{-5} M, no further reduction in Tl uptake occurs in either normal or chloride-free solutions. The subsequent experiments were performed using 10^{-4} M-ouabain to demonstrate ouabain-sensitive uptake in both normal and chloride-free Krebs–Henseleit-type solution. The inhibition of Tl uptake by ouabain is similar to the inhibition of K^+ uptake by ouabain in taenia coli (Brading & Widdicombe, 1974).

The effect of Tl on ^{204}Tl uptake

The effect of differing concentrations of Tl on the 20 min uptake of Tl is shown in Fig. 4*A* and the ouabain-sensitive uptake is shown in Fig. 4*B*. As would be expected,

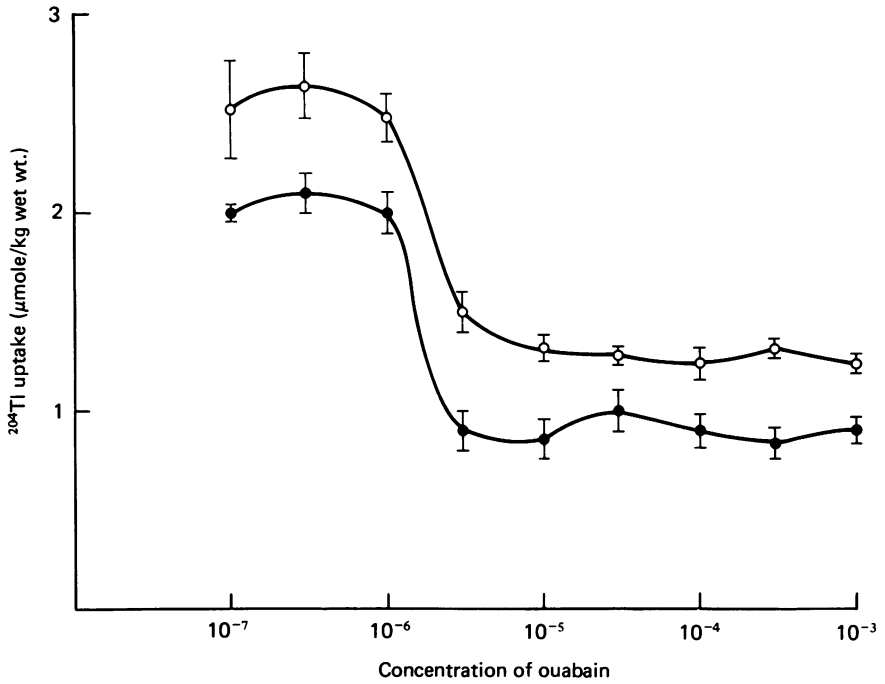

Fig. 3. The 20 min uptake of ^{204}Tl in the rabbit myometrium in chloride-free (●—●) and normal (○—○) Krebs at different ouabain concentrations. The values shown are the mean of twelve experiments on six animals. The vertical bars show the standard error of the mean.

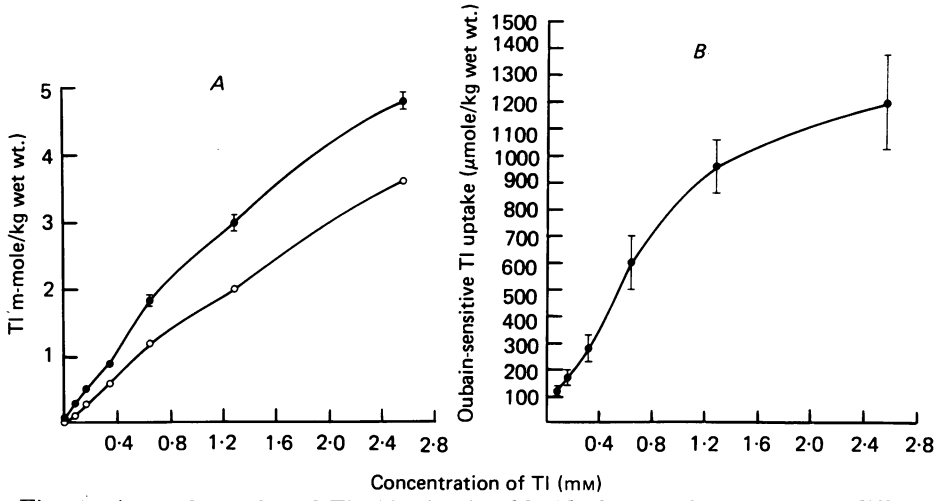

Fig. 4. *A*, total uptake of Tl (20 min) in chloride-free Krebs solution at differing external Tl concentrations in the presence (○—○) and absence (●—●) of 10^{-4} M-ouabain. The values shown are the mean of at least twelve tissues from six animals. Standard error of the mean is shownwhen larger than the symbols. *B*, ouabain-sensitive uptake of Tl (20 min) in chloride-free Krebs solution. The values shown are the mean ± standard error of the mean of twelve observations in six animals.

if thallium were entering the tissue by diffusion, the uptake of Tl in the presence of ouabain was linear. The ouabain-sensitive uptake, however, is sigmoidal, which in other systems has been taken as evidence that more than one Tl ion is being transported by the pump.

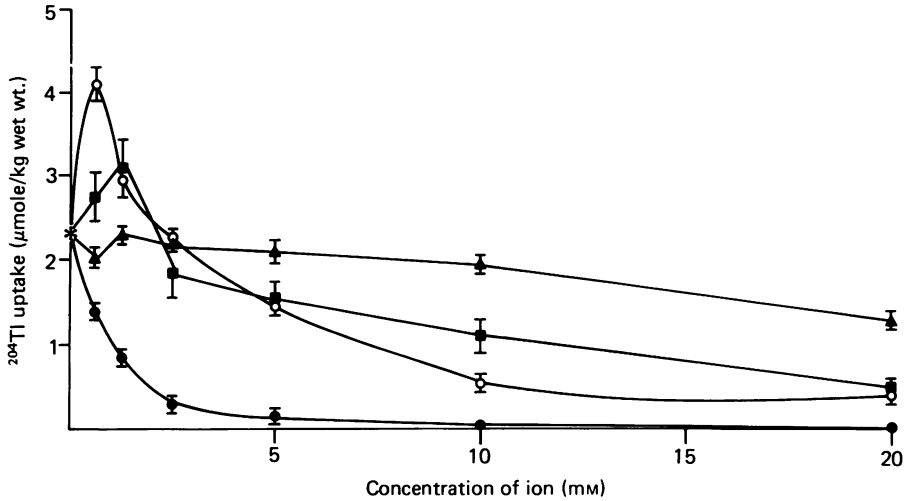

Fig. 5. The effects of different ions on the 20 min ouabain-sensitive uptake of ^{204}Tl by rabbit myometrium in chloride-free Krebs solution. K (○—○), Tl (●—●), Rb (■—■) and Cs (▲—▲). The value shown (*) is the uptake in the absence of all the ions mentioned and is the mean value of thirty-five experiments from eighteen animals. Other values are the mean ± standard error of twelve values from six animals.

The effect of alkali cations on ^{204}Tl uptake

The effects of Tl^+, K^+, Rb^+ and Cs^+ on the uptake of ^{204}Tl were investigated. The results are shown in Fig. 5. It can be seen that the inhibition of the ouabain-sensitive ^{204}Tl uptake by these cations was in the order of $Tl^+ > K^+ = Rb^+ > Cs^+$ at 5 mM, which is similar to the order in which alkali cations inhibit ^{42}K uptake in the taenia coli (Widdicombe, 1977). In these experiments the tonicity was maintained in the solution by adjusting the sodium concentration. K and Rb at low concentrations tend to stimulate the uptake of Tl compared to K-free Krebs solution, but it can be seen that at 10 mM concentration, the order of potency for the different ions is $Tl^+ > K^+ > Rb^+ > Cs^+$ and the approximate concentration producing 50% inhibition of the K-free value was Tl, 0·09 mM; K, 6·8 mM; Rb, 9·6 mM; and Cs, 22·5 mM.

The effect of Tl on mechanical activity

Exposure of the rabbit myometrium to K-free solution increases spontaneous activity, presumably by inhibition of the Na–K pump. Readdition of K then produces an inhibition of spontaneous activity which is prevented by ouabain, suggesting that the extracellular K causes a hyperpolarization of the smooth muscle due to activation of the electrogenic Na–K pump (Johns & Paton, 1974). In the rabbit myometrium bathed in K and chloride-free Krebs–Henseleit-type solution, both K and

Tl produced inhibition of spontaneous contractility. A typical trace from such an experiment is shown in Fig. 6. The inhibition by Tl occurred at a lower concentration than K, suggesting that, in this system, Tl is about twice as potent as K in turning on the electrogenic pump. The inhibitory effect of Tl on electrogenic pumping was completely inhibited by exposure of the tissue to 10^{-4} M-ouabain. The inhibitory effect of Tl is therefore similar to K, Rb and Cs in rabbit myometrium (Johns & Paton, 1974) and the order for electrogenic Na pumping is $Tl^+ > K^+ = Rb^+ > Cs^+$ as it is for Tl uptake.

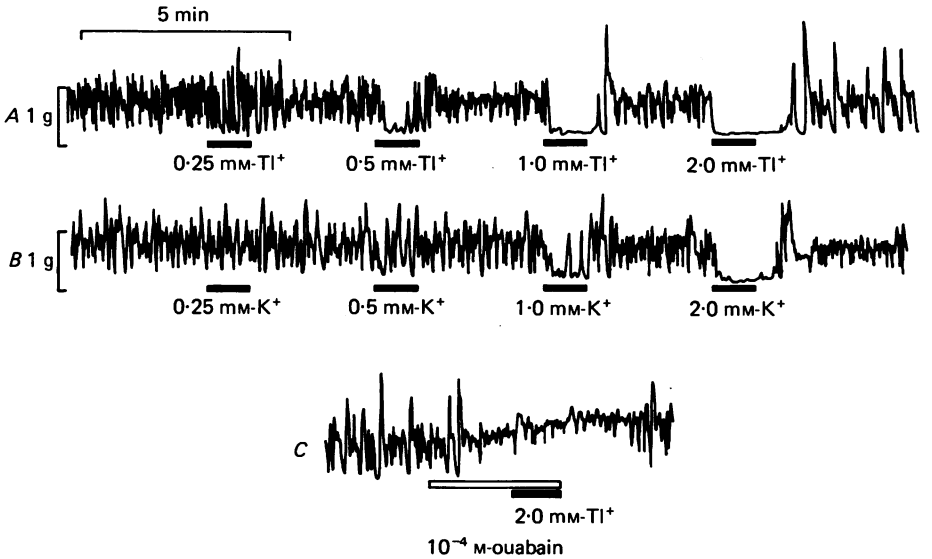

Fig. 6. The effects of addition of differing concentration of Tl (*A*) and K (*B*) on the mechanical activity of rabbit uterus bathed in chloride-free, K-free Krebs solution. Trace *C* shows the effect of 2 mM-Tl nitrate on the mechanical activity in the presence of 10^{-4} M-ouabain.

Efflux of ^{204}Tl

The efflux of ^{204}Tl from tissues loaded for 1 hr in either normal Krebs or normal Krebs + ouabain (10^{-4} M) is shown in Fig. 7. The efflux can be divided into two exponential functions in both these efflux curves with the one-half times for exchange of each component shown in Table 1.

The half-time for exchange in normal Krebs solution is faster than that for K^+ or Rb^+ fluxes in rat uterus (Hodgson & Daniel, 1972) and, since efflux of Rb is slower than that of K, it should be expected that Tl^+ efflux would be faster than K^+ efflux.

The efflux of ^{204}Tl from tissues loaded in chloride-free Krebs ± oubain (10^{-4} M) is shown in Fig. 8. Again, the efflux can be divided into two exponential functions with the half-times shown in Table 1.

From this data it would seem that the efflux of Tl into normal Krebs solution is faster than the efflux into chloride-free solution. Casteels (1970) showed that, when chloride was replaced by nitrate, efflux of K^+ increased. Since the experiments by Casteels were performed in a different manner and in a different tissue, it is not possible to draw any conclusions on the meaning of this change in permeability.

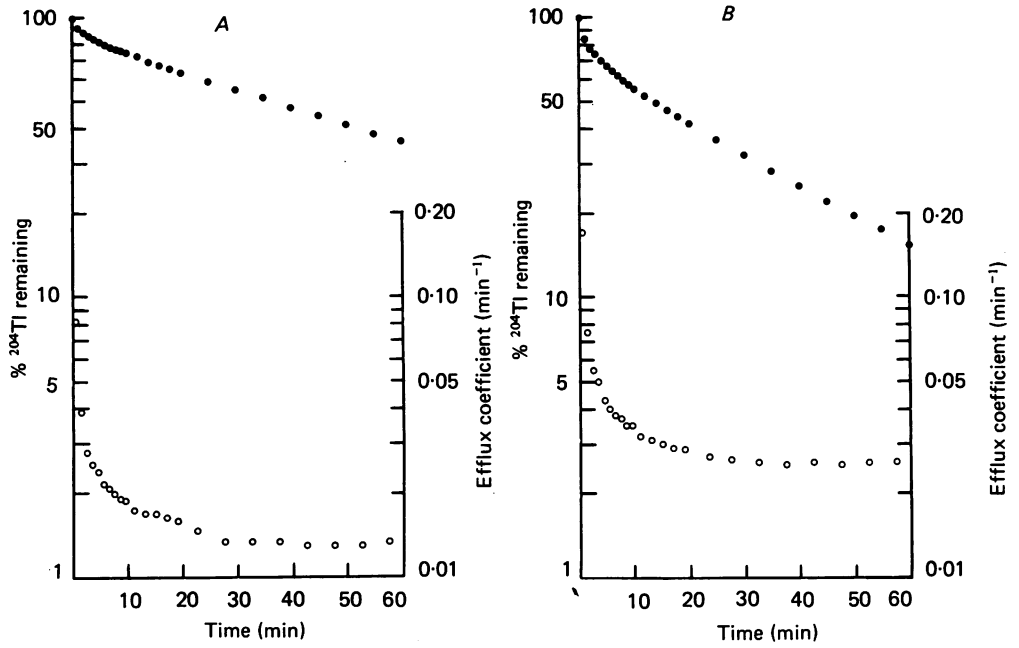

Fig. 7. *A*, the efflux of ^{204}Tl from rabbit myometrium loaded and effluxed into normal Krebs. The points shown are the mean percent of ^{204}Tl remaining in tissue (●) and efflux coefficients (○) of eleven experiments. Standard errors of the means are smaller than the symbols. *B*, the efflux of ^{204}Tl from rabbit myometrium loaded and effluxed into normal Krebs containing 10^{-4} M-ouabain. The points shown are the mean percent of ^{204}Tl remaining in tissue (●) and efflux coefficients (○) of eight experiments. Standard errors of means are smaller than symbols.

The effects of furosemide on ^{204}Tl uptake

The ouabain-insensitive uptake of thallium in normal chloride-containing solutions has been shown to be greater than in chloride-containing solutions. The chloride-sensitive, ouabain-insensitive Tl influx is greatly inhibited by 10^{-3} M-furosemide (Fig. 9*A*). Only in chloride-containing solution does furosemide inhibit the uptake of Tl by the smooth muscle. In normal chloride-containing solution, furosemide inhibits Tl uptake by $26{\cdot}9 \pm 2{\cdot}3\%$ ($n = 12$) and inhibits the ouabain-insensitive uptake by $50{\cdot}5 \pm 1{\cdot}6\%$ ($n = 12$). Ouabain alone inhibits uptake at $26{\cdot}9 \pm 2{\cdot}3\%$ ($n = 12$). In chloride-free Krebs solution, ouabain alone inhibits by $67{\cdot}2 \pm 3{\cdot}1\%$ ($n = 12$) and this compares to $63{\cdot}7 \pm 2{\cdot}3\%$ ($n = 12$) inhibition by ouabain and furosemide in normal chloride-containing solution.

Fig. 9*B* shows the effects of ouabain and ouabain + furosemide on the uptake of Tl both in high-K Krebs and in K-free Krebs. It can be seen that in the high-K solution there is no ouabain-sensitive uptake and furosemide has no significant effect on the uptake of Tl. In K-free solution, however, both ouabain and ouabain + furosemide inhibit the uptake of Tl. Ouabain alone inhibits Tl uptake by $52{\cdot}6 \pm 2{\cdot}6\%$ ($n = 12$) and furosemide inhibits ouabain-insensitive Tl uptake by $57{\cdot}0 \pm 5{\cdot}7\%$ ($n = 12$).

DISCUSSION

Thallous ion has a crystal radius (0·144 nm) which lies between that of the K ion (0·133 nm) and the Rb ion (0·148 nm). Tl has been shown to behave like K at the level of the Na–K pump and in the passive leak processes in the red blood cell (Skulskii, Manninen & Järnefelt, 1978), in squid axon (Lansdowne, 1975), in frog nerve (Hille, 1973) and in ascite tumour cells (Bakker-Grunwald, 1979). In smooth muscle, Tl is

TABLE 1. The half-times for the loss of ^{204}Tl from rabbit myometrium in the different solutions shown. The values shown are the mean ± standard error of the mean of the number of animals shown in parentheses. The fastest exchanging compartment is designated compartment I and the slowest, compartment II

	Half-times for ^{204}Tl efflux (min)	
	Compartment I	Compartment II
Norm Krebs	2·1 min ± 0·1 (11)	49·05 ± 2·3 (11)
Normal Krebs + ouabain	2·0 min ± 0·1 (10)	26·85 ± 1·5 (10)
Chloride-free Krebs	2·2 min ± 0·2 (8)	64·25 ± 5·0 (8)
Chloride-free Krebs + ouabain	2·0 min ± 0·2 (9)	32·39 ± 4·5 (9)

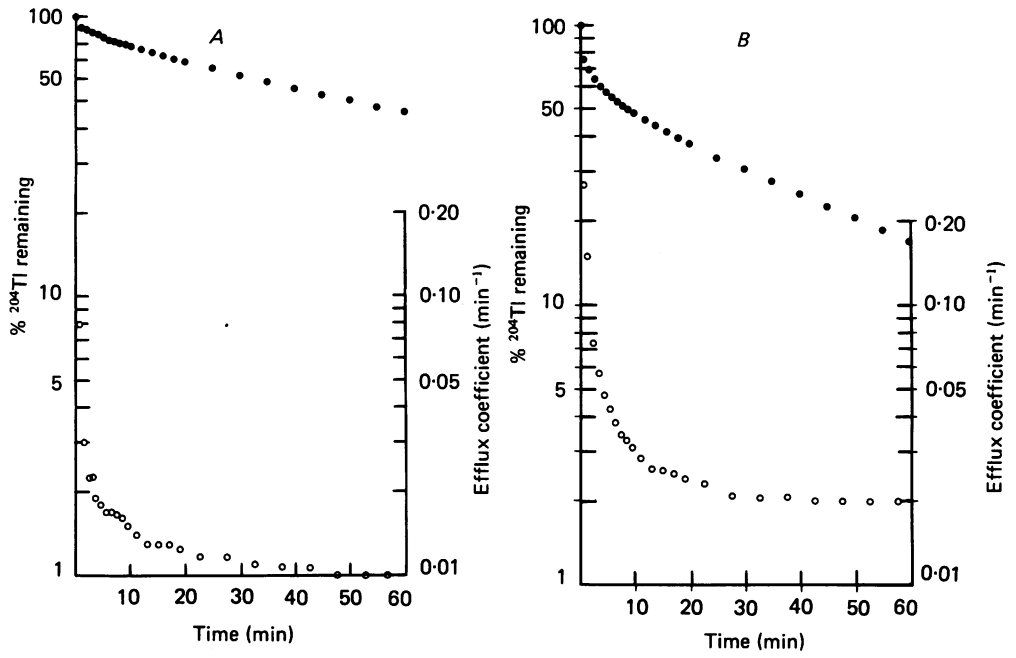

Fig. 8. *A*, the efflux of ^{204}Tl from rabbit myometrium loaded and effluxed for 1 hr in chloride-free Krebs. The points shown are the mean percent of ^{204}Tl remaining in tissue (●) and efflux coefficients (○) of eight experiments. Standard errors of means are smaller than symbols. *B*, the efflux of ^{204}Tl from rabbit myometrium loaded and effluxed into chloride-free Krebs + 10^{-4} M-ouabain. The points shown are the mean percent of ^{204}Tl remaining in tissue (●) and efflux coefficients (○) of nine experiments. Standard errors of the means are smaller than the symbols.

transported in a fashion similar to K in that it is concentrated over twofold by 30 min in both chloride-free and normal (chloride-containing) solution. In the presence of ouabain, however, transport of Tl is greatly inhibited and the concentration of ouabain necessary to inhibit transport maximally is similar to that for inhibition of K accumulation in the taenia coli (Brading & Widdicombe, 1974).

In all the experiments reported here, it is unlikely that Tl on its own had any

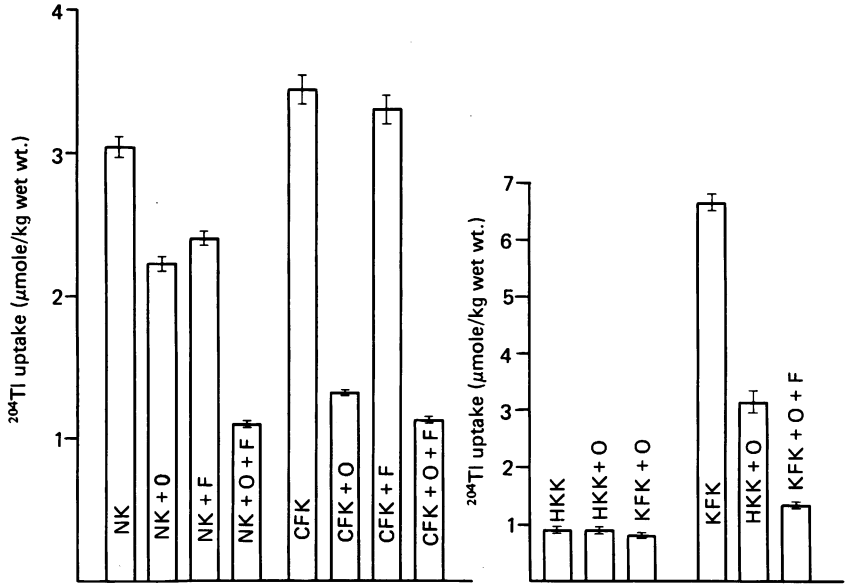

Fig. 9. The effect of 10^{-4} M-ouabain (+ O) 10^{-3} M-furosemide (+ F) and 10^{-4} M-ouabain + 10^{-3} M-furosemide (+ O + F) on the 45 min uptake of ^{204}Tl by rabbit myometrium in normal chloride-containing Krebs Henseleit (NK), chloride-free Krebs Henseleit (CFK), high K Krebs Henseleit (HKK) and K-free Krebs (KFK). The values shown are the mean of twelve experiments from six animals. The vertical bar represents the standard error of the mean.

stimulatory effects on the Na–K pump. Cavieres & Ellory (1974) showed that Tl could stimulate the Na–K pump only in solutions where the external K was below 0·1 mM. Widdicombe (1977) also showed alkali cation able to stimulate the uptake of $^{42}K^+$ when extracellular K was below 0·2 mM. In all the experiments reported (with the exception of the effect of alkali cations on ^{204}Tl uptake), the extracellular K concentration was 5·4 mM so stimulation of the Na–K pump is unlikely.

The ouabain-sensitive uptake of Tl provides a measure of the normal activity of the Na–K pump in normal tissue. In chloride-free solution, however, the ouabain-sensitive uptake of Tl is greater than in chloride-containing solution. This difference is due to a greater ouabain-insensitive uptake of Tl which is against a concentration gradient and is chloride-dependent. Similar findings have been reported in squid axon and in ascite tumour cells (Lansdowne, 1975; Bakker-Grunwald, 1979). This ouabain-insensitive, chloride-sensitive uptake is completely inhibited by furosemide in smooth muscle and in ascites cells (Bakker-Grunwald, 1979). Bakker-Grunwald (1979) suggested that, in the ascites cell, this represented Tl–K exchange. In smooth

muscle, Brading (1975) showed that Na–Na exchange was inhibited by a similar compound, ethacrynic acid. The ouabain-insensitive, chloride-sensitive uptake of Tl could, therefore, be due to this exchange pump, since both systems are inhibited by the same compound. Lansdowne (1975) suggested that, in chloride solution, only $\simeq 30\%$ of the Tl would be in the form of thallous ions and that the non-charged ion pair of thallous chloride could enter the cell on some form of carrier.

The furosemide-sensitive Tl uptake is unlikely to be due to Tl–K exchange as suggested by Bakker-Grunwald (1979) since, in high-K Krebs solution where the tissue after 1 hr would have virtually no intracellular Na, there is no furosemide-sensitive Tl uptake. In tissue bathed in K-free Krebs for 1 hr the furosemide-sensitive uptake is increased, as would be the intracellular Na concentration. The furosemide-insensitive uptake therefore is inhibited by absence of chloride and by absence of intracellular Na.

In chloride-free solution the ouabain sensitive uptake of Tl against Tl concentration shows a sigmoidal relationship, suggesting that more than one Tl ion is transported at a time. This sigmoidal relationship is similar to that reported for the uptake of K^+ and Rb^+ by the smooth muscle of the taenia coli (Widdicombe, 1977).

The ouabain-sensitive uptake of ^{204}Tl in chloride-free solution is inhibited by Tl and by K, Rb and Cs. In these experiments the K concentration of the loading media was 0·0 mM so it is to be expected that some stimulation of the pump could have occurred at low ion concentrations. At 5 mM ion concentration, however, there was no stimulation of Tl uptake, which suggests that at this concentration, Tl does not stimulate the Na–K pump. The order of potency of the inhibition of ^{204}Tl ouabain-sensitive uptake is $Tl^+ > K^+ > Rb^+ > Cs^+$ which is the same order of potency as these cations inhibit $^{42}K^+$ uptake in the smooth muscle of the taenia coli (Widdicombe, 1974).

Efflux of Tl from the myometrium is a simple two exponential process with a half-time for the slower component of $49{\cdot}05 \pm 2{\cdot}3$ min ($n = 11$). The efflux of Tl from smooth muscle is therefore faster than the efflux of K from the taenia coli (Casteels, 1970, 1971) and the efflux of K and Rb from the rat myometrium (Hodgson & Daniel, 1972). The order for the efflux of these different ions is therefore $Tl^+ > K^+ > Rb^+$. In chloride-free media, the efflux of Tl from the myometrium is decreased, the slower component having a half-time of $64{\cdot}25 \pm 5$ min ($n = 8$); this decrease in efflux is significantly different ($P < 0{\cdot}001$). The average efflux coefficient in chloride-containing solution decreased from 0·0133 min^{-1} to 0·0108 min^{-1} in chloride-free solution. The efflux of Tl therefore differs considerably from the efflux of K described in the taenia coli by Casteels (1970, 1971). Casteels (1970) showed that replacement of chloride with nitrate led to an increase in K efflux in normal solutions and a more dramatic increase in K-free solutions (Casteels, 1971). The opposite result obtained with Tl is difficult to interpret. It could be due to the longer exposure of the tissues to chloride-free solution in the Tl experiments causing a depolarization of the cell membrane; however, Csapo & Kuriyama (1963) have shown that hyperpolarization seen in myometrium bathed in nitrate solutions persists for long periods of time. The effect of chloride-free solution on Tl efflux was, however, not significantly different in the experiments where efflux was followed in the presence of ouabain, suggesting that the chloride-induced changes in Tl efflux are linked to the Na–K

pump. The decrease in Tl efflux in chloride-free solutions could be related to the greater activity of the Na–K pump in chloride-free solution, reducing efflux by recapture of the Tl leaving the cells.

Tl is also capable of substituting for K in electrogenic Na pumping in the rabbit myometrium. Johns & Paton (1974) showed that, when rabbit myometrium was bathed in K-free Krebs solution, addition of K, Rb and Cs led to an inhibition of spontaneous activity which was blocked by ouabain and, at high ion concentrations, reversed into a contractile response. In the experiments reported here, Tl was shown also to cause inhibition of spontaneous contractility in tissues bathed in K-free, chloride-free solution. Tl was also shown to be about twice as effective as K in this system. These responses were blocked by ouabain and would suggest that Tl can substitute for K in turning on the electrogenic Na pump.

All the evidence presented supports the view that Tl is actively transported into smooth muscle cells against a concentration gradient by two processes. One process, which is chloride-insensitive, is inhibited by ouabain and shows all the ion selectivity of the Na–K pump. This system shows a greater affinity for Tl than for K. The other process for Tl uptake is chloride-sensitive, is dependent on intracellular Na and is inhibited by furosemide. The importance of this uptake system, however, is not known at present.

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