Transport of Divalent Cations with Tetracycline as Mediated by the Transposon Tn10-encoded Tetracycline Resistance Protein*

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Tetracycline uptake into inverted membrane vesicles from Tn10-bearing Escherichia coli cells required divalent cations. The degree of the stimulation of tetracycline uptake by various divalent cations showed the following decreasing order: Co<sup>2+</sup> > Mn<sup>2+</sup> > Mg<sup>2+</sup> > Cd<sup>2+</sup> > Ca<sup>2+</sup>. This order is consistent with the increasing order of the dissociation constants for metal chelate complexes of tetracycline. The Hill constants for the tetracycline uptake rate with various divalent cation concentrations were one. These observations strongly suggested that a 1:1 complex of tetracycline and a divalent cation was transported by a tetracycline resistance protein.

This notion was confirmed by our observations that <sup>60</sup>Co<sup>2+</sup> was actively taken up with tetracycline by the membrane vesicles prepared from resistant cells. In the absence of tetracycline, no uptake of <sup>60</sup>Co<sup>2+</sup> was observed. It is clear that the <sup>60</sup>Co<sup>2+</sup> uptake was mediated by the tetracycline resistance protein, because the membrane vesicles from tetracycline-sensitive cells did not show the uptake of <sup>60</sup>Co<sup>2+</sup> and tetracycline. The <sup>60</sup>Co<sup>2+</sup> uptake was inhibited in the presence of tetracycline, indicating that these cations are also transported with tetracycline by the tetracycline resistance protein.

Among the mechanisms underlying bacterial resistance to antibiotics, the tetracycline resistance mediated by a plasmid-encoded resistance gene is a unique system, because the resistance is based on the active efflux of the drug out of the cells (1, 2). Similar mechanisms based on efflux are known for the bacterial resistance to some poisons and heavy metals (3-8). Arsenate and arsenite efflux systems (8, 9) coded by genes on plasmids are primary ATP-driven anion pumps (8, 10), whereas cadmium (3) and ethidium (5) are excreted by cation/proton antiporters coded by the resistance plasmids. Tetracycline is excreted by similar antiporters coupled with proton influx in resistant cells (2, 11). Tetracycline molecules are mainly present as the protonated (neutral) or monoanionic form at physiological pH (12). However, the exchange between tetracycline and protons was an electrically neutral reaction for the bacterial resistance to some poisons and heavy metals (3-8). 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When the initial rate of the tetracycline uptake in the presence of a constant tetracycline concentration (10 μM) was plotted against cation concentrations, a saturation curve was observed with all cations tested (Fig. 2A). The kinetic constants (Km and Vmax) of the tetracycline uptake with these cations were estimated from the initial uptake rate by means of three methods (Lineweaver-Burk plotting, Hanes-Woolf plotting, and Eadie plotting) (Table I). Except for Cd++ ion, the three methods gave similar values for each cation. On the other hand, the kinetic constants for the uptake with Cd++ varied significantly depending on the method used, suggesting that the uptake did not follow simple Michaelis-Menten type kinetics. Among the cations tested, Co++ showed the smallest Km and the largest Vmax values (Table I), consistent with the results shown in the figure 1. Both the increasing order of the Km value and the decreasing order of the Vmax values (Table I) were in agreement with the decreasing order of the stimulating effect (Fig. 1). Excess tetracycline could not be used for this assay, because high concentration of tetracycline increased the non-carrier-mediated permeation of tetracycline across the membrane (data not shown). Thus, Km values for divalent cations estimated above may reflect the stability of metal-tetracycline complexes.

Next the initial rate of tetracycline uptake in the presence of an excess divalent cation (500 μM) was plotted against tetracycline concentrations by the method of Hanes-Woolf plotting (data not shown). In this case, Km values for tetracycline were approximately similar (20-50 μM) regardless of the cation species present (Table II). Thus, the affinity of the carrier protein to tetracycline or its metal-chelate complex was not affected by the carrier species. On the other hand, the turnover rate of the transport carrier protein for tetracycline (Vmax) was dependent on the cation species (Tables I and II).

The initial rate of tetracycline uptake at a constant tetra-


TABLE II

| Cation | $K_m$ for tetracycline (μM) | $V_{max}$ (nmol/mg/min) |
|--------|---------------------------|-------------------------|
| Co$^{2+}$ | 24                        | 87                      |
| Mn$^{2+}$ | 22                        | 4.9                     |
| Mg$^{2+}$ | 49                        | 2.6                     |
| Ca$^{2+}$ | 23                        | 0.5                     |

TABLE III

Dissociation constants for metal chelate complex of tetracycline

Concentrations of metal-chelate complexes were determined in the presence of 10 μM tetracycline and various concentrations (5-3000 μM) of divalent cations. Dissociation constants ($K_d$) were calculated from the slope of the Scatchard plot.

| Cation | $K_d$ (μM) |
|--------|------------|
| Co$^{2+}$ | 20         |
| Mn$^{2+}$ | 266        |
| Mg$^{2+}$ | 427        |
| Ca$^{2+}$ | 726        |

Divalent Cation Transport by the Tetracycline Resistance Protein

The rates of [3H]tetracycline uptake for initial 15 s were measured at 500 μM of divalent cations and various concentrations (2-40 μM) of tetracycline as described under “Experimental Procedures.” The net uptake rate was calculated by subtracting the rate in the absence of divalent cations. The data were plotted to tetracycline concentration by Hanes-Woolf plot, and the kinetic constants were calculated from the plot.

![Graph](http://www.jbc.org/)

**Fig. 3.** Cobalt ion uptake by inverted membrane vesicles from the tetracycline resistant cells (A) or sensitive cells (B). Symbols: □, without NADH and tetracycline; ▲, 2.5 mM NADH; ○, 10 μM tetracycline; ●, 10 μM tetracycline and 2.5 mM NADH; ■, 10 μM tetracycline, 2.5 mM NADH and 20 μM CCCP.

**Fig. 4.** Inhibition of $^{60}$Co$^{2+}$ uptake by Mg$^{2+}$. The uptake for initial 1 min by inverted membrane vesicles from the resistant cells was measured under the indicated concentrations of MgSO$_4$.

The tetracycline molecule has three dissociable protons (18). The major molecular species at pH 7.5 are the monovalent anion (TH$^-$) and the neutral form (TH,). The anionic form of tetracycline easily forms a chelate complex with a wide variety of divalent cations (13, 19-21). The concentration of a chelate complex in 50 mM MOPS-KOH buffer (pH 7.5) was measured, and the dissociation constant ($K_d$) of the metal-tetracycline complex was estimated from Scatchard plots (Table III). The $K_d$ value for the complex differed widely depending on the cation species. The increasing order of the $K_d$ values was in agreement with the decreasing order of the stimulation of the tetracycline uptake by these cations. It seems unlikely that the free tetracycline molecules are a substrate for the transport carrier protein, because a lower $K_d$ value should result in a lower concentration of free tetracycline. The coincidence between the orders of the $K_d$ and $K_m$ values for various cations (Table I) indicates that the substrate of the carrier protein is a metal-chelate complex of tetracycline, and the differences in the $K_m$ value is due to a difference in the stability of the metal-tetracycline complex.

**Cobalt Ion Uptake by Inverted Membrane Vesicles from Tetracycline-resistant Cells**—The uptake of $^{60}$Co$^{2+}$ by inverted membrane vesicles prepared from tetracycline resistance cells was measured in the presence and absence of an energy source (NADH) and tetracycline (Fig. 3A). In the absence of tetracycline, no significant uptake of $^{60}$Co$^{2+}$ was detected, although the reaction mixture was well supplied with NADH. When 10 μM tetracycline was present, a very little, but significant, amount of $^{60}$Co$^{2+}$ was taken up even in the absence of NADH (possibly downhill transport of Co$^{2+}$-tetracycline complex). This $^{60}$Co$^{2+}$ uptake was greatly stimulated by the addition of NADH. The $^{60}$Co$^{2+}$ uptake due to the addition of NADH was completely inhibited by the addition of CCCP. Therefore, it is clear that the $^{60}$Co$^{2+}$ was taken up with tetracycline driven by a proton motive force. $^{60}$Co$^{2+}$ uptake by vesicles prepared from tetracycline-sensitive cells was not observed (Fig. 3B). These results indicate that the $^{60}$Co$^{2+}$ uptake was mediated by the tetracycline resistance gene.

**Inhibition of Cobalt Ion Uptake by the Magnesium Ion**—If $^{60}$Co$^{2+}$ is taken up by inverted vesicles as a metal-chelate complex with tetracycline, the $^{60}$Co$^{2+}$ uptake should be inhibited by the addition of other chelate-forming cations. When Mg$^{2+}$ was added to the assay mixture, the uptake of $^{60}$Co$^{2+}$ was competitively inhibited (Fig. 4) without concomitant inhibition of the tetracycline uptake (data not shown). $^{60}$Co$^{2+}$ uptake in the presence of Mg$^{2+}$ was approximately proportional to the concentration of Co$^{2+}$-tetracycline complex calculated from the dissociation constants of the Co$^{2+}$-tetracycline and Mg$^{2+}$-tetracycline complexes. These results indicated that the Mg$^{2+}$-tetracycline complex was formed and taken up into vesicles.

**The Effect of Ionophores on the Transport of Cobalt Ion with Tetracycline**—Tetracycline uptake into inverted vesicles is inhibited by CCCP or nigericin, but valinomycin rather stimulates the uptake (11). $^{60}$Co$^{2+}$ uptake into inverted vesicles showed the same behavior; CCCP or nigericin inhibited the uptake, whereas valinomycin stimulated the uptake by a
factor of about 1.4 in the presence of 0.1 M KCl (data not shown), indicating the electrically neutral nature of the Co²⁺-tetracycline transport driven by antiport with proton.

When tetracycline and Co²⁺ uptake was stopped by the addition of CCCP (or nigericin), tetracycline leaked out slowly from the vesicles without any significant leakage of Co²⁺ (Fig. 5), possibly due to the binding of Co²⁺ at the inner surface of the vesicles. On the other hand, when gramicidin S was added to the reaction mixture, both Co²⁺ and tetracycline rapidly leaked out from the vesicles (Fig. 5), because gramicidin S competitively removes bound cations from a membrane (22) due to its polycationic nature. Gramicidin D, which is an ionophore similar to gramicidin S but has no polycationic nature, caused no such rapid efflux of Co²⁺ and tetracycline (data not shown).

**DISCUSSION**

The experiments described in the present paper showed that a divalent cation was transported with tetracycline by the TnlO tetracycline resistance protein, probably as a metal-chelate complex. The Kₐ values for divalent cations reflected the dissociation constants (Kd) for the metal-chelate complex. The Kₐ values for divalent cations were varied with the cation species even in the presence of excess cations. The Vₘₐₓ values may be affected by the Stokes radius of the divalent cations through the difference in the size of the metal-chelate complexes. The Stokes radius of the cations used in this study shows the following increasing order: Co²⁺ < Mn²⁺ < Mg²⁺ < Ca²⁺ (23), and this order is in agreement with the decreasing order of the Vₘₐₓ values.

The uptake of øCo²⁺ was about 2-fold greater than the [³H]tetracycline uptake under the same conditions. This is clearly different from the 1:1 stoichiometry indicated by the Hill plot.

The discrepancy may be due to the leakage of free tetracycline molecules, by diffusion, out of the vesicles through the lipid bilayer (22), as a result, the observed tetracycline uptake is underestimated. This was essentially confirmed by the fact that tetracycline actually leaked out by downhill diffusion from the vesicles without any significant leakage of Co²⁺ when the uptake was stopped by the addition of CCCP (Fig. 5), although the efflux rate was slower than that expected from the discrepancy probably due to cancelling the pH gradient by CCCP. The pH gradient is not only favorable to the TetA-mediated uptake of the chelation complex but also favorable to the diffuse back out of free tetracyclines from the vesicles. The ΔpH-driven quick diffusion of tetracycline across lipid bilayer membranes was observed in liposomes made from E. coli phospholipids.²

The reason why the carrier-mediated efflux of Co²⁺ with tetracycline from the vesicles did not occur when CCCP was added (Fig. 5B) may be as follows: the metal-chelate complexes taken up into vesicles possibly dissociate into cations and free tetracycline molecules and then cations bind to the inner surface of the vesicles, whereas free tetracycline diffuse out slowly from the vesicles through lipid bilayers (22). This assumption was supported by the observation that the rapid efflux of both the Co²⁺ and tetracycline from the vesicles occurred on the addition of gramicidin S (Fig. 5), which removes cations from the membrane due to the replacement of membrane-bound cations by the antibiotic (24), resulting in the reformation of metal-tetracycline complexes and then the rapid efflux of the complexes mediated by the transport carrier proteins.

In intact E. coli cells, energy-dependent accumulation of tetracycline is known to be driven by ΔpH but not Δψ (25) and inhibited by Mg²⁺.³ Argast and Beck (26) claimed that tetracycline permeates into the cytoplasm by diffusion, and they presented a direct evidence supporting the tetracycline diffusion through phospholipid bilayers (24). We also confirmed that tetracycline was accumulated in liposomes driven by ΔpH.² The inhibitory effect of Mg²⁺ on the uptake into the cells is probably due to the decrease in free tetracycline concentration in the medium. The resistant cells also have such a mechanism for tetracycline accumulation, although the accumulated tetracycline is actively excluded from the cells.

We propose here a model for "the tetracycline transport cycle" in the resistant cells (Fig. 6). A tetracycline molecule penetrates into the cells through lipid bilayer of the cytoplasmic membrane as a neutral form (TH₄). The diffused TH₄ dissociates into TH⁻ and proton in the cytoplasm, because intracellular pH is usually higher than that in the medium. The high intracellular concentration of Mg²⁺ (1-4 mM) may also facilitate the dissociation by the formation of Mg²⁺-tetracycline chelate complex, resulting in an intracellular accumulation of tetracycline. In the resistant cells, the chelate complex is then excluded as the substrate for the efflux system mediated by the tetracycline-resistant protein coupling with proton influx. One-to-one complex of monoanionic tetracycline and divalent cation should be a true substrate for the efflux system, because the exchange of this monocationic

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² A. Yamaguchi, H. Ohmori, and T. Sawai, unpublished observations.
³ A. Yamaguchi, H. Ohmori, and T. Sawai, unpublished data.
chelate complex for proton was electrically neutral, confirming our previous observation (11). This model was also consistent with our observation that the cells harboring TnlO showed higher level of tetracycline resistance (minimum inhibitory concentration, 200 µg/ml) at pH 6.0 than that at pH 7.0 (minimum inhibitory concentration, 120 µg/ml).

It is known that cobalt ion is taken up into E. coli cells via Mg²⁺ (14, 27) or Cd²⁺ (28) transport systems. However, the tetracycline-dependent ⁶⁰Co²⁺ uptake into the inverted membrane vesicles is independent of these systems, because Co²⁺ transport mediated by these intrinsic systems should be carried out only from inside to the outside of the inverted vesicles as these vesicles have opposite orientation from cells. The inverted vesicles from tetracycline-sensitive cells actually did not show the uptake of ⁶⁰Co²⁺ dependent on respiration.

Although the origin of the tetracycline resistance gene on plasmids is not obvious, McMurry et al. (29) reported that a very weak tetracycline efflux was induced in the susceptible E. coli cells when the cells were grown in the nutrient rich medium. The tetracycline transport mediated by the resistance gene may be originated from such intrinsic efflux systems and such systems may be in general for exclusion of toxic compounds or waste products from the cells as Mg²⁺-chelate complex.

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