Angoline and Chelerythrine, Benzophenanthridine Alkaloids That Do Not Inhibit Protein Kinase C*

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Starting with an extract derived from the stem of *Macleaya cordata* (Papaveraceae) that was active in the process of inhibiting phorbol 12,13-dibutyrate binding to partially purified protein kinase C (PKC), the benzophenanthridine alkaloid angoline was isolated and identified. This discovery appeared in context, as a related benzophenanthridine alkaloid, chelerythrine, has been reported to mediate a variety of biological activities, including potent and selective inhibition of protein kinase C (PKC). However, in our studies, angoline was not observed to function as a potent inhibitor of PKC. Moreover, we were unable to confirm the reported inhibitory activity of chelerythrine. In a comprehensive series of studies performed with various PKC isozymes derived from a variety of mammalian species, neither chelerythrine nor angoline inhibited activity with high potency. To the contrary, chelerythrine stimulated PKC activity in the cytosolic fractions of rat and mouse brain in concentrations up to 100 μM. In addition, chelerythrine and angoline did not inhibit [³²P]phorbol 12,13-dibutyrate binding to the regulatory domain of PKC at concentrations up to 40 μg/ml, and no significant alteration of PKC activity was observed with human leukemia (HL-60) cells in culture. Further, chelerythrine did not inhibit 12-O-tetradecanoylphorbol 13-acetate-induced ornithine decarboxylase activity with cultured mouse 308 cells, but angoline was active in this capacity with an IC₅₀ value of 1.0 μg/ml. A relatively large number of biological responses have been reported in studies conducted with chelerythrine, and alteration of PKC activity has been considered as a potential mechanism of action. In light of the current report, mechanisms independent of PKC inhibition should be considered as responsible for these effects.

Protein kinase C (PKC),¹ a serine/threonine kinase, has been extensively studied due to its central role in cellular signal transduction (1). Various mitogens, growth factors, and transmitters of secondary messengers have been shown to mediate their effects through PKC. PKC subtypes have been grouped as (i) conventional (α, β₁, βⅡ, and γ), which are activated by calcium, phospholipids, diacylglycerol, and 12-O-tetradecanoylphorbol 13-acetate (TPA); (ii) novel (δ, η, θ, and μ), which do not require calcium for activation; and (iii) atypical (ζ and λ), which are activated by phospholipids but not by calcium, diacylglycerol, or TPA (2, 3). It is likely that these isozymes have distinct and distinguishable functions (4–7). Since PKC has been elaborated as a major intracellular phorbol ester receptor (8, 9), it has become clear that this protein plays an important role in the process of tumor promotion (10). Accordingly, inhibition of PKC can be viewed as a rational method of blocking or inhibiting tumor promotion, and several natural product inhibitors have been identified. Examples include staurosporine (11), UCN-1028C (12), and isoquiniolinesulfonamide H-7 (13). In addition, the benzophenanthridine alkaloid, chelerythrine, was described as a potent and selective inhibitor of PKC, with an IC₅₀ value of 0.66 μM illustrated with enzyme derived from rat brain (14). Biological responses mediated by chelerythrine, such as cytotoxic activity with L-1210 tumor cells (14) and antiplatelet activity (15), have been ascribed to inhibition of PKC. Additional activities mediated by chelerythrine include inhibition of alanine aminotransferase (16), inhibition of Na⁺,K⁺-ATPase (17), and antibacterial effects (18).

In searching for novel natural product cancer chemopreventive agents, the benzophenanthridine alkaloid angoline was obtained from an extract of *Macleaya cordata* (Papaveraceae); this plant extract had previously been shown to antagonize the interaction of [³²P]phorbol 12,13-dibutyrate (PDBu) with PKC receptor. Due to the structural similarity of angoline and chelerythrine, we undertook a series of studies to investigate the activity of angoline, especially in the context of affecting PKC-mediated responses. As reported herein, neither angoline nor chelerythrine were effective inhibitors of PKC. Alternate mechanisms should be taken into account when considering the biological responses mediated by these compounds.

EXPERIMENTAL PROCEDURES

Materials

Phosphatidylserine, PDBu, histone type IIIa, ATP, pyridoxal phosphate, dithiothreitol, 1,2-diolein, Triton X-100, and staurosporine were obtained from Sigma. [γ-³²P]ATP (6000 Ci/mmol, 10 mCi/ml) was from Amer sham Pharmacia Biotech, and [20-³²P]Hphorbol 12,13-dibutyrate ([³²P]PDBu) (20 Ci/mmole) was purchased from NEN Life Science Products. S-minimal essential medium, RPMI 1640, non-essential amino acid solution (10 mM, 100×), trypsin-EDTA solution (1×), and penicillin-streptomycin, antibiotic-antimycotic solution were purchased from Life Technologies, Inc. Dialyzed fetal bovine serum was obtained from...
PKC-independent Mechanism Mediated by Benzophenanthridines

HyClone (Logan, UT). Monoclonal anti-PKC (α, β, and γ) antibodies were purchased from Transduction Laboratories (Lexington, KY).

Angirole and Chelerythrine

Angirole was isolated from the stem of M. cordata (Willd.) R. Br. (syn. Bocconia cordata Willd.) (Papaveraceae). Briefly, the stem bark of M. cordata (600 g) was extracted with methanol (3 × 3 liters). The resultant extract (50 g) was defatted with petroleum ether (300 ml), suspended in 100 ml of H2O, and partitioned with ethyl acetate (3 × 400 ml) to afford 8 g of an ethyl acetate residue. Further purification was performed by silica gel column chromatography using CHCl3 and CHCl3 with an increasing amounts of methanol (0–25%) as eluents. Through repeated column chromatography of the subfractions, angirole (1) (also known as 9-methoxychelerythrine) was isolated with a melting point 212–215 °C (literature: 210 °C; Ref. 19), (Fig. 1) (also known as 9-methoxychelerythrine) was isolated with melt-}

PKC Preparations and Analysis of Activity

The purification of PKC-α from calf brain and the PKC assay was performed essentially as described by Da Silva et al. (23). Briefly, fresh calf brain homogenates were centrifuged at 100,000 × g for 60 min. The supernatant was concentrated using an ultrafiltration cell (Amicon, France).

Preparation and Fractionation of HL-60 Cells—HL-60 cells in loga-

Assessment of TPA-induced Ornithine Decarboxylase (ODC) Activity with ME 308 Cells

Mouse epidermal 308 cells were cultured in S-minimal essential medium containing non-essential amino acids (1×), dialyzed fetal bovine serum (5%), Ca2+ (0.05 mM), and antibiotic-antimycotics (1×) at 37 °C in a 5% CO2 atmosphere. For determination of TPA-induced ODC activity, cells were distributed to 24-well plates at an initial density of 2 × 104 cells/well/plate. After an 18-h preincubation, test materials dissolved in Me2SO for 1 h were added to duplicate (5 μl, 0.5% final Me2SO concentration) before the induction of ODC activity with TPA (200 nM). After an additional incubation period of 6 h, plates were washed twice with phosphate-buffered saline and stored at −80 °C until tested. ODC activity was assayed directly in the 24-well plates as described previously (25). In brief, frozen cells were lysed by quickly thawing the bottom of the culture plates in a warm water bath (37 °C, 2 min). A substrate and cofactor mixture (200 μl containing 2 μl of 1-13C-ornithine (200 nCi), 56 mCi/mmol, 100 μCi/ml), 50 μl of sodium phosphate buffer (0.2 mM, pH 7.2), 16 μl of EDTA (12.5 mM), 10 μl of dithiothreitol (50 mM), 4 μl of pyridoxal phosphate (5 mM in 10 mM NaOH) and 118 μl of unlabeled L-ornithine (78 μmol) were added to each well. Released [13C]CO2 was captured by paper discs, which were moistened with 30 μl of 1% NaOH during incubation of plates at 37 °C for 1 h while shaking. A substrate and cofactor mixture (200 μl containing 2 μl of 1-13C-ornithine (200 nCi), 56 mCi/mmol, 100 μCi/ml), 50 μl of sodium phosphate buffer (0.2 mM, pH 7.2), 16 μl of EDTA (12.5 mM), 10 μl of dithiothreitol (50 mM), 4 μl of pyridoxal phosphate (5 mM in 10 mM NaOH) and 118 μl of unlabeled L-ornithine (78 μmol) were added to each well. Released [13C]CO2 was captured by paper discs, which were moistened with 30 μl of 1% NaOH during incubation of plates at 37 °C for 1 h while shaking. A substrate and cofactor mixture (200 μl containing 2 μl of 1-13C-ornithine (200 nCi), 56 mCi/mmol, 100 μCi/ml), 50 μl of sodium phosphate buffer (0.2 mM, pH 7.2), 16 μl of EDTA (12.5 mM), 10 μl of dithiothreitol (50 mM), 4 μl of pyridoxal phosphate (5 mM in 10 mM NaOH) and 118 μl of unlabeled L-ornithine (78 μmol) were added to each well. Released [13C]CO2 was captured by paper discs, which were moistened with 30 μl of 1% NaOH during incubation of plates at 37 °C for 1 h while shaking. A substrate and cofactor mixture (200 μl containing 2 μl of 1-13C-ornithine (200 nCi), 56 mCi/mmol, 100 μCi/ml), 50 μl of sodium phosphate buffer (0.2 mM, pH 7.2), 16 μl of EDTA (12.5 mM), 10 μl of dithiothreitol (50 mM), 4 μl of pyridoxal phosphate (5 mM in 10 mM NaOH) and 118 μl of unlabeled L-ornithine (78 μmol) were added to each well. Released [13C]CO2 was captured by paper discs, which were moistened with 30 μl of 1% NaOH during incubation of plates at 37 °C for 1 h while shaking. A substrate and cofactor mixture (200 μl containing 2 μl of 1-13C-ornithine (200 nCi), 56 mCi/mmol, 100 μCi/ml), 50 μl of sodium phosphate buffer (0.2 mM, pH 7.2), 16 μl of EDTA (12.5 mM), 10 μl of dithiothreitol (50 mM), 4 μl of pyridoxal phosphate (5 mM in 10 mM NaOH) and 118 μl of unlabeled L-ornithine (78 μmol) were added to each well. Released [13C]CO2 was captured by paper discs, which were moistened with 30 μl of 1% NaOH during incubation of plates at 37 °C for 1 h while shaking. A substrate and cofactor mixture (200 μl containing 2 μl of 1-13C-ornithine (200 nCi), 56 mCi/mmol, 100 μCi/ml), 50 μl of sodium phosphate buffer (0.2 mM, pH 7.2), 16 μl of EDTA (12.5 mM), 10 μl of dithiothreitol (50 mM), 4 μl of pyridoxal phosphate (5 mM in 10 mM NaOH) and 118 μl of unlabeled L-ornithine (78 μmol) were added to each well. Released [13C]CO2 was captured by paper discs, which were moistened with 30 μl of 1% NaOH during incubation of plates at 37 °C for 1 h while shaking.
RESULTS

Effects of Chelerythrine and Angoline on PKC Activity—
Based on the structural similarity of angoline and chelerythrine (Fig. 1), initial studies were performed to assess the potential of angoline, isolated from \textit{M. cordata}, to inhibit the catalytic activity of PKC. Surprisingly, angoline demonstrated little inhibitory activity with calf brain PKC; IC$_{50}$ values for basal and PDBu-stimulated activity were approximately 100 µg/ml (Fig. 2). We then examined chelerythrine in this assay system. In contrast to the results of Herbert \textit{et al.} (14), chelerythrine did not mediate potent inhibitory activity with calf brain PKC. IC$_{50}$ values were approximately 60 and 80 µg/ml with basal and PDBu-stimulated activity, respectively (Fig. 2). The lack of efficacious inhibition by chelerythrine was not due to the nature of the stimulator, since similar dose-response patterns were observed in the presence of either PDBu or diolein (Fig. 3). Using the same experimental conditions, staurosporine (133 ng/ml) inhibited activity over 90%, irrespective of which stimulator was employed (data not shown). Chelerythrine was also ineffective as an inhibitor using mouse and rat brain cytosol fractions as sources of PKC. In fact, with these preparations, chelerythrine enhanced PKC activity in concentrations ranging up to 100 µM (Fig. 4).

Effects of Chelerythrine and Angoline on PDBu Binding—In order to investigate the effect of chelerythrine and angoline on the regulatory domain of PKC, PDBu binding activity was assessed with crude calf brain particulate as a source of PKC. At concentrations of 2 µg/ml, chelerythrine and angoline enhanced [3H]PDBu binding. This was followed by diminution of binding to the levels of control. When tested at a concentration 200 µg/ml, chelerythrine and angoline reduced PDBu binding to levels corresponding to 60 and 45% of control, respectively (Fig. 5). Using other sources of soluble PKC, including mouse, rat, dog, chicken, and rabbit brain cytosol, chelerythrine and angoline did not show inhibitory effects at concentrations ranging up to 20 µg/ml (data not shown). In each experiment, unlabeled PDBu (0.4 µM) inhibited [3H]PDBu binding to PKC by over 95% (data not shown). Therefore, chelerythrine and angoline did not affect binding to the regulatory domain of PKC with strong potency.

Effects of Test Compounds on PKC Translocation—In order to evaluate the potential of chelerythrine and angoline to affect PKC translocation, Western blot analyses were performed with preparations derived from cultured HL-60 cells treated with test compounds. Mouse anti-PKC-α, -β, or -γ antibodies were used as probes (Fig. 6). As expected, treatment with TPA (200 nM) for 3 h induced translocation of PKCs from the cytosol to particulate fractions (Fig. 6, A and B), and increasing exposure time to 24 h resulted in down-regulation (Fig. 6, C and D). When tested at concentrations as high as 1.0 µg/ml, however, alterations in PKC levels or distribution patterns were not facilitated by chelerythrine or angoline (Fig. 6). When co-incubated with TPA for 24 h, down-regulation of PKCs was slightly potentiated by the test compounds.

Effects of Chelerythrine and Angoline on TPA-induced ODC Activity—ODC is the key enzyme in the biosynthesis of poly-amines and is inducible by stimuli such as growth factors, hormones, and tumor promoters, including phorbol esters (26). Activity is controlled by various factors, including expression, stability and transcription rate of ODC mRNA, stability and translation rate of the ODC enzyme, and post-translational modifications (27, 28). Using mouse 308 cells as a model system, chelerythrine did not inhibit TPA-induced ODC activity.

FIG. 1. \textit{Chemical structures of chelerythrine and angoline.}

FIG. 2. \textit{Effect of chelerythrine and angoline on purified calf brain protein kinase C activity.} PKC activity was determined in the presence of the indicated concentrations of angoline (○) or chelerythrine (●) in the absence of stimulator (PKC basal activity), or in the presence of PDBu (0.4 µM) (angoline (▲) or chelerythrine (△)). Basal and PDBu-induced specific activities of 32P incorporation were 9.7 ± 0.3 and 45.9 ± 1.3 pmol of 32P/mg of protein/min, respectively. Values represent the mean percent ± S.D. of the respective solvent-treated controls of two independent experiments.

FIG. 3. \textit{Effect of chelerythrine on calf brain PKC activity treated with PDBu or diolein.} PKC activity was measured in the presence of the indicated concentrations of chelerythrine (●) or chelerythrine (▲) or diolein (△, 180 µM). Results were expressed as a percentage, relative to the corresponding solvent-treated control incubations. Diolein (180 µM), TPA (200 ng/ml), and PDBu (200 ng/ml) enhanced basal activity by 450 ± 31, 490 ± 23, and 480 ± 65%, respectively. Basal specific activity was 10.5 ± 1.0 pmol of 32P/mg of protein/min.
within the non-cytotoxic range (IC$_{50}$ > 1.0 µg/ml), but promoted a slight enhancement of activity at lower concentrations. Angoline did not alter the TPA-induced effect at lower concentrations, but reduced activity by approximately 50% at a test concentration of 1.0 µg/ml (Fig. 7).

**DISCUSSION**

Since PKC plays an important role in signal transduction and phorbol ester-promoted tumorigenesis, various inhibitors have been studied in detail. One such substance, chelerythrine, has been reported as a potent and specific inhibitor. The phosphorylation reaction mediated by PKC was reduced with an IC$_{50}$ value of 0.66 µM. Inhibition was competitive with respect to phosphate acceptor (histone IIIs), and noncompetitive with respect to ATP. No substantive competition was observed with respect to [3H]PDBu binding, thus suggesting interaction does not occur at the regulatory site of PKC. Other kinases, such as protein kinase A, tyrosine protein kinase, and Ca$^{2+}$/calmodulin-protein kinase, were not inhibited with great efficacy, indicating specificity for PKC (14).

Accordingly, when we obtained angoline from a plant extract demonstrating antagonism of PDBu binding with PKC, it was suspected that this substance would function in a mode similar to chelerythrine. However, angoline was found ineffective as an inhibitor of PKC activity. Thus, as a positive control, the inhibitory potential of chelerythrine was investigated, obtaining this substance from a commercial source (Sigma). However, in repeated attempts, chelerythrine was found to be practically inactive as an inhibitor of partially purified calf brain PKC. Although the compound appeared pure and stable (HPLC anal-

![FIG. 4. Effect of chelerythrine on the catalytic activity of PKC derived from various sources. PKC activity was determined in the presence of the indicated concentrations of chelerythrine using diolein (180 µM) as an activator. Cytosolic fractions (12,000 × g, supernatant) from rat brain (●), calf brain (●) or mouse brain (△), were used as sources for PKC. Diolein-induced incorporation of $^{32}$P with each respective enzyme source was 63.2 ± 9.2, 42.9 ± 1.9, and 39.9 ± 1.4 pmol of $^{32}$P/mg of protein/min. Data represent the mean percent ± S.D. of control (diolein-induced level). Tests were performed in duplicate.](image)

![FIG. 5. Effect of angoline and chelerythrine on [3H]PDBu binding. The binding of [3H]PDBu to partially purified PKC from calf brain was measured in the presence of the indicated concentrations of angoline (■) or chelerythrine (□). Specific binding activity of the control group was 3.10 ± 0.14 pmol of [3H]PDBu/mg of protein, and this was reduced to 0.15 ± 0.01 pmol of [3H]PDBu/mg of protein by the addition of unlabelled PDBu (0.4 µM). Data represent the average percent of control. Tests were conducted in duplicate.](image)

![FIG. 6. Effect of chelerythrine and angoline on translocation of PKC. Human leukemia HL-60 cells were treated with solvent (Me$_2$SO, 0.2% final concentration), chelerythrine (1.0 µg/ml), or angoline (1.0 µg/ml) in the presence or absence of TPA (200 nM) for 3 or 24 h. As described under "Experimental Procedures," cytosol and membrane-associated particulate fractions were obtained by differential centrifugation. Protein samples (50 µg per lane) were analyzed by Western blotting with monoclonal antibodies specific for PKC-α, -β, or -γ. A, cells were incubated with solvent (Me$_2$SO) or chelerythrine in the presence or absence of TPA for 3 h. Lane 1, control cytosol; lane 2, control particulate; lane 3, TPA cytosol; lane 4, TPA particulate; lane 5, chelerythrine cytosol; lane 6, chelerythrine particulate; lane 7, chelerythrine in the presence of TPA cytosol; lane 8, chelerythrine in the presence of TPA particulate. B, cells were incubated with solvent (Me$_2$SO) or angoline in the presence or absence of TPA for 3 h. Lane 1, control cytosol; lane 2, control particulate; lane 3, TPA cytosol; lane 4, TPA particulate; lane 5, angoline cytosol; lane 6, angoline particulate; lane 7, angoline in the presence of TPA cytosol; lane 8, angoline in the presence of TPA particulate. C, treatment conditions were the same as in A, except the incubation period was 24 h. D, treatment conditions were the same as in B, except the incubation period was 24 h.](image)
PKC-independent Mechanism Mediated by Benzophenanthridines

**Effect of chelerythrine or angoline on TPA-induced ODC activity.** Mouse 308 cells were simultaneously treated with TPA (200 nM) and the indicated concentrations of angoline (■) or chelerythrine (□) for a period of 6 h. ODC activity was then determined as described under "Experimental Procedures." ODC activity of TPA-treated solvent control was 1.80 ± 0.08 nmol of [14C]CO2/mg of protein/h; without TPA treatment, ODC activity was 0.070 ± 0.005 nmol of [14C]CO2/mg of protein/h. Data represent the average percent ± S.D. of the TPA-treated control group. Tests were performed in duplicate.

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