Studies on the crystalline lens

XVIII. Kinetics of thallium (Tl^+) transport in relation to that of the alkali metal cations

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^{204}Tl accumulates rapidly in cultured rabbit lenses reaching concentration levels greatly in excess of those present in the bathing media, thus suggesting that it enters the lens by active transport. The parameters describing kinetics of thallium transport were evaluated by fitting theoretical curves to experimental data showing the movement of ^{204}Tl into and out of cultured rabbit lenses in the presence of various concentrations of nonlabeled thallium. Curves were calculated on the assumption that movement occurs in accordance with a theoretical model of a pump-leak system which states that active transport into the lens involves a carrier-mediated system and passive transport dependent on diffusional flux along both electrical and chemical gradients. Values of Km and Vmax for the carrier system are 0.15 mM and 0.375 μmoles per hour per lens, respectively. The coefficient for active transport Kp, for the pump, under physiologic conditions, is 2.25 hours^{-1} and for the leak Kd, 0.105 hour^{-1}, both about three times that for potassium. Theoretical curves calculated from the aforementioned transfer coefficients for thallium, and found previously for potassium, rubidium, and cesium, adequately describe both inhibition of ^{204}Tl transport by varying concentrations of the alkali cations and inhibition of transport of alkali cations by different levels of thallium, thus providing strong evidence for the identity of the carrier system responsible for the transport of all four cations. The apparent affinity of thallium for the carrier is approximately seven times that of potassium and rubidium and almost 25 times that for cesium, whereas the magnitude of Vmax is about one quarter that for the alkali cations. Ki for ouabain for the thallium transport system is the same as that of potassium and not significantly higher than that observed elsewhere for the inactivation of Na-K ATPase and the uptake of rubidium. This is further evidence of the similarity between the carrier for thallium and the alkali cations and is in accord with the belief that the active transport system is dependent upon the action of the enzyme Na-K ATPase. The permeability of the lens membranes to thallium, relative to the alkali cations, is unrelated to ion size, suggesting that, like the latter, permeability is dependent upon absorptive rather than frictional forces. Toxicity of thallium is manifest by opacity which develops in all lenses that have accumulated thallium to levels of about 30 mM.

Key words: lens, thallium, alkali cations, cation transport, kinetics of transport, permeability, diffusion, Na-K ATPase, carrier systems

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The thallous ion (Ti^+) has properties in common with the alkali metal ions as well as those of Group III in the periodic table and tends to replace them in compounds such as complex salts. It has an ionic radius intermediate between potassium and rubidium and an electronic configuration like cesium. In water its conductance is almost identical to that of potassium but significantly higher than sodium, indicating that the hydrated ion is similar in size to that of potassium but smaller than sodium.

Movement of thallium and potassium in various animal tissues appears to occur by related mechanisms. Thus, following infusion of potassium sulfate in rabbits[1] or dogs,[2] renal clearance of thallium increases as does excretion of this ion in rats when the turnover rate of potassium is increased.[2, 3] Penetration of thallium and potassium in both resting and active membranes of sartorius muscle fibers is indistinguishable when the concentration of thallium is kept low.[4]

Like potassium, thallium moves in other organ systems and activates enzymes concerned with transport. For instance, in rabbit erythrocytes both ions are transported by the same mechanism, and both ions activate Na-K ATPase from red blood cells of rats.[5] In fact, not only can thallium replace potassium in the activation of ATPase obtained from rabbit kidney, but its affinity for the potassium-activating site is approximately ten times greater than that for potassium itself.[6] Its affinity for acetylphosphatase and p-nitrophylphosphatase of beef brain microsomes is also significantly greater than that for potassium.[7]

The dual objectives of the present study are to evaluate the parameters that describe the kinetics of transport of thallium in rabbit lenses and to determine whether this ion is actively transported into the lens by the same carrier system that is responsible for the transport of the alkali cations.

The first objective will be accomplished by fitting theoretical curves to data showing movement of ^{204}Tl into and out of the lens in the presence of various concentrations of nonlabeled species of this ion. The second will be attained by demonstrating that curves based on a hypothesis of a single carrier system and calculated from transfer coefficients determined for thallium alone, and found previously for potassium, rubidium, and cesium,[8] adequately describe movement not only of thallium (substrate) into and out of the lens in the presence of varying concentrations of the alkali cations (inhibitors), but also that of the individual alkali cations (substrates) in the presence of varying concentrations of thallium (inhibitor).

Methods

Mathematical. Theoretical curves of the rate of accumulation of labeled thallium, potassium, rubidium, or cesium in lenses and the net efflux from lenses preloaded with tracer ion are fitted to data obtained by culturing lenses in the presence of varying concentrations of nonlabeled species of each of the four ions. The curves are calculated on the basis of a theoretical model of the pump-leak hypothesis describing movement of substances into and out of the lens.[9] The model takes into account the effect of concentration of both substrate and inhibitor on the pump (Kp) and the effects of both the electric and the chemical gradients across the bounding membranes on the leak (Kd).

Equation 1 describes the change in concentration of a labeled ion in the lens. The concen-

$$\frac{d[^*S]_L}{dt} = Kp\,[^*S]_M + P\beta\left([^*S]_M\,\alpha - [^*S]_L\right) \quad (1)$$

tration of labeled ions in the medium decreases proportionately to the rate of accumulation in the lens and inversely with the volume of the medium; its rate of change is described by Equation 2. In these equations $[^*S]_L$ and $[^*S]_M$

$$\frac{d[^*S]_M}{dt} = -\frac{Vol._L}{Vol._M}\frac{d[^*S]_L}{dt} \quad (2)$$

= the concentrations of the labeled ion (substrate) in the lens and medium, respectively. Kp = transfer coefficient for the pump. $Vol._L$ = volume lens water, $Vol._M$ = volume medium (5 ml.), $P\beta$ = Kd, the transfer coefficient by diffusion (leak) in which permeability coefficient

$$P = \frac{\pi DA}{\Delta x\ Vol._L},\quad \beta = \frac{\frac{nF}{RT}V}{1-\alpha},\quad \text{and}\quad \alpha = e^{-\frac{nF}{RT}V}$$

V = bioelectric potential, i.e., difference between the inside (negative) and outside of the lens, as determined with glass microelectrodes, π = partition coefficient between "membrane" and medium, D = diffusion coefficient, A = area, Δx = thickness of "membrane," n bears sign of formal charge, RT and F have their usual significance.

Consideration is given to the separate effects on the pump of the substrate and the inhibitor. The former is the ion whose movement is being determined and the latter the ion thought to compete with the substrate for the carrier by Michaelis-Menten kinetics. The transfer coefficient for the pump, defined in terms of substrate and one inhibitor,* is expressed by the relation shown in Equation 3.

$$Kp = \frac{Vmax_S}{Vol._L}\left(\frac{Ki}{KmKi + Ki[S]_M + Km[I]_M}\right) \quad (3)$$

In these terms the rate of change in concentration of the labeled substrate ion is that

$$\frac{d[^*S]_L}{dt} = \frac{Vmax_S\ Ki[^*S]_M}{Vol._L\ (Km\ Ki + Ki[S]_M + Km[i]_M)}$$

$$+ P_S\beta\ ([^*S]_M\ \alpha - [^*S]_L) \quad (4)$$

shown in Equation 4, in which $Vmax_S$ = maximum velocity of the pump for the substrate, Km = Michaelis-Menten constant, and Ki = Michaelis-Menten constants for inhibitor.

The rates of change of concentration of nonlabeled substrate and inhibitor in the lens and medium are described by equations analogous to Equations 4 and 2. In all, six equations are solved simultaneously with an analog computer using methods of successive approximation.

Treating data by this method takes into account the effect of changes in concentration of both labeled and nonlabeled substrate as well as inhibitor in the medium and also the effect of potassium which leaks out of the lens.

Experimental. Lenses from albino rabbits weighing between 1.8 and 2.2 kilograms were removed aseptically from the posterior portion of enucleated eyes and cultured at 37° C. in 5 ml. of medium under sterile conditions by the method of Merriam and Kinsey.[10] The effect of concentration of thallium, potassium, rubidium, and cesium on the net influx and efflux of each ion was established from experiments in which rates of movement of labeled species were determined in the presence of four or five different concentrations of nonlabeled ions. The latter were added to medium of the same composition as KEI-4[11, 12] except that sodium salts were substituted for potassium to make the basic medium free of the latter ion. Thallium was added as the nitrate,* the other ions as chlorides. Isotonicity was maintained by adjusting the concentration of sodium chloride.

The maximum concentration of thallium employed was 3 mM, since at higher concentrations difficulty was experienced in keeping it in solution, presumably because of the low solubility of thallous chloride.

The rates of accumulation of ^{204}Tl, ^{42}K, ^{86}Rb, and ^{137}Cs in lenses cultured for 24 hours were determined by assaying the amount of radioactivity present in extracts made by homogenizing lenses in 2 ml. of ten per cent trichloroacetic acid. An end-window flow gas counter was used to determine radioactivity, which for ^{42}K was corrected for loss by decay. Accumulation of tracer in lenses is expressed as a ratio of concentration of labeled ion in lens water (65 per cent of wet weight) to that present in the medium at the beginning of culture. Larger lenses deplete the medium of isotope more rapidly than do smaller ones for a given velocity of transport, thus reducing the quantity available for the pump disproportionately. Accordingly, to make valid comparisons of the effect of concentration of substrate or inhibitor on the velocity of the pump in lenses of one weight group with those of another, the ratio of C_l/C_m for each lens was determined and then recalculated as though all lenses weighed 308 mg., i.e., as though each contained 0.200 ml. of water. The method employed in making this conversion is described elsewhere.[8]

Net efflux of all four cations was determined over a period of six hours after preculturing lenses for approximately 15 hours in KEI-4 medium containing radioactive isotopes of the ions.

Values for the bioelectric potentials (inside versus outside of lens) used to calculate α and β in Equation 1 were those reported recently for lenses cultured for 24 hours in medium containing different concentrations of potassium, rubidium, or cesium.[13] The bioelectric potentials of lenses cultured in 1, 2, and 3mM thallium were determined by similar procedures, except that the microelectrodes were filled with KNO_3 in place of KCl and found to be 42, 40, and 38 mv., respectively.

*In four instances two inhibitors are present as well as tracer concentrations of substrate; this occurs when transport of thallium is inhibited by rubidium or cesium or the converse; the second inhibitor is potassium which leaks out of the lens. In which instance:

$$Kp = \frac{Vmax_S\ Ki_1}{Vol._L\ Km}\left(\frac{Ki_2}{Ki_1\ Ki_2 + Ki_2\ [I_1]_M + Ki_1\ [I_2]_M}\right) \quad (5)$$

*The accumulation of ^{42}K and ^{86}Rb was not affected when 5mM NaCl in KEI-4 was replaced by the same concentration of $NaNO_3$.

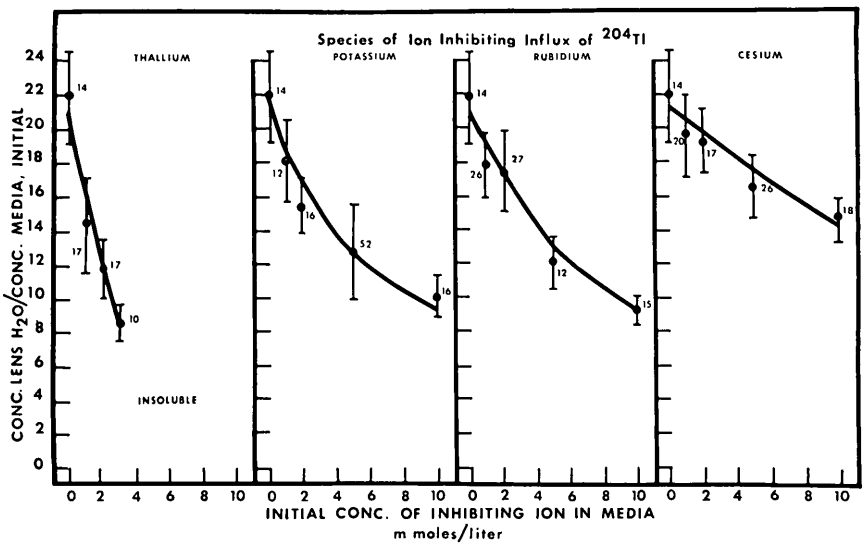

Fig. 1. Effect of concentration of thallium, potassium, rubidium, or cesium on accumulation of ^{204}Tl in rabbit lenses cultured for 24 hours.

Results

^{204}Tl accumulates in cultured lenses avidly, reaching a concentration 22 times that present in the medium initially within 24 hours. Accumulation decreases sharply with increasing concentration of nonlabeled thallium (Fig. 1, Column 1). The filled circles in this graph and all related ones correspond to the experimental data. The solid line is drawn through values of C_l/C_m at the same concentrations calculated by solving equations referred to under the Mathematical section. The method of successive approximation was applied until theoretical fits agreed closely both with the ratios obtained experimentally and, with approximately the same degree of accuracy, with data describing net efflux from lenses cultured under the same conditions (Fig. 2, Column 1).

Values for Km and $Vmax_S$ that produced fits to the data for thallium are shown on Line 1 of Table I. Those for Ki and $Vmax_i$ for the alkali cations used to calculate the theoretical rate of accumulation and net efflux of ^{204}Tl in the presence of potassium, rubidium, or cesium were assumed to be identical with Km and $Vmax_S$ for these ions determined in a previous study and are shown in Lines 2 to 4 of Table I.

Columns 2 to 4 of Fig. 1 show that potassium, rubidium, and cesium also reduce accumulation of ^{204}Tl, potassium and rubidium having the greatest effect and cesium the least, in accord with their relative values of Ki.

The same values for the parameters P, β, and α found to fit data showing accumulation of ^{204}Tl in the absence of nonlabeled thallium were used to calculate the diffusional flux of nonlabeled thallium. Analogous values for nonlabeled alkali cations were taken from a preceding study.[8]

The net efflux of ^{204}Tl from lenses cultured for six hours in medium containing varying concentrations of thallium or one of the alkali cations is shown in Fig. 2. The results are expressed as a percentage of total radioactivity present initially in the lens. The lines were also drawn by the analog computer which was programmed to solve the equations with the use of the same values for the coefficients that were employed to calculate the rates of accumulation in the lens under the same conditions.

The progressive increase in the net rate of efflux with concentration of all the cations is apparent and represents the combined effects of saturating or inhibiting the pump, decreasing the bioelectric po-

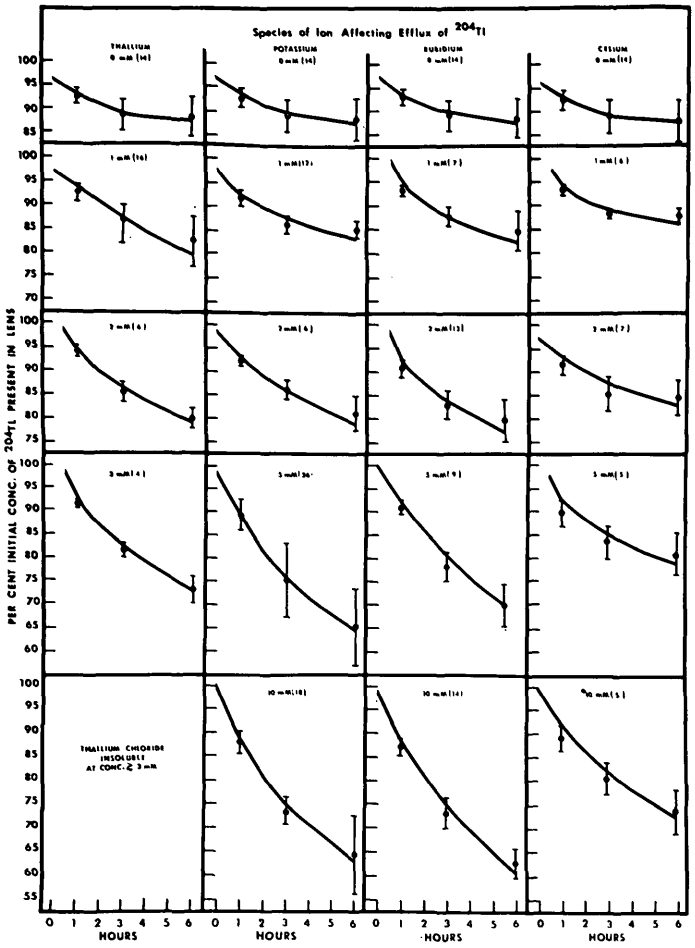

Fig. 2. Effect of concentration of thallium, potassium, rubidium, or cesium on net efflux of ^{204}Tl in rabbit lenses.

tential of the lens, and altering the permeability properties of the lens membranes.

The effect of concentration of all four cations in the culture medium on the permeability coefficient for thallium, determined from the values of Kd that provide fits to the experimental data, is shown in Fig. 3. Permeability of the lens to thallium is not affected appreciably by concentrations ranging from 0 to 3mM; it increases significantly with concentration of potassium in the range of 0 to 10mM, less with the same concentrations of rubidium and is relatively unaffected by cesium.

The effect of nonlabeled thallium in concentrations of 0 to 3mM on accumulation of ^{42}K, ^{86}Rb, and ^{137}Cs in 24 hours is shown in Columns 2 to 4 of Fig. 4 in comparison with that on accumulation of ^{204}Tl (Column 1). The inhibitory effect on all of the cations is conspicuous. The theoretical curves representing accumulation of radioactive isotopes of the alkali cations were calculated with the use of identical

Table I. Apparent Michaelis-Menten constants and maximum velocity of the carrier concerned with active transport of thallium in rabbit lenses compared with those of potassium, rubidium, and cesium

Saturating ion	*Km (mM)*	*Vmax$_S$ (μmoles/hr./lens)*
Tl	0.15	0.375
K	1.1	1.0
Rb	1.1	1.0
Cs	3.6	1.0

values of Vmax and the Michaelis-Menten constants that produced theoretical fits to the data showing the fluxes of ^{204}Tl in the presence of various concentrations of each cation. In the present instance, however, thallium is the inhibiting ion and the alkali metal ions are the substrates.

The net efflux of the alkali cations in the presence of the same concentrations of nonlabeled thallium is shown in Fig. 5. Again, all of the theoretical curves for the movement of the alkali cations fit the data within one standard deviation. The loss of all the cations from the lens appears to be accelerated by increasing the concentration of thallium.

The effect of different concentrations of thallium on the permeability coefficients of the cations studied is shown in Table II. The permeability of the lens membranes to potassium and thallium (shown graphically in Fig. 3) is not affected significantly by differences in concentration of thallium in the range of 0 to 3mM, but the permeability of the lens to rubidium and cesium is more than doubled.

Values for the transfer coefficients of the pump-leak system for the movement of thallium into and out of the lens under physiologic conditions, i.e., when the concentration of potassium is 5mM, are shown in Table III in comparison with those for the alkali cations. Kp was calculated from Equation 3 with data shown in Table I, and Kd, which is equal to $P\beta$, was calculated from the value P (0.256 $hour^{-1}$) that was found to fit the data showing the net efflux of ^{204}Tl in KEI-4, in which $\beta = 0.41$. The magnitude of the coefficient of active transport Kp for thallium is almost three times that of potassium, despite a significantly lower value of Vmax, because of the extremely high apparent affinity of thallium for the carrier. The value for Kd for thallium is also about three times that of potassium which has the largest turnover rate of the three alkali cations.

The effect of ouabain on thallium transport in lenses under physiologic conditions is shown in Table IV. The apparent Ki for

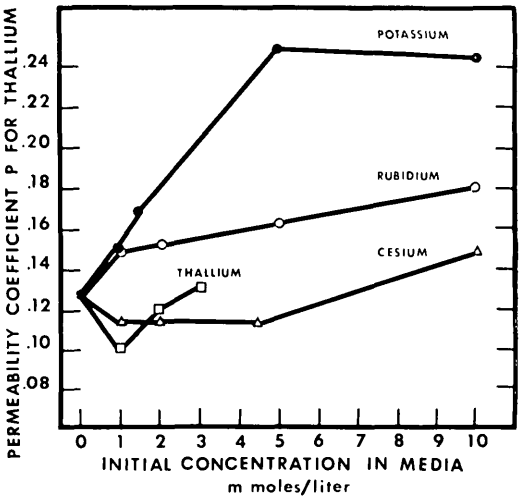

Fig. 3. Effect of concentration of thallium, potassium, rubidium, or cesium on permeability coefficient of thallium in rabbit lenses.

ouabain is $1.5 \times 10^{-6}M$. This glycoside in concentrations up to $10^{-5}M$ does not affect the rate of net efflux of ^{204}Tl; however, it does decrease the permeability coefficient from a normal value of 0.25 to 0.15 $hour^{-1}$ and lowers the bioelectric potential from 43 mv. to approximately 20 mv. after a latent period of several hours,[13] thus increasing β from 0.41 to 0.68. These and related data at other concentrations of ouabain were employed in calculating the values of Kp shown in Table IV.

Many of the lenses cultured in the presence of thallium developed cloudiness that extends deep into the cortex. This occurred both in the absence and presence of potassium or rubidium. The percentage of cloudy lenses increases with the quantity of thallium the lens accumulates and all of the lenses became cloudy when the estimated concentration within the lens is 30mM (Fig. 6), assuming all of the thallium remains in solution.

Discussion

In man, one case of cataract has been observed following thallium poisoning, and some young rats fed 0.1 mg. thallium acetate daily for about six weeks develop subcapsular cataract.[14] An explanation for the toxic effect of thallium as manifest by lens opacity is not apparent. That it is due

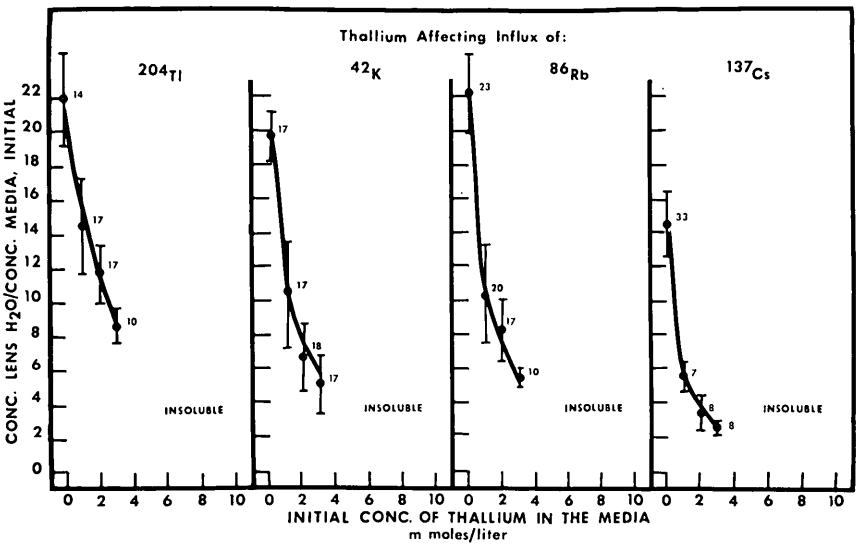

Fig. 4. Effect of concentration of thallium on accumulation of ^{204}Tl, ^{42}K, ^{86}Rb, or ^{137}Cs in rabbit lenses cultured for 24 hours.

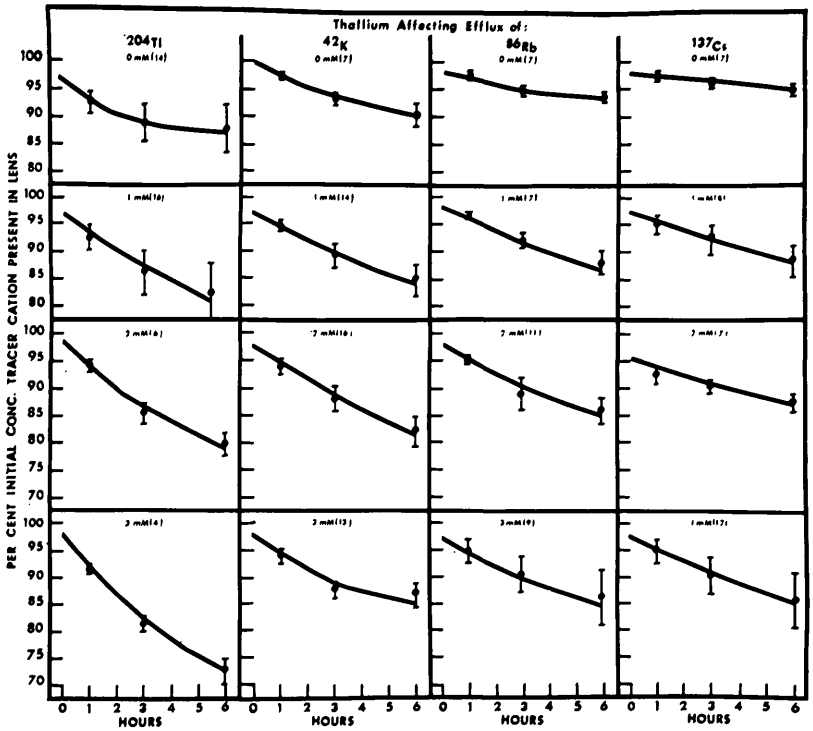

Fig. 5. Effect of concentration of thallium on net efflux of ^{204}Tl, ^{42}K, ^{86}Rb, or ^{137}Cs in rabbit lenses.

to inhibition of potassium transport seems unlikely because few lenses become cloudy when cultured in the presence of ouabain in doses that produce similar or greater reduction in potassium uptake. One possibility, suggested by preliminary evidence from electron microscopy, is that thallium comes out of solution in the lens, because the concentration of thallium exceeds the limits of solubility of some of its salts, e.g., TlCl.

Theoretical fits were obtained to data

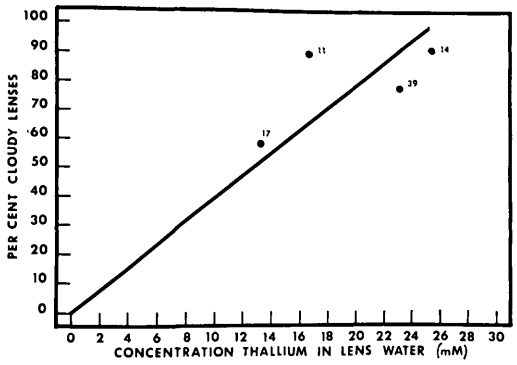

Fig. 6. Opacity resulting from accumulation of thallium in rabbit lenses cultured for 24 hours.

Table II. Effect of concentration of thallium on the permeability coefficients of thallium and the alkali cations

Saturating ion, Tl (mM)	*Permeability coefficient P (hr.$^{-1}$) for:*			
	Tl	*K*	*Rb*	*Cs*
0	0.13	0.07	0.03	0.02
1	0.10	0.07	0.07	0.04
2	0.12	0.08	0.08	0.04
3	0.13	0.08	0.08	0.05

Table III. Transfer coefficients of active transport and diffusion coefficients for thallium and alkali cations in rabbit lenses under physiologic conditions

Cation	*Pump, Kp (hr.$^{-1}$)*	*Leak, Kd (hr.$^{-1}$)*
Thallium	2.25	0.105
Potassium	0.82	0.039
Rubidium	0.82	0.023
Cesium	0.27	0.010

showing rates of accumulation of thallium at 24 hours. Values for the transfer coefficients employed were assumed to give rise to theoretical curves that would also fit accumulation at intermediate periods. The validity of this assumption was first tested by determining accumulation of ^{204}Tl at various times in medium containing a physiologic concentration of potassium (5mM). The data are shown in Fig. 7 in which the line is a theoretical curve calculated with the same values of Vmax and Km that were used to obtain fits to all of

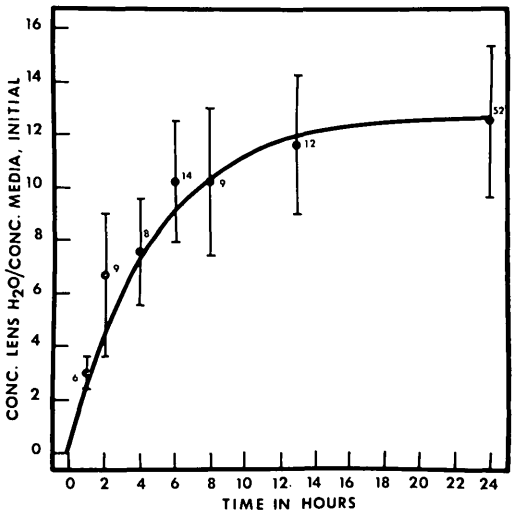

Fig. 7. Accumulation of ^{204}Tl in rabbit lenses cultured in a physiologic medium (KEI-4).

Table IV. Effect of ouabain on active transport of thallium in rabbit lenses for 24 hours under physiologic conditions

Concentration x 10^{-6}M	$\frac{C_i}{C_m}$*	*Kp (hr.$^{-1}$)*	*No. lenses*
0	12.7	2.25	52
0.5	12.0	1.90	3
1	10.1	1.40	7
2	8.3	0.96	4
5	5.1	0.42	3
10	3.3	0.20	6

*Ratio of concentration in lens water to that in medium, initially.

the data pertaining to thallium transport obtained at 24 hours only, namely Vmax = 0.375 μmoles per hour per lens and Km = 0.15 mM. The curve corresponds to the experimental data within one standard deviation throughout the whole time course; however, it is lower than the means for all of the points up to and including six hours.

The discrepancy between data and theory at early time periods was slightly greater in other experiments in which the culture medium contained 10 mM. potassium despite almost perfect agreement at 24 hours, e.g., at 6 hours C_i/C_m is 8.4 ± 1.2 compared with a calculated value of 6.4. When accumulation was determined in lenses cultured in the absence of potassium,

the difference was in the opposite direction, i.e., the predicted values were higher than those found experimentally. When intermediate concentrations of potassium (0.5, 1.0, and 2.0 mM) were employed, experimental data agreed with theory throughout the 24 hour time course.

Preculturing of lenses in medium containing potassium in concentrations of 0 or 10 mM for six hours before adding tracer thallium did not affect the rates of accumulation, thus apparent variations in Kp with time seem to be related to factors affecting movement of thallium directly rather than to any change in the distribution of potassium within the lens consequent to changing its concentration in the medium. Whatever the explanation, the differences between rates of accumulation found experimentally and those predicted theoretically were not of sufficient magnitude to cast serious doubt on the general validity of the mathematical model used for the calculations. They do suggest, however, the importance of measuring fluxes over a relatively extended period when attempting to characterize parameters governing transport systems in the lens.

In some instances the rate of net efflux appeared to be biphasic with a transitory rapid component followed by a persistent slower one; all of the theoretical curves were fitted to the latter since they probably give a truer picture of efflux from within the lens.

In accord with observations on other cells,[4-6] the results of this study demonstrate that thallium is actively transported into the lens by the same carrier system responsible for transport of the alkali cations, i.e., each ion acts at the carrier site in the same manner whether it is considered as substrate or inhibitor. Thus it was observed that the same values of $Vmax_S$ and Km found to describe the movement of alkali cations into the lens would correctly predict their individual inhibitory effect on the accumulation of ^{204}Tl (Fig. 1). Conversely, theoretical curves, calculated on the assumption that Km is equal to Ki for each of the ions, were also shown to fit experimental data on accumulation of ^{42}K, ^{86}Rb, and ^{137}Cs in the presence of varying concentrations of thallium.

The low value of Km for thallium transport system accounts for both the remarkable rapidity with which thallium enters the lens and the effectiveness of low concentrations in inhibiting the transport of potassium, rubidium, and especially cesium. The affinity of thallium for the carrier appears to be about seven times that of potassium, if it is assumed that the reciprocal of Km is an adequate approximation of affinity. Thus the relative affinity of the two ions is essentially that found for the activation of Na-K ATPase from rabbit kidney[6] or beef brain.[7]

The magnitude of Vmax for thallium is much lower than that for the alkali cations, suggesting that the breakdown of the carrier complex in the epithelium may be slow compared with the analogous complex formed with the latter ions because of stronger binding of thallium to the carrier.

The active transport system of thallium in the lens, similar to that for the alkali cations, appears to be either identical or very closely related to Na-K ATPase.[15] The Ki for the inhibition of thallium transport by ouabain under physiologic conditions is 1.5×10^{-6}M, which is the same as that found by the present investigators under the same conditions for potassium and probably not significantly greater than that reported both for the inhibition of Na-K ATPase when determined in the presence of 5mM potassium[15] or for the uptake of rubidium by rabbit lenses.[16] Moreover, the system must be located primarily in the epithelium where transport of the alkali cations takes place[12] and where Na-K ATPase in the lens is concentrated.[15] The latter conclusion is supported by present observations made on the accumulation of ^{204}Tl in lenses from which the epithelium and capsule have been removed. Cl/Cm after 20 hours of culture is

2.2 ± 0.9 (30 lenses) compared with 22 ± 2.4 in intact lenses. However, it may be that the lens fiber membranes possess some capacity for active transport, since ouabain (10^{-5}M) reduces the ratio to 1.5 ± 0.4 (ten lenses). It is possible, too, that thallium may bind slightly to lens proteins since the ratio still remains above one.

The physical-chemical property of thallium and the alkali cations responsible for activating Na-K ATPase is not apparent. Thus, although Britten and Blank[6] conclude that thallium might be expected to mimic the biological behavior of potassium more closely than that of sodium, the unique characteristic that enables thallium to substitute for potassium in activating the enzyme is not known. Clues are also lacking as to the property of thallium that enables it to share the transport system in the lens with the alkali cations. However, because the enzyme and carrier are similar, if not identical, only a single characteristic of thallium is needed to account for its interaction with both.

While thallium and the alkali cations both affect Na-K ATPase and the carrier system, in each instance the affinity for thallium is much greater than that for the latter ions. The observations reported in the present paper also show that the permeability for thallium is significantly greater than that for any of the alkali metal ions, suggesting that affinity for the carrier and selectivity of the lens membrane responsible for limiting diffusional exchange could possibly involve similar types of interaction, as proposed by Eisenman.[17] Because the carrier system is surely located chiefly in the epithelium and the membranes separating the interior of the lens from its fluid environment include also the fiber membranes, both within the lens and at its posterior surface, further studies designed to measure permeability characteristics of only the anterior surface are needed before meaningful conclusions can be drawn concerning the significance of any correlation between affinity for the carrier and lens membranes for cations.

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