High Glucose Increases Prostaglandin E₂ Synthesis in Human Peritoneal Mesothelial Cells: Role of Hyperosmolarity

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Abstract. Peritoneal mesothelial cells are considered the predominant source of peritoneal prostanoid formation because they represent the largest resident cell population in the peritoneal cavity. The present study was designed to evaluate the effect of α-glucose, which is widely used in commercially available peritoneal dialysis fluids as an osmotic compound, on the synthesis of prostaglandins in cultured human mesothelial cells (HMC). Analysis of eicosanoid synthesis in HMC by reversed-phase HPLC revealed that 6-keto-PGF₁α, the spontaneous hydrolysis product of prostacyclin (PGI₂), and prostaglandin E₂ (PGE₂) were the main eicosanoids produced. Addition of α-glucose resulted in a time- and concentration-dependent (30 to 120 mM) increase in PGE₂ production in HMC (24 h, 90 mM: 3.9 ± 0.5 ng/10⁵ cells versus 2.3 ± 0.3 in untreated cells; P < 0.05). Mannitol (90 mM) or L-glucose (90 mM), nonmetabolizable osmotic compounds, also led to a significant (P < 0.05) but less intense increase in PGE₂ synthesis (3.3 ± 0.4 and 3.2 ± 0.5 ng/10⁵ cells, respectively). Increased PGE₂ synthesis was completely blunted by coincubation with the specific protein kinase C (PKC) inhibitor Ro 31-8220 or downregulation of PKC activity by preincubation with phorbol myristate acetate for 16 h. Furthermore, coincubation with PD 98059, an inhibitor of the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, also inhibited increased PGE₂ synthesis by α-glucose or mannitol. In contrast, the iso-osmolar glucose polymer icodextrin, which is used as an alternative to α-glucose in peritoneal dialysis solutions, had no effect on PGE₂ synthesis. These data indicate that α-glucose and metabolically inert sugars increase PGE₂ synthesis in HMC at least in part by hyperosmolarity and that this effect requires activation of PKC and the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway of intracellular signaling.

Human mesothelial cells (HMC) line the peritoneal cavity and form an active biological barrier through which transport of water and solutes occurs during peritoneal dialysis (1). These cells play a central role in maintaining peritoneal homeostasis and controlling intraperitoneal inflammation. To this end, it has been demonstrated that HMC synthesize phospholipids (2), cytokines (3), fibrinolytic system components (4,5), and prostaglandins (6–8). Long-term exposure to nonphysiologic dialysis solutions adversely affects function and structure of the peritoneal membrane (9), resulting in increased peritoneal permeability and loss of ultrafiltration (10). Although the precise mechanisms leading to changes in peritoneal permeability are poorly understood, it has been suggested that vasoactive prostaglandins play a central role in the control of fluid movement and the pathophysiology of increased protein permeability (11). In addition, analysis of peritoneal fluid has demonstrated increased levels of prostaglandin E₂ (PGE₂) during peritonitis (12,13), which may serve as a negative feedback loop by inhibiting cytokine release from intraperitoneal macrophages (14). This might be an important control mechanism in the downregulation of inflammation. In this respect, studies on arachidonic acid metabolism by cultured mesothelial cells have demonstrated that prostaglandin release is stimulated in the presence of inflammatory cytokines and that prostacyclin and PGE₂ are the predominant prostaglandins produced in this cell type (8). It has therefore been postulated that mesothelial cells may be the main source of intraperitoneally produced prostaglandins.

This study was designed to evaluate the effect of α-glucose, osmotic solutes, and the glucose polymer icodextrin on the synthesis of PGE₂ by cultured HMC. The metabolic effect of α-glucose as well as its hyperosmolar concentration in the dialysate have been shown to compromise the function and metabolism of HMC (15,16). However, the effect of α-glucose or other osmotic solutes on HMC prostaglandin synthesis has not yet been investigated. We report that α-glucose and metabolically inert osmotic compounds increase prostaglandin production in HMC by a signaling pathway requiring protein kinase C (PKC) and mitogen-activated protein kinase (MAPK) activity.

Materials and Methods

Materials

M199 medium and newborn calf serum were obtained from Life Technologies (Eggenstein, Germany); tissue culture plates were from...
Human peritoneal mesothelial cells (HMC) were isolated from the omental tissue of consenting patients undergoing elective surgery, as described (5). Briefly, 1-cm² samples were washed in sterile phosphate-buffered saline, pH 7.4, and incubated with 1 mg/ml collagenase type II for 15 min at 37°C with continuous agitation. Digested pieces of omentum were then discarded, and the cell suspension was centrifuged at 800 g for 5 min. The cell pellet was washed and cells were grown in fibronectin-coated dishes in M199 medium supplemented with 25 mM Hepes, pH 7.3, 2 mM glucose, 10% (vol/vol) newborn calf serum (heat-inactivated), endothelial cell growth factor (20 µg/ml), penicillin (100 IU/ml), and streptomycin (100 µg/ml) at 37°C under 5% CO₂/95% air atmosphere. The medium was replaced every 2 to 3 d. Subcultures were obtained by trypsin/ethylene diamine tetra-acetic acid treatment at a split ratio of 1:3. To characterize cells from omental tissue as pure mesothelial cells, immunofluorescence staining of mesothelial cell antigens was performed on cell monolayers that were grown on coverslips and fixed in 80% (vol/vol) acetone for 10 min at 4°C. The cells were incubated for 30 min with monoclonal antibodies against cytokeratins 8 and 18 and against vimentin. To exclude a contamination with microvascular endothelial cells, incubation was also done with a monoclonal antibody against the endothelial cell marker PAL-E and a polyclonal antibody against human von Willebrand factor. FITC-labeled goat anti-mouse IgG was used as a second antibody. The absence of von Willebrand factor and PAL-E and the uniform positive staining for cytokeratins 8 and 18 and for vimentin characterized cells as mesothelial cells (4,7). For the experiments, confluent cultures were used at the second or third passage, and cells were always reseeded the day before the experiment with M199, supplemented with 25 mM Hepes, pH 7.3, 2% (vol/vol) human serum, and antibiotics. Incubation of cells with doses of tested compounds for up to 24 h did not have any significant effect on cell viability as tested by vital cell staining with acridine orange and ethidium bromide, where living cells show green and dead cells show red fluorescence, when analyzed by fluorescence microscopy (cell viability exceeds 95%). For determination of eicosanoids by reversed-phase HPLC, cells were grown to confluence in 20-cm² dishes. They were incubated for 4 h with control medium (containing 2% human serum) or medium containing TNFα (500 U/ml). Then cells were washed and stimulated in 4 ml of buffer containing (in mM): 1.0 CaCl₂, 2.7 KCl, 25.0 NaHCO₃, 1.4 KH₂PO₄, 20.0 Hepes, 120.0 NaCl, 0.7 MgSO₄, 10.0 glucose, pH 7.4, supplemented with the Ca²⁺ ionophore A23187 (10 µM) or its vehicle DMSO. At the same time, ³H-arachidonic acid (AA) (0.5 µCi for 1 × 10⁶ cells) and nonradioactive AA were added to give a final concentration of 10 µM. After 15 min, the reaction was stopped by addition of 4 ml of ethanol (100%) to each well. Cells were scraped and eicosanoids were extracted (see below). For PGE₂ determination, cells were grown in 2-cm² dishes treated as indicated at 37°C for 6 to 36 h with 0.5 ml of incubation medium containing the appropriate concentration of the test compound or stock solvent. The medium was then centrifuged 5 min (800 × g) to remove cellular debris, and samples were frozen at −20°C until analysis by enzymelinked immunosorbent assay.

³H-Thymidine Incorporation Assay
Proliferation of confluent HMC in the absence or presence of human serum was measured by ³H-thymidine incorporation. Cells were plated onto 24-well plates and cultured in the presence of 10% newborn calf serum and 10% human serum until they reached confluence. Afterward, the medium was removed and cells were incubated for 24 h in 2% human serum-containing medium or for 48 h in 0.1% fetal calf serum-containing medium. The medium was then removed and cells were exposed to 0.5 µCi/ml ³H-thymidine (specific activity, 117 Ci/mmol) in the absence or presence of 2% human serum for 24 h at 37°C. At the end of exposure, cells were washed with phosphate-buffered saline and precipitated with 20% TCA. The precipitate was dissolved in 0.5N NaOH, and radioactivity was measured in a beta liquid scintillation counter (Wallac 1410, Pharmacia, Freiburg, Germany).

Analysis of Eicosanoids
Eicosanoids from cells prelabeled with ³H-AA were extracted as described elsewhere (20). In brief, after acidification to pH 3.5 with acetic acid, eicosanoids were extracted twice with chloroform. Samples were dried under vacuum and resuspended in acetonitrile:water (32:68; vol:vol), pH 4.0. Reversed-phase HPLC was performed using a Waters 600 Multisolvent Delivery System (Waters, Eschede, Germany) with a Beckman Ultrasphere ODS C18 column (4.6 mm × 25 cm; Beckman, Munich, Germany). Eicosanoids were detected by ultraviolet absorption using a Gynkotek Diode Array Detector spectrophotometer (Gynkotek, Germaning, Germany) and by monitoring radioactivity with a Berthold HPLC Radiotrace Monitor LB 506 C (Berthold, Munich, Germany). AA metabolites were eluted with acetoni-trile/water, pH 4.0, using a discontinuous gradient from 32% acetoni-trile to 100% acetoni-trile. Substances were identified by their retention times and by the coelution of standard compounds (Biomol, Hamburg, Germany). The eicosanoids were quantified by normalizing the radioactivity in each peak to the recovery of total radioactivity per sample.

A quantitative assay of PGE₂ in conditioned medium was performed using the enzyme-linked immunosorbent assay obtained from Assay Designs, Inc. (Ann Arbor, MI), according to the manufacturer’s description. Aliquots of the cell supernatants, diluted 1:20, were assayed without prior purification.

Statistical Analysis
Data are given as mean ± SD or SEM as indicated. Statistical analysis was performed using the Wilcoxon matched-pairs signed rank test for nonparametric data, and a P value < 0.05 was considered to indicate statistically significant differences.
Results

Characterization of the Cell Culture Model

HMC obtained by collagenase treatment of omental tissue grew to confluence in 4 to 5 d. All experiments were done with confluent monolayers as shown in Figure 1A. To establish the mesothelial nature of these cells and to exclude contamination with fibroblasts or macrophages, the presence of cytokeratins 8 and 18 was shown with monoclonal antibodies by immunofluorescence microscopy (Figure 1B).

To demonstrate that HMC, after they have reached confluence, are in a nonproliferative state in our experimental conditions (M199, 2% human serum), the medium containing 20% serum was removed, and cells were incubated for 24 h in 2% human serum or for 48 h in 0.1% fetal calf serum. In the later condition, HMC have been described to be in a nonproliferative state (8). Thereafter, the medium was removed and HMC were exposed for 24 h to 3H-thymidine in serum-free conditions or in the presence of 2% human serum. As shown in Table 1, 3H-thymidine incorporation in the presence of 2% human serum did not differ significantly ($P > 0.05$) from serum-free conditions in confluent cells. These results indicate that HMC used for the following experiments were in a nonproliferative state in the presence of 2% human serum.

Characterization of Eicosanoid Synthesis in Cultured HMC in the Presence of Exogenous Arachidonic Acid

The spectrum of prostanoids produced in HMC was characterized by reversed-phase HPLC. Figure 2A shows the radioactive AA metabolites extracted from unstimulated HMC. In the absence of exogenous stimuli, HMC produced metabolites that coeluted with the standard for 6-keto-PGF$_{1\alpha}$ (peak 2) and PGE$_2$ (peak 4). No radioactivity was detected at the retention time of thromboxane B$_2$ (TxB$_2$) or prostaglandin F$_2\alpha$ (PGF$_{2\alpha}$). To potently activate prostanoid synthesis, HMC were incubated for 4 h with TNF$\alpha$ and stimulated with the Ca$^{2+}$ ionophore A23187 for 15 min. As shown in Figure 2B, maximal stimulation of HMC with TNF$\alpha$ and A23187 resulted in a 2.5-fold increase in the generation of PGE$_2$. The production of PGF$_{1\alpha}$ almost doubled, and a small peak was present at the same retention time as TxB$_2$ (peak 3). In both conditions, variable amounts of eicosanoids eluting at the retention times of mono-hydroxyeicosatetraenoic acids (peak 5) were detected.

$\gamma$-Glucose Increases PGE$_2$ Formation in HMC

Because PGE$_2$ is the eicosanoid most responsive to exogenous stimulation and may be the most important in modulating inflammatory peritoneal processes, the effect of $\gamma$-glucose used in peritoneal dialysis on PGE$_2$ synthesis in HMC was assessed. $\gamma$-glucose dose dependently increased PGE$_2$ formation, with a maximal effect at 90 and 120 mM, concentrations used in dialysis fluids (Figure 3A). In parallel with $\gamma$-glucose, the same effect was observed for mannitol (Figure 3B), indicating that high extracellular osmolarity and not cellular metabolism of the monosaccharide was responsible for enhanced PGE$_2$ formation.

The stimulatory effects of $\gamma$-glucose (90 mM) and mannitol (90 mM) on PGE$_2$ synthesis were time-dependent. As demonstrated in Figure 4, $\gamma$-glucose stimulated PGE$_2$ synthesis only in the first 8 h, reaching a plateau thereafter. In parallel, mannitol (90 mM) also increased PGE$_2$ formation only in the

<p>| Table 1. $^3$H-Thymidine incorporation in human mesothelial cells$^a$ |
|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Preincubation</th>
<th>24-h $^3$H-Thymidine Incubation</th>
<th>cpm/10$^6$ Cells</th>
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<tbody>
<tr>
<td>24 h: 2% human serum</td>
<td>+2% human serum</td>
<td>469 ± 101</td>
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<tr>
<td></td>
<td>+0% serum</td>
<td>434 ± 35</td>
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<tr>
<td>48 h: 0.1% FCS</td>
<td>+2% human serum</td>
<td>483 ± 92</td>
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<tr>
<td></td>
<td>+0% serum</td>
<td>399 ± 71</td>
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$^a$ Values are means ± SD from six experiments. Differences are statistically not significant. FCS, fetal calf serum.

Figure 1. (A and B) Phase-contrast photomicrograph of confluent human mesothelial cells (HMC) obtained from omental tissue cultured in M199 containing 10% human serum and 10% newborn calf serum after one passage ($\times 70$) (A). Immunofluorescence staining of HMC using antibodies against cytokeratin 8 ($\times 175$) (B).
Elution time [min]  

Figure 2. (A and B) Reversed-phase-HPLC analysis of 3H-arachidonic acid (AA) metabolism in cultured HMC without (A) or after (B) treatment with tumor necrosis factor-α (500 U/ml for 4 h) plus stimulation with the Ca2+ ionophore A23187 (10 µM for 15 min). For details, see Materials and Methods. Retention times of AA metabolites were determined by coelution of authentic standards. Peaks are: 1: polar lipids; 2: 6-keto-prostaglandin F1α (PGF1α); 3: thromboxane B2 (TxB2); 4: PGE2; 5: hydroxyeicosatetraenoic acids.

due at least in part to increased extracellular osmolarity without being specific for D-glucose.

Effect of Alternative Sugars on PGE2 Formation in HMC

To further relate the stimulatory effect of D-glucose and mannitol to their osmotic activity, the effect of L-glucose, another osmotic compound, and of icodextrin, a nonmetabolizable and nonosmotic sugar, was determined. D-Glucose significantly (P < 0.05) increased PGE2 formation (3.9 ± 0.6 ng/10^5 cells) compared with untreated cells (2.3 ± 0.3 ng/10^5 cells, P < 0.05). Mannitol (3.3 ± 0.5 ng/10^5 cells) and L-glucose (3.2 ± 0.5 ng/10^5 cells) also enhanced PGE2 formation, although to a smaller degree (Figure 5). In contrast, icodextrin (7.5%) did not stimulate PGE2 production (2.3 ± 0.3 ng/10^5 cells). These results indicate that increased PGE2 synthesis in response to high monosaccharide concentrations is due at least in part to increased extracellular osmolarity without being specific for D-glucose.

Role of PKC and MAPK in Monosaccharide-Induced PGE2 Synthesis

To assess the role of PKC and the MAPK cascade in monosaccharide-induced PGE2 synthesis, we used a specific inhibitor of PKC, Ro 31-8220 (17–21), and downregulation of PKC by active phorbol esters as well as PD 98059, an inhibitor of the MEK (mitogen-activated protein kinase [MAPK]/extracellular signal-regulated kinase [ERK] kinase) pathway of the MAPK system (18–22). Exposing cultured HMC to phorbol myristate acetate (PMA) at a concentration of 20 nM for 24 h...
resulted in an almost 15-fold increase in PGE2 production (Figure 6). Coincubation of the cells with the PKC inhibitor Ro 31-8220 (Figure 6A) or downregulation of PKC activity by preincubation of HMC with PMA (1000 nM) for 16 h (Figure 6B) completely inhibited the stimulatory effect of PMA on PGE2 production. In parallel, suppressing MEK activity by addition of PD 98059 also abrogated increased PGE2 formation caused by PMA in a concentration-dependent manner (Figure 6C). These results indicate that PKC and further downstream the MEK pathway are required to mediate PMA-induced PGE2 synthesis.

Activation of the PKC and the MEK pathways of intracellular signal transduction were also required for increased PGE2 synthesis in response to d-glucose and mannitol (90 mM each). As shown in Figure 7A, Ro 31-8220 inhibited increased PGE2 formation induced by both monosaccharides. As evidence of this, downregulation of PKC activity by preincubation with PMA (1000 nM) for 16 h also inhibited the stimulatory effect of d-glucose and mannitol on PGE2 production (Figure 7B). Furthermore, coincubation of the cells with the MEK inhibitor PD 98059 prevented the rise in PGE2 synthesis (Figure 7C) by d-glucose and mannitol. These data strongly indicate that activation of PKC and further downstream of MEK are involved in mediating the effect of hyperosmolar d-glucose and mannitol on PGE2 synthesis.
been shown to increase during episodes of peritonitis (11,13),

\[\text{TNF}_{\alpha}\text{-treated HMC with the Ca}^{2+}\text{ionophore A23187 in the cells from human and other species (7,8,23). Stimulation of products that have been found in human peritoneal fluids (12). PGF}_{\alpha}, \text{POE}, \text{and TxB}_{2}. \text{These are the major cyclo-oxygenase}

\[\text{presence of exogenous AA resulted in the release of 6-keto-POE}, \text{POE}, \text{and PGE}_{2}. \text{These findings are consistent with previous observations in mesothelial and PGE}_{2} \text{were the predominant AA metabolites. These findings demonstrate that increased PGE}_{2} \text{concentration is related to the increase in osmolarity: d-Glucose, mannitol, and l-glucose, causing the same osmolar stress, enhance PGE}_{2} \text{formation to a similar extent. In contrast, icodextrin, a high molecular weight glucose polymer that is used to generate an ultrafiltration gradient in an iso-osmolar dialysis fluid by the process of colloid osmosis (19), has no effect on PGE}_{2} \text{formation.}

The molecular mechanism underlying the action of osmotic solutes has not been clearly delineated. As has been demonstrated in rat liver macrophages, hyperosmolar compounds could induce expression of cyclo-oxygenase-2 (29) and subsequently formation of prostanoids. Topley et al. (8) confirmed that HMC have the capacity to express inducible cyclo-oxygenase-2 after treatment with the cytokine TNF\(_{\alpha}\). However, given the observations that PGE\(_2\) formation is only increased over a rather short period of 8 h after treatment with hyperosmolar compounds and that the activity of inducible cyclo-oxygenase-2 can be detected in most cell types for almost 24 h after induction of its expression (8,29–31), it seems more likely that hyperosmolar compounds increase PGE\(_2\) formation by other mechanisms. Because the rate-limiting factor of cyclo-oxygenase-1 and -2 activity is the level of free AA, increased phospholipase A\(_2\) activity also enhances PGE\(_2\) formation (32). Cytosolic phospholipase A\(_2\) is activated by PKC and MAPK in many cell types (33–35), suggesting a key role for PKC in the regulation of AA release. To evaluate the role of PKC in cultured HMC, we used the active phorbol ester PMA, a strong activator of PKC, and Ro 31-8220, a specific inhibitor of PKC activity (17,21). Since PMA, glucose, and mannitol increased PGE\(_2\) production, whereas Ro 31-8220 and down-regulation of PKC with PMA completely reversed this effect, our observations indicate that in cultured HMC, a PKC-dependent pathway is involved in increased PGE\(_2\) synthesis. Furthermore, monosaccharide-induced PGE\(_2\) synthesis also depends on activation of MAPK/MEK pathway, as inhibition of MEK by PD 98059 completely abrogated the increase in PGE\(_2\) synthesis. Since the MAPK/MEK pathway can be activated by PKC via phosphorylation of Raf-1 (36), it is intriguing to speculate that in HMC the kinase cascade PKC \(\rightarrow\) Raf-1 \(\rightarrow\) MEK \(\rightarrow\) ERK is activated to mediate the stimulatory effect of glucose and mannitol on PGE\(_2\) synthesis. This assumption is

\[\text{Discussion}

Peritoneal mesothelial cells are considered to account for the major part of peritoneal prostanoid formation because they are the largest resident cell population in the peritoneal cavity (8). HPLC analysis demonstrated that cultured HMC release prostanoids in the absence of exogenous stimulation and that PGI\(_2\) and PGE\(_2\) were the predominant AA metabolites. These findings are consistent with previous observations in mesothelial cells from human and other species (7,8,23). Stimulation of TNF\(_{\alpha}\)-treated HMC with the Ca\(^{2+}\) ionophore A23187 in the presence of exogenous AA resulted in the release of 6-keto-PGF\(_{1\alpha}\), PGE\(_2\), and TxB\(_2\). These are the major cyclo-oxygenase products that have been found in human peritoneal fluids (12).

Because the PGE\(_2\) concentration in dialysis effluents has been shown to increase during episodes of peritonitis (11,13), we decided to focus on this prostanoid, which is known to influence extracellular matrix deposition and cytokine release (14,24). The present study demonstrates that hyperosmolar concentrations of d-glucose, l-glucose, or mannitol markedly enhance basal PGE\(_2\) production. This increase occurs within 8 h of exposure. Similar observations have been made in mesangial cells, in which elevated PGE\(_2\) levels were detected in medium containing high d-glucose concentrations, but not in the presence of mannitol (25). Therefore, it is concluded that this effect is specific for d-glucose, which may directly activate PKC by the generation of diacylglycerol (25,26), and is not related to hyperosmolality. In contrast, hyperosmolality has been shown to modify cellular functions, such as cell viability and cell growth, in different cell types (16,27,28), but the effect of osmotic solutes on prostanoid synthesis has not yet been investigated. Our results demonstrate that increased PGE\(_2\) concentration is related to the increase in osmolarity: d-Glucose, mannitol, and l-glucose, causing the same osmolar stress, enhance PGE\(_2\) formation to a similar extent. In contrast, icodextrin, a high molecular weight glucose polymer that is used to generate an ultrafiltration gradient in an iso-osmolar dialysis fluid by the process of colloid osmosis (19), has no effect on PGE\(_2\) formation.

![Figure 7](https://example.com/figure7.png)

**Figure 7.** (A) Inhibition of glucose-induced or mannitol-induced (90 nM) PGE\(_2\) production by the PKC inhibitor Ro 31-8220 (Ro: Ro 31-8220 [3 \(\mu\)M]; wo/Ro: without Ro 31-8220). (B) Depletion of PKC activity by preincubation with PMA (1000 nM) for 16 h followed by stimulation with glucose or mannitol (90 nM for 24 h) (pre: preincubation with PMA [1000 nM] for 16 h; wo/pre: without preincubation). (C) Inhibition of glucose-induced or mannitol-induced (90 mM) PGE\(_2\) production by the MEK inhibitor PD 98059 (1 to 30 \(\mu\)M). PGE\(_2\) was determined in culture medium by a specific ELISA after incubating HMC for 24 h in M199 with 2% human serum supplemented as indicated. The values represent the mean \(\pm\) SEM of six independent experiments. *\(P < 0.05\) compared with control conditions (wo).
dependent mechanism, as has been recently shown by Haneda et al. (37). Furthermore, in various tissues, hyperosmolarity has been shown to activate MAPK (38,39).

In summary, the present study indicates that PGE$_2$ production by cultured HMC can be stimulated by D-glucose, as well as by metabolically inert osmotic monosaccharides, through a PKC- and MEK-sensitive pathway. These observations suggest that hyperosmolar D-glucose stimulates PGE$_2$ production at least in part due to its osmotic effects, although we cannot exclude additional metabolic effects of D-glucose by the generation of diacylglycerol. In contrast, the iso-osmolar glucose polymer icodextrin does not affect eicosanoid metabolism in HMC. Current dialysis fluids containing D-glucose as an osmotic agent may induce at least a transitory increase of intraperitoneal PGE$_2$ levels. Since the passage of proteins across the peritoneal membrane is related to the prostaglandin content of dialysis fluids, increased intraperitoneal secretion of PGE$_2$ may enhance protein loss (11). In addition, high levels of PGE$_2$ may disturb the intraperitoneal cytokine network by downregulation of macrophage cytokine release (14), and may thus be important in the inflammatory process of acute peritonitis.

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