Suppression of 15-Hydroxyprostaglandin Dehydrogenase Messenger RNA Concentration, Protein Expression, and Enzymatic Activity during Human Ureteral Obstruction

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ABSTRACT

Prostanoids produce significant effects in the ureter, particularly in response to obstruction. Ureteral obstruction is associated with increased prostanoid synthesis via cyclooxygenase induction; however, prostaglandin degradation mediated by 15-hydroxyprostaglandin dehydrogenase (PGDH) has not been evaluated in the ureter. The purpose of this study was to determine whether PGDH steady-state mRNA, protein, and enzyme activity are altered in the human ureter during obstruction. Human ureteral segments from patients undergoing donor nephrectomy (normal segments) or ureteral stricture repair (obstructed segments) were obtained with proper informed consent. We evaluated PGDH steady-state mRNA relative to ribosomal protein S26 reference gene by reverse transcription-polymerase chain reaction and Vistra Green fluorimaging. We determined PGDH protein content relative to glyceraldehyde-3-phosphate dehydrogenase by immunoblotting and PGDH localization by immunohistochemistry. PGDH enzymatic activity was determined by measurement of conversion of 15-hydroxy- to 15-keto-prostaglandin using thin layer chromatography separation. We found that PGDH mRNA and protein were decreased 4- to 6-fold, and enzyme activity was decreased >3-fold in obstructed human ureter relative to normal controls. PGDH was localized to the urothelial cells, with little or no expression in smooth muscle. Our results indicate that PGDH mRNA, protein, and enzyme activity are suppressed in the human ureter during obstruction. Increased concentrations of prostanoids subsequent to ureteral obstruction seem to be due to decreased degradation as well as increased synthesis. Modulation of prostanoid degradation may have therapeutic relevance in obstructive disorders of the ureter.

Obstructive diseases of the ureter are among the most painful conditions experienced by humans and can have deleterious effects in the urinary tract (Gulmi et al., 1998). Despite this, our understanding of ureteral physiology and function subsequent to obstruction remains limited. This gap in knowledge is a significant barrier to improved treatment of these patients. Urinary calculi are by far the most common cause of ureteral obstruction, but obstruction can also be caused by ureteral strictures, tumors, sloughed papilla, primary megaureter disease, pregnancy, vascular anomalies, and introduction of foreign bodies such as stents (Young et al., 1999). Thirteen percent of Americans will experience ureteral obstruction at some point in their life (Ramello et al., 2000), and societal costs of this disease total over $2 billion annually (Clark et al., 1995).

Prostanoid release significantly effects ureteral function through increased contractility, pressure, and pain. Prostanoids are synthesized by cyclooxygenases (COXs), and our laboratory recently reported an up-regulation of the inducible isof orm (COX-2) during human ureteral obstruction (Nakada et al., 2002). Prostanoids mediate the pathophysiology associated with ureteral obstruction by two identified biochemical mechanisms: 1) prostanoid receptor activation, resulting in increase or decrease of smooth muscle tone and contractility (Cole et al., 1988); and 2) direct hypersensitization of nociceptors, potentiating sensory afferent neuron stimulation by pain mediators such as substance P and br-
dykinin (Cesare and McNaughton, 1997). Blockade of prostanoid synthesis with nonselective COX inhibitors has been used successfully to treat severe pain associated with ureteral obstruction (Basar et al., 1991), but serious side effects, including gastric ulceration, renal insufficiency, and platelet dysfunction remain significant concerns (Perlmutter et al., 1993; Colletti et al., 1999).

Although most investigations of prostanoids in the ureter have focused on increased prostanoid synthesis, prostanoid degradation in the ureter remains largely undescribed. The primary pathway of prostanoid metabolism occurs in three major steps (Fig. 1): 1) dehydration of the 15-hydroxyl group; 2) saturation of the Δ13 double bond; and 3) β-oxidation (Anggard and Oliw, 1981). The first step of this process (the rate-limiting step) is catalyzed by 15-hydroxyprostaglandin dehydrogenase (PGDH; Bakhle, 1983). Two isoforms of PGDH have been identified and are characterized by cofactor dehydrogenase (PGDH; Bakhle, 1983). Two isoforms of PGDH have been identified and are characterized by cofactor dependence is considerably less than that of the NAD-dependent isoform are considerably less than that of the NAD-dependent isoform. The NAD-dependent (type I) PGDH is considered the primary source of prostanoid metabolism in most tissues, particularly for metabolism of PGE$_2$ and PGF$_{2\alpha}$ (Chung et al., 1987).

PGDH is regulated in organ systems in which precise control of prostanoid concentration is critical for homeostasis or biological function. This is particularly true in initiation of labor and regulation of menstrual cycle, inflammation, glaucoma, and encephalitis. In addition, reduction of PGDH activity in hydronephrotic kidneys is believed to play a role in modulating renal blood flow (Wong et al., 1985). The purpose of this study was to determine whether PGDH mRNA expression, protein expression, and activity are regulated in the human ureter in response to obstruction.

**Fig. 1.** Mechanism of PGE$_2$ metabolism. Prostanoids are metabolized readily in most tissues to inactive metabolites. In the primary cascade of prostanoid metabolism, the first step is the conversion of physiologically active 15-hydroxyprostanoids to inactive 15-keto prostanoids. This is considered the rate-limiting step in prostanoid degradation, and it is catalyzed by PGDH. In a secondary cascade, PGE$_2$ can be converted to PGF$_{2\alpha}$ by prostaglandin 9-keto reductase.

**Materials and Methods**

All chemicals were purchased from Acros/Fisher Scientific (Pittsburgh, PA) unless otherwise stated.

**Collection and Preparation of Human Ureteral Segments**

Human ureteral tissues were obtained from excess segments of ureters from patients undergoing donor nephrectomy (normal ureters) or ureteral stricture repair procedures (obstructed ureters). Tissue use was approved by the appropriate institutional review board and was obtained with informed patient consent. Ureteral segments were placed immediately in Krebs' physiological salt solution (pH 7.4; composition 119 mM NaCl, 1 mM NaH$_2$PO$_4$, 4.7 mM KCl, 2.5 mM CaCl$_2$, 0.5 mM MgCl$_2$, 25 mM NaHCO$_3$, and 25 mM glucose) and transported to the laboratory (approximately 5 min). Adherent tissues were removed, and tubular ureteral segments were isolated as rings, 3–4 mm in length, weighing approximately 0.1 g. Segments were either snap frozen in liquid nitrogen and stored at −70°C to prevent degradation of RNA or fixed in phosphate-buffered formalin (10%) for immunohistochemical analysis.

**Evaluation of PGDH mRNA Concentrations in the Ureter**

**RNA Extraction.** Snap frozen segments were placed in 1 ml of TRIzol solution (acid guanidium thiocyanate phenol; Invitrogen, Carlsbad, CA) and kept at 4°C while homogenized (1 min). Homogenates were incubated at room temperature for 5 min, and 0.2 ml of 100% chloroform was added. Homogenates were cooled to 4°C and centrifuged at 11,000g. The supernatant was collected, and 0.5 ml of 100% isopropanol was added. After a 10-min incubation at 20°C, samples were centrifuged and supernatant was discarded. A 75% ethanol wash was performed, and the RNA was collected after centrifugation and evaporation of supernatant. RNA yield was quantified using a DU 640B spectrometer (Beckman Coulter Inc., Fullerton, CA).

**Reverse Transcription.** Extracted total RNA was added to excess Moloney murine leukemia virus reverse transcriptase (Promega, Madison, WI) in buffer supplied by the manufacturer along with excess random hexamers and dNTPs. After a 1-min denaturation period at 65°C, reverse transcription was performed at 37°C for 2 h.

**Polymerase Chain Reaction.** Oligonucleotide primers for PGDH and ribosomal protein S26 were designed from the published human sequences: human PGDH: sense, ACCCTCAGAAGACTCTGA, and antisense, CGTGCTCTCAAGATGACAAA, and antisense, TAAAATCGGGTGTTGGGTGTT. cDNA equivalent to 50 ng of untranscribed RNA was amplified in a 50-µl volume using 1.25 U of TaqDNA polymerase (PerkinElmer Life Sciences, Boston, MA) in PCR reaction buffer (10 mM Tris HCl, 50 mM KCl, and 1.5 mM MgCl$_2$, pH 8.3) with an excess of the primers listed above and dNTPs. The following cycle parameters were used: denaturing at 94°C for 30 s, annealing at 61°C for 30 s, and elongation at 72°C for 60 s. To calculate the ratio of PGDH to S26 housekeeping gene, PCR amplification of cDNA to the linear range was performed: 20, 22, and 24 cycles and 25, 27, and 29 cycles for S26 and PGDH, respectively. Reactions were performed using a RoBoCycler Gradient 40 (Stratagene, La Jolla, CA), in triplicate.

**Quantification of PCR Products.** After amplification, PCR products were identified by Vistra Green (Amersham Biosciences Inc., Piscataway, NJ) agarose gel electrophoresis and quantified using a Storm 860 fluororimeter and ImageQuant 5.0 software (Amersham Biosciences Inc.). Band intensity was evaluated for each amplification, and ratios of intensities of PGDH/S26 were determined at the following relative number of cycles within the linear range for each cDNA: 25/20, 27/22, and 29/24. Thus, amplification ratios were determined at three points in the linear range of amplification that were consistent for obstructed and normal groups. The average ratio within the three points was determined and reported.
as one data point, with all coefficients of variation less than 0.30. The ratios for each group (obstructed and normal; n = 4) were averaged and compared. Statistical evaluation was done using an unpaired Student’s t-test, with p < 0.05 indicative of statistical significance.

Evaluation of PGDH Protein Concentrations in the Ureter

Immunoblot Analysis of PGDH Protein Concentration. Obstructed and normal ureteral segments were homogenized in protease inhibitor containing lysis buffer (150 mM NaCl, 10 mM Tris, 1 mM EDTA, 1 mM phenylmethylsulfonyl fluoride, and 10 μg/ml each of leupeptin, aprotinin, and antipain). Triton X-100 was added to a concentration of 1.0% (v/v), and the homogenate was incubated for 30 min at 4°C. The homogenate was centrifuged and the supernatant collected. Total protein concentration was determined using BCA assay (Pierce Chemical, Rockford, IL). Twenty-five micrograms of protein extract was heat denatured in SDS running buffer (125 mM Tris, pH 6.8, 1% (w/v) SDS, 10% (v/v) glycerol, 5% (v/v) β-mercaptoethanol, 0.1% (w/v) bromphenol blue) for 10 min at 100°C and re-solved by SDS-polyacrylamide gel electrophoresis (12% polyacrylamide Tris HCl gels; Bio-Rad, Hercules, CA). Resolved proteins were transferred to nitrocellulose blotting membranes (Bio-Rad) using a semidiary blotter and blocked with blotto-B solution (1% (w/v) nonfat dry milk, 1% (w/v) bovine serum albumin, 0.05% (w/v) NaN3, and 0.05% Tween 20 in 1× phosphate-buffered saline) for at least 1 h. Membranes were then incubated with rabbit polyclonal anti-PGDH for 18 h (1:2000 in blotto-B; Cayman Chemical, Ann Arbor, MI) or mouse anti-GAPDH (1: 30,000 in Blotto B; Biogenesis, Poole, Dorset, UK) for 1 h to evaluate equivalence of protein loading. The nitrocellulose blots were washed six times with phosphate-buffered saline + 0.05% Tween 20 and incubated with either goat anti-rabbit (PGDH blots) or goat anti-mouse (GAPDH blots) IgGs (Pierce Chemical) conjugated to horseradish peroxidase in Blotto B (minus NaN3) for 1 h. Peroxidase activity was detected via chemiluminescence (SuperSignal West Femto luminol substrate and peroxide buffer; Pierce Chemical). Photoimages were analyzed by NIH Image Scion software, and ratios of PGDH to GAPDH protein were determined and compared between obstructed and normal tissues. Statistical analysis was performed via unpaired Student’s t-test; p values of less than 0.05 were considered statistically different.

Immunohistochemical Analysis of Protein Localization. Specimens were fixed at room temperature in 10% buffered formalin and processed routinely in graded ethanol, cleared in xylene, and embedded in paraffin. The segments were imbedded longitudinally, and serial cross sections (5 μm) were obtained. Immunostaining for PGDH was performed using a 4-plus horseradish peroxidase-diaminobenzidine detection kit according to the manufacturer’s instructions (Biocare Medical, Walnut Creek, CA). Briefly, slides were deparaffinized in xylene and rehydrated through immersion in ethanol gradient. Endogenous peroxidase activity was inactivated and slides were washed in Tris-buffered saline and subjected to antigen retrieval in 0.01 M EDTA-80% glycerol buffer. After washing in Tris-buffered saline, slides were incubated with blocking solution for 30 min, followed by incubation with primary antibody overnight at 4°C. Primary antibody was rabbit anti-PGDH (Cayman Chemical), and the negative control was species-specific immunoglobulin G at 5 μg/ml. Slides were washed, and antibody localization was identified using an avidin-biotin system with diaminobenzidine and peroxide as the indicator. A dark brown precipitate indicated positive antibody localization.

Evaluation of PGDH Enzymatic Activity in the Ureter

PGDH Activity Assay and Media Extraction. Normal and obstructed human ureteral segments (0.1 g) were incubated for 1 h at 37°C in 1 ml of Krebs’ buffer, with buffer changed every 15 min. Tissues were then incubated for 1 h with 1 μM indomethacin (Sigma-Aldrich, St. Louis, MO) to inhibit endogenous prostanoid production. Buffer was replaced with fresh Krebs’ (1 ml) containing [3H]PGE2 [5,6,8,11,12,14,15-3H(N); 0.5 μCi/ml; 3 nM PGE2; New England Biolabs, Beverly, MA], 1 μM indomethacin, and tissues were incubated for 3 h at 37°C. One vial containing buffer without tissue was used as an autooxidation control. The buffer (1 ml) was collected every hour up to 3 h and transferred to glass-stoppered tubes. HCl (1.0 N, 30 μl) was added, along with 3 ml of 100% ethyl acetate. The solution was thoroughly vortexed, centrifuged to achieve phase separation, and the organic phase collected and dried at 45°C under a stream of nitrogen. The product was reconstituted in 100 μl of ethyl acetate and assayed via thin layer chromatography (TLC) for product content. Radioactivity within the aqueous phase before and after extraction was quantified via scintillation to determine an extraction efficiency ratio. Total protein in each tissue was calculated by BCA assay in conditions recommended by the manufacturer (Pierce Chemical).

TLC. Silica gel TLC plates (20 × 20 cm, aluminum backed) were prerun in chloroform to remove impurities and air-dried. Plates were spotted 1 cm from the bottom with all extracted product from the PGDH activity assay and autooxidation controls, in addition to known concentrations of [3H]PGE2, to derive a standard curve. Nonradioactive PGE2 and 15-keto PGE2 (0.10 mg/ml) were added to each plate as visualized standards. The plates were placed in TLC tanks containing the water-saturated organic phase of TLC running buffer (39% ethyl acetate, 18% isooctane, 7% glacial acetic acid, and 36% water). The plate was chromatographed for 13 cm and air-dried. The plates were placed in a TLC tank containing iodine crystals to reveal the PGE2 and 15-keto PGE2 standards. Locations on plates corresponding to identified standards were excised, placed in scintillation cocktail, and processed for quantification of radioactivity.

Quantification of PGE2 Degradation. Disintegrations per minute of each collection were compared with the standard curve of [3H]PGE2 and picomoles of PGE2 per milliliter were calculated. This value was compared with the 3 nM concentration added to the sample, and a picomoles per milliliter reduction in [3H]PGE2 was calculated. The autooxidation (buffer only) reduction rate in PGE2 was calculated and an autooxidation ratio ([3H]PGE2/3 nM at each time point) was determined. The picomoles per milliliter [3H]PGE2 reduction rate for each sample was multiplied by the autooxidation ratio, followed by the organic extraction efficiency ratio (extractions with efficiency ratios of <0.9 were not used in this study), and an adjusted picomoles per milliliter [3H]PGE2 reduction rate was calculated. This was divided by the total protein in each tissue, and picomoles [3H]PGE2 converted per gram total protein was reported. The picomoles [3H]PGE2/g protein converted per hour for obstructed and normal ureter was determined at 1, 2, and 3 h of incubation, and results for obstructed and normal ureter were compared with unpaired Student’s t-test.

Results

PGDH mRNA Concentrations. In all ureteral segments analyzed, PCR amplification of S26 cDNA at 20, 22, and 24 cycles fell into a linear range of amplification. Similarly, amplification of PGDH cDNA at 25, 27, and 29 cycles produced a linear range of amplification (Fig. 2). Amplification beyond these cycle numbers produced nonlinear increases in DNA product, indicating saturation of the reaction.

All PCR reactions used for quantification were completed in triplicate and repeatable with coefficient of variation values of less than 0.3. ImageQuant 5.0 analysis and ratio determination demonstrated that the ratio of PGDH mRNA concentrations to S26 in the linear ranges of amplification was 2.0 ± 0.12 in normal ureter compared with 0.67 ± 0.15 in the obstructed ureter (n = 4 both groups). This difference was statistically significant (p = 0.001).
PGDH Protein Concentrations. Immunoblotting of ureteral protein preparations for PGDH detected a single protein band at 29 kDa, the molecular mass of PGDH (Fig. 3). Blotting for GAPDH detected a single band at 38 kDa, the molecular mass of GAPDH. Obstructed ureter exhibited significantly reduced PGDH relative protein concentrations, because the ratio of PGDH/GAPDH was 1.78 ± 0.22 in the normal ureter and 0.33 ± 0.14 in the obstructed ureter (n = 5; p = 0.001).

Immunohistochemical staining of normal and obstructed ureters revealed strong positive localization of PGDH in the urothelial cells of normal ureter, whereas less intense detection was observed in the obstructed ureter (Fig. 4). PGDH was not detected in the smooth muscle or adventitia of the ureter.

PGDH Enzymatic Activity. Scintillation counting of selected regions of the gels revealed that normal ureters converted 17.7 ± 4.8 pmol of [3H]PGE$_2$ per gram of protein per hour in the first hour of reaction, 14.5 ± 4.5 in hour 2, and 7.8 ± 2.5 in hour 3 (Fig. 5). This activity was repressed in the obstructed ureter to 4.5 ± 2.5 pmol/g/h in hour 1, 2.9 ± 1.1 in hour 2, and 1.5 ± 0.5 in hour 3. These data were obtained in tissues pretreated with indomethacin (1 µM) to prevent saturation of the cellular PGDH enzymes with endogenous prostanoids. Tissues not treated with indomethacin converted less than 10% of this amount and meaningful data were not calculated. Immunoblotting of indomethacin-treated normal and obstructed ureter showed that indomethacin had no effect on detectable PGDH protein concentrations, because the ratio of PGDH/GAPDH was 1.10 ± 0.18 in normal ureters treated with indomethacin and 0.95 ± 0.05 in nontreated tissues (n = 3).
Discussion

Although PGDH expression and activity have been evaluated in the urinary tract previously (Wong et al., 1985; Chang et al., 1991), our report is the first to describe PGDH expression and activity in the ureter in response to obstruction. Our data indicate that PGDH mRNA expression, protein expression, and enzymatic activity are suppressed 3- to 6-fold during human ureteral obstruction. Suppression of PGDH expression occurred in all four ureters evaluated in mRNA analysis, all five ureters in immunoblotting analysis, and all four ureters used in enzyme activity analysis, indicating that this regulation is a consistent response of the human ureter to obstruction. The consistent suppression of PGDH mRNA, protein concentrations, and enzymatic activity suggest that PGDH repression occurs primarily at the transcriptional or post-transcriptional level and that neither protein synthesis nor enzymatic efficiency is affected.

In analysis of PGDH enzymatic activity, we used 1 μM indomethacin to inhibit prostanooid production and reduce saturation of PGDH with endogenous prostanoids, thereby potentiating the effect of PGDH on radiolabeled prostanoids. It has been reported that indomethacin can induce PGDH expression in a concentration- and time-dependent manner (Frenkian et al., 2001). However, we evaluated PGDH protein via immunoblot with and without 1 μM indomethacin for the 3-h period of the incubation and observed no effect of indomethacin on PGDH expression. Therefore, the observed enhancement of PGE2 metabolism in the presence of indomethacin is likely due to blockade of endogenous prostanooid production rather than induction of the enzyme, at least in the concentrations and time points used in our study.

Three additional aspects of prostanooid metabolism during ureteral obstruction remain unresolved by this study. The first is the relative oxidation/reduction (redox) state of the urothelial cells during ureteral obstruction. The effect of ureteral obstruction on the redox state of urothelial cells is undetermined, yet redox changes in intact cells can have profound effects on dehydrogenase activity in intact cells and tissues. Future work stemming from this study should include determining the redox state of urothelial cells in response to obstruction and determining what effect redox potential has on PGDH activity in this condition. Second, the present study does not resolve the role of 15-ketoprostaglandin-13-reductase during ureteral obstruction. Although PGDH is considered the rate-limiting step in prostanooid metabolism and oxidation of the 15-hydroxy to 15-keto renders prostaglandins inactive, obstruction could regulate the expression of 15-ketoprostaglandin-13-reductase, which may have effects on overall prostanooid metabolism in urothelial cells. Finally, the transport of prostanooids into cells where PGDH resides could be regulated by ureteral obstruction. This could have effects on the overall metabolism of prostanooids, as has been observed in lipopolysaccharide-induced fever (Ivanov et al., 2003).

Suppression of PGDH expression represents the second known distinct mechanism of prostanooid elevation during ureteral obstruction. We have reported previously that ureteral obstruction is associated with a 4-fold increase in COX-2 expression (Nakada et al., 2002). The finding that prostanooid metabolism is concurrently suppressed suggests that the concentrations of biologically active prostanooids in the diseased ureter is dramatically enhanced in a bimodal manner. Prostanoid synthesis has been a long-standing target of pharmacological intervention, and COX inhibitors have clinical efficacy for treatment of symptomatic ureteral obstruction. Our data suggest that enhancing the metabolism of active prostanoids may also be a logical target of drug action.

This report adds to the known physiological processes in which PGDH expression is regulated. The best-studied physiological processes involving PGDH regulation are pregnancy and birth. Uterine PGDH expression increases significantly throughout the course of pregnancy, most likely to inhibit excess prostanoids from inducing premature labor (Schoof et al., 2001). At term, PGDH expression in uterine tissue is decreased dramatically (Patel and Challis, 2002). The result of this repression is substantially increased prostanooid concentrations and induction of uterine contraction. Reduced PGDH is particularly apparent in the uterine ambion layer and cytотrophoblasts where PGDH seems to be nonexistent during delivery (Sangha et al., 1994). In animal studies, PGDH expression is tightly regulated in the ovary and uterus throughout the estrous cycle (Silva et al., 2000). PGDH expression seems even further suppressed in the infected uterus (van Meir et al., 1997). Infection is also associated with inhibition of PGDH in the lung (Ivanov et al., 2003) and skin (Hahn et al., 1999). In addition, reduced PGDH has been associated with urinary bladder carcinoma (Gee et al., 2001), further implicating prostanoid regulation as a primary factor in cancer cell proliferation. Our study is the first to identify an association between distension of a visceral tissue and decreased PGDH; this may also have implications in cancer biology because stretch and distension are known to induce proliferation of bladder cancer cells in vivo in a prostanooid-dependent manner (Park et al., 1999).

Elucidation of cell signaling mechanisms of PGDH regulation in ureteral obstruction may lead to identification of potential therapeutic targets directed at maintaining PGDH levels. Although the mechanisms of PGDH regulation are poorly studied, analysis of the promoter region of mouse PGDH has revealed several intriguing possibilities (Matsumoto et al., 1997). The promoter contains response elements for Sp1, CAM, glucocorticoids, activator proteins 1 and 2, nuclear factor-interleukin (IL)-6, and steroid hormones. Although the role of steroid hormones in PGDH regulation has been extensively studied (Chang and Tai, 1985; Greenland et al., 2000; Tong and Tai, 2000a) this is an unlikely mechanism of regulation in response ureteral obstruction. Because ureteral obstruction is associated with stretch and distension, as well as inflammatory and recovery events, signaling pathways involved in these processes are more plausible. Inflammatory cytokines such as IL-1β and tumor necrosis factor-α repress PGDH expression; this is reversed by the anti-inflammatory cytokine IL-10 (Pomini et al., 1999). The Sp1 or nuclear factor-IL-6 elements of the PGDH promoter may be involved in these cascades. This possibility is strengthened by the discovery that LPS-induced fever down-regulates PGDH and prostaglandin transporters, both of which contain an Sp1 regulation element (Ivanov et al., 2003). In addition, stretch and distension might elevate intracellular cAMP concentrations. Induction of cyclic nucleotides represses PGDH expression in trophoblasts (Lennon et al., 1999). Several compounds enhance PGDH expression or block
PGDH activity. Cell culture models have demonstrated that phorbol ester and 1,25-dihydroxyvitamin D3 increase PGDH concentrations (Pichaud et al., 1997; Tong and Tai, 2000b). Numerous compounds have been shown to inhibit PGDH, including arachidonate-derived 13-hydroperoxycytadecacenic acid (Sakuma et al., 1993), the sulfasalazine derivative Ph CL28 [2-hydroxy-5(3,5-dimethoxy-carbonyl-benzoyl)-benzene acetic acid] (Berry et al., 1985), and natural product derivatives such as thiazolidinediones, genistein, and sofalcone (Kobayashi et al., 1992; Rao et al., 1997; Cho and Tai, 2002).

In summary, PGDH mRNA expression, protein expression, and enzymatic activity are suppressed 4- to 6-fold during human ureteral obstruction. Suppression of PGDH combined with induction of COX-2 represent two distinct mechanisms by which prostanoid concentrations are increased during ureteral obstruction. The physiological effects of increased prostanoid concentrations include increased nociception, ureteral hypercontractility, inflammation, and cell proliferation. Future research should be aimed at identification of the cellular mechanisms involved in PGDH regulation and development of specific pharmacological agents targeting PGDH.

References


Chang CC, Lin SN, Chen FS, and Chang WC (1991) 15-Hydroxyprostaglandin dehydrogenase activity. Cell culture models have demonstrated that PGDH expression, protein expression, and enzymatic activity are suppressed 4- to 6-fold during human ureteral obstruction. Suppression of PGDH combined with induction of COX-2 represent two distinct mechanisms by which prostanoid concentrations are increased during ureteral obstruction. The physiological effects of increased prostanoid concentrations include increased nociception, ureteral hypercontractility, inflammation, and cell proliferation. Future research should be aimed at identification of the cellular mechanisms involved in PGDH regulation and development of specific pharmacological agents targeting PGDH.