Enhanced de Novo Ceramide Generation through Activation of Serine Palmitoyltransferase by the P-Glycoprotein Antagonist SDZ PSC 833 in Breast Cancer Cells

Hongtao Wang, Armando E. Giuliano, and Myles C. Cabot
John Wayne Cancer Institute, Saint John’s Health Center, Santa Monica, California 90404

Abstract
SDZ PSC 833 (PSC 833), a P-glycoprotein-targeted multidrug resistance modulator, sensitizes cancer cells to chemotherapy. Here we show that PSC 833 also potentiates the formation of ceramide. Because ceramide is a second messenger in chemotherapy-induced apoptosis, knowledge of the lipid pathways influenced by PSC 833 is of relevance. In intact MDA-MB 468 breast cancer cells, ceramide generation increased 3-fold 1 h after PSC 833 addition (5.0 μM). Cyclosporine A, a structural analogue, failed to impact ceramide metabolism. Spinganine, the upstream precursor of ceramide, also increased in response to PSC 833, and this could be blocked by adding L-cycloserine, a serine palmitoyltransferase (SPT) inhibitor. Exposure of cultured cells to PSC 833 (30 min to 4 h; 1–10 μM), followed by isolation of microsomes for in vitro assay, increased SPT activity 60%, whereas palmitoyl-CoA synthetase and ceramide synthase activities were not altered. SPT activity was also heightened by pretreating cells with either paclitaxel, N-(4-hydroxyphenyl)retinamide, etoposide, or daunorubicin; however, activation was half that attained by PSC 833. PSC 833 stimulated ceramide generation in other breast cancer cell lines as well, including BT-20, MDA-MB 231, Hs 578T, T-47D, and MCF-7. In summary, several types of anticancer agents and the P-glycoprotein modulator PSC 833 share the ability to increase cellular ceramide levels by activation of SPT, the rate-limiting enzyme in the de novo pathway of ceramide synthesis. These data provide novel insight in the area of lipid-mediated cell death.

Introduction
Multidrug resistance is the major cause of cancer treatment failure (1, 2). Overexpression of P-gp, a M170,000 transmembrane protein that functions as a drug efflux pump, is one of the most consistent alterations of the MDR phenotype (3). Numerous agents have been studied in an effort to overcome P-gp-mediated MDR, tamoxifen, PSC 833 (Valspodar), verapamil, cyclosporine A, and VX-710, among them (4–9). MDR modulators bind directly to P-gp and thereby interfere with cellular export of anticancer drugs. This approach appears to be a useful avenue for restoring cytotoxicity in drug-resistant cells; however, results from clinical trials are as yet inconclusive.

Ceramide, the lipid backbone of sphingomyelin and glycolipids, is an important second messenger of apoptosis (10, 11). Many chemotherapeutic agents stimulate the production of ceramide, an upstream signal of apoptosis (12–15), and it is now becoming apparent that initiation of programmed cell death may have greater therapeutic value than antiproliferative routes. Our previous studies show that the P-gp modulator, PSC 833, also activates ceramide generation, and that the effect of PSC 833 on ceramide metabolism correlates with an increase in cell death and a dampening of MDR in breast cancer cells (16–18). These results suggest that part of the cytotoxic activity of PSC 833 is associated with ceramide formation.

Ceramide levels may be increased by hydrolysis of membrane-resident sphingomyelin by sphingomyelinase or by de novo synthesis at the level of the endoplasmic reticulum (19–23). Previous studies on the involvement of ceramide in the activation of apoptotic pathways elicited by tumor necrosis factor-α, Fas, and ionizing radiation show that intracellular ceramide elevation results from sphingomyelin hydrolysis (24–26). However, a recent report showed that ceramide increases in response to PSC 833 treatment were not accompanied by depletion of sphingomyelin (16, 17). Several enzymes, including palmitoylCoA synthetase, SPT, and ceramide synthase, contribute to catalyze de novo formation of ceramide (21–23). Although our previous data showed that the ceramide synthase inhibitor, FB1, blocked ceramide generation induced by PSC 833 (17), details of the enzyme activation pathway remained unknown.

Because the ceramide de novo pathway inhibitor, FB1, has been shown to block daunorubicin-induced ceramide formation and retard apoptosis in murine leukemia (21), it has been...
widely accepted that the enzyme, ceramide synthase, is the sole target for various anticancer agents that use ceramide. More recent studies have, however, demonstrated that some anticancer drugs activate SPT (23), and we have shown in work with neuroblastoma that 4-HPR (or fenretinide) activates both SPT and ceramide synthase (15). Here, we have focused our studies on assessing the target of PSC 833, and we have demonstrated that this P-gp modulator activates SPT, the rate-limiting enzyme in the de novo pathway (Fig. 1), in a cell line devoid of P-gp. We also show in breast cancer cells that other anticancer drugs, among them paclitaxel, 4-HPR, and etoposide, share this activity.

Materials and Methods

**Materials.** PSC 833 was a gift from Novartis Pharma AG (Basel, Switzerland). The human breast cancer cell lines MDA-MB 468, MDA-MB 231, T-47D, BT-20, and Hs 578T were purchased from the American Type Culture Collection (Rockville, MD). The human breast carcinoma cell lines, MCF-7 and MCF-7 AdrR (MCF-7/AdR), were obtained from Drs. Kenneth Cowan (University of Nebraska Medical Center Eppeley Cancer Center, Omaha, NE) and Merrill E. Goldsmith (National Cancer Institute, Bethesda, MD). Culture media were products of Life Technologies, Inc. (Grand Island, NY), and FBS was from HyClone (Logan, UT). Paclitaxel, daunorubicin, and etoposide were from Sigma Chemical Co. (St. Louis, MO). 4-HPR was kindly provided by R. W. Johnson Pharmaceuticals (Spring House, PA). FB, and L-cycloserine were purchased from Biomol (Plymouth Meeting, PA). Ceramide and sphingomyelin (brain derived) were from Avanti Polar Lipids (Alabaster, AL). Sphinganine (N-erythro-dihydrosphingosine in pure form) was from Matreya (Pleasant Gap, PA). [9,10-3H(N)]Palmitic acid (50 Ci/mm) was from DuPont/NEN (Boston, MA). [5,6-3H]Sphinganine (60 Ci/mm) and L-[3H(O)]serine (20 Ci/mm) were from American Radiolabeled Chemicals, Inc. (St. Louis, MO). Silica Gel G TLC plates were purchased from Analtech (Newark, DE). Monoclonal antibody, C219, to P-glycoprotein was from Signet Laboratories (Dedham, MA). Fluorescein-conjugated secondary antibody against mouse was from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA). Other chemicals were from Sigma Chemical Co. (St. Louis, MO).

**Cell Culture.** MDA-MB 468, MDA-MB 231, MCF-7 and MCF-7/AdrR cells were cultured in RPMI 1640 containing 10% FBS and 584 mg/liter l-glutamine. T-47D cells were cultured in RPMI 1640 containing 10% FBS, 2 mM l-glutamine, 10 mM HEPEs (pH 7.3), 1.0 mM sodium pyruvate, and 7 µg/ml bovine insulin. Hs 578T cells were cultured in DMEM containing 10% FBS, 4.5 g/liter glucose, and 10 µg/ml bovine insulin. BT-20 cells were cultured in minimum essential medium Eagle’s with 2 mM l-glutamine and Earle’s balanced salt solution, adjusted to contain 1.5 g/liter sodium bicarbonate, 0.1 mM nonessential amino acids, 1.0 mM sodium pyruvate, and 10% FBS. All cell culture media contained 100 units/ml penicillin and 100 µg/ml streptomycin. Cells were grown in a humidified 5% CO2 tissue culture incubator at 37°C and subcultured using 0.05% trypsin/0.53 mM EDTA solution. For the experiments, cells were subcultured into 6- or 96-well plates, or 6- or 10-cm dishes, and the FBS content of the medium was lowered to 5%. Stock solutions of PSC 833 (10 mM) were prepared in ethanol in 1-dram glass vials and stored at –20°C. Culture media containing PSC 833 or other drugs were prepared just before use. Ethanol vehicle was present in controls.

**Metabolic Labeling and Analysis of Cellular Lipids.** After radiolabeling (1.0 µCi [3H]palmitic acid/ml culture medium for the specified times, 0.1-ml aliquots of media were removed and analyzed by LSC to determine cellular uptake of fatty acid. The culture medium was aspirated, and monolayers were rinsed twice with ice-cold PBS. Ice-cold methanol containing 2% acetic acid was added, and cells were scraped free of the substratum (plastic scraper) for lipid extraction in 1-dram glass vials as described (13, 14). The resulting organic layer of the biphasic extraction was withdrawn, transferred to a glass vial, and evaporated to dryness under a stream of nitrogen. [3H]Ceramide was resolved from other radiolabeled lipids by TLC using a solvent system containing chloroform/acetone (90:10, v/v). [3H]Sphinganine, sphingosine, and glucosylceramide were resolved by TLC in chloroform/methanol/acetic acid/water (60:30:7:3, v/v/v/v). After iodine vapor visualization, the lipids of interest were scraped from the TLC plate for tritium quantitation by LSC using Ecolume (13).

**Isolation of Microsomal Membranes.** Cultures, at 80% confluence in 10-cm dishes, were placed on ice, rinsed twice with ice-cold PBS, and scraped into 0.5 ml of homogenization buffer [20 mM HEPS (pH 7.4), 5 mM DTT, 5 mM EDTA, 2 mM leupeptin, and 20 µg/ml aprotinin]. Cell suspensions were sonicated over ice for 60 s (20% output, alternating 15-s sonication and 20-s pause) using a Micro Ultrasonic Cell Disruptor from Kontes (Vineland, NJ). Lysates were centrifuged at 10,000 × g for 10 min. The postnuclear supernatant was isolated and centrifuged at 100,000 × g for 60 min.
at 4°C. The microsomal membrane pellet was resuspended in 100 µl of homogenization buffer by sonication for 5 s and frozen at −80°C (27).

**SPT Assays.** Enzymatic activity was determined by measuring the incorporation of [3H]serine into 3-ketosphinganine. Each tube (final volume, 0.1 ml) contained 0.1 mM HEPES (pH 8.3), 2.5 mM EDTA, 50 µM pyridoxal phosphate, 5 mM DTT, 1.0 mM L-serine, and 100 µg of microsomal protein. After preincubation at 37°C for 10 min, the reaction was initiated by simultaneous addition of palmitoyl-CoA (0.2 mM) and 1.0 µCi [3H]serine. Control tubes contained either boiled microsomes or no protein. The reaction was incubated at 37°C for 7 min and terminated by addition of 0.2 ml of 0.5 N NH₄OH. Organic-soluble products were isolated by addition of 3 ml of chloroform:methanol (2:1), 25 µg of sphingosine carrier, and 2.0 ml of 0.5 N NH₄OH. The washed organic phase was isolated, and 1.0 ml was dried under a stream of nitrogen and analyzed by LSC (27).

**Ceramide Synthase Assays.** For assaying ceramide synthesis (28), [3H]sphinganine was used as radiolabeled precursor. The reaction mixtures contained 25 mM HEPES (pH 7.4), 2 mM MgCl₂, 0.5 mM DTT, 10 µM sphinganine, and 100 µg of microsomal protein. Sphinganine was dried under nitrogen from a stock solution in chloroform:methanol (2:1) and dissolved with sonication in the reaction mixture before addition of microsomal protein. The total reaction volume was 0.1 ml. Assays were initiated by simultaneous addition of palmitoyl-CoA (0.1 mM) and 0.5 µCi [3H]sphinganine, followed by incubation at 37°C for 40 min with gentle shaking. Controls were as above. The reaction was terminated by lipid extraction, and dihydroceramide was isolated and quantitated by TLC and LSC.

**Palmitoyl-CoA Synthetase Assays.** We used a slight modification of a method described previously (29). Microsomal protein (100 µg) was added to a buffer mixture containing 200 mM Tris-HCl (pH 7.5), 2.5 mM ATP, 8 mM MgCl₂, 2 mM EDTA, 20 mM NaF, 0.1% Triton X-100, and 10 µM palmitic acid. Reactions were initiated by simultaneous addition of acetyl-CoA (0.1 mM) and 1.0 µCi [3H]palmitic acid. The reaction, 0.5-ml total volume, was incubated at 37°C for 10 min with gentle shaking and terminated by the addition of 1.5 ml of isopropanol:heptane:2 N H₂SO₄ (40:10:1, v/v/v). After addition of 0.65 ml of H₂O and 1.5 ml of heptane containing 5 mg/ml palmitic acid, the mixtures were vortexed, and the organic phase was removed. The aqueous phase, containing palmitoyl-CoA formed during reaction, was washed three times with 2 ml of heptane containing 5 mg/ml palmitic acid, and 0.2 ml was analyzed by LSC. In control experiments, either the microsomes or acetyl CoA was omitted.

**P-gp Expression.** P-Glycoprotein expression was evaluated by immunofluorescence staining using C219 monoclonal antibody. Cells were grown on sterile coverslips in 6-well tissue culture plates. The coverslips were incubated in 4% paraformaldehyde for 5 min, fixed with cold acetone for 5 min, and preincubated with horse serum for 30 min. The coverslips were then incubated with C219 monoclonal antibody (diluted 1:100) in a humidified chamber at 4°C overnight. After washing with PBS, coverslips were incubated for 5 min, and preincubated with horse serum for 30 min. The washed coverslips were then incubated with C219 monoclonal antibody (diluted 1:100) in a humidified chamber at 4°C overnight. After washing with PBS, coverslips were incubated for 30 min with fluorescein-conjugated secondary antibody against mouse (diluted 1:200). Immunofluorescence staining was evaluated using an Olympus IX70 fluorescence microscope (Olympus, Inc., Tokyo, Japan). Coverslips were incubated with PBS instead of the primary antibody as a negative control. MCF-7/AdrR cells were used as positive controls.

**Results**

The main pathways for cellular production of ceramide are shown in Fig. 1. L-Cycloserine and FB₁ are inhibitors of de novo enzymes. Our study was conducted to determine the avenue by which PSC 833 enhances ceramide production in breast cancer cells. The influence of PSC 833 on ceramide metabolism in MDA-MB 468 breast cancer cells is shown in Fig. 2. Intracellular ceramide increased as early as 15 min after the addition of drug, and by 1 h ceramide levels had risen 3-fold over control. The effect of PSC 833 on ceramide metabolism was also dose dependent and plateaued at ~5 µM (Fig. 2, inset).

Results using inhibitors of SPT and ceramide synthase indicated that PSC 833 targeted de novo ceramide synthesis upstream of ceramide synthase. As shown in Fig. 3A, PSC 833 alone activated sphinganine formation by 1.5-fold. Exposure of cells to FB₁, a ceramide synthase inhibitor, promoted sphinganine build-up that was 5-fold over control. When FB₁ was added to block conversion of sphinganine to ceramide, sphinganine increased nearly 10-fold in response to PSC 833 addition; however, when L-cycloserine was added, sphinganine formation was halted in response to PSC 833. Under the same conditions, PSC 833 increased cellular ceramide levels 2.5-fold over control (Fig. 3B). FB₁
treatment decreased basal ceramide synthesis by ~40%, and FB, also decreased the formation of ceramide in response to PSC 833 treatment (PSC 833 + FB); Fig. 3B). Inhibition of SPT by l-cycloserine reduced the amount of baseline ceramide generated and severely retarded PSC 833-induced ceramide formation. Myriocin, a more specific SPT inhibitor, was also used to confirm the role of SPT in the PSC 833-governed lipid response. The addition of myriocin (0.25 μM) inhibited PSC 833-induced sphinganine formation by 80% and ceramide formation by 95%. Whereas this work demonstrates that PSC 833 accelerates ceramide synthesis through SPT/sphinganine, the experiments were conducted with cultured cells, and the data are not intended to relate kinetic or stoichiometric information.

The contributions of de novo synthesis and sphingomyelin hydrolysis to the production of ceramide by PSC 833 were compared by differential radiolabeling of cellular lipid pools. Twenty-four h prelabeling of cellular sphingomyelin with [3H]palmitic acid followed by a wash to deplete cytoplasmic tritium and subsequent PSC 833 treatment yielded no increase over control in intracellular [3H]ceramide (Fig. 4, left). However, when [3H]palmitic acid and PSC 833 were added simultaneously, before palmitate was incorporated into sphingomyelin, intracellular [3H]ceramide levels increased 4-fold over control (Fig. 4, middle). By the same token, combining both of the radiolabeling techniques, 24 h prelabeling of sphingomyelin pools followed by simultaneous addition of PSC 833 with a fresh bolus [3H]palmitic acid, yielded the same 4-fold increase in [3H]ceramide (Fig. 4, right). These experiments show that equilibrium radiolabeling of sphingomyelin does not enhance ceramide formed in response to PSC 833 exposure, demonstrating that sphingomyelin is not contributory to ceramide production when PSC 833 is present.

Because ceramide can be hydrolyzed by ceramidase and glycosylated to form glucosylceramide by glucosylceramide synthase, we also investigated the impact of PSC 833 on these metabolic pathways. Treatment of MDA-MB-468 cells with PSC 833 (10 μM) for 4 h in the presence of [3H]palmitic acid increased the cellular glucosylceramide fraction. This would represent glycosylation of newly formed ceramide generated by PSC 833 exposure and as such demonstrates that the elevation of ceramide after PSC 833 exposure is not through glucosylceramide synthase inhibition. On the other
hand, PSC 833 had no impact on cellular ceramidase activity, because no changes in levels of sphingosine, the product of ceramidase, were apparent with treatment. Both PSC 833 and cyclosporine A are P-gp substrates and structurally nearly identical (Fig. 5A); however, a comparison of both agents shows that only PSC 833 increases cellular ceramide levels (Fig. 5B). After a 4-h exposure to PSC 833 (10 μM), cellular levels of [3H]ceramide were 4-fold control values. PSC 833 also promoted formation of sphinganine, 50% over control (Fig. 5B), whereas cyclosporine A was without influence. The results from immunofluorescent staining showed that MDA-MB 468 cells are P-gp negative; therefore, these experiments also illustrate that the influence of PSC 833 on ceramide production is independent of P-gp.

Cell-free experiments were carried out to assess whether exposure of intact cells to PSC 833 would modify enzyme activity in vitro. MDA-MB 468 cells were cultured with PSC 833 before harvesting and isolation of microsomes for in vitro assays. Of the major enzymes in the de novo synthesis pathway (see Fig. 1), only SPT activity was enhanced by pretreatment of cells with PSC 833 (Table 1). SPT activity, measured by sphinganine formation, was 57 ± 0.2 and 91 ± 7.1 pmol/mg protein/min in control and PSC 833-treated cells, respectively, accounting for a 60% increase in enzymatic activity. Palmitoyl-CoA synthetase and ceramide synthase activities were not influenced. Further studies revealed that stimulation of SPT by PSC 833 was both time and dose dependent (Fig. 6). SPT activation was biphasic with regard to time (Fig. 6A), with an early peak at 15 min (17% increase) followed by prolonged and greater activation thereafter (50% increase).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pal-CoA Syn</th>
<th>SPT</th>
<th>Cer syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>476 ± 12</td>
<td>57 ± 0.2</td>
<td>157 ± 3.3</td>
</tr>
<tr>
<td>PSC 833</td>
<td>451 ± 13</td>
<td>91 ± 7.1</td>
<td>155 ± 4.6</td>
</tr>
</tbody>
</table>

*Pal-CoA syn, palmitoyl-CoA synthetase, palmitoyl-CoA formed; SPT, sphinganine formed; Cer syn, ceramide synthase, ceramide formed. Statistically significant from control, *P* < 0.01.
Figure 7. Effects of PSC 833 on ceramide generation in various human breast cancer cell lines. Experiments were performed at ~90% confluence. The cells were treated with 5 μM PSC 833 for 1 h, before the addition of [3H]palmitic acid (1.0 μCi/ml medium), for an additional 3 h. Total lipids were extracted, and ceramide was quantitated by TLC and LSC. Data represent the means of triplicate samples; bars, SD. These experiments were conducted two times, both yielding similar results.

Discussion

PSC 833, a second generation P-gp antagonist developed to treat MDR, is being evaluated in patients with advanced cancers including acute myeloid leukemia and refractory ovarian carcinoma (30–32). Many studies demonstrate that PSC 833 retards drug efflux (5, 33); however, our group has determined that PSC 833 also activates ceramide formation in cancer cells (16, 17). Because ceramide has been linked with apoptosis pathways elicited by chemotherapy drugs (reviewed in Ref. 11), it is reasonable to hypothesize that the cytotoxic principle of PSC 833 is in part associated with ceramide. Results from other laboratories mirror this idea. In acute myeloid leukemia, PSC 833 acts independently of P-gp to enhance apoptosis through sphingomyelin/ceramide-linked events (34), and in prostate cancer cells, it was concluded that PSC 833 alone or in combination with estramustine, etoposide, ketoconazole, suramin, or vinorelbine exerted anticancer effects by an avenue divorced from pump interaction (35). Whether strictly P-gp-directed or otherwise, PSC 833 and similar MDR modulators hold promise as co-drugs in cancer therapy, and therefore knowledge of mechanisms and targets is essential for furthering therapeutics in this area.


ceramide causes MDA-MB-468 cell death with an EC_{50} of <2.0 μM (data not shown). With drugs that generate ceramide such as etoposide (23), daunorubicin (21), and paclitaxel (14), the inclusion of ceramide synthesis inhibitors has been shown to reverse drug cytotoxicity. Recently, it has been reported that de novo ceramide synthesis inhibitors also significantly reduce PSC 833-induced apoptosis in the human T leukemia cell lines, Mol-4 and Jurkat (36). In the current study, use of de novo ceramide synthesis inhibitors did not reduce PSC 833-induced apoptosis in MDA-MB-468 cells. These dissimilar findings may be reflective of cell type-specific responses to PSC 833.

Experiments using the ceramide synthase inhibitor, FB1, and SPT inhibitors, L-cycloserine and myriocin, indicate that PSC 833 enhances de novo ceramide synthesis, targeting upstream of ceramide synthesis. The FB1 used in this study was 98% pure by TLC. We used a level that was not cytotoxic for MDA-MB-468 cells but that would also decrease the PSC 833-enhanced complement of ceramide production.
through ceramide synthase (PSC 833 + FB1; Fig. 3B). Depending on the cell line, some cells are extremely sensitive to FB1. The 50 μM concentration was optimal for inhibition of ceramide synthesis while not being cytotoxic in MDA-MB 468 cells. The in vitro enzymology experiments demonstrate that PSC 833 promotes ceramide formation by enhancing SPT activity and not by stimulation of ceramide synthase or palmitoyl CoA synthetase activities. Therefore, both the use of inhibitors and in vitro assays support the idea that PSC 833 targets SPT.

Our preliminary studies show that no gross changes occur in the levels of mRNAs coding for the SPT subunits in response to PSC 833 treatment (data not shown). This suggests that a posttranscriptional avenue of enzyme activation is likely. The rapid activation time (Figs. 2 and 6) is further support for a nontranscriptional effect of PSC 833 on SPT. Although P-gp is not required for ceramide formation (18), influences on lipid transport and substrate localization caused by PSC 833 may play a role in enhancing ceramide formation in intact cells. MDR3 P-gp can function as a phosphatidylcholine translocase (37). Similarly, PSC 833 has been shown to influence sphingolipid translocation in CHO cells (38). Similar physical effects may be in operation at the ER/Golgi level with PSC 833; however, the enhanced SPT activity in cell-free incubations using exogenously added radiolabeled substrate (Fig. 6) would argue against physical changes contributing to SPT activation in intact cells.

Several known chemotherapy drugs also stimulated ceramide generation through SPT in MDA-MB 468 cells. The degree of enhancement (Table 2 and in vitro SPT results) may simply be reflective of drug lipophilicity enhancing cellular uptake. SPT may be a common target in the cytotoxic mechanism of some anticancer agents, because other studies show similar results. In Molt-4 human leukemia cells, etoposide enhances ceramide formation in intact cells. MDR3 P-gp can function as a phosphatidylcholine translocase (37). Similarly, PSC 833 has been shown to influence sphingolipid translocation in CHO cells (38). Similar physical effects may be in operation at the ER/Golgi level with PSC 833; however, the enhanced SPT activity in cell-free incubations using exogenously added radiolabeled substrate (Fig. 6) would argue against physical changes contributing to SPT activation in intact cells.

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Molecular Cancer Therapeutics

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