Novel Anion Dependence of Induced Cation Transport in Malaria-infected Erythrocytes*

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Following invasion by the malaria parasite there appear in the parasitized erythrocyte new ("induced") permeation pathways that mediate the transport of a wide variety of small solutes. Although anion-selective, these pathways have a significant cation permeability and cause a substantial increase in the basal leak of cations into and out of the infected cell. In this study of human erythrocytes infected in vitro with Plasmodium falciparum it was shown that the transport of monovalent cations (Rb⁺ and choline), but not that of a nonelectrolyte (sorbitol) or a monovalent anion (lactate), via the malaria-induced pathways is strongly dependent on the nature of the anion in the suspending medium. Substitution of NO₃⁻ for Cl⁻ resulted in a 4-6-fold increase in the unidirectional influx and efflux of Rb⁺, and a 2-3-fold increase in the influx of choline via the induced pathways. By contrast, replacement of Cl⁻ with NO₃⁻ caused a slight (although not significant) decrease in the malaria-induced influx of sorbitol and lactate. Hemolysis experiments with a range of K⁺ salts revealed that the net influx of K⁺ into infected cells showed the same novel anion dependence as seen for the unidirectional flux of Rb⁺ and choline, with hemolysis occurring much faster in iso-osmotic KNO₃ and KSCN solutions than in KCl, KBr, or KI solutions. Hemolysis in the corresponding Na⁺ salt solutions was very much slower, consistent with the induced pathways being selective for K⁺ over Na⁺, and raising the possibility that the efflux of cell K⁺ via these pathways may play a role in host cell volume regulation. A number of models that would account for the anion dependence of malaria-induced cation transport are considered.

Human erythrocytes infected with the mature (trophozoite) form of the malaria parasite, Plasmodium falciparum, show increased permeability to a diverse range of small solutes including polyols, amino acids, nucleosides, and monovalent anions and cations (reviewed by Ginsburg (1988, 1990, 1994), Cabantchik (1990), Gero and Upston (1992), Gero and Kirk (1994), and Elford et al. (1995)). The available data is consistent with the view that much of this increase is mediated by a singletype of broadspecificity permeation pathway. This pathway has not yet been identified at a molecular level but has the properties of an anion-selective pore or channel (Ginsburg et al., 1985) and shows functional characteristics similar in at least some respects to those of anion-selective channels in the plasma membranes of other cell types (Kirk et al., 1993, 1994).

Despite being strongly anion-selective, the malaria-induced pathway, like a number of anion-selective channels elsewhere (Franciolini and Petris, 1990), has a significant permeability to monovalent cations. The membrane of the normal erythrocyte has a very low cation permeability and the flux of cations via the induced pathway represents a relatively large increase in the basal leak of cations into and out of the infected cell. In this study we have investigated the characteristics of malaria-induced cation permeation in infected erythrocytes. The induced transport of monovalent cations, unlike that of the nonelectrolyte sorbitol and the monovalent anion lactate, was found to vary dramatically with the nature of the permeant anion in the suspending medium, increasing markedly when Cl⁻ was replaced with either NO₃⁻ or SCN⁻. Mechanisms that might account for the unusual ion permeability properties of the malaria-induced pathway are considered.

EXPERIMENTAL PROCEDURES

Materials—[86Rb]Cl was from DuPont NEN. [14C]Choline chloride, [14C]sorbitol, and sodium L-[14C]lactate were from Amersham International. Furosemide, DIDS,¹ and p-chloromercuribenzenesulfonic acid (pCMBS) were from Sigma.

Cell Culture—Human erythrocytes (type O) infected with the ITO4 line of P. falciparum (Berendt et al., 1989) were cultured under conditions described previously (Kirk et al., 1992a). All experiments were carried out using synchronized suspensions of trophozoite-infected cells (approximately 35 post-invasion; 20-22% parasitemia), prepared using a combination of sorbitol hemolysis (Lambros and Vanderberg, 1979) and gelatin flotation (Pasvol et al., 1978). In experiments comparing uninfected cells with malaria-infected material, erythrocytes (from the same donor) were incubated in parallel with the infected cell cultures under identical conditions for at least 24 h prior to the experiment. Cell counts were made using either an improved Neubauer counting chamber or a Coulter Multisizer. Parasitemia was estimated from methanol-fixed Giemsa-stained smears.

Radioisotope Influx Measurements—The unidirectional influx of K⁺ (5 mM), choline (1 mM), sorbitol (1 mM), and lactate (1 mM) into infected and uninfected erythrocytes was estimated from the uptake of [86Rb]⁺, [14C]choline, [14C]sorbitol, and L-[14C]lactate, respectively. All radioisotope flux experiments were carried out using cells washed (× 4) then resuspended in a HEPES-buffered saline constituted using either Cl⁻ salts (125 mM NaCl, 5 mM KCl) or NO₃⁻ salts (125 mM NaNO₃, 5 mM KNO₃), together with 25 mM HEPES and 5 mM glucose with pH adjusted to 7.4.

Influx measurements were made under conditions designed to minimize fluxes via the normal host erythrocyte transport systems. In [86Rb]⁺ influx experiments cells were pretreated (for >10 min) with 0.1 mM ouabain to inhibit the Na⁺/K⁺ pump, 0.01-0.1 mM bumetanide to inhibit the NaKCl₂ cotransporter, and 0.01-0.02 mM nitrendipine to inhibit the Ca²⁺-activated K⁺ channel (Ellory et al., 1992). In choline influx experiments the use of an extracellular choline concentration of 1 mM ensured that the endogenous erythrocyte choline carrier (which

¹ The abbreviations used are: DIDS, 4,4′-disothiocyanostilbene-2,2′-disulfonic acid; pCMBS, p-chloromercuribenzenesulfonic acid.
has a $K_{m}$ of approximately 10 μM) was fully saturated and therefore contributed little to choline uptake (Kirk et al., 1994). Lactate influx into malaria-infected cells was measured in cells pretreated (for 10 min) with 0.01-0.02 mM DIDS to inhibit transport via the erythrocyte band 3 anion exchanger and 0.1 mM pCMBS to block the normal erythrocyte monocarboxylate transporter (Poole and Halayesrap, 1993). Unidirectional influx rates for all substrates were estimated from the amount of radiolabel accumulated by the cells during a fixed incubation period, found in preliminary experiments to fall within the initial linear phase of the uptake time course. For $^{86}$Rb$^{+}$ and $[^{14}$C]choline the incubation period was 10 min, for sorbitol, 1 min, and for lactate, 5-10 s. Influx experiments were carried out at room temperature (~22°C) unless otherwise stated.

Radionuclide solution was measured using two different protocols. For $^{86}$Rb$^{+}$ and choline, influx experiments commenced with the addition of $^{86}$Rb$^{+}$ or $[^{14}$C]choline, together with unlabelled substrate, to a microcentrifuge tube containing cells (± furosemide). The final sample volume was 0.5 ml, the final cell concentration typically $2 \times 10^{8}$ cells/ml, and the final concentration of radioactivity was 1 μCi/ml. The flux was terminated by transferring aliquots (0.11 ml) of the suspension to microcentrifuge tubes containing 0.8 ml of ice-cold stopping solution (HEPES-buffered, Cl$^{-}$ containing saline supplemented with 0.1 mM furosemide; Kirk et al. (1994)) layered over 0.5 ml of dibutylphthalate. The tubes were centrifuged immediately ($10,000 \times g, 20$ s) to sediment the cells below the oil. For the more rapidly transported substrates, sorbitol and lactate (Kanaani and Ginsburg, 1991), influx was measured using an alternative approach. A microcentrifuge tube containing 0.15 ml of saline (with radiolabeled substrate, unlabelled substrate and, where appropriate, transport inhibitors), layered over 0.2 ml of dibutylphthalate, was placed in a microcentrifuge. The flux commenced with the addition of an aliquot of cell suspension, giving a final cell concentration of approximately $2 \times 10^{8}$ cells/ml and a final concentration of radioactivity of 1 μCi/ml. The flux was terminated at the appropriate time by starting the centrifuge ($10,000 \times g, 20$ s), thereby sedimenting the cells below the oil. The time taken between starting the centrifuge and termination of the flux was estimated as 2 s (by extrapolation of data from short time course experiments) to infer the half-life.

In all experiments, following sedimentation of the cells below the oil, the aqueous supernatant solution was removed by aspiration and the radioactivity remaining on the walls of the tube removed by rinsing the tubes four times with water. The dibutylphthalate was aspirated, then the cell pellet was lysed with 0.1% (v/v) Triton X-100 (0.5 ml) and deproteinized by the addition of 5% (w/v) trichloroacetic acid (0.5 ml), followed by centrifugation (10,000 $\times g, 10$ min). Radioactivity was measured using a $\beta$-scintillation counter.

In the $^{86}$Rb$^{+}$ and $[^{14}$C]choline influx experiments, the extracellular space in the cell pellets was estimated from the amount of $^{86}$Rb$^{+}$ or $[^{14}$C]choline in pellets derived from aliquots of the flux suspension sampled (into microcentrifuge tubes containing 0.8 ml of ice-cold stopping solution layered over 0.5 ml of dibutylphthalate) and centrifuged within a few seconds of combining the cells and radiolabel. In the shorter sorbitol and lactate influx experiments, the amount of radiolabel trapped in the extracellular space within the cell pellets was estimated from the amount of $[^{14}$C]sorbitol or $[^{14}$C]lactate in pellets sampled (within <2 s of combining the cells and the radiolabeled substrate) from suspensions containing 0.1 mM furosemide to block influx (Kirk et al., 1994).

In order to average data obtained in experiments done on different parasitized cell cultures, the measured transport rates were corrected for parasitemia. The malaria-infected cell component was calculated by subtracting the flux measured in uninfected cells from that measured in infected cell cultures. The degree of parasitemia was estimated by the addition of either the solid salt or the hypo-osmotic HEPES + glucose solution to lie within the range 298–306 mosmol kg$^{-1}$ H$_2$O$^{-1}$.

Prior to beginning the time courses, cells in RPMI (supplemented with 40 mM HEPES, 10 mM glucose, and 2 mM glutamine) were pretreated for 10–20 min at room temperature with ouabain (0.1 or 0.5 mM ouabain and 0.1 mM furosemide) or with 10 mM bumetanide (both for 5 min) to inhibit the erythrocyte Na$^{+}/K^{+}$ pump and Ca$^{2+}$-activated $K^{+}$ channel, respectively (Ellory et al., 1992). Time courses commenced with the addition of a 0.2-ml aliquot of the infected cell suspension to 3.3 ml of iso-osmotic Na$^{+}$ or K$^{+}$ solutions (containing 0.1 mM ouabain and 0.01 mM nitrendipine) to give a cell concentration of approximately 0.5 $\times 10^{8}$ cells/ml. At predetermined intervals, 0.5-ml aliquots of the suspension were transferred to microcentrifuge tubes containing 0.5 ml of ice-cold stopping solution (400 mM sucrose in H$_2$O). The tubes were centrifuged for 30 s then 0.9 ml of the supernatant solution was transferred to another tube for the subsequent spectrophotometric (A$_{540}$) estimation of hemoglobin concentration.

In all such experiments the A$_{540}$ value corresponding to full hemolysis of trophozoite-infected erythrocytes was estimated from the final A$_{540}$ value achieved in the supernatant solution from infected cells suspended in an iso-osmotic sorbitol solution (Ginsburg et al., 1985; Kirk et al., 1994).

RESULTS

Human erythrocytes infected with P. falciparum trophozoites show increased rates of transport of a diverse range of solutes. The available data is consistent with the view that much of the increased transport is via a single type of pathway that is inhibited by the anion transport blocker, furosemide (Kirk et al., 1994). The phenomenon is illustrated in Fig. 1 which shows the rates of influx of four different solutes (two monovalent cations (K$^{+}$ and Na$^{+}$) and choline), a nonelectrolyte (sorbitol), and a monovalent anion (lactate) into uninfected cells and infected cells (± furosemide) in the presence of reagents that inhibit the endogenous transport systems of the normal human erythrocyte. As is clear from the relative influx rates, induced transport is anion-selective: the furosemide-sensitive flux of the monovalent anion, lactate, was several orders of magnitude greater than that of the monovalent cations K$^{+}$ and choline, with that of the uncharged polyol, sorbitol, falling in between.

The malaria-induced influx of the two cations, but not that of...
sorbitol or lactate, increased markedly on replacement of Cl\(^-\) with NO\(_3\)\(^-\) in the suspending medium. This is illustrated in Fig. 2 which shows the furosemide-sensitive flux component for the four solutes in the two different media. The influx of K\(^{+}\)(86Rb\(^{+}\)) via the furosemide-sensitive pathway was 4–6-fold higher in the NO\(_3\)\(^-\) solution than in the Cl\(^-\) solution (p = 0.001, paired two-tail t-test). The induced influx of sorbitol was also substantially (2–3-fold) higher in NO\(_3\) than in Cl\(^-\) (p = 0.005). By contrast, the induced influx of both sorbitol and lactate was marginally (although not significantly) slower in the NO\(_3\) solution than in the Cl\(^-\) solution.

The data in Fig. 2 are from experiments carried out at 22 °C. In experiments at 37 °C (not shown) a very similar (4–6-fold) stimulation of 86Rb\(^+\) influx and (2–3-fold) stimulation of sorbitol influx was seen on replacement of Cl\(^-\) with NO\(_3\)\(^-\).

One possible explanation for the stimulatory effect of NO\(_3\) on the malaria-induced cation influx is that the replacement of Cl\(^-\) with NO\(_3\) caused a hyperpolarization of the cell membrane, resulting in an increased electrical driving force for the influx of cations via a conductive pathway. To investigate this possibility we tested the effect of NO\(_3\) on the influx of 86Rb\(^+\) via the malaria-induced pathway. Fig. 3 shows representative time courses for the influx of 86Rb\(^+\) from cells preloaded with radio-label, washed in isotonic Cl\(^-\) or NO\(_3\)\(^-\) medium, then resuspended in the same solution with or without furosemide. The inset shows the rate constants for the furosemide-sensitive component of 86Rb\(^+\) efflux, averaged from four experiments on cells from different donors. As in the influx experiments (Fig. 2), replacement of Cl\(^-\) with NO\(_3\) caused a 4–6-fold increase in furosemide-sensitive 86Rb\(^+\) efflux (p < 0.001). The stimulatory effect of NO\(_3\) on cation influx was therefore not due to a change in electrical driving force but represents a genuine increase in the cation permeability of the induced transport mechanism.

The concentration dependence of the effect of NO\(_3\) on the influx of 86Rb\(^+\) via the malaria-induced pathway is shown in Fig. 4. Furosemide-sensitive 86Rb\(^+\) influx increased in a slightly curvilinear manner with increasing NO\(_3\) and decreasing Cl\(^-\) concentration.

The effect of different anions on the induced cation permeability of malaria-infected erythrocytes was investigated in more detail using a hemolysis technique that has been used previously to investigate the induced permeability of malaria-infected erythrocytes (Ginsburg et al., 1985; Kirk et al., 1994). On suspension of cells in an iso-osmotic solution of a compound that is more permissive than the intracellular solutes, influx of solute into the cells exceeds efflux. This leads to uptake of water, cell swelling, and eventual lysis, the rate of which provides a semi-quantitative measure of the rate of influx of the extracellular solute(s).

Trophozoite-infected cells suspended in iso-osmotic sorbitol solution at 22 °C hemolyzed within 30 min, consistent with the high permeability of the malaria-induced pathway to this polyol (Fig. 5). Infected cells suspended in an iso-osmotic KNO\(_3\) solution (Fig. 5B) were almost fully hemolyzed within 3 h but were protected against hemolysis by 0.1 mM furosemide, consistent with a role for the furosemide-sensitive pathway in mediating the influx of KNO\(_3\). Cells in KSCN hemolyzed at a similar rate to those in KNO\(_3\) while those in KI, KBr, and KCl lysed more slowly. Uninfected cells were stable in all of the media tested (not shown). The data indicate that the malaria-induced transport of K\(^+\), like that of Rb\(^+\), was strongly dependent on the nature of the permeant anion present, being substantially greater in NO\(_3\) than in I\(^-\), Br\(^-\), or Cl\(^-\).

Fig. 5A shows the results of a similar experiment carried out...
The membrane of the normal (uninfected) human erythrocyte has a relatively low permeability to cations. Thus, although the pathway that mediates the increased permeability of \textit{P. falciparum}-infected erythrocytes shows a marked preference for anions and nonelectrolytes over cations (Ginsburg et al., 1985; Kirk et al., 1994; Figs. 1 and 2 of the present study), the low but significant flux of cations via this pathway represents a large relative increase in the basal cation permeability of the infected cell.

In this study, the rate of transport of monovalent cations in malaria-infected cells was found to be strongly dependent upon the nature of the anion present. The unidirectional influx and efflux of $^8$Rb$^+$ via the induced pathway increased 4–6-fold on replacement of Cl$^-$ with NO$_3^-$ in the medium (Figs. 2–4). The same maneuver caused a 2–3-fold increase in induced choline influx (Fig. 2). The observation that both the influx and efflux of $^8$Rb$^+$ were affected to the same extent indicates that the effect cannot be explained in terms of altered electrical driving forces following anion substitution, but represents a genuine difference in the cation permeability of the pathway in the presence of the different anions.

The time courses of hemolysis of parasitized cells in iso-osmotic solutions of a range of different K$^+$ salts (Fig. 5B) indicate that the net flux of K$^+$ via the malaria-induced pathway showed a similar anion dependence to that seen in the (unidirectional) $^8$Rb$^+$ flux experiments. They also provide further information on the effects of different anions on the pathway: induced K$^+$ transport was substantially greater in NO$_3^-$ and SCN$^-$ than in I$^-$, Br$^-$, or Cl$^-$ media.

The anion dependence of K$^+$, Rb$^+$, and choline transport via the malaria-induced pathway is quite unlike that of the well known cation/anion cotransporters which, in contrast to the induced pathway, carry cations much better in the presence of Cl$^-$ and Br$^-$ than in the presence of NO$_3^-$ or SCN$^-$. In marked contrast to the situation in the various iso-osmotic K$^+$ salt solutions, trophozoite-infected cells in iso-osmotic solutions of the corresponding Na$^+$ salts showed little if any hemolysis over a 3-h period (Fig. 5A). Without knowing the respective rates of Na$^+$ and K$^+$ ions once inside the infected erythrocyte, it is not possible to draw quantitative conclusions about the rates of transport of these two cations. However, the data are consistent with the malaria-induced pathway having a substantially higher permeability to K$^+$ than to Na$^+$. It is unclear how a pathway that is permeable to molecules as large as nucleosides (Kirk et al., 1994; Upston and Gero, 1995) might discriminate between these two alkali metal cations. However, whatever the physical basis of this apparent selectivity, it may have important implications for the physiological role of the induced pathway. Any “leak” pathway that is present in the cell membrane and that is selective for K$^+$ over Na$^+$ has the potential to play a role in cell volume regulation. Under physiological conditions such a pathway would mediate the net efflux of K$^+$ (with Cl$^-$), down its electrochemical gradient (while not allowing a corresponding influx of Na$^+$), resulting in a loss of cell water and a consequent decrease in cell volume. The present results therefore raise the possibility that the induced transport pathway plays an important role in host cell volume regulation, mediating the net efflux of K$^+$ from the parasitized cell (as well as that of amino acids resulting from the digestion of hemoglobin; Zarchin et al. (1986)), thereby countering the effect on cell volume of the growth of the intracellular parasite.

In contrast to the dramatic increase in the rate of induced cation transport on replacement of Cl$^-$ with NO$_3^-$ (or SCN$^-$), the induced transport of the nonelectrolyte, sorbitol, and the monovalent anion, lactate, was slightly (although not significantly) slower in NO$_3^-$ than in Cl$^-$ media (Fig 2). Any model of the malaria-induced pathway should therefore account for why the permeation of cations is strongly anion-dependent, whereas the permeation of nonelectrolytes and anions is not. Fig. 6A shows a schematic representation of the induced pathway in which it is represented as an anion-selective channel bearing a positive charge or dipole, as well as a hydrophobic region, represented by the shaded area. The positive charge or dipole would provide the anion-selectivity filter, allowing the passage of anions and uncharged solutes, but repulsing cations. The hydrophobic region would account for the previously described preference of the pathway for hydrophobic over similarly sized hydrophilic solutes (Ginsburg et al., 1985; Ginsburg and Stein, 1987; Kirk et al., 1994).
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There are a number of ways in which anions might facilitate the passage of cations via a channel of this sort, by interacting either with the channel or with the permeating cation. As represented in Fig. 6, B (i), a permeant anion may enter the channel and bind at the cationic site, thereby shielding the cationic site and neutralizing its charge. Similarly, in model (ii) the nature of the anion is unlikely to affect the permeation of nonelectrolytes and anions, unless the cation:anion pairs have some tendency to block the pathway.

In summary, the transport of cations but not that of nonelectrolytes or anions via the pathway induced in human erythrocytes by the malaria parasite showed a marked dependence on the nature of the anion in the suspending medium, increasing severalfold when Cl\(^{-}\) was replaced by NO\(_3\)\(^{-}\) or SCN\(^{-}\). A number of models of ion permeation might account for this effect. A comparison of the rates of hemolysis of malaria-infected cells suspended in iso-osmotic solutions of a range of Na\(^+\) salts indicates that the new permeation pathway is selective for K\(^+\) over Na\(^+\). This is consistent with a physiological role for this pathway in mediating the volume regulatory efflux of K\(^+\) from the malaria-infected cell and thereby playing an important role in host cell volume control.

**Fig. 6.** Alternative models of solute permeation through the malaria-induced pathway. A, the pathway is represented as a channel containing a hydrophobic region (shaded area) and a positive charge or dipole which provides the anion selectivity filter, allowing the passage of anions and uncharged solutes, but repulsing cations. In the model represented by B, (i), permeant anions enter the channel and bind at the positive site, thereby neutralizing it and allowing the flux of cations through the pathway. In the model represented by B, (ii), cations permeate the channel as electronneutral cation:anion pairs. Both models would account for the pronounced anion dependence of cation permeation of the induced pathway, as well as the observation that the transport of nonelectrolytes and anions is little affected by anion substitution. C, shows the interaction of an inhibitor with the channel. The most potent inhibitors so far identified of malaria-induced solute transport (including furosemide) are all monovalent anions with a carboxylate group at one end and a relatively large hydrophobic “tail.” The anionic carboxylate group would be expected to interact with the cationic site on the channel and the hydrophobic tail with the hydrophobic region of the pathway.

Both models would account for the lack of stimulation of the flux of nonelectrolytes and anions via the pathway under conditions in which cation transport is increased. If, in model (ii), the permeant anion interacting with the cationic site actually restricts the passage of solutes through the pathway, substitution of Cl\(^{-}\) with an anion that spends a greater time at this site might slow the flux of non-cationic solutes through the pathway (as was observed for sorbitol and lactate on substitution of Cl\(^{-}\) with NO\(_3\)\(^{-}\); Fig. 2). In model (ii) the nature of the anion is unlikely to affect the permeation of nonelectrolytes and anions, unless the cation:anion pairs have some tendency to block the pathway.

Fig. 6C shows a representation of the interaction of an inhibitor with the channel. The most potent inhibitors so far identified of malaria-induced solute transport (including furosemide) are all monovalent anions with a carboxylate group at one end and a relatively large hydrophobic “tail.” The anionic carboxylate group would be expected to interact with the cationic site on the channel and the hydrophobic tail with the hydrophobic region of the pathway. A recent structure-activity analysis with a series of analogues of the widely used Cl\(^{-}\) channel blocker, 5-nitro-2-(3-phenylpropylamino)benzoic acid, indicated that the potency with which these compounds inhibited the malaria-induced pathway increased with the length and hydrophobicity of the tail (Kirk and Horner, 1995). This is consistent with the present model in which increasing the hydrophobicity of the inhibitor might be expected to strengthen the hydrophobic interaction between the inhibitor and the channel.

The basic features of the model represented in Fig. 6 are not fundamentally different from those of the model proposed by Ginsburg and Stein (1987), in which the malaria-induced pathway and those of a number of anion-selective channels elsewhere (e.g. Kirk et al. (1992)), it is perhaps worth considering whether a similar model (in which solutes traverse the membrane via a pathway formed at a protein-lipid interface) might be applicable to some of these other channels.

**Acknowledgments**—We are grateful to Barry Elford, Clive Ellory, and Chris Newbold for numerous stimulating discussions and for their ongoing interest and support.

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