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The effects of pentoxifylline on renal function and free radical production in unilateral ureteral obstruction

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Abstract There is an ongoing discussion about ureteral obstruction-related renal dysfunction. In this study, we aimed to test the effect of pentoxifylline (PTX) on both kidneys in unilateral ureteral obstruction (UUO), and to determine its interaction of with prostaglandin E_2 (PGE_2), and diclofenac sodium (DIS). A sham operation was performed in group 1. Placebo, PTX, DIS, and PTX + DIS were administrated to groups 2, 3, 4 and 5, respectively. The left ureter was ligated in all groups except group 1. At 24 h, technetium 99m diethylenetriamine penta-acetic acid scintigraphy was performed to determine renal function. Additionally, the tissue levels of thiobarbituric acid reactive substances (TBARS) and PGE_2 in both kidneys were measured to determine cytotoxic and cytoprotective mechanisms. When the ipsilateral kidneys were evaluated: (1) UUO significantly reduced DTPA uptake and none of the medications used prevented the reduction, (2) UUO significantly increased TBARS production, and only PTX prevented the increase, (3) UUO caused a significant increase in PGE_2 production, and only DIS significantly decreased this. When the contralateral kidneys were evaluated: (1) UUO significantly increased DTPA uptake but DIS and PTX + DIS prevented this, (2) UUO significantly elevated TBARS levels and DIS and PTX + DIS caused an additional elevation, (3) UUO significantly increased PGE_2 production, and only DIS prevented this. In conclusion, UUO caused ipsilateral renal hypofunction and contralateral hyperfunction, which are related to increased TBARS and PGE_2 levels. PTX markedly decreased free radical activity in the ipsilateral kidney. While PTX showed a placebo effect, DIS prevented the compensatory contralateral renal response through increased TBARS and decreased PGE_2 levels. The beneficial effect of PTX on the ipsilateral kidney, and the hazardous effect of DIS on the contralateral kidney may be explained by more complex interactions among TBARS, PGE_2, PTX, DIS and UUO-related renal dysfunction.

Keywords Ureteral obstruction · Pentoxifylline · Diclofenac · Free radicals · PGE_2

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Introduction

Complete unilateral ureteral obstruction (UUO) causes a temporary increase in renal blood flow and renal parenchymal function and then a steady decrease or renal ischemia [17]. Data suggest that a decline in vasodilatory prostaglandin E_2 (PGE_2), increases vasoconstrictors thromboxane A_2 (TxA_2) and angiotensin II which are responsible for some of the renal hemodynamic changes in the ipsilateral (IL) kidney, probably resulting in hydronephrotic atrophy [28]. Although angiotensin II-blocking agent and papaverin infusion reverse arteriolar vasoconstriction in the glomeruli, cyclooxygenase inhibitors have negative effects on renal functions [9]. The administration of non-steroid anti-inflammatory drugs (NSAIDs) to patients with renal damage results in a decrease in the renal plasma flow and glomerular filtration rate by inhibiting the cyclooxygenase pathway of arachidonic acid metabolism and hence decreasing prostaglandin and thromboxane production [18]. However, whether pentoxifylline (PTX), a peripheral vasodilator and stimulator of tissue PGE_2

production, obstructs the detrimental effect of ureteral obstruction is unknown.

PTX has been shown to be valuable in preventing the ischemic tissue damage which accompanies various vascular diseases [1]. Additionally, Berens and Luke [2] have shown that the glomerular filtration rate and urine flow increased in kidneys administered PTX following renal artery occlusion in a model of kidney transplantation. In the present study, the objective was to assess the potential value of PTX on renal function (RF) and free radical production in both IL and contralateral (CL) kidneys. Also, diclofenac sodium (DIS) was administered to another group of kidneys to evaluate the potential relationship between PTX and prostaglandins, and DIS. Stepaniuk et al. [22] reported that intragastric combined administration of diclofenac with pentoxifylline reduced the ulcerogenic effect and nephrotoxicity of diclofenac. On the other hand, pretreatment of rats with a phosphodiesterase inhibitor, PTX, theophylline, or rolipram, significantly improved the macroscopic intestinal ulceration caused by diclofenac administration [19].

Materials and methods

The study was initiated after approval by the Animal Investigation Committee of our institute. The animals (female Swiss-Albino rats) weighing 210–260 g were kept under standard laboratory conditions and all rats were given only water 1 day before any experimental procedures.

Surgical procedure

Anesthesia was induced with xylazine 10 mg/kg and ketamine 50 mg/kg. Rats were divided into five different groups according to surgical procedure: group I (sham, $n=10$) underwent a sham operation with a midline incision and exploration of the left ureter. Saline (0.9%) was injected intramuscularly 1, 12 and 23 h after laparotomy. In group II (placebo, $n=10$) complete ureteral obstruction was created by ligation of the left upper ureter with 5-0 silk. As in group I, saline was injected at 1, 12 and 23 h following laparotomy. PTX (10 mg/kg), DIS (10 mg/kg) and PTX + DIS was respectively injected into groups III, IV, and V, at 1, 12, and 23 h after UUO. All rats were re-anesthetized immediately after injection at 23 h, and their femoral veins were catheterized for scintigraphic analysis. Table 1 summarizes the the treatments.

Evaluation of renal function

There is a strong linear correlation between creatinine clearance and renal uptake (0.5–1.5 min after injection) of technetium 99m diethylenetriamine penta-acetic acid (Tc-99m DTPA) in rats [15]. Therefore, we evaluated the renal function by using Tc-99m DTPA scintigraphy as previously reported [11]. All renal scintigraphies were performed after the injection of 37 MBq Tc-99m DTPA (<0.3 ml) via the femoral vein 24 h after laparotomy. Images were obtained at 15 s intervals for 10 min from the posterior position and were recorded on a disk for analysis. A Toshiba GCA-602 digital gamma camera equipped with a "low energy all purpose collimator" was used (Toshiba, Medical System Division, Tokyo, Japan). Renal uptake of DTPA was quantified from 0.5–1.5 min interval images and was expressed as a percentage of the administered activity. These values were corrected for tissue attenuation using renal depth. The following formula was used to estimate renal depth [11]: $y=6.61+0.1238x$. Where x is the body weight in grams and y is the depth (cm) of the center of the kidney from the posterior skin surface.

After DTPA scintigraphy, both the IL and CL kidneys were removed and kept frozen at −80°C until tissue levels of PGE_2 and thiobarbituric acid reactive substances (TBARS) were estimated.

Lipid peroxidation assay

Free radical production is accompanied by polyunsaturated fatty acids. TBARS was analyzed as a marker of lipid peroxidation and hence free radical activity. To measure TBARS content in the kidney, the tissue specimen was twice frozen on dry ice with a tissue disrupter (TRI-R STIR-R, Model K43) driven at 4,000 rpm for 30 s. Tissue homogenates at a final concentration of 10% w/v were prepared in homogenization fluid, and TBARS was measured in homogenates by the thiobarbituric acid method of Stocks and Dormandy [23]. An external standard, tetramethoxypropane (Sigma, St Louis, Mo., USA) was used, and the lipid peroxide level was expressed in nm malondialdehyde. Proteins were determined by the method of Lowry.

Measurement of tissue PGE_2

Tissue PGE_2 levels were measured according to the method described by Cockrell and Ellis [4] by using high performance liquid chromatography (Varian, model 5000: Varian Instrument Group, Walnut Creek, Calif., USA). Renal tissue specimens that were removed from each animal were frozen rapidly in liquid nitrogen and kept at −80°C until PGE_2 estimation was completed. Tissue homogenization was performed using an homogenizer (TRI-S STIR-R, model K43) with 2 ml of saline solution. The protein content in the tissue homogenate was precipitated with 500 µl of acetone, and pH adjusted to 3 with 0.4% formic acid. The homogenate was then extracted twice with 2 ml of ethyl acetate. The ethyl acetate extract was dried under a stream of nitrogen, dissolved in 1 ml of chloroform, and filtered with a 0.45 µm Millipore filter. The chloroform was then removed with nitrogen and the residue dissolved in 1 ml of mobile phase consisting of water-acetonitrile-benzene-acetic acid (767:230:2:1, by volume). A total of 10 µl of each sample was loaded onto a reverse phase column, MicroPak SP C18-3 (Varian, 15×4 cm, 3 mm particle size). The final recovery in percent of the initial PGE_2 present in the specimen was 77%. The lower detection limit was 10 pM (3.52 pg/ml) PGE_2 and the coefficient of variation was 14.29%. The flow rate of the mobile phase was 1 ml/min. The peak of PGE_2 was

Table 1 A summary of the group characteristics

Group	Surgical procedure	Substance injected	Time of injection –(h after surgery)
I (Sham)	Exploration of left ureteral	Saline	1, 12, 23
II (Placebo)	Complete unilateral ureteral obstruction	Saline	1, 12, 23
III (PTX)	Complete unilateral ureteral obstruction	Pentoxifylline (10 mg/kg)	1, 12, 23
IV (DIS)	Complete unilateral ureteral obstruction	Diclofenac (10 mg/kg)	1, 12, 23
V (PTX + DIS)	Complete unilateral ureteral obstruction	Pentoxifylline plus diclofenac (10 mg/kg)	1, 12, 23

determined by UV absorbance at 254 nm and 28°C by comparison with the retention time of the PGE_2 standard. Quantitative integration of chromatographic separation was established using a Varian integrator (Model 4290) and the PGE_2 standard as a reference.

Statistical Analysis

Data were presented as means ± SEM. The results were subjected to one-way analysis of variance for repeated measures, and the statistical significance was determined using the LSD test to compare groups (SPSS 9.0 for Windows). Differences were considered significant when $P < 0.05$.

Results

The results are summarized in Table 2.

Renal function

In all UUO groups, IL-RF was found to be significantly decreased when compared with the sham group ($P < 0.001$) (Fig. 1). Ipsilaterally, PTX treated animals had higher RF than the other UUO animals. However, the difference between them was not significant.

In the sham group, no significant difference between IL-RF and CL-RF was found. Nevertheless, CL-RF was significantly higher in the placebo group than in the sham group ($P < 0.01$). On the CL side, PTX administration caused a significant increase in RF compared to DIS and PTX + DIS treated rats ($P < 0.001$), but there was no difference compared to the placebo group. Contralaterally, RF was significantly lower in DIS treated rats than in PTX and placebo rats ($P < 0.001$), while there was no significant difference between DIS and sham rats. In addition, in comparison with the other UUO groups, the PTX + DIS treatment significantly decreased CL-RF ($P < 0.001$).

Tissue levels of TBARS

Although there was no significant difference between the PTX and sham groups ipsilaterally, PTX administration resulted in a significant decrease in tissue levels of TBARS compared with the other UUO groups ($P < 0.001$) (Fig. 2). Also, in PTX animals, IL-TBARS was significantly lower than CL-TBARS ($P < 0.01$).

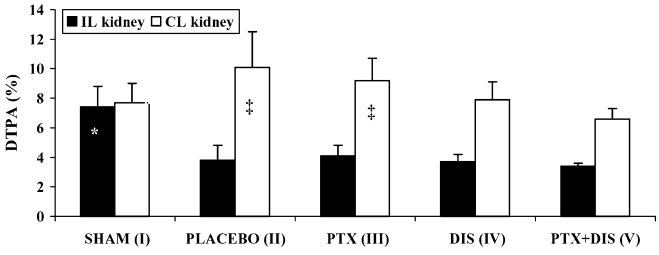

Fig. 1 Diethylenetriamine penta-acetic acid (*DTPA*) levels, an index of renal function, are summarized for all groups. An *asterisk* indicates $P < 0.001$ ipsilaterally, group 1 vs groups 2, 3, 4, 5. A *vertical double plus* indicates $P < 0.001$ contralaterally, groups 2, 3 vs groups 1, 4, 5. Values are means ± SE. *PTX*, pentoxifylline; *DIS*, diclofenac sodium; *IL*, ipsilateral; *CL*, contralateral; *PTX + DIS*, pentoxifylline plus diclofenac sodium

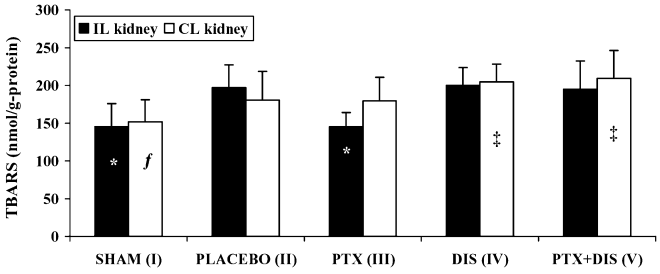

Fig. 2 Tissue levels of thiobarbituric acid reactive substances (*TBARS*), a marker of lipid peroxidation, are shown for all groups. An *asterisk* indicates $P < 0.001$ on the IL kidney groups 1, 3 vs groups 2, 4, 5; and also $P < 0.01$) ipsilaterally group 3 vs contraletarally group 3; *f* indicates $P < 0.01$ on the contralateral side group 1 vs groups 2, 3, 4, 5. A *vertical double plus* indicates $P < 0.001$ contralaterally, groups 4, 5 vs 1, 2, 3. Values are means ± SE. *PTX*, pentoxifylline; *DIS*, diclofenac sodium; *PTX + DIS*, pentoxifylline plus diclofenac sodium

Except for the PTX group, in the other UUO groups IL-TBARS was significantly higher than in sham animals ($P < 0.001$). On the IL side, the DIS and PTX + DIS groups were not different from the placebo group in tissue levels of TBARS.

Statistical analysis between placebo and PTX rats did not identify a significant difference on the CL side. Contralaterally, TBARS levels were significantly greater in all groups with UUO than in sham rats ($P < 0.01$). Treatment with DIS or PTX + DIS caused a significant increase in the level of CL-TBARS when compared with the other groups ($P < 0.001$).

Table 2 Data are summarized as mean ± SD

Group	DTPA		TBARS		PGE_2	
	IL	CL	IL	CL	IL	CL
I (Sham)	7.4 ± 1.4	7.7 ± 1.3	144.9 ± 30.8	152 ± 29.1	15.3 ± 4.3	15.9 ± 3.2
II (Placebo)	3.8 ± 1	10.1 ± 2.4	197 ± 30.2	180.6 ± 37.7	20.1 ± 3.8	20.3 ± 3.3
III (PTX)	4.1 ± 0.7	9.2 ± 1.5	145.1 ± 19.2	179.5 ± 31.3	20.9 ± 2.4	19.6 ± 2.8
IV (DIS)	3.7 ± 0.5	7.9 ± 1.2	200.2 ± 23.6	204.7 ± 23.4	16.9 ± 2.8	17.4 ± 2.7
V (PTX + DIS)	3.4 ± 0.2	6.6 ± 0.7	195 ± 37.3	209.1 ± 37.1	20.1 ± 2.5	20.3 ± 2.5

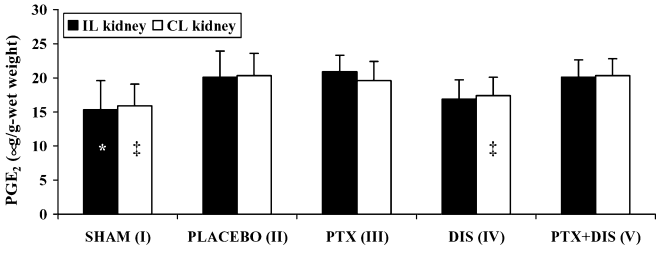

Fig. 3 Tissue levels of PGE_2 were measured using high performance of liquid chromatography. An *asterisk* indicates $P < 0.01$) on the IL kidney groups 1, 4 vs groups 2, 3, 5. A *vertical double plus* indicates $P < 0.01$ on the CL kidney groups 1, 4 vs 2, 3, 5. Values are means ± SE. *PTX*, pentoxifylline; *DIS*, diclofenac sodium; *PTX + DIS*, pentoxifylline plus diclofenac sodium

Tissue levels of PGE_2

On the IL side, PGE_2 levels in rats given PTX and PTX + DIS did not show a significant difference from placebo rats (Fig. 3). However, PGE_2 levels were significantly lower in the DIS group ($P < 0.01$), but there was no significant difference between the DIS and sham groups.

Similarly, CL-PGE_2 was significantly decreased in the DIS group compared with the other UUO groups ($P < 0.01$), but there was no significant difference between the contralateral and ipsilateral PGE_2 levels.

Discussion

For the IL kidney, metabolic and hemodynamic changes due to UUO have been described in three phases [20]: (1) 0–1.5 h, UUO increases renal blood flow, GFR, release of PGE_2, and induces afferent arteriole vasodilation, (2) 1.5–5 h, increase of angiotensin II and TxA_2 associate with efferent arteriole vasoconstriction, (3) 5–18 h, although PGE_2 originating from the kidney continues to rise, a preponderance of TxA_2 and angiotensin II causes afferent arteriole vasoconstriction. There is obviously a decline in the renal blood flow, GFR and RF. Following the release of a 24-h obstruction, renal function may return to normal [7]. UUO exceeding 1 week may result in permanent renal damage leading to hydronephrotic atrophy [29]. However, contralaterally, although UUO stimulates the production of PGE_2 and thromboxane, renal function is not impaired as much as for the IL kidney.

Various pharmacological agents were administered to limit the renal damage due to UUO. Even though captopril increased renal blood flow until the end of the second phase, neither denervation or the use of an alpha-receptor blocking agent, nor an angiotensin II-blocking agent could reverse renal function in the experimental models with UUO at 7 h, 1, 2 or 3 weeks [10]. However, the effect of PTX on renal pathophysiological changes, which commence after UUO, is unclear.

The parent compound of PTX has a half-life 0.4–0.8 h and plasma half lives of its metabolites vary from 1.0 to 1.6 h [27]. The active metabolites have respective plasma concentrations five and eight times greater than PTX. Therefore, we used PTX 1, 12, 23 h after UUO at equal dosages of 10 mg/kg.

In experimental studies, it has been suggested that UUO progressively decreases renal plasma flow (RF) immediately after the second phase for UUO [20]. Likewise, the presented study revealed that UUO of 24 h dramatically reduced IL-RF. On the other hand, Vadiei et al. [24] reported that a single dose of PTX decreased the incidence of mortality compared to control rats 48 h following the induction of acute renal failure with mercuric chloride. In our study, although PTX raised RF on the IL side when compared with the other obstruction groups, there was no significant difference between them, and this finding demonstrated the failure of PTX on IL-RF. Contralaterally, RF rose significantly in both the placebo and PTX treated rats in comparison with the sham rats, and this result points out the compensatory increase in CL-RF. However, PTX did not cause a significant increase in either IL or CL renal functions.

The use of NSAIDs, including indomethacin, diclofenac, naproxen, and ketorolac, in the management of renal colic is becoming increasingly common. However, in an UUO model the effect of DIS on RF is not clear. DIS was added in a separate group in the presented study to determine the possible relationship between PTX and PGE_2. In a renographic study, Kinn et al. [12] reported that DIS treatment may cause an overestimation in ureteral colics by delaying renal excretion bilaterally. In our study, DIS and PTX + DIS rats had less RF than those of sham rats ipsilaterally, but on the CL side DIS significantly reduced RF compared to PTX and placebo rats. Moreover, CL-RF decreased significantly with PTX + DIS compared to the other obstruction groups. Consequently, DIS inhibited the compensatory renal response on the CL side, even when DIS was combined with PTX.

Renal damage resulting from UUO may be stimulated by reactive oxygen species, which are produced by a variety of processes [17]. For instance, damaged cellular membrane and intracellular components stimulate neutrophil and macrophage chemotaxis leading to the production of superoxide free radicals, which are known to be responsible for further tissue damage. In studies related to ischemia/reperfusion, a rise in TBARS, index of lipid peroxidation or reactive oxygen species production, is regarded as signifying free radical release [18]. Kinter et al. [13] showed that renal tissue levels of TBARS were increased by 3 days of UUO. Young et al. [30] showed that a rise in free radicals occurred in renal venous blood after UUO, and that there was a marked released during the first 30 min after relief of UUO. This release was partially attenuated by allopurinol pretreatment. Also, vitamin E and probucol led to a significant decrease in both plasma and renal cortical tissue free radical content in UUO animals [21, 23]. Similarly to the methylxanthines such as theophylline and caffeine, PTX may prevent the effects of adenosine on the

renal vasculature, but the effect of PTX on free radical production following UUO is unknown. Experimental studies have shown that PTX checks cytokine and free radical release after ischemia/reperfusion injury, and increases tissue perfusion [24]. In the presented study, although CL tissue levels of TBARS did not show a significant difference in PTX rats compared to placebo rats, PTX significantly reduced IL tissue levels of TBARS. This finding demonstrates that PTX reduced free radical production on the IL side following UUO of 24 h. On the other hand, in placebo treated rats, tissue levels of TBARS rose significantly in both kidneys.

Although DIS rats were no different from placebo rats in terms of IL-TBARS, DIS treatment caused a significant increase of CL-TBARS compared to PTX and the placebo animals. In PTX + DIS rats, tissue levels of TBARS were not different from those of DIS rats. Consequently, DIS markedly stimulated CL free radical activity, and PTX combined with DIS could not prevent the increase of free radicals.

From other studies, the effects of NSAIDs on renal free radical production are unclear during and after ureteric obstruction. In the presented study, we showed that DIS, a NSAID, led to significantly increased free radical release following 24-h UUO compared to placebo and PTX treatments. Weglarz et al. [26] stated that drug treatment (indomethacin, phenylbutazone, acetylsalicylic acid and hydrocortisone) resulted in decreased activity of the antioxidant enzymes in rat kidneys. On the other hand PGE_2, a cytoprotective prostaglandin, may limit the hazardous effect of macrophages and other immune-activated cells by modulating the production of, for example, cytokines and free radicals. Prostaglandins are produced by both cortical and medullary elements of the kidney, and have been shown to be natriuretic, diuretic, and to increase renal blood flow. The inhibition of prostaglandin synthesis causes a marked decrease in renal blood flow and renal function [18].

UUO results in IL activation of renal PGE_2. Yanasigawa et al. [28] showed that UUO causes an increase in PGE_2 levels in the glomeruli of both the IL and CL kidneys. Frøkiaer et al. [8] demonstrated that UUO was associated with an increase in the urinary excretion of PGE_2. Likewise, in this study PGE_2 significantly increased in both the CL and IL kidneys from placebo rats. However, on the CL and IL sides, PGE_2 markedly decreased in DIS rats. PGE_2 is a valuable agent in both hemodynamic changes of UUO and pain, which is manifested as renal colic. In this respect, the detrimental effects of NSAIDs on renal function are not avoided, even if the inhibition of prostaglandin production may provide an advantage for pain control.

On the other hand, PGE_2 levels did not show a significant difference in PTX rats compared to placebo and PTX + DIS rats. Nevertheless, PTX indirectly induced renal PGE_2, which significantly increased in PTX + DIS rats compared to DIS rats, despite the cyclooxygenase inhibition by DIS. Various studies have been performed to explain the effects of PTX on prostaglandin synthesis [7]. Sinzinger [21] confirmed that a single dose of PTX enhanced prostacyclin generation by vascular and renal tissues. However, in an ureteral obstruction model, the effect of PTX on renal PGE_2 had not been described until the presented study. The mechanism of amelioration of PTX on IL renal lipid peroxidation during UUO most likely involves not only the indirect stimulation of renal vasodilator prostaglandins but also the intracellular elevation of cAMP and inhibition of tumor necrosis factor (TNF). The increase in cAMP, which follows PGE_2 induced activation of adenylatecyclase, adds to the cAMP increase deriving from the direct inhibition of phosphodiesterase by PTX [3]. Also, PTX attenuates the hazardous effect of NSAIDs on the stomach by suppressing TNF production.

In summary, although the rats treated with pharmacological doses of PTX did not show an improvement in renal function following UUO of 24 h, PTX markedly decreased free radical production in the IL kidney. DIS and PTX + DIS contralaterally both inhibited the compensatory elevation of renal function, and caused an additional increase of TBARS levels. For both kidneys, the potential relationship between PTX and DIS is somewhat confusing, but is most likely explained with complex interactions among PGE_2, the adenosine pathway and TNF. Nevertheless, further investigation on these interactions is needed to evaluate the relationship between PTX and DIS in complete or partial ureteral obstruction.

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