Membrane vesicles prepared from cells expressing the multidrug resistance-associated protein (MRP) transport glutathione S-conjugates of hydrophobic substrates in an ATP dependent manner. Purified MRP possesses ATPase activity which can be further stimulated by anticancer drugs or leukotriene C4. However, the detailed relationship between ATP hydrolysis and drug transport has not been established. How the ATPase activity of MRP is regulated in the cell is also not known. In this report, we have examined the effects of different nucleotides on the ATPase activity of purified MRP. We have found that pyrimidine nucleoside triphosphates have little effect on enzymatic activity. In contrast, purine nucleotides dATP, dGTP, and adenosine 5′-(β,γ-imido)triphosphate function as competitive inhibitors. Somewhat unexpectedly, low concentrations of all the nucleoside diphosphates (NDPs) tested, except UDP, stimulate the ATPase activity severalfold. ADP or GDP at higher concentrations was inhibitory, reflecting NDP binding to the substrate site. On the other hand, the enhancement of hydrolysis at low NDP concentrations must reflect interactions with a separate site. Therefore, we postulate the presence of at least two types of nucleotide binding sites on the MRP, a catalytic site(s) to which ATP preferentially binds and is hydrolyzed and a regulatory site to which NDPs preferentially bind and stimulate hydrolysis. Interestingly, the stimulatory effects of drugs transported by MRP and NDPs are not additive, i.e. drugs are not able to further stimulate the NDP-activated enzyme. Hence, the two activation pathways intersect at some point. Since both nucleotide binding domains of MRP are likely to be required for drug stimulation of ATPase activity, the two sites that we postulate may also involve both domains.

The multidrug resistance-associated protein (MRP) gene was cloned from a multidrug-resistant cell line, H99AR, which was obtained by stepwise selection in increasing concentration of doxorubicin (1). A single open reading frame of 1531 amino acids was defined, and the protein was found to be a member of the ABC superfamily of transport systems (1). The multidrug resistance-associated Protein by Nucleoside Diphosphates* Stimulation of ATPase Activity of Purified Multidrug Resistance-associated Protein by Nucleoside Diphosphates

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† To whom correspondence should be addressed: Mayo Clinic Scottsdale, S. C. Johnson Medical Research Center, Mayo Clinic Scottsdale, Scottsdale, Arizona 85259

From the S. C. Johnson Medical Research Center, Mayo Clinic Scottsdale, Scottsdale, Arizona 85259

Xiu-Bao Chang, Yue-Xian Hou, and John R. Riordan

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Stimulation of ATPase Activity of Purified Multidrug Resistance-associated Protein by Nucleoside Diphosphates

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EXPERIMENTAL PROCEDURES

Materials—Tissue culture materials were from Life Technology, Inc. ATP, AMP, ADP, GDP, CTP, UTP, ITP, GTP, dADP, dGDP, UDP, CDP, dCDP, ATP-γS, AMP-PNP, AMP-CP, GSH, doxorubicin, and sheep brain lipid (5-α-phosphatidylethanolamine) were purchased from Sigma. [α-32P]ATP, [α-32P]dATP, [α-32P]GTP, wheat germ lectin-Sepharose 6MB, dATP, dGTP, dCTP, and dTTP were purchased from Amershams Pharmacia Biotech. His-Bind Resin was purchased from Novagen. Formic acid was purchased from Fisher. n-Dodecyl-β-D-maltoside was from Calbiochem. Polyethyleneimine cellulose plates were purchased from either J. T. Baker or Fisher.

Cell Lines, Cell Culture, and MRP Protein Purification—A baby hamster kidney cell line stably expressing human MRP (3) was utilized for the purification of MRP. The cells were cultured at 37 °C in 5% CO2 in the presence of 500 μM methotrexate. MRP was purified by two affinity chromatography steps as described previously (3). Briefly, the crude membrane was prepared from the MRP-expressing cells and solubilized in 1% n-dodecyl-β-D-maltoside. MRP was then bound and eluted from His-Bind Resin column and further purified by a second step affinity chromatography on wheat germ lectin-Sepharose 6MB.

Assay of ATPase Activity—ATPase activity was assayed employing a thin layer chromatography method to separate the substrates and products in the reaction mixture enabling the measurement of [α-32P]ADP

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production from the \(\alpha\)-\(32\)P\(\text{ATP}\). Unless otherwise indicated in the figure legends, the assay was carried out in a 30-mL reaction mixture containing 40 mM Tris-HCl (pH 7.4), 1 mM dithiothreitol, 10 mM MgCl\(_2\), 1 mM \(\alpha\)-\(32\)P\(\text{ATP}\), and 4 mM \(\alpha\)-\(32\)P\(\text{ATP}\). Reaction mixtures were incubated at 37 °C for 1 h, stopped by the addition of 30 mL of a solution containing 1 M formic acid and 0.5 M LiCl and transferred to ice. One-mL aliquots were spotted on a polyethyleneimine-cellulose plate and chromatographed with 0.5 M LiCl and 1 M formic acid as the solvent. The amounts of \(\alpha\)-\(32\)P\(\text{ATP}\) and \(\alpha\)-\(32\)P\(\text{ADP}\) in each reaction mixture were determined by electronic autoradiography using a Packard Instant Imager (Packard). The assay was performed in the same fashion using \(\alpha\)-\(32\)P\(\text{dATP}\) or \(\alpha\)-\(32\)P\(\text{GTP}\) as the substrate.

**RESULTS**

**Influence of Nucleoside Triphosphates on MRP ATPase—**

Initially the influence of pyrimidine nucleotides at increasing concentrations on ATP hydrolysis was examined. Neither the

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**TABLE I**

Influence of ADP on ATPase, \(\text{dATPase, and GTPase activity of purified MRP protein}

| Nucleotides       | \(V_{\text{max}}\) (\(\mu\)mol/mg MRP/min) | \(K_m\) (m M) | Hill constant |
|-------------------|-----------------------------------------|---------------|--------------|
| ATP               | 0.47                                    | 2.95          | 0.987 ± 0.076 |
| ATP + 250 \(\mu\)M ADP | 1.00                                    | 1.44          | 0.958 ± 0.099 |
| \(\text{dATP}\)   | 0.09                                    | 0.87          | 1.036 ± 0.068 |
| \(\text{dATP} + 250 \(\mu\)M ADP\) | 1.16                                    | 3.77          | 0.984 ± 0.025 |
| GTP               | 0.67                                    | 3.37          | 1.018 ± 0.046 |
| GTP + 250 \(\mu\)M ADP | 0.88                                    | 3.66          | 1.000 ± 0.049 |

The enzyme assays were performed in the presence or absence of 250 \(\mu\)M ADP and the amounts of ATP, \(\text{dATP, or GTP as substrate hydrolyzed were determined as described under “Experimental Procedures.” The \(V_{\text{max}} \text{ and } K_m \text{ values were derived from Lineweaver-Burk plots. Hill constants were calculated based on the formula } \log \left( \frac{V}{V_{\text{max}}} \right) = h \times \log[S] - \log K_m, \text{ where } v \text{ is the velocity determined under the conditions described in Fig. 2; } [S] \text{ is the nucleoside triphosphate concentration; } h \text{ is Hill constant.} \)
ribonucleotides, CTP and UTP, nor the deoxyribonucleotides, dCTP and dTTP, had a great influence on activity, except at the highest concentration of 16 mM, which exceeded the MgCl₂ concentration (10 mM; Fig. 1A). However, the mild inhibition by the deoxy compounds was stronger than that caused by the ribonucleotides. When purines were tested, dATP and dGTP inhibited more strongly (Fig. 1B), further indicating that deoxyribonucleotides are recognized by MRP. When the purine ribonucleotides, ITP or GTP, were added, there was an unexpected enhancement of activity at intermediate concentrations and inhibition at higher concentrations. This inhibition may reflect substrate competition as these two purine triphosphates are reasonable substrates for many ATPases (25–28). A non-hydrolyzable analogue of ATP, AMP-PNP, appeared to cause strictly competitive inhibition (Fig. 1C), exhibiting a $K_i$ of 1.64 mM ± 0.22.

Hydrolysis of GTP and dATP—Since both these compounds had strong effects on ATP hydrolysis by MRP, their capacity to serve as substrates was also examined. The results expressed as Michaelis-Menten curves and compared with those with ATP are shown in Fig. 2. As these curves indicate, GTP and ATP behave very similarly as substrates ($K_m$ and $V_{max}$ values are given in Table I). dATP is hydrolyzed at a greatly reduced rate, but its affinity for the catalytic site would seem to be considerably higher than that of the purine ribonucleotides on the basis of the relative $K_m$ values determined from these data (Table I). This is consistent with the ability of the deoxyribonucleoside triphosphates to inhibit ATP hydrolysis (Fig. 1, A and B).

Influence of Nucleoside Diphosphates on Hydrolysis of Triphosphate—The effects of NDP products of NTP hydrolysis on the process were investigated for two reasons. First, consistent with the proposed formation of a Mg-ADP-Pᵢ enzyme transition state complex in ATP hydrolysis by P-glycoprotein (29, 30), Mg-ADP is a strong competitive inhibitor of that reaction (25). Second, we wished to test whether the stimulatory influence of the hydrolyzable nucleoside triphosphates (Fig. 1B, ITP and GTP) was a consequence of their direct action or of their products. In view of the strong competitive inhibition of other ATPases by ADP (25), the results shown in Fig. 3A were surprising. While no influence was detected below 10 μM, both ADP and GDP at concentrations between 0.1 and 1 mM were strongly stimulatory, with the maximal effect at approximately 250 μM ADP or GDP. At concentrations in the 2 mM range, activity was not different from that with no added NDP. Only at 4 mM and higher is hydrolysis inhibited. It is notable that these biphasic curves relating activity to NDP concentration are qualitatively similar to those showing dependence on NTP concentration (Fig. 1B), the former just left-shifted with respect to the latter. Combined with the fact that the nonhydrolyzable NTP analogue, AMP-PNP, was not stimulatory (Fig. 1C), these observations suggest that the primary ability of the NDPs to promote hydrolysis might also be responsible for the apparently similar effects of the NTPs. In addition to the NDP formed during the reaction, its presence as a contaminant in...
NTP preparations might contribute. Fig. 3B indeed indicates that NDP contamination was substantial in the NTP solutions that were most stimulatory (ITP and GTP), as it was in a weakly hydrolyzable ATP analogue, ATPγS. To further test the apparent correlation between the presence of NDP and stimulation, the effect of ATPγS on the hydrolysis of ATP was evaluated (Fig. 3C). In contrast to AMP-PNP, which appeared free of NDP and acted strictly as a competitive inhibitor (Fig. 1C), the ADP-contaminated ATPγS had an effect quite similar to ITP or GTP.

Hence, it would appear that NDPS either formed during hydrolysis of the purine NTPs that are substrates of MRP ATPase or present as contaminants are able to stimulate NTP hydrolysis. This strongly suggests the presence of regulatory site(s) with higher affinity for NDPS than for NTP substrates, separate from hydrolytic site(s) specific for NTPs. As these NTP substrates include deoxyribonucleoside triphosphates, we wondered if dNDPS were active at the regulatory site. Fig. 3D indicates that they apparently are as 250 μM or 1 mM dADP or dGDP are as stimulatory as ADP. CDP, dCDP, and the nonhydrolyzable ADP analogue, AMP-CP, also exerted stimulatory effects (Fig. 3D). Of all the nucleoside diphosphates examined, UDP was the only one that was not stimulatory (Fig. 3D).

In contrast to NTPs and NDPS, AMP neither stimulated nor inhibited the ATPase activity (Fig. 3A), indicating that the nucleoside monophosphate was not recognized by the regulatory or hydrolytic site(s).

Since GTP and dATP are also substrates, the response to the NDP products of their hydrolysis was assessed as well. The results summarized in Table I indicate that addition of 250 μM ADP does increase hydrolysis of both of these NDPS, although its effect on kinetic parameters is not identical for each substrate. Whereas the enhancement of ATP hydrolysis was reflected as a 2-fold increase in V_max and decrease in K_m, the V_max of dATP hydrolysis was elevated more than 10-fold, even though the apparent K_m increased substantially as well. The influence of ADP on GTP hydrolysis is less pronounced, probably because of GDP present in the GTP and formed during hydrolysis. Nevertheless, the maximal rates of hydrolysis of all three substrates are similar at approximately 1 μmol/mg/min ± 20% in the presence of 250 μM added ADP. This suggests a very strong interaction between the NDP-specific regulatory site and the catalytic site, which in the absence of NDP recognizes dATP with high affinity (low K_m), but hydrolyzes it less well (low V_max) than the ribonucleotides. When ADP is added, the hydrolysis of dATP becomes as efficient as that of ATP. Thus, occupation of the NDP regulatory site seems to bring about an elevation in the rate of hydrolysis of different substrates to a similar ceiling level. However, no matter whether the 250 μM ADP is present or absent, the Hill constants are always approximately 1 (Table I), indicating that an apparent lack of any positive or negative cooperativity between the two nucleotide binding sites.

Effect of Nucleoside Diphosphates on Drug Stimulation of MRP ATPase—We had previously shown that MRP ATPase is inhibited the ATPase activity (Fig. 3). In contrast to NTP substrates, separate from hydrolytic site(s) specific for NTPs. As these NTP substrates include deoxyribonucleoside triphosphates, we wondered if dNDPS were active at the regulatory site. Fig. 3D indicates that they apparently are as 250 μM or 1 mM dADP or dGDP are as stimulatory as ADP. CDP, dCDP, and the nonhydrolyzable ADP analogue, AMP-CP, also exerted stimulatory effects (Fig. 3D). Of all the nucleoside diphosphates examined, UDP was the only one that was not stimulatory (Fig. 3D).

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Effect of Nucleoside Diphosphates on Drug Stimulation of MRP ATPase—We had previously shown that MRP ATPase is stimulated by compounds which it is believed to be able to transport (3). To assess how this stimulation relates to the unanticipated activation by NDPS, we tested the effect of an anthracycline and a Vinca alkaloid in the absence and presence of 250 μM ADP (Fig. 4). Strikingly, stimulation by either doxorubicin or vincristine did not occur in the presence of 250 μM ADP. This was the case even when glutathione, which enhances drug stimulation of MRP, was added together with the drugs. The lack of additivity of activation by NDPS and transported drugs may be just due to the fact that the NDP has caused maximal stimulation of hydrolysis or it may reflect some commonality in the mechanisms of stimulation by the different agents.

DISCUSSION

The purpose of this work was to determine the effects of different nucleotides on the ATPase activity of purified MRP. As shown in Fig. 2, MRP can hydrolyze not only ATP, but also GTP and dATP. This is consistent with the fact that GTP can support transport by MRP (13, 14). It also indicates that, like P-glycoprotein (25–28), substrate specificity is not restricted to just nucleotides containing adenosine and ribose moieties. However, as shown in Fig. 1, A and B, dATP and dGTP are stronger inhibitors than are CTP, UTP, dCTP, or dTTP, indicating these two purine nucleotides have much higher affinity than the pyrimidine nucleotides and implying that the base structure of the nucleotide plays an important role in binding. The sugar also is a determinant of the nucleotide binding, since CTP, for example, did not have any inhibitory effect until concentrations of 4 mM and higher were used, while dCTP inhibited 20% of the ATPase activity at 4 mM. This indicates that the deoxyribonucleotide has higher affinity for the MRp than the ribonucleotide. The much lower K_m for dATP than ATP (Table I) also confirmed that the deoxyribonucleotide has higher affinity for MRp than the ribonucleotide. The effect of different phosphate chain length on the nucleotide binding is not clear because of the unexpected NDP stimulatory effect. However, comparing the effects of adenosine monophosphate with the di- or triphosphates at 4 mM, AMP inhibited about 10%, ADP, 30%, and dATP or AMP-PNP, 40%. This suggests that at least the diphosphate is necessary in order to efficiently compete with ATP binding.

The stimulation by ADP was surprising and suggests that...
there is an ADP binding site in the protein separate from the ATP binding and hydrolytic site. ATP, dATP, or GTP cannot prevent the stimulatory effect of 250 μM ADP. This lack of effect of up to a 32-fold excess of NTP suggests that this site must have a strong preference for NDP. Hence, we postulate that there are two different kinds of nucleotide binding sites in the MRP, one an ADP binding site (regulatory site) and the other an ATP binding site (ATP hydrolytic site). ADP at lower concentrations binds to this ADP binding site, perhaps causing a conformational change which stimulates the ATPase activity. ADP at higher concentrations not only binds to this ADP binding site, but also to the ATP binding site(s) and inhibits the ATPase activity.

All those NDPs tested, except UDP, can stimulate ATPase activity (Fig. 3D), further indicating that the length of the phosphate chain is extremely important to NDP binding. ADP and GDP are more stimulatory at the 250 μM concentration than at the 1 mM concentration, whereas dADP and dGDP stimulate more at the 1 mM concentration than at the 250 μM concentration, presumably reflecting different affinities of those nucleotides for the ADP binding site. CDPP and dCDP can also stimulate ATPase activity (Fig. 3D), indicating that pyrimidine nucleotides, except UDP, can also bind to this regulatory site. Since the nonhydrolyzable ADP analogue, AMP-CP, can also stimulate the ATPase activity, ADP hydrolysis is not required for this stimulation.

Although the relevance of these findings to the cellular function of MRP is unknown, the biphasic sensitivity to ADP may be an effective modulator of its enzymatic activity. ADP concentrations between 10 μM and 2 mM were stimulatory, whereas higher concentrations inhibited activity. Since the stimulatory range covers the concentrations in the cell during reasonable changes in energy charge, stimulation of MRP may enhance its efficiency. When the energy charge of the cell becomes unusually low, i.e., low ATP and high ADP, activity would be inhibited. Overall the turnover of substrate would be accelerated under most conditions but reduced if the level of product became unusually high.

The suggestion of an NDP regulatory site separate from the catalytic site is of interest from several points of view. First, the relationship of these two sites to the two nucleotide binding domains of the protein is intriguing. In the case of P-glycoprotein both of these domains have been shown to hydrolyze ATP (31). However, it is not yet known if that is the case with MRP. Mutagenesis of crucial residues in these domains of MRP will help to address the location of both hydrolytic and regulatory sites. Occupation of the NDP regulatory site appeared to fully activate NTP hydrolysis by MRP so that substrates of transport had no further effect. To again draw on information from P-glycoprotein (32, 33), it may be reasonable to assume that the drug binding and transport sites in MRP are in membrane associated domains and very recent data confirm this (34). Thus mediation of the stimulatory conformational change, which presumably occurs on drug binding, to the site(s) of hydrolysis may be similar to the allosteric signal from the NDP binding site(s). Precise mapping of this site(s) in relation to drug binding site(s) should provide additional insight into the mechanism of MRP ATPase stimulation by substrates for transport and conversely the ATP-driven transport step.

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