Kinetics of Thallium Exchange in Cultured Rat Myocardial Cells

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SUMMARY. The kinetics of thallium exchange in cultured rat myocardial cells were studied and compared to those of potassium in the same tissue. Studies were carried out using low concentrations (10 nM to 5 μM) of thallium-204, approximating those likely to be encountered during clinical myocardial scintigraphy. Both thallium uptake and release could be described by a single exponential with a half-time of exchange which was approximately half that of potassium and which was largely independent of extracellular thallium concentration. Some 60% of thallium uptake occurred via an "active" or ouabain-inhibitable mechanism which, in the absence of extracellular potassium, could be activated by low concentrations (10 nM to 5 μM) of thallium. The apparent Km for thallium on this active transport mechanism was 2-7 μM. Increasing extracellular potassium from 0-10 mM caused significant, concentration-dependent decreases in both the total and the active component of the thallium influx. Similarly nonradioactive thallium (0.10 μM to 0.10 mM) caused a concentration-dependent decrease in active potassium influx. Analysis of these results by both Lineweaver-Burk plots and Dixon plots confirmed competitive inhibition, potassium on thallium influx and vice versa, for the active component of the fluxes, and noncompetitive in the remainder. These findings indicate that active transport accounts for the greater portion of the influx of thallium and potassium, and that this active transport occurs via a common mechanism. If, as the results suggest, the receptor for thallium and potassium is the same, then the analysis by Dixon plots would indicate that the affinity of the receptor for thallium is 260 to 900 times greater than for potassium. This would therefore explain the rapid accumulation of thallium-201 by the myocardium, in vivo, from the low circulating concentrations of the isotope. (Circ Res 56: 370-376, 1985)

THALLIUM-201 myocardial imaging has become an accepted diagnostic tool in cardiology, impairment of thallium-201 uptake commonly being used to detect and assess the extent of myocardial ischemia. Thallium ions (Tl+) and potassium ions (K+) are generally considered to behave in an analogous manner in a variety of biological systems (Mullins and Moore, 1960; Gehring and Hammond, 1964; Britten and Blank, 1968; Kashket, 1979), and Tl+ can both activate (Britten and Blank, 1968) and be transported by (Landowne, 1975; Skulski et al., 1978) membrane Na+,K+-ATPase. However, the Km for Tl+ of Na+,K+-ATPase, 0.16 mM (Britten and Blank, 1968), is considerably smaller than that for K+. Most studies to date have examined the kinetics of Tl+ transport when applied in concentrations between 0.01 and 1.0 mM to various enzyme or membrane systems, and little attention has been paid to myocardial thallium kinetics and exchange when the ion is used in concentrations (<1 μM) likely to be encountered during thallium-201 scintigraphy.

We therefore conducted the present study to examine the characteristics of cellular Tl+ exchange, using low concentrations of the ion (10 nM to 5 μM), in cultured rat heart cells. The preparation used was chosen because of the presence of a single, rapidly exchangeable, extracellular compartment, which greatly facilitates flux determination, and because many of the cell's membrane characteristics (McCall, 1979; Wheeler et al., 1982) are similar to those of other myocardial preparations.

Methods

Myocardial Cell Cultures

Primary cultures of rat myocardial cells were prepared from the hearts of 1- to 2-day-old rats as previously described (McCall, 1979). Using only ventricular tissue, to obtain as nearly as possible a homogeneous population, the hearts were each cut into approximately six pieces and disaggregated to single cells by repeated trypsinization. After separation of fibroblasts (McCall, 1979) the cell suspension was seeded in Petri dishes, 6 cm in diameter (Falcon), and incubated at 37°C in an atmosphere of 5% CO2 in air. All studies on the myocardial cells were carried out after 4-5 days growth in minimum essential medium containing 10% calf serum. By this time each Petri dish contained a synchronously contracting monolayer of 1.0-1.5 x 10^6 cells. In all cultures used, myocardial cells accounted for at least 80% of the total cell population (McCall, 1979).

Ion flux studies were carried out with cultures whose initial intrinsic concentration frequency lay in range 120-140/minute to minimize a rate-dependent effect. The val-
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ues for cell surface area, cell volume, and volume of cell water previously reported (McCall, 1979) were used for all flux calculations.

Solutions Used

Because the pH of the growth medium depends on an atmosphere of 5% CO2 in air, it could not be kept constant during the flux experiments, when cultures were continually being removed from, and replaced in, the incubator. All experiments were therefore carried out with the cells in a modified balanced salt solution (BSS) containing (mm): Na+, 136.80; K+, 5.35; Ca2+, 2.25; Mg2+, 1.03; Cl-, 148.22; PO43-, 0.43; glucose 11.10; plus calf serum, 5%, and phenol red, 0.0002% (pH 7.2). The cells were allowed to equilibrate in BSS, which could maintain cell viability for at least 24 hours, for 2–3 hours before any measurements were made.

The K+-free solutions used were obtained by omitting the K+ salts and using dialyzed calf serum. No osmotic replacement for the K+ salts was required, and during the K+-free flux studies, the solution was continuously replaced to prevent accumulation of K+ which could leak from the cells. Tl+ solutions were prepared with Tl NO3, because of its greater solubility; the final concentrations represent the combination of 204Tl and the nonradioactive ion.

Ion flux Measurements

The technique employed in determining ionic content and fluxes in the cells have been described in detail elsewhere (Lamb and McCall, 1972; McCall, 1979). The K+ and Tl+ contents were measured after equilibration in BSS containing 42K or 204Tl. After cell loading, an isotonic K+-free calcium-sorbitol solution at 0°C was used to wash the cells free of extracellular tracer, thereby permitting determination of intracellular radioactivity (McCall, 1979).

Influx determinations for K+ were made and calculated as previously described (McCall, 1979). Initial studies of Tl+ exchange showed that, like K+, the uptake and release of Tl+ could be described by a single exponential. The half-time of Tl+ exchange was around 5 minutes compared to 12 minutes in the case of K+. Subsequent determinations of Tl+ influx were therefore made in the same way as for K+ fluxes—in this case, after the cells had been exposed for 2 minutes to 2M Tl+.

Separation of each influx into its "active," or ouabain-sensitive, and passive components was achieved from parallel measurements made in the presence and absence of 10-3 M ouabain (McCall, 1979). In each case, the cells were pretreated with ouabain for 10 minutes prior to the influx determination (Lamb and McCall, 1972) to ensure adequate Na pump inhibition. Efflux was measured by equilibrating the cells with the appropriate isotope tracer and then observing its loss into a nonradioactive solution by measuring the amount left in the cells at various times (McCall, 1979). For these studies, the nonradioactive solution at 37°C was continually replaced at 30–60 ml/min, which was not rate limiting to the efflux process. All flux determinations were made at 37°C (McCall, 1979).

Materials

204Tl (5 Ci/g of Tl+) was purchased from New England Nuclear. For the present study, 204Tl was used because of its longer half-life and, as a consequence, its easier handling. Biologicals were from Flow Laboratories, and all chemicals from Mallincrodt were of analytical grade.

Statistical Analysis

Student’s t-tests for paired data were used to test for significant differences between groups. Linear regression analysis was done by least-squares fit. All results are presented as mean ± SEM.

Results

Thallium Uptake and Exchange

The uptake of Tl+ by cultured myocardial cells, over the range of Tl+ concentrations tested (10 nM to 10 μM), could be described by a single exponential. The half-time of uptake in the absence of extracellular K+ was largely independent of the Tl+ concentration, and the mean half-time of the exchange was 4.95 ± 0.51 minutes. This value is considerably less than the half-time of exchange for K+ in the same preparation, which has a mean value of 12.05 minutes (McCall, 1979). The curve describing Tl+ uptake was clearly asymptotic, intracellular Tl+ reaching an equilibrium value within 20–40 minutes of exposure of the cells to the tracer.

Equilibration of intracellular Tl+ ([Tl+]i) with respect to extracellular Tl+ ([Tl+]o) is confirmed by the determination of the rate of loss of previously accumulated 204Tl from the cells into a nonradioactive solution. These studies showed, over the range of Tl+ concentrations tested and under equilibrium conditions, that the net Tl+ efflux was almost identical to the net Tl+ influx, mean half-time of 204Tl loss being 5.09 ± 0.46 minutes (n = 15). Like the Tl+ influx, the rate of Tl+ loss under these conditions was unaffected by the concentration of Tl+ to which the cells had been exposed during the loading period, and could be fitted to a single exponential.

Effect of Ouabain on Tl+ Influx

The possibility that all or part of the Tl+ uptake by myocardial cells could occur via the Na pump was assessed by measuring 204Tl influx (2-minute exposure method) in the presence of ouabain, 10-9 to 10-3 M. As shown in Figure 1, ouabain effected a concentration-dependent decrease in Tl+ uptake, very similar to that on the K+ influx. None of the concentrations of ouabain used had any demonstrable effect on the Tl+ efflux rate. Half-maximal inhibition of the Tl+ influx was produced by 2 × 10-5 M ouabain, and the drug maximally inhibited some 60% of the total Tl+ influx (Fig. 1). These findings are very similar to those found with the K+ influx (McCall, 1979) where ouabain maximally inhibited 75% of the flux, with half-maximal inhibition occurring at a concentration of 10-6 M. The inhibitory effect of ouabain on the Tl+ influx was significant (P < 0.001) for all concentrations of ouabain in excess of 10-7 M. This pattern of inhibition held true for all concentrations of Tl+ tested, up to and including, in this case, 0.1 μM.

This finding strongly suggests that 60% of the Tl+ influx represents active transport via the Na pump,
so that in all subsequent studies the flux was divided into its "active" and passive components on the basis of ouabain sensitivity.

**Effect of [K+]o on Tl+ Exchange**

Although the rate constant of Tl+ uptake was independent of [Tl+]o, it was markedly affected by changes in [K+]o. The rate constant, λ, of Tl+ uptake in the absence of extracellular K+ was 0.14 ± 0.02 min⁻¹ (n = 5). Increasing [K+]o to 2 mM and 5 mM, for example, decreased λ to 0.09 ± 0.01 and 0.06 ± 0.02/min respectively (for each n = 5), both values being significantly (P < 0.001) less than the control. Similar progressive decreases in the rate constant were seen as [K+]o was increased toward 10 mM.

Separation of the Tl+ influx into its constituent components (Fig. 2) revealed that [K+]o had a significant effect on all three components, total, active and passive, of the flux. For example (Fig. 2), using a [Tl+]o of 2 mM, the total Tl+ influx (mol⁻¹/cm² per sec) declined from a control (K+-free conditions) of 13.56 ± 0.59 (n = 10) to 3.88 ± 0.11 (n = 10) and 2.10 ± 0.15 (n = 5) in 5.3 mM and 10 mM K+, respectively (for each P < 0.001). At the same time, the passive or ouabain-insensitive influx (mol⁻¹/cm² per sec) declined from 2.86 ± 0.07 (n = 10) to 1.49 ± 0.04 (n = 10) and 0.84 ± 0.05 (n = 5), again in both cases the difference from the control being highly significant. By subtraction, this gives a net "active" Tl+ influx (mol⁻¹/cm² per sec) of 10.70 in the absence of extracellular K+; 2.40 at [K+]o = 5.3 mM, and 1.26 at [K+]o = 10 mM. The inhibitory effect of extracellular K+ on both active and passive Tl+ influx was apparent for all concentrations of Tl+ tested in this way (0.1–2.0 μM).

The principal effect of changes in [K+]o on Tl+ exchange was to modify the Tl+ influx. Increasing [K+]o from 0 to 5 mM or 10 mM had little or no effect on the rate constants describing the loss of previously accumulated ¹²⁴Tl from the myocardial cells.

**Tl+ and K+ Interrelationship in Myocardial Cells**

From the above data, it is apparent that more than half of the cellular Tl+ uptake, like that of K+, occurs via a ouabain-sensitive mechanism, presumably the Na pump. Further, it is apparent that extracellular K+ can act as an inhibitor of Tl+ uptake, suggesting that both ions may enter the cell by a common pathway. It has also been shown previously (Britten and Blank, 1968) that Tl+ is capable of functioning as an activator of Na+,K+-ATPase. For these reasons, it was felt that attempts to analyze the above data by Lineweaver-Burk, or double-reciprocal plots, where [Tl+]o = S and Tl+ influx = V, could be helpful in further clarifying the interaction of the two ions.

Using Lineweaver-Burk, or double reciprocal, plots to analyze the data for total Tl+ influx, with K+ as inhibitor, we obtained a pattern representative of mixed inhibition. Similar treatment of the non-ouabain-sensitive fluxes produced data in keeping with noncompetitive inhibition. However, when the active or ouabain-sensitive Tl+ influx data were subjected to this analysis (Fig. 3), the results were in keeping with strictly competitive inhibition of the Tl+ influx by K+. From the data presented in Figure 3, the intercept on the y axis, representing the reciprocal of the maximum active Tl+ influx, gives a value of 0.05, suggesting a maximal ouabain-sensitive Tl+ influx of 20 mol⁻¹/cm² per sec. The x intercept of the [K+]o = 0 line (Fig. 3) would represent the reciprocal of the Michaelis constant (Km) of Tl+ on the active Tl+ influx. The value for Km obtained in the
FIGURE 3. Double-reciprocal plot of $[\text{Tl}^+]_o$ and active $\text{Tl}^+$ influx, myocardial cells at 37°C in the absence ($[\text{K}^+] = 0$) and presence of two concentrations (5.3 and 10 mM) $\text{K}^+$. Each point is the mean of six observations, and lines shown are calculated linear regression lines, for each $r > 0.94$ (P < 0.001).

The present study was therefore of the order of 2 $\mu$M. This latter value was rather surprising in light of previously reported values (Britten and Blank, 1969) for the $K_m$ of $\text{Tl}^+$ on Na$^+$, K$^+$-ATPase (0.16 mM).

In view of the apparent differences between the present findings and those previously reported, further studies were carried out to determine the relationship between $[\text{Tl}^+]_o$ and active $\text{Tl}^+$ influx over the range of $\text{Tl}^+$ concentrations from 10 nM to 0.1 mM. This showed, in the absence of extracellular $\text{K}^+$, a sigmoid relationship reaching saturation at around 0.1 mM $\text{Tl}^+$ with a maximum active $\text{Tl}^+$ influx of 30 mol/cm$^2$ per sec. This latter value is some 50% higher than the calculated maximum active $\text{Tl}^+$ influx (Fig. 3), and the apparent $K_m$ is of the order of 7 $\mu$M compared with the previously calculated value of 2 $\mu$M.

The $\text{Tl}^+$:K$^+$ interrelationship in the myocardial cells was further explored using a Dixon plot (Dixon, 1953) of the inhibitor ($\text{K}^+$) against the reciprocal of the active, or ouabain-sensitive, $\text{Tl}^+$ influx (Fig. 4). This also confirmed competitive inhibition between $\text{K}^+$ and $\text{Tl}^+$ with respect to the active $\text{Tl}^+$ influx, and also permitted the calculation of the inhibitor constant ($K_i$) for $\text{K}^+$, the $\text{K}^+$ concentration at the point of intersection of the graphed lines being $-K_i$. The value for the $-K_i$ of $\text{K}^+$ on the active $\text{Tl}^+$ influx was found to be 1.2 mM (Fig. 4), which compares very favorably with the calculated $K_m$ of $\text{K}^+$ on the active $\text{K}^+$ influx (Fig. 5) at 1.8 mM. The values used in Figure 5 were derived from the $^4\text{K}$ influx from solutions containing various concentrations of $\text{K}^+$ from 1–5.4 mM, measured in the presence and absence of $10^{-2}$ M ouabain.

FIGURE 4. Dixon plot of active $\text{Tl}^+$ influx, from two concentrations of $\text{Tl}^+$, and various concentrations of $[\text{K}^+]_o$. Each point is mean of six observations and lines shown are calculated linear regression lines ($r > 0.95$, P < 0.001).

Effect of $[\text{Tl}^+]_o$ on K Influx

To test the competitive nature of the $\text{Tl}^+$:K$^+$ interrelationship further, the effect of varying concentrations of nonradioactive $\text{Tl}^+$ on the $^4\text{K}$ uptake was determined. As in the other studies, the K$^+$ influx was separated into its active and passive components using $10^{-2}$ M ouabain. It was found that $\text{Tl}^+$ in concentrations from 0.10 $\mu$M to 0.10 mM produced a concentration-dependent decrease in both total and active K$^+$ influx (Fig. 6), the decrease being significant (P < 0.01) at 1 $\mu$M and highly significant (P < 0.001) at all concentrations in excess of 1 $\mu$M. Thallium-induced decreases in K$^+$ influx could be

FIGURE 5. Double reciprocal plot of active $^4\text{K}$ influx and $[\text{K}^+]_o$ myocardial cells at 37°C. Each point is mean of 5–10 observations, and the line shown is the calculated linear regression line ($r = 0.97$, P < 0.001). Open symbol from data previously reported (McCall, 1979).
observed in the presence of each level of [K+]o tested, from 1–5 mM.

By subjecting these data to the same analysis as that used for the Tl+ flux data, we were able to confirm the presence of competitive inhibition by Tl+ on K+ influx (Fig. 7). The Kt for the K+ influx at 6 μM was similar to the apparent Kt for the active Tl+ influx (Fig. 3) described above.

The possibility that Na+ loading, or changes in contraction frequency, during K+-free treatment of the cells, modified Tl+ influx, was evaluated in a series of studies in which both 24Na content and contraction frequency were measured at various times after exposure to K+-free or K+-free + 1 μM Tl+ BSS (Fig. 8). In K+-free solution, there was a rapid gain in intracellular 24Na, the initial rate of which was in keeping with previously reported Na+ flux data (McCall, 1979). After 5 minutes, however, the rate of Na+ accumulation declined, possibly indicating activation of alternative pathways of Na+ extrusion, such as Na+-Ca++ exchange, or a concentration-dependent decline in Na+ influx. In the presence of 1 μM Tl+ (Fig. 8), the gain in cellular Na+ was much less rapid, in keeping with, or supporting, the contention that low concentrations of Tl+ can at least partially activate the Na pump. A similar pat-
tern was observed in the effects of the two solutions on contraction frequency (Fig. 8) in that the response to a K+ free solution was much more immediate than that to a solution containing 1 μM Tl+.

Since most determinations of Tl+ influx were made over a 2-minute period, it is unlikely that either Na+ loading or contraction frequency had a significant bearing on Tl+ influx since, in the presence of 1 μM Tl+, [Na+] had risen from 12.3 ± 0.3 mM to only 16.9 ± 0.5 mM (n = 5) during this time, and contraction frequency had declined by less than 10%. Nonetheless, determinations of 56Cu influx after 30 seconds (using a 30-second influx measurement), 2 minute (using a 2-minute influx measurement) and 30 minutes (2-minute influx) of exposure to either a K+-free or K+-free + 1 μM Tl+ solution were made. The results are summarized in Table 1.

Although there was a modest, but significant (Table 1), decline in 204Tl influx after 30 minutes of treatment with either solution, it is unlikely that either Na+ loading or contraction frequency significantly influenced the results, since most Tl+ influx determinations were made over a 2-minute period, and following, at most, 10 minutes of Na pump inhibition (ouabain experiments). The data from Table 2 also serves to validate further the 2-minute 204Tl influx measurements, since the values obtained are not significantly different from those obtained from a 30-second 204Tl influx determination.

Discussion

The present study represents an attempt to define the kinetics of Tl+ exchange in cultured myocardial cells, using concentrations of Tl+ more closely approximating those likely to be encountered during clinical myocardial scintigraphy. Prior evaluations of Tl+ exchange (Mullins and Moore, 1960; Gehring and Hammond, 1964; Skulskii et al., 1978), Streptococcus lactis (Kashket, 1979), frog skeletal muscle (Mullins and Moore, 1960), and squid axon (Landowne, 1975). In addition, it is worth noting that the absolute values obtained for Tl+ fluxes in the present study are very similar to those found by Mullins and Moore (1960) in skeletal muscle.

In the present study, myocardial cells accumulated Tl+ rapidly until a steady state with respect to [Tl+] was reached within 20–30 minutes. Under these steady state conditions, net Tl+ influx and Tl+ efflux were equal. Equilibrium times appear to be longer in both skeletal muscle (Mullins and Moore, 1960) and red cells (Gehring and Hammond, 1964), the difference in both tissues being attributable to a small, slowly exchanging component not seen in the myocardial cells or in Streptococcus lactis (Kashket, 1979). At equilibrium, the cells contained significantly higher concentrations of Tl+ than that in the incubation medium, confirming that myocardial tissue, like other tissues, is capable of concentrating the ion. For all concentrations of [Tl+], tested, the [Tl+] of [Tl+] ratio, at equilibrium and in the absence of extracellular K+, was approximately 50:1 (Table 2). Gehring and Hammond (1964) found a ratio, [Tl+] of [Tl+] ratio, at equilibrium of 8.66:1, whereas a much higher ratio, 500:1, was demonstrated in S. lactis preparations (Kashket, 1979). Although the reason for these differences is not clear, the lower ratio in erythrocytes may reflect the much lower Na pump density in these cells, compared to cultured heart cells (McCall, 1979), and/or the lower membrane potential of the cells.

Ouabain (10-2 M) maximally inhibited approxi-
mately 60% of the Tl\(^+\) influx in cultured heart cells, a finding similar to that in both squid axon (Landowne, 1975) and red blood cells (Skulskii et al., 1978). Although not infallible (Baker et al., 1969), ouabain sensitivity is generally accepted to be the most reliable indication that an ion flux is dependent on Na pump activity. As such, it can therefore be assumed that the greater part of myocardial Tl\(^+\) influx is dependent on membrane Na\(^+\),K\(^-\)-ATPase. Further, the present study shows that the putative Na pump-dependent Tl\(^+\) movement can be activated by low concentrations (10 nM to 5\(\mu\)M) of Tl\(^+\) in the absence of extracellular K\(^+\).

Although no direct measurements of Na\(^+\),K\(^-\)-ATPase activity were made in the present study, certain inferences regarding the activity of the enzyme can be made. If all of the ouabain-inhibitable Tl\(^+\) influx represents Na\(^+\),K\(^-\)-ATPase activity, then the results of this study would yield an apparent K\(_m\) for Tl\(^+\) on the enzyme activity of 2–7 \(\mu\)M. This is considerably different than the K\(_m\) of Tl\(^+\) on renal Na\(^+\),K\(^-\)-ATPase of 0.17 \(\mu\)M found by Britten and Blank (1968) and Grisham et al. (1974). The latter authors, however, noted K\(_m\) of Tl\(^+\) on Na\(^+\),K\(^-\)-ATPase of 29 \(\mu\)M in the absence of Mn\(^++\), a value not greatly different from that of the present study. Since isolated and purified ATPase was not studied in this preparation, the results are not strictly comparable. Nonetheless, it is clear that the K\(_m\) of Tl\(^+\) for the active Tl\(^+\) influx presented here is considerably less than that for the isolated enzyme system (Britten and Blank, 1968; Grisham et al., 1974). Several explanations could account for the difference, (1) the present experiments were carried out at 37\(^\circ\)C compared to 21–23\(^\circ\)C for the others (2) much lower concentrations of Tl\(^+\) were used in the present studies (3) the preparation, having a single, rapidly exchangeable extracellular compartment, allows accurate flux determinations without contamination from trapped inhibitors such as K\(^+\), and, finally, (4) the active transport properties of the preparation itself could be unique. The last factor is least likely since it has been shown (McCull, 1979; Wheeler et al., 1982) that cation transport by cultured myocardial cells is similar to that in other myocardial preparations. This is further supported by the observation in this study that the K\(_m\) of Tl\(^+\) on the active K\(^+\) influx is 1.8 \(\mu\)M, identical to that for both Na pump activity and ATPase activity (Glynn, 1968; Glitsch et al., 1978; Gadsby, 1980) in a wide variety of tissues. It seems most likely, therefore, that the present observation stems from a combination of the very low concentrations of Tl\(^+\) used and the ability to measure fluxes accurately, free from inhibitor. Whatever the reason, the very low value for K\(_m\) of Tl\(^+\) in the present study is consistent with the myocardial Tl\(^+\) uptake observed in vivo in which the heart is exposed to very low concentrations of this ion.

An interrelationship between Tl\(^+\) and K\(^+\) has been shown in a variety of preparations (Mullins and Moore, 1960; Gehring and Hammond, 1964, 1967; Landowne, 1975; Kashket, 1979). This study has defined a competitive inhibition of active Tl\(^+\) influx by K\(^+\), and also of active K\(^+\) influx by Tl\(^+\). These findings suggest that active transport of both ions occurs via a common pathway, presumably the Na pump, and further suggests a common receptor for both on the enzyme system. The present data therefore support the concept that Tl\(^+\) behaves as a K\(^+\) analog in cultured myocardial cells.

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