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Anion-Dependent Transport of Thallous Ions through Human Erythrocyte Membrane

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Summary. Unidirectional fluxes of $^{204}Tl^+$ through the human red blood cell membrane were measured. The inward rate coefficient measured in a K^+-free saline was 15.6 ± 0.6 hr^{-1}. The influx of Tl^+ could be partially inhibited with 0.1 mM ouabain (by 28%), 0.1 mM DIDS (by 50%) or 1 mM furosemide (by 51%). The inhibitory effects of ouabain and DIDS or furosemide were additive. Half-maximal responses were seen at 0.72 μM and 0.22 mM concentrations of DIDS and furosemide, respectively. A similar action of these blockers on Tl^+ influx was observed in the erythrocytes incubated in $MgCl_2$-sucrose media. The outward rate coefficient of ^{204}Tl was also inhibited by DIDS and furosemide (by 65 and 52%, respectively). Rate coefficients of ^{204}Tl influx and efflux decreased significantly in the red cells exposed to Cl^--free media ($NaNO_3$ or $Mg(NO_3)_2$-sucrose). Under these conditions addition of DIDS and furosemide led to only a small inhibition of Tl^+ fluxes. There was a linear increase in Tl^+ influx with rising of external Cl^- concentration within 80–155 mM or HCO_3^- concentration from 20 to 40 mM when the sum of anions was kept constant (155 mM) with NO_3^-. The HCO_3^--stimulated Tl^+ influx was completely blocked by 0.05 mM DIDS but only 67% by 1 mM furosemide. The present study provides direct evidence for the occurrence of Cl^- (HCO_3^-)-dependent, DIDS-sensitive movement of Tl^+ across the human erythrocyte membrane in both directions. Under physiological conditions, about half of net Tl^+ fluxes occurs due to an anion exchange mechanism. Our data fail to detect a contribution of the Na-K-Cl cotransport system to Tl^+ transport in human erythrocytes.

Key Words thallium transport · anion exchanger · human erythrocytes

Introduction

Thallous ion (Tl^+) is known as a substitute of K^+ in various mechanisms of ion membrane transport. It was shown that Tl^+ is able both to activate the Na,K-ATPase and to be transported by the Na,K pump [9, 11, 27, 39]. Tl^+ can replace K^+ in Na-K-Cl cotransport in smooth muscle and Ehrlich ascites cells [3, 21, 30]. Potassium channels in various tissues are more permeable to Tl^+ than to K^+ [8, 14, 18, 19]. Transport of K^+ through the inner mitochondrial membrane was inhibited by Tl^+ in a competitive manner [4, 13].

In human erythrocytes, the inward and outward rate coefficients for Tl^+ are about two orders of magnitude higher than those for alkali metal ions [11, 31, 33, 34]. Mechanisms of Tl^+ movement across the erythrocyte membrane, except for the Na,K pump, remain to be established. Recent studies revealed the major role of erythrocyte anion exchange protein (Band 3) in transport of some cations, such as Pb^{2+} [32], Zn^{2+} [22, 36] and Cu^{2+} [2]. In the earlier works [5, 10, 16, 17], it has been shown that in human erythrocytes the entry of both Na^+ and Li^+ is mediated by a HCO_3^--dependent mechanism sensitive to inhibitors of anion transport. Transport of the above-mentioned cations via anion exchanger is believed to occur in the form of negatively charged ion pairs. Taking into account the ability of Tl^+ to form ion pairs and complexes [25, 26, 28], an involvement of the anion exchange in Tl^+ transport may be expected.

The main purpose of the present investigation was to estimate the contribution of the anion exchange mechanism to the total transfer of Tl^+ through the human erythrocyte membrane. It was found that about half of Tl^+ flux is mediated by protein Band 3 and can be inhibited by DIDS and furosemide. No evidence was obtained for the contribution of Na-K-Cl cotransport in Tl^+ movement across the human red blood cell membrane.

Materials and Methods

Red Cell Preparation

Freshly drawn heparinized human blood was centrifuged at 2700 × *g* for 5 min at 4°C to remove plasma and buffy coat. The cells used the same day were washed three times with a 10-fold

volume of buffered (pH 7.4) solution containing (in mM): A. 145 NaCl, 10 Tris-HCl; B. 145 $NaNO_3$, 10 Tris-HNO_3; C. 75 $MgCl_2$, 85 sucrose, 10 Tris-HCl; and D. 75 $Mg(NO_3)_2$, 85 sucrose, 10 Tris-HCO_3. Red cells to be used the next day were washed and stored overnight in cold solution containing (in mM): 140 KCl, 10 NaCl, 10 Tris-HCl, and 10 glucose (pH 7.4 at 4°C).

Tl^+ Influx Measurements

Washed red blood cells were suspended to 40–50% hematocrit in the flux medium "A," "B," "C" or "D" with addition of 10 mM glucose. Aliquots of the suspension were added to the medium to a final hematocrit of 2–5%, and after 2 min for cell adaptation, the influx experiment was initiated by adding ^{204}Tl (1.2 μCi/ml suspension) at zero time. Low concentrations of cold Tl^+ (0.02 mM) were added to media together with ^{204}Tl in all influx experiments. Such a concentration of Tl^+ was used because of the low solubility of TlCl and in order to avoid saturation of Tl^+ transport [27, 34]. In experiments with ouabain the cells were preincubated for 30 min to bind the inhibitor to erythrocyte membrane. The cells were exposed to ^{204}Tl for 1 min in control and for 2 min in the presence of inhibitors. Then aliquots of the suspension were injected into a 10-fold volume of the ice-cold stop solution (145 mM NaCl, 10 Tris-HCl, pH 7.4) and centrifuged at 2700 × g for 2 min at 4°C. Samples of supernatant were pipetted into counting tubes to measure ^{204}Tl in the medium. The sedimented cells were washed with the same stop solution, lysed in distilled water and counted for radioactivity. The radioactivity of the media and lysates was measured using a crystal scintillation counter detecting soft e—capture radiation of ^{204}Tl. Preliminary studies have shown that the ^{204}Tl influx remains linear for the first 2 min of the study. Tl^+ influx rate coefficient (K_{in}) was calculated from the equation

$$K_{in} = A_{cell}/A_{medium} \cdot t \quad (1)$$

where A_{cell} and A_{medium} represent the radioactivity of 1 ml of originally packed erythrocytes and 1 ml of medium, respectively, and t represents the time of incubation with ^{204}Tl.

Tl^+ Efflux Measurements

Washed erythrocytes were suspended to a 40% hematocrit in the flux medium with ^{204}Tl (10 μCi/ml medium) and incubated at 37°C for 30 min to ensure Tl^+ equilibration. Cells were washed three times at 4°C with nonradioactive flux medium to remove external ^{204}Tl. The loaded cells were added (2% final hematocrit) at zero time to a prewarmed (37°C) efflux media containing (in mM): 140 NaCl, 5 KCl, 10 Tris-HCl (pH 7.4 at 37°C), and 10 glucose. In some experiments Cl^- was replaced with NO_3^-. Aliquots of the suspension were pipetted into a 10-fold volume of ice-cold medium at 3, 6 and 9 min and quickly centrifuged for 1 min at 4°C. Supernatant was aspirated and the cells were lysed in distilled water. The initial content of ^{204}Tl in cells (A_0) was determined by measuring the suspension aliquot radioactivity. The outward rate coefficient (K_{out}) was calculated graphically from the equation

$$\ln(A_t/A_0) = -K_{out} \cdot t \quad (2)$$

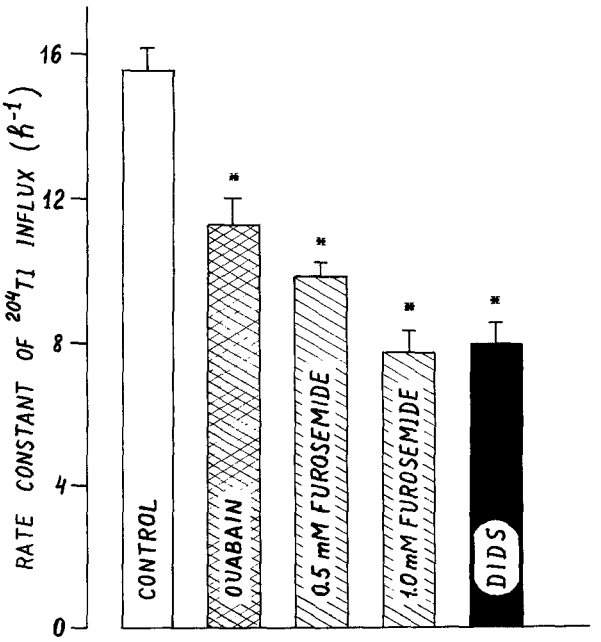

Fig. 1. Inhibition of the Tl^+ influx by ouabain, furosemide and DIDS in human erythrocytes. Incubation media contained (in mM): 145 NaCl, 10 glucose, and 10 Tris-HCl (pH 7.4 at 37°C). The cells were preincubated at 2–5% hematocrit at 37°C for 1–2 and for 30 min in the presence of ouabain. ^{204}Tl uptake for 1–2 min was measured, and influx rate constant was calculated (*see* Materials and Methods). Each column represents mean ± SE for seven experiments. *$P < 0.001$ as compared with the control.

where A_t and A_0 represent radioactivity of 1 ml of packed cells at "0" and "t" time.

Chemicals

Ouabain, furosemide and DIDS (4,4'-diisothiocyanostilbene-2,2'-disulphonic acid) were purchased from Sigma Chemical. Ouabain was dissolved in flux medium to make 10-mM stock solution. Stock solutions of furosemide (100 mM) and DIDS (5 mM) were prepared by dissolving in DMSO and in ethanol, respectively. The same amounts of DMSO or ethanol were added to flux medium in control experiments. ^{204}Tl was obtained from "ISOTOP" (USSR).

Results

Effects of Ouabain, Furosemide and DIDS on Tl^+ Influx

Rapid uptake of Tl^+ was observed in red blood cells incubated in K^+-free control saline. The inward rate coefficient of Tl^+ was 15.6 ± 0.6 hr^{-1} (means ± SE, $n = 7$). The influx of Tl^+ was significantly decreased in the presence of ouabain, furosemide and DIDS (Fig. 1). DIDS is a well-known selective inhibitor of

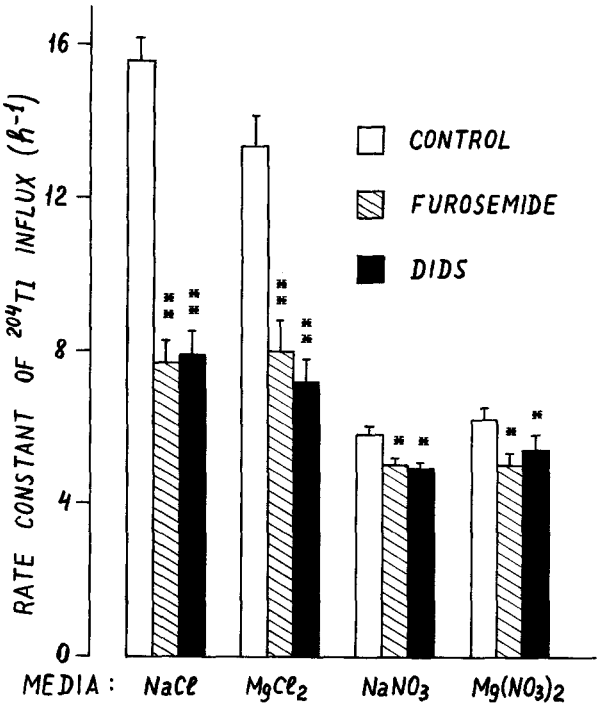

Fig. 2. Effect of furosemide (1 mM) and DIDS (0.1 mM) on ^{204}Tl influx in erythrocytes in various media. The cells were washed and incubated in isotonic media as described in Materials and Methods. After 2-min preincubation at 37°C, ^{204}Tl was added and 1–2 min uptake was measured. The values are means ± SE for 5–7 experiments. $^*P < 0.01$, $^{**}P < 0.001$ as compared with the control (paired t test).

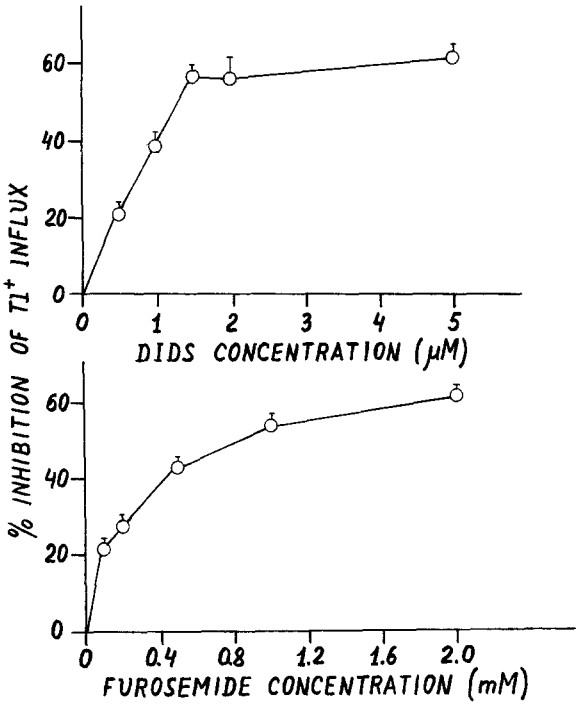

Fig. 3. Dose-response curves for the inhibition of ^{204}Tl influx by DIDS and furosemide. Erythrocytes were preincubated at 37°C for 2 min in media containing (in mM): 145 NaCl, 10 glucose, 10 Tris-HCl (pH 7.4 at 37°C) and various concentrations of inhibitors. I_{50} values were estimated graphically (0.72 μM for DIDS and 0.22 mM for furosemide).

anion transport through erythrocyte membrane. The effect of furosemide could be attributed to the inhibition of Na-K-Cl cotransport or Cl^- transport via anion exchanger [1, 3, 7, 10, 20, 24]. Further experiments were designed to investigate the effects of the inhibitors when extracellular Na^+ or Cl^- were replaced by Mg^{2+} or NO_3^-, respectively. In Na^+-free $MgCl_2$-sucrose medium the inward rate coefficient was 13.4 ± 0.8 hr^{-1} (n = 7). Under these conditions ouabain, furosemide and DIDS caused a marked inhibition of Tl^+ transport by 29, 41, and 46%, respectively (Fig. 2). The inhibitory effects of ouabain plus furosemide or ouabain plus DIDS were additive, decreasing the Tl^+ influx by 67–69% (the rate coefficients were 4.4 ± 0.5 and 4.2 ± 0.4 hr^{-1}, respectively).

Substitution of Cl^- by NO_3^- resulted in a considerable reduction of the inward rate constant down to 5.8 ± 0.2 (n = 4) and 6.2 ± 0.3 hr^{-1} for $NaNO_3$ and $Mg(NO_3)_2$-sucrose media. In Cl^--free media furosemide and DIDS produced little change in Tl^+ transport. Figure 2 shows the effects of these blockers on the rate coefficient for Tl^+ influx in various incubation media. The action of ouabain on Tl^+ transport was independent on ion composition of the media (*data not shown*). It is noteworthy that under all conditions the inhibitory effect of 1 mM furosemide was equal to that of 0.1 mM DIDS (Fig. 2). Moreover, simultaneous addition of both blockers to media did not produce an additive effect on the rate coefficient of ^{204}Tl influx (6.1 ± 0.6 hr^{-1} for DIDS and 5.7 ± 0.7 hr^{-1} for DIDS + furosemide, n = 4). In further experiments the inhibitory potency of these blockers was estimated.

Figure 3 shows the concentration-dependent effects of DIDS and furosemide on Tl^+ influx in the red cells incubated in normal saline. Furosemide produced detectable inhibition on Tl^+ transport at 0.1 mM and 50% inhibition at 0.22 ± 0.02 mM. Maximal inhibitory effect was observed at a 2-mM concentration of furosemide (60.8 ± 1.3%). The near maximal effect was achieved at 1 mM furosemide (54.0 ± 0.8%). DIDS caused a maximal effect on Tl^+ transport at a concentration of 1.5–5.0 μM (57.9 ± 2.3%): the concentration for a half-maximal inhibition was 0.72 ± 0.04 μM. Thus, DIDS was three orders of magnitude more potent in inhibition of Tl^+ transport than furosemide, but maximal effects of both blockers were similar. Taken together, the obtained data suggest the existence of a Cl^--dependent

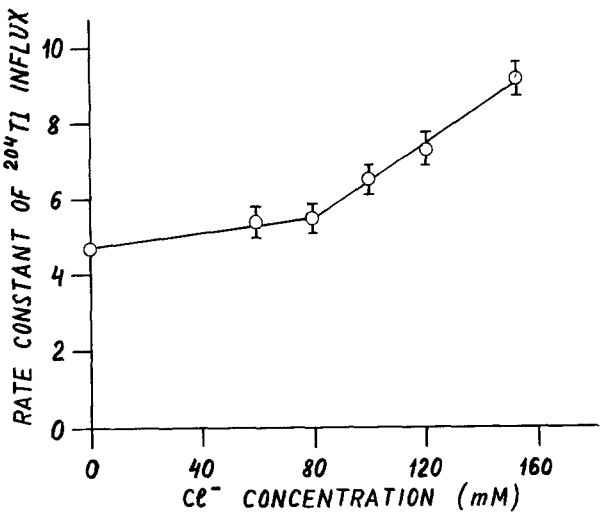

Fig. 4. Effect of chloride concentration on Tl^+ influx in human erythrocytes. The cells were washed and suspended in medium containing (in mM): 140 $NaNO_3$, 5 KNO_3, and 10 Tris-HNO_3 (pH 7.4 at 37°C). Then the suspension was added to media with various Cl^- concentrations (the sum of NO_3^- + Cl^- concentration was kept constant, 155 mM). Each point represents mean ± SE for three independent experiments.

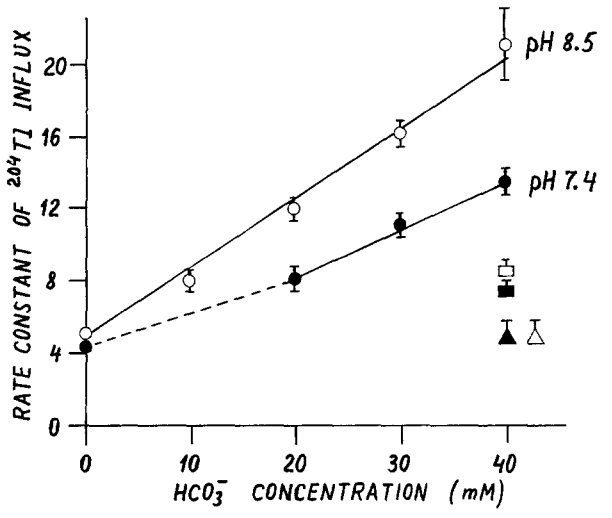

Fig. 5. Effect of bicarbonate concentration on Tl^+ influx in human erythrocytes. The erythrocytes were washed and suspended in the medium containing (in mM): 140 $NaNO_3$, 5 KNO_3, and 10 Tris-HNO_3 (pH 7.4 at 37°C) or 10 Tris-HNO_3 (pH 8.5 at 37°C). Incubation media were prepared immediately before the experiment by mixing suspending medium with 150 mM $NaHCO_3$ solution. Erythrocytes were preincubated in media for 2 min and then ^{204}Tl was added. Each point represents mean ± SE for four independent experiments. (□ and ■): effect of 1 mM furosemide in the red cells incubated with 40 mM HCO_3^- at pH 7.4 and pH 8.5, respectively. (△, ▲): effect of 0.05 mM DIDS in media with 40 mM HCO_3^- at pH 7.4 and pH 8.5. Effect of HCO_3^- concentration below 20 mM at pH 7.4 was not studied (broken line).

pathway for Tl^+ entry in human erythrocytes inhibited by DIDS and furosemide. It is known that DIDS-sensitive transport of some cations (Na^+, Li^+, Pb^{2+}, and Zn^{2+}, Cu^{2+}) in human red blood cells is coupled with HCO_3^- and occurs via an anion exchanger [2, 5, 10, 22, 32]. Special experiments were carried out to estimate the ability of Cl^- and HCO_3^- in activation of Tl^+ transport.

Dependence of Tl^+ Influx on Concentration of Cl^- and HCO_3^-

Erythrocytes were washed and suspended in $NaNO_3$ medium. Then they were transferred to incubation media containing various concentrations of Cl^- or HCO_3^- (the sum of NO_3^- and Cl^- or HCO_3^- being constant, 155 mM). Active transport of Tl^+ was inhibited by 5 mM K^+ in the media [34]. Figure 4 shows that the increase of Cl^- concentration up to 60 and 80 mM caused only a small activation of Tl^+ influx (5.4 ± 0.4 hr^{-1} and 5.5 ± 0.3 hr^{-1}, respectively) as compared with Cl^--free media (4.7 ± 0.2 hr^{-1}). The rate coefficient of Tl^+ influx increased linearly with the Cl^- concentration from 80 to 155 mM, with a slope of 0.048 hr^{-1} (mM Cl)$^{-1}$.

The addition of HCO_3^- to $NaNO_3$ medium caused considerable activation of Tl^+ influx (Fig. 5). The inward rate coefficient increased from 4.4 ± 0.2 hr^{-1} in NO_3^--medium to 8.2 ± 0.4 hr^{-1} in the presence of 20 mM HCO_3^-. The increase of HCO_3^- concentration up to 30 and 40 mM led to a linear rise of Tl^+ influx with the slope of 0.27 hr^{-1} per mM HCO_3^-. The increase of Tl^+ influx stimulated by 40 mM of HCO_3^- was eliminated by 0.05 mM DIDS to the value of 4.9 ± 0.2 hr^{-1} which did not differ from the control level in HCO_3^--free medium. Under similar conditions furosemide inhibits the HCO_3^--stimulated Tl^+ influx by only 66%. The stimulating effect of HCO_3^- on the Tl^+ influx was larger at pH 8.5 as compared with normal pH 7.4. At pH 8.5 the slope was 0.40 hr^{-1} per mM HCO_3^-. The effects of 10 mM HCO_3^- at pH 8.5 and of 20 mM HCO_3^- at pH 7.4 were the same. The addition of DIDS to the medium containing 40 mM HCO_3^- at pH 8.5 decreased the rate constant of Tl^+ influx to control level, while 1 mM of furosemide inhibited the Tl^+ influx by only 79% (Fig. 5).

Two experiments were carried out with erythrocytes of the same donor to compare the effect of 40 mM HCO_3^- in the presence of either Cl^- or NO_3^-. In the former case HCO_3^- increased the rate coefficient from 10.1 to 27 hr^{-1} while in NO_3^- media the influx rose from 5.2 to 15.4 hr^{-1}. Therefore, the HCO_3^--dependent component of the Tl^+ influx in Cl^- medium was higher than the NO_3^- medium (16.9 and 10.2 hr^{-1}, respectively).

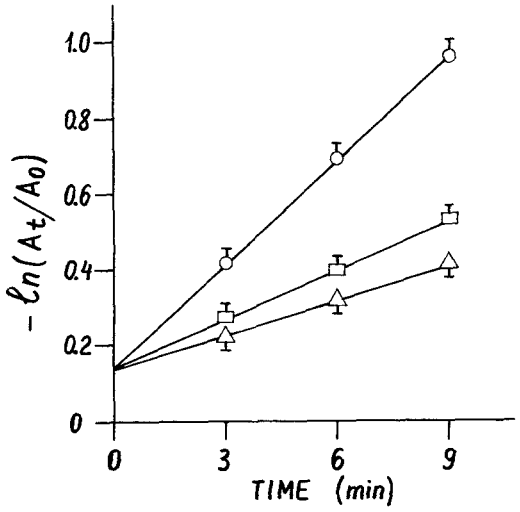

Fig. 6. Effect of DIDS and furosemide on Tl^+ efflux from human erythrocytes. Efflux was measured at 37°C in the red cells loaded with ^{204}Tl as described in Materials and Methods. Each point represents mean ± SE for three independent experiments. The zero-time intercept on the vertical axis represents the fraction of radioactivity leaking inevitably from the ^{204}Tl-loaded cells before the aliquot of suspension was injected to the efflux medium at zero time. This fraction of extracellular activity may be subtracted from the value of A_0; in this case, meanings for efflux rate coefficients would be the same.

Effects of Furosemide and DIDS on the Efflux of Tl^+

Figure 6 shows that the outward rate constant for Tl^+ was decreased by furosemide to 2.5 ± 0.2 hr^{-1} and by DIDS to 1.9 ± 0.2 hr^{-1} as compared with the control level (5.3 ± 0.2 hr^{-1}), when red cells were incubated in normal saline. In $NaNO_3$ medium the outward rate constant was 2.6 ± 0.2 hr^{-1} (n = 3). The addition of 1 mM furosemide or 0.05 mM DIDS caused no effect on the efflux of ^{204}Tl (3.2 ± 0.3 hr^{-1} and 2.7 ± 0.2 hr^{-1}, respectively).

Discussion

To our knowledge, the evidence presented here is the first demonstration of Tl^+ transport in human erythrocytes mediated by DIDS-sensitive anion exchanger. Anion-dependent transport of Tl^+ through the red cell membrane was also blocked by furosemide, known as an inhibitor of the Na-K-Cl cotransport. However, furosemide also inhibits Cl^- transport in various types of cells including human erythrocytes [1, 7, 10, 20, 24, 29]. Data from the present study demonstrate that furosemide and DIDS inhibit the same component of Tl^+ transport in human red blood cells. This conclusion is based upon the following observations. First, the effect of furosemide on Tl^+ influx does not depend on the presence of external Na^+ and K^+. Second, action of both blockers depends on the presence of Cl^- ions, being similar in the magnitude of inhibitable fluxes (Fig. 2). Third, concentrations of DIDS (0.72 μM) and furosemide (0.22 mM) providing a half-maximal inhibition of Tl^+ influx are close to those required for the inhibition of Cl^- transport across the human red cell membrane [7, 20, 23]. Last, furosemide and DIDS inhibit both the influx and efflux of Tl^+ in Cl^- media. The maximal effects of these inhibitors were similar, but DIDS proved to be much more potent compared to furosemide. The latter in a concentration of 1 mM failed to cause a complete inhibition of the HCO_3^--stimulated transport of Tl^+ as well as the Tl^+ efflux in Cl^- medium (Figs. 5 and 6).

In the present study the DIDS-sensitive transport of Tl^+ occurs in the presence of Cl^- or HCO_3^-, suggesting formation of ion pairs of Tl^+ with these anions. The DIDS-sensitive influx of Tl^+ is twofold activated after increasing of Cl^- concentration from 80 to 155 mM in the medium or HCO_3^- concentration from 20 to 40 mM (Figs. 4 and 5). These results are associated with the data [20, 23, 38] that the anion exchanger possesses a relatively low affinity to Cl^- as compared with HCO_3^- ions. The value of HCO_3^--dependent Tl^+ influx was found to be higher at pH 8.5 than at pH 7.4. This difference could be due to the increase of HCO_3^- (CO_3^{2-}) concentration and, as a consequence, to the increase of concentration of ion pairs.

It has been demonstrated [2, 5, 10, 32, 36] that transport of some cations (Na^+, Li^+, Pb^{2+}, Zn^{2+}, and Cu^{2+}) across the human erythrocytes membrane may be mediated by the anion exchange transporter. Na^+ and Li^+ are transported through this DIDS-sensitive mechanism coupled with HCO_3^- [16]. Recently, there appeared several reports [6, 12, 15, 35, 37] demonstrating the existence of electrogenic $Na(HCO_3^-)_n$ transport via membrane of various tissues. Marked stimulation of DIDS-sensitive uptake of Pb^{2+} and Zn^{2+} by red cells can be found only in the presence of both Cl^- and HCO_3^- [22, 32, 36]. In our experiments, small activation of Tl^+ influx (1.7-fold) is observed in the red cells incubated in the simultaneous presence of both Cl^- and HCO_3^- in the medium, which cannot be explained by the stimulating influence of each of these anions. Similar to Tl^+, DIDS-sensitive Cu^{2+} uptake by human erythrocytes is also significantly stimulated by Cl^- or HCO_3^-, although a small component of this Cu^{2+} transport is observed in NO_3^- medium [2]. Cu^{2+} transport via anion exchanger is also inhibited by 0.5–1.0 mM furosemide. Our study failed to detect the saturation

of ^{204}Tl tracer transport via the anion exchanger with increasing Cl^- concentration to 155 mM or HCO_3^- concentration to 40 mM (Figs. 4 and 5). DIDS-sensitive influx of Na^+ and Li^+ in red cells was shown to be almost a linear function of HCO_3^- concentration up to 150 mM [10, 16]. Taken together, the data provide evidence for the involvement of anion exchange protein Band 3 in transport of some cations across the erythrocyte membrane. There was marked difference in transport rate via this pathway among studied anions and cations. Although chloride tracer fluxes in human red cells (rate coefficient for ^{36}Cl exchange is about 10 sec^{-1}) are $2 \cdot 10^3$-fold greater than the DIDS-sensitive fluxes of ^{204}Tl, the net flux rate of chloride [20, 23] and ^{204}Tl are comparable. On the other hand, DIDS-inhibitable influx of Pb^{2+} [32] is much faster ($4 \cdot 10^3$ hr^{-1}) than ^{204}Tl influx. Movement of alkali metals (Na^+, Li^+) through the DIDS-sensitive mechanism in the presence of HCO_3^- [5, 10, 16, 17] occurs with a low rate (about 0.02 hr^{-1}).

We succeeded in demonstrating the DIDS-sensitive Tl^+ efflux from human erythrocytes. In contrast to Tl^+ transport, the role of the anion exchange mechanism in the efflux of Pb^{2+}, Zn^{2+} and Cu^{2+} was not revealed due to the binding of these cations with intracellular proteins [2, 32, 36]. Obtained data indicate that the anion exchanger plays an important role in Tl^+ transport across human erythrocyte membrane in both directions. DIDS had no effect on steady-state distribution of ^{204}Tl over erythrocyte membrane (I.A. Skulskii, G.P. Gusev, A.O. Sherstobitov & V. Manninen, *unpublished data*).

The results obtained indicate that the anion-dependent transport of Tl^+ in human red blood cells is not mediated by the Na-K-Cl cotransport system. In contrast to our findings, several studies [3, 21, 30] have revealed Tl^+ movement via a furosemide-sensitive Na-K-Cl cotransport system in the other tissues. It should be noted that Tl^+ transport by anion exchanger, found in our study, and Tl^+ movement across the Na-K-Cl cotransport system are both Cl^- dependent and furosemide inhibitable. In smooth muscle, the involvement of the Na-K-Cl cotransport system to Tl^+ transport comes from its dependence on intra- and extracellular Na^+ concentration [21]. Cl^--dependent Tl^+ uptake by canine iliac artery also required external Na^+ and was not sensitive to DIDS [30]. However, furosemide-inhibitable, Cl^--dependent transport of Tl^+ in Ehrlich ascites cells [3] may be attributed to Na-K-Cl cotransport as well as the anion exchange transporter. It is possible that in human red cells Tl^+ fluxes through the Na-K-Cl system are too small to be observed as compared with a high rate of Tl^+ transport via other pathways. It is interesting to note that the similarity of Tl^+ and K^+ movement via different transport mechanisms [3, 9, 27] was not revealed in the case of anion-dependent transport in human red blood cells.

In summary, these studies lead to the conclusion that there are at least three distinct pathways of Tl^+ transport in human erythrocyte membrane: (i) ouabain-sensitive active transport through the Na,K pump, (ii) DIDS (furosemide)-inhibitable transport via the anion exchanger which is modulated by the concentration of Cl^- and HCO_3^-, and (iii) passive diffusion. Under physiological conditions (i.e., in the presence of 4 mM K^+ and 25 mM HCO_3^-) the ouabain-sensitive transport of Tl^+ is blocked by K^+ and more than 50% of Tl^+ entry in human erythrocytes occurs via anion exchanger protein Band 3.

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