2-Arachidonoylglycerol: A Novel Inhibitor of Androgen-Independent Prostate Cancer Cell Invasion

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Abstract

Endocannabinoids have been implicated in cancer. Increasing endogenous 2-arachidonoylglycerol (2-AG) by blocking its metabolism inhibits invasion of androgen-independent prostate cancer (PC-3 and DU-145) cells. Noladin ether (a stable 2-AG analog) and exogenous CB1 receptor agonists possess similar effects. Conversely, reducing endogenous 2-AG by inhibiting its synthesis or blocking its binding to CB1 receptors with antagonists increases the cell invasion. 2-AG and noladin ether decrease protein kinase A activity in these cells, indicating coupling of the CB1 receptor to downstream effectors. The results suggest that cellular 2-AG, acting through the CB1 receptor, is an endogenous inhibitor of invasive prostate cancer cells.

Introduction

2-Arachidonoylglycerol (2-AG) is a monoacylglycerol derivative of arachidonic acid (AA) that can be synthesized from AA-enriched membrane phospholipids such as phosphatidylinositol and phosphatidylglycerol lipase (1). Fatty acid amide hydrolase (2) and monoacylglycerol lipase (3, 4) can hydrolyze 2-AG to AA and diacylglycerol lipase (1). Fatty acid amide hydrolase (2) and monoacylglycerol lipase (3, 4) can hydrolyze 2-AG to AA and glycerol. 2-AG is an endogenous ligand (endocannabinoid) for the central cannabinoid (CB1) receptors (5) and for the peripheral cannabinoid (CB2) receptors (6) in some cells. Studies have implicated endocannabinoids and cannabinoid receptors in tumorigenesis. 2-AG inhibits proliferation of rat C6 glioma cells (7) and prolactin-induced DU-145 cells (8). It reduces the growth of colon cancer (9). These 2-AG activities in DU-145 cells and colon cancer involve the CB1 receptors. 2-AG inhibits a rapid, transient elevation of intracellular Ca2+ concentration in neuroblastoma × glioma hybrid NG108-15 cells (10), similar to the cannabinoid agonist WIN55,212-2, and the cannabinoid CB1 receptor antagonist SR141716 blocks this effect. On the other hand, exogenous 2-AG stimulates migration of CB2-overexpressing myeloid leukemia cells and normal splenocytes (11). 2-AG also induces the migration of microglial cells through CB2 receptors (12).

In these studies, 2-AG was applied as a chemoattractant in the bottom compartment of the Transwell. A different mechanism could be responsible for 2-AG functions in these cells than other cells. Whereas exogenous 2-AG inhibits proliferation of prolactin-induced DU-145 cells, the effects of endogenous 2-AG have not been studied. We investigated the roles of endogenous 2-AG and cannabinoid receptors in regulating invasion of human prostate cancer cells. Androgen-independent (PC-3 and DU-145) and androgen-dependent (LNCaP) prostate cancer cells were used to determine whether 2-AG functions differently in hormone-refractory prostate cancer cells.

Materials and Methods

Cells and Cell Culture. Androgen-independent (PC-3 and DU-145) and androgen-dependent (LNCaP) human prostate cancer cells were obtained from American Type Culture Collection (Manassas, VA). Cells were maintained in Eagle’s minimal essential medium (RPMI 1640) supplemented with 10% fetal bovine serum, l-glutamine (2 mmol/L), streptomycin (100 μg/mL), and penicillin (100 units/mL). Cells were grown in 75-cm² polystyrene tissue culture flasks at 37°C in 5% CO2 to about 60% to 70% confluence before use.

Cell Invasion Assay. Cells were incubated overnight with [methyl-3H]-thymidine (1 μCi/mL; Applied Biosystems, Foster City, CA) in media containing 10% fetal bovine serum. Cells were rinsed once with fresh complete medium to remove unbound [methyl-3H]-thymidine, and fresh complete medium was added to each flask. Cells were then detached from the flask by using Pucks buffer (150 mmol/L NaCl, 5 mmol/L KCl, 10 mmol/L HEPES, 5 mmol/L NaHCO3, 1 mmol/L acid-free EDTA, 5 mmol/L glucose, and 0.25% trypsin) at 37°C for 5 minutes. The cells were centrifuged at 200 × g and resuspended in 3 mL of serum-free RPMI 1640. The experiments were performed in 24-well plates containing Transwells with 8.0-μm pore polyvinylpyrrolidone-free polycarbonate filters (Corning Inc., Corning, NY) coated with Matrigel (BD Biosciences, Bedford, MA) on the top compartments. Cell suspension (100 μL; 50,000 cells) containing the vehicle control or pharmacological agents [2-AG and noladin ether (Cayman Chemical, Ann Arbor, MI), methyl arachidonyl fluorophosphonate (MAFP; Tocris, Ballwin, MO), diazamethylandrochidone ketone (DADK; synthesized in our laboratory; ref. 13), RHC-80267 (Calbiochem, San Diego, CA), SR141716 and SR144528 (Research Triangle Institute, Research Triangle Park, NC), WIN55,212-2 (Sigma, St. Louis, MO), (R)-(+-)methanandamide (RBI, Natick, MA)] at various concentrations was added to each upper compartment. Fibroblast conditioned-media (400 μL) was added in the bottom compartment of the well as a chemoattractant. Normally, 6 wells per treatment were performed for each batch of experiments. An additional 6 wells without Matrigel and Transwell but containing the identical number of cells and pharmacological agents were used for the “control counts” of [methyl-3H]-thymidine. Cells were incubated at 37°C in the incubator for 5 hours. Plates were centrifuged at 1,450 × g at 22°C for 30 minutes. The cells passed into the lower compartment media were detached with Pucks buffer containing 0.75% trypsin and placed in vials. The bottom side of the filter and the lower compartment were rinsed with 400 μL of Pucks buffer, incubated at 37°C for 20 minutes to remove adherent cells, combined in the corresponding vials, and counted for radioactivity. Each treatment was performed at least three times. The invasion was reported as the percentage of the invasion of the control cells.

Determination of 2-Arachidonoylglycerol in Prostate Cancer Cells by Liquid Chromatography-Electrospray Ionization-Mass Spectrometry. Cells were grown in T-75 flasks, rinsed with 5 mL of HEPES buffer (pH 7.4), and treated with RHC-80267 (100 nmol/L) or vehicle in HEPES buffer at 37°C for 15 minutes (14). The cells were lysed, scraped, and transferred into 15-mL tubes for sample preparation by solid phase extraction. An aliquot of 100 μL was saved for protein determination using Bio-Rad (Hercules, CA) protein assay. [3H]-2-AG (15 ng; Cayman Chemical) was added to the samples as an internal standard. The samples were extracted by solid phase extraction as
described previously (14), redissolved in 20 μL of acetonitrile, and analyzed or kept at -80°C. Samples were analyzed by using liquid chromatography-electrospray ionization-mass spectrometry (Agilent 1100 LC-MSD, SL model; ref. 14). Briefly, the samples were separated on a reverse phase C18 column (Kromasil; 250 × 2 mm; Phenomenex) using water/acetonitrile containing 0.005% acetic acid as a mobile phase at a flow rate of 0.2 mL/min. The gradient started at 35% acetonitrile, increased linearly to 100% acetonitrile in 35 minutes, and held at 100% acetonitrile for 10 minutes. Drying gas of the electrospray chamber was 12 L/min, drying gas temperature was 350°C, nebulizer pressure was 35 psig, vaporizer temperature was 350°C, and fragmentor voltage was 90 V. The detection was made in the positive mode. For quantitative measurement, m/z 379 and 387 were used for 2-AG and [2H8]2-AG, respectively. The concentrations of 2-AG were calculated by comparing their ratios of peak areas to the standard curves. The results were normalized to the protein content. 

**Determination of 2-OG Hydrolysis.** Cells were grown in T-75 flasks to 60% to 70% confluence. Then, the medium was replaced by 100 μL of 100 mmol/L PBS (pH 7.4), after cells were washed twice with PBS buffer. Cells were homogenized by pulling them through a 27-gauge needle a few times. The membrane proteins were separated by centrifugation at 20,000 × g at 4°C for 30 minutes, and cytosolic proteins were separated by centrifugation at 60,000 × g at 4°C for 60 minutes. The membrane protein pellet was resuspended in 150 μL of PBS buffer. The hydrolysis of 2-oleoyl-[3H]glycerol (2-OG) by cytosolic and membrane proteins (96 μg each) was determined according to the previously described method (4), with modifications. The final volume of the assay was 0.5 mL of 100 mmol/L PBS buffer (pH 7.4) in the absence and presence of MAFP (100 nmol/L) or DAK (1 μmol/L). 2-Oleoyl-[3H]glycerol (20 Ci/mmol; American Radiolabeled Chemical, St. Louis, MO) at 10,000 dpm was used as a substrate. Incubations were carried out at 37°C for 30 minutes.

**Western Blot Analysis of Cannabinoid Receptors.** Cells were lysed as described above in the presence of a protease inhibitor. Membrane proteins (50 μg) were separated by SDS-PAGE (Ready Gels) and transferred to a 0.7-micron nitrocellulose (Bio-Rad) membrane. Proteins were incubated with the CB1 and CB2 antibodies. Anti-CB1 and anti-CB2 receptor antibodies raised in rabbit from Cayman Chemical and Affinity BioReagents (Golden, CO) were used. Then, goat antirabbit IgG-horseradish peroxidase (Zymed Laboratories Inc., South San Francisco, CA) was used to complex with the primary antibodies. The detection was made by using Western Lightning Chemiluminescence Reagent (Perkin-Elmer, Boston, MA) and captured by Fuji X-ray film (Tokyo, Japan).

**Results and Discussion**

**Cellular Synthesis of 2-Arachidonoylglycerol and Its Effects on Cell Invasion.** Prostate cancer PC-3, DU-145, and LNCaP cells produced 2-AG at high concentrations (in the ng/mg protein range), and RHC-80267 (100 nmol/L), a diacylglycerol lipase inhibitor, significantly inhibited 2-AG production in these three cell lines (Fig. 1A). Treatment of cells with RHC-80267 (10, 100 nmol/L) increased the invasion of PC-3 and DU-145 cells (Fig. 1B). Of the two cell lines,
Effects of MAFP (1 μmol/L) and RHC-80267 (100 nM) on invasion of PC-3, DU-145, and LNCaP cells. Values are mean ± SE (n = 6).

PC-3 cells (4.2-fold increase) were more sensitive to RHC-80267 (100 nM) than DU-145 cells (2.0-fold increase). RHC-80267 did not affect invasion of LNCaP cells. These results suggest that 2-AG is a potential endogenous inhibitor of invasion of androgen-independent prostate cancer cells. To test the inhibitory effect of 2-AG, cells were incubated with exogenous 2-AG (1 μmol/L), and cell invasion was measured. However, exogenous 2-AG did not inhibit invasion of PC-3, DU-145, and LNCaP cells, but it reversed the cell invasion increase by RHC-80267 in PC-3 and DU-145 cells to a level similar to that of the control cells (without RHC-80267). Analysis of radiolabeled species obtained after incubation of these cells with [14C]2-AG for 15 minutes indicates that the added [14C]2-AG was rapidly converted to [14C]AA (data not shown). These results suggest that exogenous 2-AG is rapidly metabolized by these cells before it binds to cannabinoid receptors and induces a signaling cascade. Therefore, noladin ether (a nonhydrolyzable analog of 2-AG; ref. 15), which is a ligand of CB1 receptors (16) and weakly binds to CB2 receptors, was studied. However, noladin ether is less potent than 2-AG in many systems studied. Noladin ether significantly inhibited invasion in a concentration-dependent manner of PC-3 (67.58 ± 3.15% and 28.89 ± 0.97% invasion at 10 and 50 μmol/L, respectively) and DU-145 cells (70.19 ± 6.13% at 50 μmol/L), but not LNCaP cells (Fig. 1C). In parallel with the effects of RHC-80267, PC-3 cells were more sensitive to the effects of noladin ether than DU-145 cells.

Hydrolysis of 2-OG. Because 2-AG can be metabolized to AA and glycerol and is less effective in inhibiting cell invasion than noladin ether, the effects of inhibition of endogenous 2-AG metabolism on cell invasion were investigated. Two characterized hydrolases, fatty acid amidohydrolase and monoacylglycerol lipase (17), and other less well-defined esterases can metabolize 2-AG to AA and glycerol. This is a terminating step of the action of endocannabinoids (3, 17). To investigate the inhibitors of 2-AG hydrolysis, the hydrolysis of 2-oleoyl-[3H]glycerol (a readily available radiolabeled analog of 2-AG) by cytosolic and membrane protein fractions of each cell type was determined. 2-OG hydrolysis occurred with both the cytosolic and membrane fractions of each cell type studied (Table 1). Interestingly, the relative hydrolysis (expressed as a percentage of conversion of 2-OG) in each fraction displayed a different pattern in the three cells: in PC-3 cells, the activity was similar in both fractions (30.45 ± 1.94% in the cytosolic fraction and 28.89 ± 0.97% in the membrane fraction); in DU-145 cells, the activity was greater in the membrane fraction (70.19 ± 6.13%) than in the cytosolic fraction (53.19 ± 1.97%); and in LNCaP cells, the activity was much greater in the membrane fraction (84.55 ± 0.71%) than in the cytosolic fraction (21.40 ± 3.76%). In all of the cells, the nonselective serine

Table 1 Hydrolysis of 2-OG by cytosolic and membrane proteins of prostate cancer cells in the absence and presence of enzyme inhibitors (100 nM MAFP and 1 μmol/L DAK)

<table>
<thead>
<tr>
<th>Cells and protein fractions</th>
<th>Control</th>
<th>MAFP</th>
<th>DAK</th>
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<tr>
<td>PC-3</td>
<td></td>
<td></td>
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<tr>
<td>Cytosolic fraction</td>
<td>30.45 ± 1.94</td>
<td>21.75 ± 0.90</td>
<td></td>
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<tr>
<td>Membrane fraction</td>
<td>21.75 ± 0.90</td>
<td>21.19 ± 1.96</td>
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<tr>
<td>DU-145</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytosolic fraction</td>
<td>76.06 ± 1.97</td>
<td>76.29 ± 3.50</td>
<td></td>
</tr>
<tr>
<td>Membrane fraction</td>
<td>76.29 ± 3.50</td>
<td>76.32 ± 3.50</td>
<td></td>
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<tr>
<td>LNCaP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytosolic fraction</td>
<td>21.40 ± 3.76</td>
<td>3.76 ± 5.18</td>
<td></td>
</tr>
<tr>
<td>Membrane fraction</td>
<td>3.76 ± 5.18</td>
<td>3.76 ± 5.18</td>
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* Significantly different from control (P < 0.001).
esterase/amidase inhibitors, MAFP (100 nmol/L) and DAK (1 μmol/L), significantly reduced but did not completely eliminate the hydrolysis of 2-OG in the cytosolic and membrane fractions. These concentrations of MAFP and DAK are the concentrations that gave the inhibition at near the maximum invasion (see Fig. 1D and E). Again, the hydrolysis activity of the membrane fractions in DU-145 and LNCaP cells remained high in the presence of MAFP and DAK at these concentrations. DAK (25 μmol/L) inhibited 2-OG hydrolysis in these cells slightly more than DAK (1 μmol/L).

These results suggest that the localization of enzymes may be important for 2-AG hydrolysis. Furthermore, these cells may contain other enzymes such as esterases that can hydrolyze 2-AG. The smaller hydrolysis activity in PC-3 cells suggests that it may be one of the factors responsible for the greater sensitivity of PC-3 cells to treatment with MAFP and DAK as compared with other cells.

**Effects of Inhibition of 2-Arachidonoylglycerol Metabolism on Cell Invasion.** Cells were incubated with MAFP and DAK to inhibit 2-AG metabolism, and invasion was determined. Both MAFP (Fig. 1D) and DAK (Fig. 1E) inhibited invasion of PC-3 and DU-145 cells but were without effect in LNCaP cells. Exogenous 2-AG alone did not inhibit invasion of PC-3 cells (probably due to its rapid metabolism). However, when PC-3 cells were incubated with 2-AG (1 μmol/L) in the presence of MAFP (1 μmol/L), 2-AG augmented the inhibition of cell invasion by MAFP (Fig. 1F; 61.87 ± 2.85% for MAFP and 46.54 ± 2.90% for MAFP and 2-AG). These results indicate that the blockade of 2-AG metabolism inhibits cell invasion, and they further support the hypothesis that endogenous 2-AG is a negative regulator of invasion in androgen-independent prostate cancer cells.

**Cannabinoid Receptors and Cell Invasion.** To investigate whether 2-AG regulation of cell invasion is CB receptor dependent, the expression of CB receptors was determined in these cells. Antibodies against CB1 and CB2 receptors from two different sources were used with identical results. Western blot analysis indicates that all three prostate cancer cell lines examined here express CB1 and CB2 receptor proteins (at 55 and 50 kDa, respectively; Fig. 2A and B) as reported previously (8, 18). CB1 receptor expression, as compared with β-actin, is higher in PC-3 cells (0.13) than in DU-145 (0.07) cells and LNCaP cells (0.06), whereas CB2 receptor expression in PC-3 cells (0.11) is similar to that in DU-145 cells (0.12) but higher than that in LNCaP cells (0.06).

To further characterize the pharmacological response of the CB receptors on cell invasion, cells were treated with WIN55,212-2 (a nonselective CB agonist), (R)-(+)methanandamide (a selective CB1 agonist), SR141716 (a selective CB1 antagonist), and SR144528 (a selective CB2 antagonist), and cell invasion was measured. Both WIN55,212-2 (Fig. 2C) and (R)-(+)methanandamide (Fig. 2D) inhibited cell invasion in a concentration-dependent manner, whereas SR141716 (Fig. 2E) increased invasion of PC-3 and DU-145 cells. These CB agonists and antagonists did not significantly affect the invasion of LNCaP cells. SR144528 did not affect the invasion of any of the cell lines (data not shown). Furthermore, SR141716 (500 nmol/L) reversed the inhibition of cell invasion by MAFP (1 μmol/L) in PC-3 cells (Fig. 2F; 63.18 ± 2.75% for MAFP and 98.76 ± 3.98% for MAFP and SR141716). These results suggest that the inhibition of cell invasion of androgen-independent prostate cancer cells by 2-AG involves a CB1 receptor pathway. A higher relative expression of CB1 receptors in PC-3 cells may be one of the reasons that this cell line is more sensitive to endogenous 2-AG, noladin ether, and CB agonists than other cells.

**Protein Kinase A Activity.** All prostate cancer cells investigated express CB1 receptors, but the inhibition of cell invasion was observed only in androgen-independent cells. Activation of the CB1 receptor leads to inhibition of adenylyl cyclase activity (19), which may result in a disruption of downstream signaling transduction pathway(s) that regulates cell invasion (20). To determine whether CB1 receptor activation inhibited adenylyl cyclase in these prostate cancer cells, cAMP-dependent PKA activity was determined in cells treated with 2-AG and MAFP or with noladin ether. Treatment with 2-AG (1 μmol/L) + MAFP (1 μmol/L) or with noladin ether (10 μmol/L) decreased PKA activity in PC-3 and DU-145 cells but slightly increased the activity in LNCaP cells (Fig. 3A). The average of PKA activities (n = 4) of cells treated with 2-AG + MAFP or with noladin ether were 62.0 ± 6.0% and 55.3 ± 10.4% of control, respectively, for PC-3 cells: 79.2 ± 12.8% and 61.8 ± 3.6% of control, respectively, for DU-145 cells; and 138.9 ± 10.1% and 118.1 ± 12.3% of control, respectively, for LNCaP cells (Fig. 3B). Furthermore, MAFP (1 μmol/L) inhibited PKA activity (73.43 ± 3.93% of control) in PC-3 cells, and SR141716 reversed this inhibition (111.71 ± 4.37% of control; Fig. 3C and D). These results suggest that inhibition of PKA activity by 2-AG and noladin ether may be one of the inhibition effects 2-AG has on androgen-independent prostate cancer cell invasion. In conclusion, prostate cancer cells produce 2-AG. A stable analog of 2-AG, blockade of 2-AG metabolism, and binding of agonists to CB1 receptors inhibited the invasion of PC-3 and DU-145 cells. Conversely, inhibition of 2-AG synthesis and blockade of CB1 recep-

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**Fig. 3. Effects of 2-AG and noladin ether on PKA activity.** A, representative photographs of nonphosphorylated bands and phosphorylated bands of PKA-specific substrate peptide (30-minute reaction time) in PC-3, DU-145, and LNCaP cells incubated with vehicle (Lane 1), 2-AG (1 μmol/L) and MAFP (1 μmol/L; Lane 2), and noladin ether (10 μmol/L; Lane 3) [15-minute electrophoretic run time]. B, the average of relative intensity of phosphorylated bands in these cells. The intensity was normalized to the control cells for each gel (as 100%). Values are mean ± SE (n = 4). *, significantly different from control, P < 0.005; #, significantly different from control, P < 0.01.
tors increased their cell invasion. Taken together, the following three observations may be responsible for a different inhibition of cell invasion in these prostate cancer cells: (a) a different activity for glycerol hydrolysis in membrane and cytosolic fractions; (b) a different relative expression of CB1 receptors; and (c) a different effect of 2-AG on PKA activity in these cells. The results from this study suggest that endogenous 2-AG possesses an anti-invasive effect in androgen-independent prostate cancer cells through a CB1-dependent pathway by inhibiting adenylyl cyclase and decreasing the activity of PKA and results in a further downstream signaling cascade that inhibits cell invasion. These results potentially lead to the understanding of mechanisms involved in metastasis and resistance to hormone therapy in prostate cancer. Furthermore, specific inhibitors of enzymes degrading 2-AG and CB1 agonists may be important therapeuti
c agents for hormone-refractory prostate cancer.

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