Competitive Interaction of Cyclosporins with the Vinca
Alkaloid-binding Site of P-glycoprotein in Multidrug-resistant Cells*

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The mechanism of reversal of resistance to Vinca alkaloids by cyclosporins is unclear. We investigated the molecular mechanism of reversal of Vinca alkaloid resistance by cyclosporin A (CsA) and its nonimmunosuppressive analog 0-acetyl C4, CsA (SDZ 33-243) in multidrug resistant DC-3F/VCRd-5L Chinese hamster cells. CsA at 3 μM increased vincristine (VCR) sensitivity and almost totally reversed VCR resistance. SDZ 33-243 at 1 μM reduced the IC50 for VCR in resistant cells from 62.0 to 0.00062 μM. CsA and SDZ 33-243 at 10 μM increased [3H]vinblastine (VBL) accumulation in DC-3F/VCRd-5L cells by 27- and 22-fold, respectively. At 10 μM, these compounds also increased [3H]VCR uptake by membrane vesicles from DC-3F/VCRd-5L cells showed high and low affinity components with Michaelis-Menten kinetics, and apparent Km values were 0.140 ± 0.0525 and 24.8 ± 0.67 μM, respectively. Kinetic analysis of [3H]VCR uptake in membrane vesicles in the presence of 0.2 μM CsA revealed that CsA competitively inhibited the high affinity [3H]VCR uptake with an apparent inhibition constant (K_i) of 0.126 ± 0.0173 μM. In addition, CsA and SDZ 33-243 inhibited VBL photoaffinity labeling of P-glycoprotein in a dose-dependent manner, with half-maximum inhibition at 0.5 and 0.4 μM, respectively, compared with that of VBL at 0.6 μM. These data confirm that cyclosporins modulate Vinca alkaloid resistance at least partially through interaction with P-glycoprotein.

Materials and Methods

Chemicals and Supplies—Eagle’s minimum essential medium with Ham’s nutrient mixture F-12 was purchased from Gibco. Fetal bovine serum was obtained from Hyclone Laboratories, Inc. (Logan, UT). Vinblastine (VBL) and VCR were gifts from Eli Lilly & Co. CsA and O-acetyl C4 CsA (SDZ 33-243) were gifts from Sandoz (Basel, Switzerland). N-Hydroxysuccinimidyl-4-azidosalicylate was obtained from Pierce Chemical Co. ATP-S was purchased from Boehringer Mannheim. [3H]VBL (specific activity 23 Ci/mmol). [3H]VCR (specific activity 6.2 Ci/mmol), and Na[3H] (specific activity 2200 Ci/mmol) were purchased from Amersham Corp. All other chemicals were obtained commercially and were reagent grade.

Cell Culture and Cytotoxicity Assays—Sensitive DC-3F Chinese hamster lung cells and variant DC-3F/VCRd-5L, cells selected for primary resistance to VCR (2400-fold) and cross-resistance to other natural product antitumor drugs (2200-fold to doxorubicin, 1000-fold to actinomycin D, and 1000-fold to colchicine) were generously supplied by Dr. June L. Biedler (Memorial Sloan-Kettering Cancer Center, New York) and were cultured in a 1:1 mixture of Eagle’s minimum essential medium with nonessential amino acids and Ham’s nutrient mixture F-12. Cells were supplemented with 5% fetal bovine serum, streptomycin (100 ng/ml) and penicillin (100 ng/ml) (26, 27). The resistant cells were maintained in growth medium containing 50 μg/ml VCR; 1 week prior to experiments these cells were cultured in the absence of drug. For drug cytotoxicity assays, 500 cells were plated in Corning six-well plates containing increasing concentrations of VCR the cell, resulting in decreased drug accumulation within cells leading to decreased drug efficacy (3, 5). Drugs involved in the MDR phenotype bind specifically to P-gp (6-10). Analysis of cDNA encoding P-gp demonstrates that this protein has two nucleotide-binding sites homologous to ATP-binding sites of bacterial transport proteins (11-15).

Several reports have documented that certain lipophilic agents are able to reverse MDR in vitro (3, 13). These agents may modulate MDR by interacting with chemotherapeutic drug-binding site(s) of P-gp (8, 14-22). Recent work by Slater et al. (23) and Twentyman (24) showed that the immunomodulating fungal undecapeptide cyclosporin A (CsA) can reverse vincristine (VCR) and doxorubicin resistance in MDR cells. Due to the relatively low toxicity of CsA at clinically achievable concentrations (25), this agent may be useful for overcoming drug resistance in cancer patients. Since the molecular mechanisms of reversing MDR by cyclosporins are not clear and since there is increasing evidence that many lipophilic agents may interact with P-gp to reverse MDR, we examined CsA and its nonimmunosuppressive analog O-acetyl C4 CsA (SDZ 33-243) (24) to determine whether interaction of these agents with P-gp is the mechanism of reversing Vinca alkaloid resistance. Our data indicate that cyclosporins may reverse Vinca alkaloid resistance by competitively interacting with the Vinca alkaloid-binding site of P-gp, and demonstrate correlations between the ability of cyclosporins to inhibit binding of Vinca alkaloids to P-gp, increase cellular retention of these drugs, and reverse Vinca alkaloid resistance.

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1. The abbreviations used are: MDR, multidrug resistance; ATP-S, adenosine-5’-O-(3-thio)triphosphate; CsA, cyclosporin A; [3H]NASV, N-[p-azido(3,5,12)N-salicyl]-N’-β-aminohydroxindestine; P-gp, P-glycoprotein; SDZ 33-243, O-acetyl C4 cyclosporin A; VBL, vinblastine; VCR, vincristine.
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in the absence or presence of 1 and 3 pm cyclosporins for 7 days. The effects of 1, 3, 5, and 10 pm cyclosporins alone on the survival of the sensitive and resistant cells were also evaluated. Colonies were fixed with 4% formaldehyde, stained with crystal violet, and colonies containing more than 50 cells were scored. Concentrations of VCR which reduced the number of colonies by 50% after 7 days treatment (IC50) in colonogenic assays were determined from triplicate experiments using 0.0001-100 pm VCR.

Drug Accumulation—[3H]VCR and [3H]VBL accumulation was determined using cell monolayers grown to 70% confluence in Corning 24-well plates in growth medium containing 50 nm [3H]VCR or [3H]VCR with or without 2.5, 5, or 10 pm cyclosporins in a 5% CO2 atmosphere. Cells in each well were incubated for 1 h at 37°C. Drug accumulation was stopped by rapid freezing of the cells twice with ice-cold phosphate-buffered saline. The cells were then trypanized, and the cell-associated radioactivity was counted in a Beckman LS-7500 scintillation counter.

Results

Cytotoxicity—The cytotoxicity of VCR on DC-3F-sensitive Chinese hamster lung cells and VCR variant DC-3F/VCRd-5L cells was evaluated by colonogenic assay. The VCR concentration that inhibited cell growth by 50% (IC50) was 0.026 mM for DC-3F and 62 mM for DC-3F/VCRd-5L cells, respectively (Table I), indicating that DC-3F/VCRd-5L cells are about 2400-fold resistant to VCR. At 5 pm, CsA alone partially inhibited the growth of sensitive and resistant cells, and no cells survived at 10 pm CsA. SDZ 33-243 alone was a more potent inhibitor of cell growth, and neither sensitive DC-3F nor resistant DC-3F/VCRd-5L cells survived at 3 pm SDZ 33-243. Addition of 3 pm CsA or 1 pm SDZ 33-243 to the sensitive DC-3F cells in the presence of increasing concentrations of VCR decreased the IC50 to 0.00075 and 0.00062 pm, respectively (Table I). CsA at 3 pm decreased the VCR IC50 of DC-3F/VCRd-5L cells from 62 to 0.28 pm. The nonimmunosuppressive analog of CsA, SDZ 33-243, was a more potent modulator of VCR resistance and at 1 pm decreased the IC50 of the resistant cells to 0.00062 pm.

Effects of Cyclosporins on [3H]VBL and [3H]VCR Accumulation—We also determined the effect of CsA or SDZ 33-243 on [3H]VBL and [3H]VCR accumulation in the parental DC-3F and MDR variant DC-3F/VCRd-5L cell lines (Fig. 1, A and B). The accumulation of both Vinca alkaloids in both cell lines reached steady-state after 30-min incubation of cells with 50 nm [3H]VBL or [3H]VCR (data not shown). After 1 h of incubation with 50 nm [3H]VBL, resistant cells accumulated 22-fold less [3H]VBL than did sensitive cells (Fig. 1A). Addition of 2.5, 5, or 10 pm CsA increased [3H]VCR accumulation in DC-3F/VCRd-5L cells by 3.4-, 16-, or 27-fold, respectively. Similarly, SDZ 33-243 enhanced [3H]VCR accumulation by 14-, 22-, or 22-fold, respectively (Fig. 1A). As shown in Fig. 1A, only 2-fold increases in [3H]VCR accumulation by sensitive cells were seen in the presence of various concentration of CsA or SDZ 33-243. Similarly, [3H]VCR accumulation (Fig. 1B) in DC-3F/VCRd-5L cells was significantly increased in the presence of 2.5, 5, or 10 pm of either CsA (1.6-, 2.4-, or 3.5-fold, respectively) or SDZ 33-243 (2.3-, 3.2-, or 4.0-fold, respectively). At 1 pm SDZ 33-243 increased [3H]VCR accumulation by 1.27-fold (data not shown). Accumulation of [3H]VCR in DC-3F cells at 2.5, 5, or 10 pm CsA was increased by 1.4-, 1.4-, or 1.6-fold, respectively, and SDZ 33-243 at these concentrations increased [3H]VCR accumulation 1.4-, 1.4-, or 1.7-fold, respectively (Fig. 1B).

Drug-resistant DC-3F/VCRd-5L cells accumulated 80% less [3H]CsA than the corresponding drug sensitive DC-3F cell line (data not shown), suggesting that cyclosporins are substrates for the outward drug transporter of MDR cells and can be effluxed by these cells.

Effect of Cyclosporins on [3H]VCR Uptake by Membrane Vesicles—[3H]VCR uptake specificity was analyzed by incubating membrane vesicles from DC-3F/VCRd-5L cells with increasing concentrations of [3H]VCR (0.03-55 pm) in the absence or presence of 500 pm unlabeled VCR. In the absence of unlabeled VCR, uptake of [3H]VCR to membrane vesicles was biphasic (data not shown), which is characteristic of both specific and nonspecific uptakes. In the presence of

\[ v = \frac{(V_0 \times S)}{(K_v + S)} + \frac{(V_0 \times S)}{(K_u + S)} \]

where \( v \) and \( s \) are specific uptake and VCR concentration in the reaction solution, respectively. \( V_0 \) and \( K_v \) are maximum uptake and half-maximum uptake VCR concentrations for the high affinity component, respectively. Similarly, \( V_0 \) and \( K_u \) represent those values for the low affinity component, respectively. The apparent inhibitory constant (K) of CsA or SDZ 33-243 was estimated from [3H]VCR uptake in the absence and presence of CsA by replacing \( K_v \) with \( K_u \) in the following equation:

\[ \text{IC}_{50} = \frac{V_0}{2} \times \frac{1}{K_u + S} + \frac{V_0}{2} \times \frac{1}{K_v + S} \]

Photosutathy Labeling—Exponentially growing cells were harvested by rubber blade. Trypan blue viable (>90%) cell suspensions (2.5 x 106 cells/assay) in Ca2+ Mg2+-free Dulbecco's phosphate-buffered saline containing 4% dimethylsulfoxide and 0.01 mM [14C]NASV (200 Ci/mmol) in a final volume of 0.05 ml were used in photolabeling experiments. This mixture was preincubated for 1 h at 25°C in the absence or presence of nonradioactive competing ligand and then irradiated for 30 min with a UV lamp equipped with two 15-watt self-filtering 366-nm lamps. Photolabeled cells were analyzed by 6-15% sodium dodecyl sulfate-polyacrylamide gel electrophoresis containing 4.5 urea followed by autoradiography (6, 7, 16). Quantitation of radiolabeling was accomplished by cutting appropriate pieces from the gel and determining radioactivity by \( \gamma \) counter.

TABLE I

| Cyclosporins | Dose (pm) | DC-3F | DC-3F/VCRd-5L | DC-3F | DC-3F/VCRd-5L |
|-------------|----------|-------|----------------|-------|----------------|
| None        |          | 100   | 100            | 0.026 | 62.0           |
| CsA         | 3        | 100   | 82             | 0.00075 | 0.28          |
|             | 5        | 50    | 52             |        |                |
|             | 10       | 0     | 0              |        |                |
| SDZ 33-243  | 1        | 100   | 100            | 0.00052 | 0.00062      |
|             | 3        | 100   | 100            | 0.00062 | 0.00062       |

* Number of colonies in the absence or presence of CsA or SDZ 33-243 were determined by colonogenic assay. Values are the average of triplicate experiments.

** Concentration of VCR which reduced the number of colonies by 50% in the absence or presence of cyclosporins after 7-day treatment. Values are the average of triplicate experiments.

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FIG. 1. Effect of CsA and SDZ 33–243 on the accumulation of [3H]VBL (A) and [3H]VCR (B) by DC-3F and DC-3F/VCRd-5L cells. [3H]VBL or [3H]VCR accumulation at the concentration of 50 nM was measured in culture medium maintained in 5% CO₂ and 37 °C for 60 min. Concentrations of CsA or SDZ 33–243 were 2.5, 5, and 10 µM. The results of DC-3F (hatched bar) and DC-3F/VCRd-5L (closed bar) cells are shown as mean ± S.E. of triplicate experiments.

excess VCR, specific [3H]VCR uptake was blocked, and the uptake of radioactivity to membrane vesicles increased linearly with a slope parallel to the terminal nonspecific linear portion of the biphasic curve. The specific [3H]VCR uptake was estimated by subtracting the nonspecific linear curve from the mixed biphasic profile. With this correction for nonspecific uptake, total specific uptake of [3H]VCR to membrane vesicles was determined and the results are shown in Figs. 2 and 3. In Figs. 2, A and B, the uptake of [3H]VCR showed saturation at low and high concentration ranges. An Eadie-Hofstee plot of the data from Fig. 2, A and B is shown in Fig. 3. As clearly shown in the plot, the specific uptake was composed of two distinct components, and the kinetic parameters for high and low affinity uptake components were estimated by nonlinear least squares analysis. The high and low affinity uptake exhibited Vₘ values of 20.1 ± 4.99 and 712 ± 126 pmol/mg protein, respectively. The Kₘ values for those uptake components were 0.140 ± 0.0523 and 24.8 ± 6.67 µM, respectively (Table II).

When experiments were performed in the presence of 3 mM ATP, 5 mM MgCl₂, and 50 nM [3H]VCR, specific uptake of [3H]VCR by membrane vesicles was 2.3 ± 0.86 pmol/mg protein. However, when ATP was replaced by ATPγS, a non-hydrolytic analog of ATP, no specific uptake was observed. Furthermore, in the presence of either 3 mM ATP or ATPγS and 6.4 µM [3H]VCR, 120 ± 6.4 and 63.5 ± 5.2 pmol [3H]VCR/mg protein were seen, indicating that approximately 50% of low affinity uptake is ATP-dependent. ATP-dependent stimulation of [3H]VCR uptake from the incubation medium to membrane vesicles suggests that these membrane vesicles were inside-out vesicles.

FIG. 2. Concentration dependence of [3H]VCR uptake by membrane vesicles of DC-3F/VCRd-5L cells. The uptake of [3H]VCR was measured in 10 mM Tris-HCl buffer, pH 7.4, containing 5 mM MgCl₂, 3 mM ATP, and 250 mM sucrose for 60 min at room temperature. The specific uptake was obtained by subtracting nonspecific uptake measured in the presence of 500 µM unlabeled VCR from the total uptake. At 0.1, 1, and 20 µM [3H]VCR, 30, 40, and 50–60% nonspecific uptake was measured. A and B represent the results obtained at the low (0.03–1.35 µM) and high (1.63–55 µM) concentrations of [3H]VCR, respectively. Each point represents mean ± S.E. of triplicate determinations.

TABLE II

| Component     | Vₘ (pmol/mg protein) | Kₘ (µM) | Kᵣ (µM) |
|---------------|----------------------|--------|--------|
| High affinity | 20.1 ± 4.99          | 0.140  | 0.126  |
| Low affinity  | 712 ± 126            | 24.8   | 6.67   |

*Inhibitory constant of CsA on the uptake of VCR. Each value represents the mean ± S.D. estimated from the nonlinear least squares analysis.

To examine whether [3H]VCR uptake by membrane vesicles was affected by CsA, we studied the effect of different concentrations of CsA on uptake of 54 nM [3H]VCR (Fig. 4). CsA inhibited [3H]VCR uptake in a dose-dependent manner.
and 50% inhibition occurred at 0.5 μM CsA. To determine whether inhibition of [3H]VCR uptake by CsA was competitive or noncompetitive, detailed kinetic analysis of [3H]VCR uptake in membrane vesicles was performed. Fig. 3 also shows the effect of CsA on [3H]VCR uptake in membrane vesicles. CsA at 0.2 μM increased the apparent high affinity uptake Kapp value while it did not affect the Vmax. These results demonstrate that CsA is a competitive inhibitor of VCR uptake at a high affinity site with an apparent Kc of 0.126 ± 0.0173 μM.

Inhibition of VBL Photoaffinity Labeling by Cyclosporins—In order to further explore the interaction of cyclosporins with Vinca alkaloid-binding site(s) of the outward drug transporter, we performed photoaffinity labeling experiments with the VBL photoactive analog [125I]NASV in the absence or presence of increasing concentrations of either unlabeled VBL or cyclosporins (Fig. 5). We have previously shown that this photoactive analog specifically binds to P-gp (6). When photoaffinity labeling was carried out with 0.01 μM [125I]NASV in the presence of increasing concentrations of unlabeled VBL (0.1–100 μM VBL), 50% inhibition of binding to P-gp occurred at 0.6 μM VBL. CsA and SDZ 33–243 were potent inhibitors of [125I]NASV binding to P-gp with IC50 values of 0.54 and 0.4 μM, respectively (Fig. 5). This is in line with our Vinca alkaloid accumulation experiments and kinetic analysis of [3H]VCR uptake in the absence or presence of cyclosporins.

**DISCUSSION**

In this study we examined the mechanism of reversal of VCR resistance by CsA and its nonimmunosuppressive analog, SDZ 33-243, in VCR/MDR variant DC-3F/VCRd-5L cells in vitro. As revealed by colchicine assay, CsA was a highly effective modulator of VCR resistance and SDZ 33–243 was even more active. Furthermore, while the effects of cyclosporins are much greater in VCR-resistant cells, some degree of sensitization in the parental DC-3F cells was also evident. CsA alone partially inhibited the growth of both sensitive and resistant cells at 5 μM and SDZ 33–243 totally inhibited growth in both cell lines at 3 μM. These results are in agreement with previous studies by Saydjari et al. (29) which described growth inhibition by CsA in a hamster pancreatic carcinoma cell line, and by Twentyman (24), who demonstrated growth inhibition of a MDR subline of the human small cell lung cancer cell line NCI-H69 by O-acetyl CsA. In this study, VCR resistance modulation occurred at dose levels which are not in themselves growth inhibitory. Therefore, it appears that there is no direct relationship between the growth inhibition by a given cyclosporin and its ability to reverse MDR. Moreover, our data and others (24, 30–32) demonstrate that the molecular mechanism of reversing MDR by cyclosporins is separate from the immunosuppressive properties of these agents.

Our drug uptake data demonstrate that VCR (Fig. 1A), VBL (Fig. 1B) and CsA accumulation are diminished in the VCR/MDR variant DC-3F/VCRd-5L cells which overexpress P-gp. The cyclosporins tested increased accumulation of [3H]VBL, [3H]VCR, and [3H]CsA in the resistant cells. Furthermore, we have shown that CsA inhibits efflux of [3H]VBL from MDR cells. These data collectively suggest that cyclosporins may reverse Vinca alkaloid resistance at least in part by interacting with the outward drug transporter in MDR cells and preventing extrusion of Vinca alkaloids from these cells. That this effect was indeed mediated by P-gp came from kinetic analysis of the uptake of [3H]VCR by membrane vesicles and photoaffinity labeling of P-gp by [125I]NASV in the presence of cyclosporins.

The results presented in Figs. 2–4 show that there is an active VCR uptake in membrane vesicles from MDR cells with high and low affinity sites and that CsA has a specific effect on [3H]VCR uptake by these membrane vesicles. The uptake of [3H]VCR was osmotically sensitive. The high affinity uptake of [3H]VCR was totally ATP- and Mg2+-dependent while only approximately 50% of the low affinity component of uptake was ATP- and Mg2+-dependent. Recently, both ATP-dependent and -independent VCR binding with apparent Kc values of 0.24 and 9.7 μM, respectively, in membrane vesicles of the human MDR K562/ADM leukemia cells was also reported (21). The kinetic parameters obtained in the presence of ATP in the present study are close to these reported Kc values, suggesting that the high and low affinity uptake in these membrane vesicles from MDR cells is very similar to that observed in other systems and that CsA may have a direct effect on the binding of VCR to P-gp. Furthermore, our kinetic analysis of [3H]VCR uptake by membrane vesicles of the resistant cells in the presence of 0.2 μM CsA revealed that this agent interacts with the drug...
transporter at the high affinity site in the MDR cells and competitively inhibits VCR uptake with an apparent \( K_c \) of 0.126 \( \pm \) 0.0175 \( \mu M \). These results suggest that the high affinity uptake component might have an important role in reversing Vinca alkaloid resistance of MDR cells by cyclosporins.

We have previously reported that photoactive analogs of VBL bound to P-gp in MDR cells (6, 9) and that many compounds which reverse MDR also bind to P-gp (8, 15-19) and inhibit binding of VBL to this protein (8, 18, 19). Further support for the interaction of cyclosporins with the Vinca alkaloid-binding site of P-gp was provided by photoaffinity labeling experiments with the photoaffinity analog of VBL, \([\text{125I}]}\)NASV. When membrane vesicles from the VCR/MDR variant DC-3F/VCRd-5L cell line were photosolated with 50 nM \([\text{125I}]}\)NASV in the presence of increasing concentrations of unlabeled VBL, CsA, or SDZ 33-243, photolabeling of P-gp was inhibited with half-maximum concentrations of 0.6, 0.5, and 0.4 \( \mu M \), respectively. These results suggest that cyclosporins interact directly with VBL on P-gp. Interestingly, the cyclosporins have used slightly higher potency than VBL in inhibiting \([\text{125I}]}\)NASV binding to P-gp. These results are also in agreement with the data in Fig. 4 in which 50% inhibition of VCR uptake in membrane vesicles occurred at 0.5 \( \mu M \) CsA. During the course of this study (32), Foxwell et al. (33) reported that a photoactive analog of CsA, \([\text{3H}]}\)cyclosporin \( \text{B} \), competitively inhibits VCR uptake with an apparent \( K_c \) of 0.5, 0.4, and 0.3 \( \mu M \), and since these cells have a low outward transport of these drugs. The weak correlation between the magnitude of the effect of cyclosporins on VCR accumulation and cell survival suggests that in addition to interaction with P-gp, these drugs may modulate VCR resistance by other mechanisms. A prospective study of MDR reversal with a greater number of cyclosporins will enable definitive conclusions regarding the structure-activity relationship for resistance modulation by these compounds and for the increased drug accumulation in sensitive and MDR cells by cyclosporins.

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