The Urotensin-II Receptor Antagonist Palosuran Improves Pancreatic and Renal Function in Diabetic Rats

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ABSTRACT

Urotensin-II (U-II) is a cyclic peptide that acts through a specific G-protein-coupled receptor, UT receptor. Urotensin-II and UT receptors have been described in pancreas and kidney, but their function is not well understood. We studied the effects of chronic treatment of diabetic rats with the orally active selective U-II receptor antagonist palosuran. Streptozotocin treatment causes pancreatic β-cell destruction and leads to the development of hyperglycemia, dyslipidemia, and renal dysfunction. Long-term treatment of streptozotocin-induced diabetic rats with palosuran improved survival, increased insulin, and slowed the increase in glycemia, glycosylated hemoglobin, and serum lipids. Furthermore, palosuran increased renal blood flow and delayed the development of proteinuria and renal damage. The U-II system is unique in that it plays a role both in insulin secretion and in the renal complications of diabetes. Urotensin receptor antagonism might be a new therapeutic approach for the treatment of diabetes.

Urotensin-II (U-II) is a cyclic peptide hormone that acts through a specific G-protein-coupled receptor, GPR14, now renamed urotensin receptor (UT) (Pearson et al., 1980; Ames et al., 1999). Urotensin-II was originally isolated from fish spinal cord (Pearson et al., 1980), and its human homolog was cloned and characterized in 1999 (Ames et al., 1999). Urotensin-II is a potent vasoconstrictor but causes a vasodilatation of low and variable magnitude. Urotensin-II also enhances vascular permeability (Gendron et al., 2004) and induces cardiac (Onan et al., 2004) and vascular muscle cell hypertrophy (Watanabe et al., 2001). Urotensin-II has not only cardiovascular effects but also metabolic effects because it inhibits glucose-induced insulin release in perfused rat pancreas (Silvestre et al., 2001). Both U-II and UT mRNA are present in human pancreas (Ames et al., 1999; Elshourbagy et al., 2002).

The U-II system is up-regulated in diabetes mellitus; plasma U-II levels are increased in type 2 diabetic patients and further increased by renal failure (Totsune et al., 2003, 2004); the S89N polymorphism in the U-II gene is associated with the development of insulin resistance and type 2 diabetes (Wenyi et al., 2003); U-II immunoreactivity is also increased in atherosclerotic vessels (Maguire et al., 2004); and finally, there is a dramatic overexpression of UT receptors in kidneys of diabetic patients, particularly in the tubular epithelium of dilated or damaged tubules, suggesting a direct role in the tubular toxicity of proteins (Langham et al., 2004). The differential expression of U-II and UT receptors in normal physiology and the pathological situation of diabetes suggest a contribution of the endogenous U-II system to the disease.

To study the role of the U-II system in diabetes mellitus, we used an accelerated rat model, which included injection of streptozotocin (STZ) and unilateral nephrectomy, without administration of insulin (Steffes et al., 1978; O’Donnell et al., 1986; Ding et al., 2003). Streptozotocin-induced diabetes is an established model of type I diabetes that has been studied extensively in rodents. Because STZ destroys pancreatic β-cells, STZ-treated rats develop insulin-sensitive hyperglycemia and associated complications, including nephropathy. The link between hyperglycemia and renal dysfunction has not been fully explained, but transplantation experiments have shown that nephropathy in STZ-treated rats is a result of the induced diabetic state rather than a direct toxic effect of STZ on the kidney (Lee et al., 1974; Churchill et al., 1993). Nephropathy typically develops 6 to 10 months after STZ treatment, but the process is accelerated after unilateral nephrectomy (Steffes et al., 1978; O’Donnell et al., 1986).

The goal of our study was to evaluate the effects of a
chronic treatment with the orally active and selective UT receptor antagonist, palosuran (ACT-058362; Actelion Pharmaceuticals Ltd., Allschwil, Switzerland) (Clozel et al., 2004) on glycemic control and on the development of diabetic nephropathy. Two consecutive protocols were applied. In a first study, we assessed whether palosuran treatment had an effect on the survival of diabetic rats compared with untreated rats. An additional goal of this first study was to help us define the optimal duration for a second study, which should be short enough to avoid a statistical bias due to uneven number of deaths between the two groups. This study assessed the effects of chronic palosuran treatment on glycemina, insulinemia, albuminuria, and in a terminal experiment in anesthetized rats, on blood pressure, renal clearances, and renal and pancreatic histology. The duration of this second study was fixed at 16 weeks.

Materials and Methods

All protocols were in accordance with the Swiss guidelines for animal experimentation and were approved by the Basel-Landschaft cantonal veterinary office.

Streptozotocin Model. Male Wistar rats (initial body weight 250–300 g) were anesthetized i.p. with a mixture of 90 mg/kg ketamine hydrochloride (Ketavet; Parke Davis, Berlin, Germany) and 10 mg/kg xylocaine (Rompun; Bayer AG, Wuppertal, Germany). A unilateral nephrectomy was performed to accelerate the development of diabetic nephropathy (Steffes et al., 1978; O’Donnell et al., 1986). After allowing the rats a 1-week recovery, diabetes was induced by an i.v. injection of STZ (Sigma-Aldrich, St. Louis, MO; 35 mg/kg in 1 ml/kg citrate buffer, 10 mM, pH 4.5). Nondiabetic rats were subjected to unilateral nephrectomy but received no STZ but the same volume of citrate buffer. No insulin was administered. At day 2, the diabetic state was confirmed by measurement of serum glucose concentrations, and an oral glucose tolerance test was performed 3 h after a single oral dose of palosuran or vehicle. At day 3, the chronic treatment with palosuran or vehicle of the 16-week study was initiated.

Survival Study. For the survival study, three groups were followed: nondiabetic rats (n = 11), diabetic rats (n = 21), and diabetic rats treated with palosuran (n = 24), for 25 weeks. Diabetic rats were randomly assigned to treatment with palosuran or vehicle. The dose of palosuran was of 300 mg/kg/day, given as food admix, since that oral dose was shown in pilot studies to prevent the development of renal failure induced by renal ischemia to a similar extent as i.v. dosing (Clozel et al., 2004). The food intake was controlled, and the amount of food was adapted, if needed, to keep the daily dose of palosuran constant.

Sixteen-Week Study. This study was designed to assess the effects of palosuran on serum glucose and insulin, as well as on renal function and the development of albuminuria. The composition of the three groups was similar to the survival study: nondiabetic rats (n = 16), diabetic rats (n = 24), and diabetic rats treated with palosuran (n = 22).

Blood samples (from the sublingual vein) and 24-h urine samples were collected at baseline and at weeks 2, 4, 6, 8, 12, and 16 after the start of palosuran treatment. Urinary albumin concentrations were determined, and serum samples were assayed for concentrations of glucose, cholesterol, and triglycerides. Blood glycosylated hemoglobin (HbA1c) and serum insulin concentration were measured at weeks 8 and 16. Serum insulin concentration was measured by radioimmunoassay (RI-13K; Linco Research, St. Louis, MO). Serum and urine glucose, cholesterol, triglycerides, and HbA1c concentrations were analyzed using a Synchronte CKX 3 PRO (Beckman Coulter, Fullerton, CA).

After 24-h urine collection, at week 16, renal clearance measurements were performed in anesthetized rats (Ding et al., 2003). A catheter was placed into the left femoral vein for infusion of synthetic plasma, inulin, and α-aminohippurate (PAH), and the left femoral artery was prepared for arterial blood pressure monitoring and periodic blood sampling. Mean arterial blood pressure and heart rate were recorded on a PowerLab (OXI Data acquisition; Emka Technologies, Paris, France), which was connected to a Dell Dimension 733R computer (Dell Inc., Round Rock, TX) equipped with Datamax software (version 1.65; Emka Technologies). Through a small, suprapubic incision, a flanged catheter was placed in the urinary bladder for collection of urine. After a 45-min equilibration period, two consecutive 20-min urine collections were performed, with midpoint arterial blood sampling. Urine volume was measured gravimetrically. Inulin concentrations in urine and plasma were determined using the anthrone method (Fuhr et al., 1955; Davidson and Sackner, 1963), and PAH concentrations in urine and plasma were measured colorimetrically (Smith et al., 1945). These measurements allowed calculation of clearances of inulin and PAH, glomerular filtration rate (GFR), renal plasma flow (RPF), renal vascular resistance (RVR), and filtration fraction (FF) (Qiu et al., 1994, 1995; Ding et al., 2003). The results of the two clearance periods were averaged.

Inulin clearance (equal to GFR) was calculated as $\frac{U_{\text{inulin}} \times V_{\text{plasma}}}{V_{\text{inulin}}}$, where $U_{\text{inulin}}$ is the urinary inulin concentration, V is urinary flow rate, and $P_{\text{inulin}}$ is plasma inulin concentration. PAH clearance was calculated as $\frac{U_{\text{PAH}} \times V_{\text{PAH}}}{P_{\text{PAH}}}$, where $P_{\text{PAH}}$ is the urinary PAH concentration, V is urinary flow rate, and $P_{\text{PAH}}$ is plasma PAH concentration. RPF was calculated as PAH clearance/PAH extraction ratio, where the PAH extraction ratio was assumed to be 0.85. RVR was calculated by the formula $(1 - Hct) \times (MAP - 5)/RPF$, where Hct is hematocrit, MAP is mean arterial pressure, and 5 is assumed to equal mean venous pressure. FF is defined as GFR/RPF.

Oral Glucose Tolerance Test. To investigate whether palosuran has a direct effect on insulin release and/or production, we examined the acute effects of palosuran on serum glucose concentrations and on the insulin response to a glucose load in diabetic rats 2 days after STZ injection.

After an overnight fasting, the rats were pretreated with either vehicle or palosuran (300 mg/kg by gavage). Three hours later, each rat was given an oral dose of 2 g/kg glucose. For measurement of serum glucose and insulin concentrations, serum samples were collected at baseline and at 30 and 60 min. Twenty-four hours after the initial palosuran or vehicle treatment, the chronic 16-week study was initiated.

Histology. At the end of the renal clearance experiments, rats were sacrificed, and the left kidney was obtained from all animals. The pancreas was obtained from one-half the animals in each group. The pancreas was obtained from one-half the animals in each group. The left kidney was cut longitudinally. Pancreas and one-half of the left kidney were fixed with 10% buffered formalin and embedded in paraffin. Sections of 4-μm thickness were stained with H&E.

The pathologist, who was blinded to experimental groups, assessed the severity of the morphological changes under light microscopy, using on-line input into the PDS PATHDATA computer system. Each section of tissue was graded for the presence/departure from the normal histological spectrum (i.e., lesions), scored on a 0 to 5 scale. Severity scores were assigned as proposed by Zbinden (1976).

Statistics. Data are expressed as mean ± SEM. Survival curves were analyzed using a log-rank test and all other data using analysis of variance (Statistics; StatSoft, Tulsa, OK). Where a significant F ratio was observed, the data were further analyzed with a Student-Newman-Keuls procedure. Statistical significance is defined as $p < 0.05$.

Results

UT Antagonism Improves Survival in Diabetic Rats. We first evaluated the effects of long-term (25 weeks) administration of the UT receptor antagonist palosuran on survival
of STZ-induced diabetic rats. Administration of palosuran more than doubled the number of rats with diabetes mellitus that survived (Fig. 1); the 25-week survival of rats treated with palosuran was 83%, compared with 33% in untreated diabetic rats ($p = 0.0011$). No rats died in the nondiabetic group during the 25 weeks of follow-up.

**UT Antagonism Improves Glucose Tolerance and Lipid Status.** A study was then performed to assess the effects of palosuran on serum glucose and insulin, as well as on renal function and the development of albuminuria. To avoid a statistical bias due to the uneven distribution of deaths between untreated and treated diabetic groups, the study duration was 16 weeks. During this 16-week observation period, two rats died in the untreated diabetic group, whereas no rats died in the nondiabetic and palosuran-treated diabetic groups. Even though both groups of diabetic rats had a much reduced body weight gain compared with nondiabetic rats, palosuran-treated rats exhibited significantly greater body weight gain compared with untreated rats (91 ± 11 and 58 ± 11 g, $p < 0.05$, respectively, versus 164 ± 7 g in nondiabetic rats).

Longitudinal measurements of serum concentrations of glucose, cholesterol, and triglycerides were performed before and during the 16-week administration of palosuran. The STZ-induced increase in glycemia was similar in both diabetic groups at the start of palosuran treatment. From week 2 onwards, chronic administration of palosuran partially prevented the further increase in glycemia, and a statistically significant difference, in comparison with untreated diabetic rats, was evident from week 6 onwards (Fig. 2a). Urinary glucose excretion was not increased by palosuran but rather decreased, suggesting that renal elimination of glucose is not increased by UT receptor antagonism (6.1 ± 0.7 versus 8.9 ± 0.7 g/24 h at week 2, $p < 0.05$). Both serum cholesterol and triglycerides levels were markedly increased in the untreated diabetic rats; palosuran halved the increase in cholesterol and largely prevented the increase in triglycerides (Fig. 2, b and c). HbA1c, an index of chronic glycemia (Nathan et al., 1984), and serum insulin concentration were assessed at weeks 8 and 16. The concentrations of HbA1c were markedly increased in untreated diabetic rats, compared with nondiabetic controls, and were slightly but significantly reduced by chronic administration of palosuran ($p < 0.05$; Fig. 3a). Serum insulin concentrations were very low in the untreated diabetic rats at weeks 8 and 16 and were significantly, albeit moderately, increased in diabetic rats treated with palosuran ($p < 0.01$; Fig. 3b).

A semiquantitative, blinded histopathological evaluation of pancreatic sections at the end of the 16-week study showed
that in untreated diabetic rats the islets of Langerhans were generally smaller and contained fewer β-cells than in nondiabetic rats. In palosuran-treated diabetic rats, islets of Langerhans were larger even though there was still a slightly reduced number of β-cells (Figs. 4 and 9a). To investigate whether palosuran has an acute effect on insulin release and/or production in diabetic rats, we evaluated the effects of a single dose of palosuran on serum glucose and on insulin responses to a glucose load, 2 days after STZ injection. At baseline, fasting glucose concentrations were 1.05 ± 0.03 (nondiabetic rats), 1.37 ± 0.11 (diabetic rats), and 1.24 ± 0.06 (diabetic rats treated with palosuran) g/l, and insulin concentrations were 0.26 ± 0.09 (nondiabetic rats), 0.11 ± 0.01 (diabetic rats), and 0.10 ± 0.01 (diabetic rats treated with palosuran) ng/ml. Three hours after oral single-dose administration, palosuran did not modify either glycemia or insulin concentration; however, after a glucose load, palosuran reduced glycemia (p < 0.001 at 30 min; Fig. 5a) and slightly increased serum insulin (p = 0.056 at 30 min; p < 0.05 at 60 min; Fig. 5b) compared with vehicle treatment.

**UT Antagonism Decreases Albuminuria and Reduces Renal Damage.** Albuminuria rapidly increased with time in the untreated diabetic rats. The development of albuminuria was attenuated, but not normalized, by chronic administration of palosuran (p < 0.01 at 16 weeks, Fig. 6). At the end of the 16-week treatment period, rats were anesthetized, and systemic and renal hemodynamics were assessed. Untreated diabetic rats had decreased mean arterial blood pressure, compared with controls (103 ± 3 versus 117 ± 2

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**Fig. 3.** Effects of chronic administration of palosuran (300 mg/kg/day as food admix) on HbA1c (a) and serum insulin concentrations (b). **+, p < 0.001; untreated diabetic rats versus nondiabetic rats. **+, p < 0.05; **+, p < 0.01; **+, p < 0.001; palosuran-treated rats versus untreated diabetic rats.**

**Fig. 4.** Effect of chronic administration of palosuran (300 mg/kg/day as food admix) on mean severity score for β-cell depletion in diabetic rats. **+, p < 0.001; untreated diabetic rats versus nondiabetic rats. **+, p < 0.05; **+, p < 0.01; **+, p < 0.001; palosuran-treated rats versus untreated diabetic rats.**

**Fig. 5.** Percent change of serum glucose (a) and insulin concentrations (b) induced by oral administration of glucose (2 g/kg) at 3 h after oral administration of vehicle or palosuran (300 mg/kg). **+, p < 0.05; **+, p < 0.01; **+, p < 0.001; untreated diabetic rats versus nondiabetic rats. **+, p < 0.05; **+, p < 0.001; palosuran-treated rats versus untreated diabetic rats.**
versus 327 Hg, p < 0.01) but no significant effect on heart rate (334 ± 8 versus 327 ± 9 beats per minute in untreated diabetic rats). Compared with nondiabetic rats, RVR (Fig. 7d) was significantly decreased in RPF (Fig. 7b) and GFR (Fig. 7a). Chronic administration of palosuran had no significant effect on RVR but significantly increased RPF and GFR in the diabetic rats. Palosuran had no effect on filtration fraction (Fig. 7c). A semiquantitative, blinded histopathological evaluation of kidney sections at 16 weeks showed that kidneys of untreated diabetic rats exhibited moderate to marked renal lesions (tubular degeneration/regeneration, tubular vacuolization, and minimal to slight glomerulosclerosis). Palosuran significantly decreased the incidence and severity of these lesions (Figs. 8 and 9b).

**Discussion**

The mammalian U-II system is of recent discovery (Coulouarn et al., 1998), and its role is still poorly understood. Since it is a tissular system, studies that rely on injecting exogenous U-II in the bloodstream may be misleading. Our study shows that antagonism of the endogenous U-II system slows the progression of diabetes and causes in diabetic rats a dual effect: an increase in glucose tolerance and a decrease in proteinuria.

We show here that antagonism of the U-II system with palosuran has acute and chronic effects on glucose control. Acutely, palosuran decreased serum glucose and increased insulin in response to a glucose load. This suggests that palosuran may directly increase the release and/or production of insulin in diabetic rats. This is in agreement with previous data showing that in isolated perfused rat pancreas, U-II significantly inhibited insulin secretion in response to increasing glucose concentration by directly influencing pancreatic β-cells (Silvestre et al., 2001). Both U-II and UT receptors are abundantly expressed in pancreas and vascular endothelial cells (Ames et al., 1999; Maguire et al., 2000; Elshourbagy et al., 2002; Totsune et al., 2003). Thus, U-II produced within the pancreas may act in an autocrine or paracrine manner on pancreatic β-cells. Circulating U-II may also contribute in an endocrine fashion since plasma U-II concentrations are increased in experimental and human diabetes. Because U-II and its receptor are also present in the liver (Elshourbagy et al., 2002; Totsune et al., 2003), and, in fish, U-II decreases liver glycogen content and increases liver glucose 6-phosphate activity (Sheridan et al., 1987), we cannot exclude that the antihyperglycemic effect of palosuran may also be related to an inhibition of glucose mobilization. However, it is not known whether this effect occurs in mammals.

After chronic administration to diabetic rats, palosuran slowed the progressive increase in serum glucose and decreased glycosylated hemoglobin, which reflects integrated mean glucose levels over a period of 2 to 3 months (Nathan et al., 1984). Palosuran slightly increased serum insulin concentrations and decreased β-cell loss in islets of Langerhans. Long-term UT receptor blockade may protect the pancreatic β-cells against cell death and enhance insulin biosynthesis in diabetic rats. To determine whether this effect of palosuran in pancreas occurs through an antiapoptotic mechanism or is related to an increase in β-cell regeneration requires further studies. This chronic, long-lasting antihyperglycemic effect of palosuran is different from the glucose-lowering effect of glibenclamide. Indeed, after glibenclamide, the initial decrease in glycemia is followed by a gradual return of glycemia to baseline levels or higher (Riddle, 2000). Thus, palosuran may promote the survival of pancreatic β-cells in diabetic rats.

Whereas the first target of action of palosuran is the pancreas, the second target of action is the kidney. Both U-II and the UT receptor genes are expressed in the kidney (Matsus-
Urotensin-II is expressed in epithelial cells of tubules and collecting ducts, capillary and glomerular endothelial cells, and endothelial and smooth muscle cells of renal arteries (Shenouda et al., 2002). The UT receptor, in contrast, is found in kidney cortex (Maguire et al., 2000; Matsushita et al., 2001; Shenouda et al., 2002). Recently, we have demonstrated that short-term i.v. administration of palosuran improves the glomerular and tubular dysfunction and renal tissue injury induced by renal ischemia/reperfusion (Clozel et al., 2004). Chronic administration of palosuran significantly attenuates the development of proteinuria, renal dysfunction, and tubular and tubulointerstitial lesions in diabetic rats. Palosuran increases renal plasma flow without changing filtration fraction. This very peculiar profile suggests a unique pre- and postglomerular vasodilation, as already suggested in ischemia-reperfusion (Clozel et al., 2004). This differentiates the role of U-II from that of angiotensin II (Anderson et al., 1986), endothelin (King et al., 1989), and calcium (Dworkin et al., 1990, 1996), the inhibition of which causes either selective postglomerular (angiotensin II, endothelin) or preglomerular vasodilation (calcium channel blockers). The antiproteinuric effect of palosuran might be due to either a decrease in glomerular pressure or a change in glomerular permeability.

Palosuran improves survival in rats with diabetes mellitus. Several factors could contribute to this long-term survival effect, in particular its antihyperglycemic effect. Hyperglycemia is recognized as the primary culprit in the pathogenesis of diabetic vascular complications since a clear association between the level of chronic glycemia and the risk

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**Fig. 8.** Effects of chronic administration of palosuran (300 mg/kg/day as food admix) on mean severity score for renal tubular degeneration/regeneration (a) and global kidney lesion score (b) in diabetic rats.***p < 0.001; untreated diabetic rats versus nondiabetic rats. **p < 0.01; palosuran-treated rats versus untreated diabetic rats.

**Fig. 9.** Effects of chronic administration of palosuran (300 mg/kg/day as food admix) on pancreatic and renal morphology in diabetic rats. (a, representative histographs (H&E-stained section, magnification ×20) of pancreatic morphology. Left, normal β-cells in nondiabetic rats; Center, in diabetic rats, moderate reduction in the size of an islet of Langerhans due to a reduced number of β-cells; vacuolar degeneration of islet cells/single cell loss (VD). Right, less severe effect on islet of Langerhans size noted in palosuran-treated diabetic rats; persistence of a slightly reduced number of β-cells; vacuolar degeneration of islet cells/single-cell loss (VD). (b, representative histographs (H&E-stained section, magnification ×20) of renal morphology. Left, normal glomerulus (NG); normal tubules (NT). Center, in diabetic rats, tubular vacuolation (TV); tubular degeneration with pronounced tubular regeneration (TD). Right, reduced severity and frequency of tubular degeneration in palosuran-treated diabetic rats, persistence of tubular vacuolation (TV).
of developing specific diabetic complications has been established (Reichard et al., 1993; De Vriese et al., 2000). Diabetes is associated with a number of other metabolic disorders such as increased sympathetic activity. Since exogenous U-II increases circulating catecholamines and cortisol and stimulates fatty acid release and lipolysis in fish (Sheridan and Bern, 1986; Douglas and Ohlstein, 2000) and sheep (Watt et al., 2003), urotensin-II may also participate in the long-term progression of diabetes by its sympathomimetic effects, either peripheral, by directly increasing catecholamine release by the adrenal medulla, or central, by stimulation of the pituitary-adrenal axis. A benefit of palosuran may, therefore, be attenuation of the increased sympathetic activity of diabetes. Finally, the increase in survival with palosuran may be due to its effect on the development and progression of diabetic nephropathy. Even though plasma creatinine concentrations over the relatively short duration of the study were not high enough to suggest that renal failure was the cause of death in untreated diabetic rats, the prevention of albuminuria and the decreased incidence of tubular and tubulointerstitial lesions by palosuran suggest that nephropathy may have contributed to the prognosis.

Overall, our results suggest that the U-II system plays a role in the progression of diabetes and contributes both to the decrease in insulin secretion and to the progression of diabetic nephropathy. Urotensin-II peptide and UT receptors are markedly up-regulated in diabetic patients. The next steps should establish if palosuran is effective in diabetic patients. Preliminary data from a series of three clinical proof-of-concept studies of palosuran in diabetic nephropathy patients do not suggest a major efficacy, at the doses used, the duration of treatment applied, for the patients examined. Further studies are needed to understand whether antagonism of the U-II system will constitute a novel therapeutic approach in diabetes.

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References


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