GI262570, a Peroxisome Proliferator-Activated Receptor γ Agonist, Changes Electrolytes and Water Reabsorption from the Distal Nephron in Rats


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ABSTRACT

Peroxisome proliferator-activated receptor-γ (PPARγ) agonists have been shown to have significant therapeutic benefits such as desirable glycemic control in type 2 diabetic patients; however, these agents may cause fluid retention in susceptible individuals. Since PPARγ is expressed selectively in distal nephron epithelium, we studied the mechanism of PPARγ agonist-induced fluid retention using male Sprague-Dawley rats treated with either vehicle or GI262570 (farglitazar), a potent PPARγ agonist. GI262570 (20 mg/kg/day) induced a plasma volume expansion. The plasma volume expansion was accompanied by a small but significant decrease in plasma potassium concentration. Small but significant increases in plasma sodium and chloride concentrations were also observed. These changes in serum electrolytes suggested an activation of the renal mineralocorticoid response system; however, GI262570-treated rats had lower plasma levels of aldosterone compared with vehicle-treated controls. mRNA levels for a group of genes involved in distal nephron sodium and water absorption are changed in the kidney medulla with GI262570 treatment. In addition, due to a possible rebound effect on epithelial sodium channel (ENaC) activity, a low dose of amiloride did not prevent GI262570-induced fluid retention. On the contrary, the rebound effect after amiloride treatment potentiated GI262570-induced plasma volume expansion. This is at least partially due to a synergistic effect of GI262570 and the rebound from amiloride treatment on ENaC expression. In summary, our current data suggest that GI262570 can increase water and sodium reabsorption in distal nephron by stimulating the ENaC and Na,K-ATPase system. This may be an important mechanism for PPARγ agonist-induced fluid retention.

Peroxisome proliferator-activated receptor-γ (PPARγ) is a member of the PPAR family of the nuclear receptor superfamily of ligand-dependent transcription factors (Evans, 1988; Desvergne and Wahli, 1999). PPARγ agonists, including thiazolidinediones (TZDs), are novel insulin-sensitizing agents that primarily improve insulin sensitivity and increase glucose disposal in insulin-sensitive tissues in diabetic animals and patients (Evans, 1988; Desvergne and Wahli, 1999; Olefsky and Saltiel, 2000). Currently, two TZDs, rosiglitazone and pioglitazone, are being widely used as therapeutic agents for type 2 diabetes.

Most type 2 diabetics treated with rosiglitazone and pioglitazone tolerated the agents well, despite modest weight gain in a subpopulation of patients. Although adipogenesis in the subcutaneous adipose tissue contributed to the weight gain, it has been documented that some patients also had increased plasma volume and fluid retention (Wang et al., 2002; Mudaliar et al., 2003). In some cases, patients even developed peripheral edema or congestive symptoms, which is reversible after drug withdrawal (Wang et al., 2002; Kermani and Garg, 2003; Tang et al., 2003). Both fluid retention and overt clinical edema typically developed within the first few weeks of treatment.

ABBREVIATIONS: PPAR, peroxisome proliferator-activated receptor; TZD, thiazolidinedione; GFR, glomerular filtration rate; GI262570, farglitazar; AVP, arginine vasopressin; q.d., daily; RT, reverse transcription; qPCR, quantitative polymerase chain reaction; ANOVA, analysis of variance; SGK1, serum- and glucocorticoid-regulated kinase 1; GR, glucocorticoid receptor; AQP, aquaporin; ENaC, epithelial sodium channel; NPR-A, type A natriuretic peptide receptor; MR, mineralocorticoid receptor; 11β-HSD, 11-β-hydroxysteroid dehydrogenase; AVP-R2, type 2 arginine vasopressin receptor.
few months of drug administration (Niemeier and Janney, 2002; Kermani and Garg, 2003). The mechanism(s) of PPARγ agonist-induced fluid retention/edema is (are) presently unclear and may involve multiple factors/systems. A balance between intake and output of water and all electrolytes in the body is maintained in a large part by the kidney. It is reasonable to hypothesize that increased sodium and water retention at the renal level plays an important role in PPARγ agonist-induced fluid retention; however, the mechanism and the driving force that lead to excessive renal sodium and water retention remains unclear. In our previous studies, we demonstrated that GI262570, a potent nonthiazolidinedione PPARγ agonist (Willson et al., 2000), caused slow accumulation of sodium (sodium intake > sodium excretion) (L. Chen, B. Yang, J. McNulty, L. Clifton, J. Binz, A. Grimes, J. Strum, W. Harrington, Z. Chen, T. Balon, S. Stimpson and K. Brown, unpublished data) but did not affect glomerular filtration rate (GFR), effective renal plasma flow, and renal filtration fraction (Yang et al., 2003). In addition, GI262570-treated rats did not show significant changes in renal hemodynamics compared with vehicle-treated controls (Gardiner et al., 2004). It is likely that PPARγ agonists cause sodium and fluid retention via a direct effect on tubular sodium reabsorption.

Renal expression of PPARs has been investigated in many species (Guan et al., 1997; Yang et al., 1999); all three PPAR isoforms have been identified in the nephron. PPARα is predominantly expressed in the proximal tubules and medullary thick ascending limbs, whereas PPARδ is found in all segments of the nephron. PPARγ is selectively expressed in the medullary collecting duct and pelvic urothelium. This expression pattern suggests that PPARγ may have effects on the reabsorption of water and electrolytes in the distal nephron, the segment of nephron that responds to the integrated effects of multiple hormones such as aldosterone, arginine vasopressin (AVP), insulin, and atrial natriuretic peptide.

In this study, we characterized the renal effects of GI262570 in rats. Our data suggest that GI262570-induced sodium retention is likely to be through the activation of sodium reabsorption by the distal nephron epithelial cells.

Materials and Methods

Drug and Material. GI262570 was synthesized by the Medicinal Chemistry Department at GlaxoSmithKline, Inc. GI262570 was suspended in 0.5% hydroxypropylmethyl cellulose and 0.1% Tween 80. This vehicle was prepared by the Pharmacy in Safety Assessment of GlaxoSmithKline. Amlodipine was purchased from Sigma-Aldrich (St. Louis, MO) and prepared in sterile water.

Animals and Drug Treatment. Male Sprague-Dawley rats (225–250 g) (Charles River, Indianapolis, IN) were housed at 72°F and 50% relative humidity with a 12-h light and dark cycle and fed standard rodent chow (Purina 5001; Harlan, Indianapolis, IN). After a 1-week acclimatization period, rats were randomly assigned to experimental groups. Animals were orally gavaged once a day at 8:00 AM. All procedures were performed in compliance with the Animal Welfare Act and U.S. Department of Agriculture regulations and were approved by the GlaxoSmithKline Animal Care and Use Committee. Study 1. Rats were treated with vehicle (0.5% hydroxypropylmethyl cellulose and 0.1% Tween 80) or 2 or 20 mg/kg/day of GI262570 for 5 days (n = 6 per group). Study 2. Rats were treated with vehicle or 2 or 20 mg/kg/day of GI262570 for 4 days (n = 6 per group). Study 3. In this study, rats were assigned to different durations of treatment (2, 4, and 10 days) each containing a vehicle and a GI262570 (20 mg/kg/day) group (n = 6 per group). An additional group of rats were treated with vehicle or GI262570 for 10 days and then off the drug for 2 days (n = 6). Study 4. Rats were treated with vehicle or GI262570 (20 mg/kg/day) for 5 days with/without amlodipine (1 mg/kg p.o., q.d.) (n = 6 per group). Study 5. Rats were treated with vehicle or GI262570 (20 mg/kg/day) for 4 days with/without amlodipine (1 mg/kg p.o., q.d.) (n = 6 per group) for 4 days. One GI262570-treated group was given amlodipine only on the 4th day. Study 6. Rats were treated with a single dose of amlodipine 6 h before sample collection (n = 5 per group).

Plasma Volume Measurement. Rats were treated with either vehicle or GI262570 (2 or 20 mg/kg q.d.) with or without amlodipine (1 mg/kg q.d.) for 5 days (studies 1 and 4). Rats were anesthetized with isoflurane 2 h after the fifth dose. One jugular vein was catheterized for sample collection and dye injection. Blood (0.2–0.3 ml) was collected for obtaining baseline plasma samples. Then 1 ml/kg of an Evans blue saline solution (2 mg/ml) was administered intravenously through the jugular vein cannulation. Five minutes later, 0.5 ml of blood was collected to measure Evans blue concentration in the plasma. Two milliliters of blood were withdrawn for plasma electrolytes. Plasma Evans blue concentrations were determined according to a standard curve generated by a serial dilution of Evans blue saline solution (2 mg/ml). Plasma volume was calculated using the dilution factors of Evans blue.

Blood Sampling and Tissue Collection. Rats were anesthetized with isoflurane 6 h after the administration of the drugs on the last day of treatment for studies 2, 3, 5, and 6. The abdominal cavity was opened via a midline incision, and blood was collected immediately from the inferior vena cava using a heparinized syringe. The medullary portion of the kidneys was carefully dissected out and placed immediately into liquid nitrogen and subsequently stored at −80°C. Plasma was obtained from the blood samples via centrifugation (10 min at 1000g). Plasma electrolytes (sodium, potassium, and chloride) were measured using the Instrumentation Laboratory Ilab600 clinical chemistry analyzer (Instrumentation Laboratory, Lexington, MA). Plasma aldosterone concentration was measured using an enzyme immunoassay kit (Cayman Chemical, Ann Arbor, MI) following the manufacturer’s instructions. To avoid the daily differences on plasma electrolytes and aldosterone levels, each GI262570-treated group had its own vehicle control group from the same day.

Tissue Total RNA Extraction, Reverse Transcription (RT), and Quantitative Polymerase Chain Reaction (qPCR). Total RNA from kidney medulla was extracted using TRIzol (Invitrogen, Carlsbad, CA). The RNA samples were then further purified using RNeasy mini column (QIAGEN, Valencia, CA) and digested with DNase (QIAOPEN) following the manufacturer’s instruction to remove DNA contamination. One microgram of cleaned total RNA was reverse-transcribed in a 100-μl reaction using the High Capacity cDNA archive kit (Applied Biosystems, Foster City, CA). qPCR was performed and analyzed using ABI PRISM 7000 Sequence Detection System (Applied Biosystems) and gene-specific primers and probes (Table 1). Data were normalized to the expression of β-actin mRNA and presented as -fold of vehicle controls.

Data Analysis. Data were presented as mean ± S.E.M. Differences between vehicle and GI262570-treated groups were analyzed by unpaired Student’s t test or ANOVA followed by Fisher’s protected least significant difference test when there was a significant difference among groups. A p value less than 0.05 was considered to be significant.

Results

GI262570 Induced a Rapid Development of Plasma Volume Expansion. Doses of GI262570 were chosen based on the previous in vivo studies that induced fluid retention in rats (B. Yang and L. Chen, unpublished data). A dose of 20 mg/kg/day is about 10-fold higher than that required to improve glycemic control in rodent models of T2DM (Brown et
Between the changes in plasma sodium and chloride concentration were found in some but not all of the time points (Fig. 3, A–D). There was a correlation of changes in plasma potassium concentration was still lower in the GI262570-treated animals (Fig. 3D). Changes in plasma electrolyte concentrations (Fig. 3, A–D). The changes in plasma electrolytes were within the normal ranges, and GI262570 had no effect on plasma osmolarity (data not shown).

The Effect of GI262570 on Plasma Aldosterone Level. Plasma aldosterone was measured in samples from study 2. Both 2 and 20 mg/kg/day of GI262570-treated rats had lower circulating aldosterone concentrations than the vehicle group (Fig. 4).

The Effect of GI262570 on Gene Expression in the Renal Medulla. To explore possible mechanisms for GI262570-induced renal electrolyte homeostasis, the mRNA expression of a selected group of genes in the kidney medulla from study 2 and the 2-day group of study 3 was determined using qPCR (Table 2). The expression of several genes changed significantly in GI262570-treated groups. Compared with the vehicle groups, the mRNA levels of PPARα and the α subunit of Na,K-ATPase (Na,K-ATPase-α) were elevated in all three GI262570-treated groups (Table 2, all p < 0.05). In addition, the mRNA expression of enzymes involved in mineralocorticoid and glucocorticoid signaling were also altered (Table 2). Similar changes were found with aquaporin 2 (AQP2) mRNA (Table 2). None of the changes in the subunits of ENaC reached statistical significance; however, the mRNA levels of ENaCα subunit (ENaCa) in GI262570-treated groups tended to be higher than that of the vehicle groups (Table 2, p = 0.215, 0.156, and 0.078 for 2 days with 20 mg/kg/day, 4 days with 2 mg/kg/day, and 4 days with 20 mg/kg/day, respectively). Meanwhile, the expression of type A natriuretic peptide receptor (NPR-A) tended to decrease after a 4-day treatment (Table 2, p = 0.273, 0.211, and 0.063 for 2 days with 20 mg/kg/day, 4 days with 2 mg/kg/day, and 4 days with 20 mg/kg/day, respectively). mRNA expression was unaltered for Nr3c1 (the mineralocorticoid receptor (MR)), 11β-HSD2, AQP3, and type 2 AVP receptor (AVP-R2). Although 11β-HSD1 mRNA was decreased in adipose tissue after GI262570 treatment (data not shown), which was consistent with a previous report (Berger et al., 2001), it was not changed in the kidney.

The Combined Effect of GI262570 and Amiloride on Plasma Volume and Electrolytes and Kidney Medullary

![Fig. 1. GI262570-induced plasma volume expansion. Rats were treated with 2 mg/kg/day of vehicle or 20 mg/kg/day of GI262570 for 5 days. Two hours after the fifth dose rats were anesthetized with isoflurane and cannulated via a jugular vein. Total plasma volume was then measured using the Evans blue method. * p < 0.05 versus vehicle (ANOVA).](image-url)
Fig. 2. GI262570 treatment affected plasma K⁺, Na⁺, and Cl⁻ concentration. Rats were treated with vehicle or GI262570 for 4 days. Six hours after the last dose rats were anesthetized with isoflurane, and blood samples were collected through inferior vena cava. Plasma sodium, potassium, and chloride concentrations were measured. *, p < 0.05; **, p < 0.01; and ***, p < 0.001 versus vehicle; ##, p < 0.05 versus 2 mg/kg/day of GI262570 (ANOVA).

Fig. 3. Time course for the effect of GI262570 treatment on plasma electrolytes. Rats were treated with vehicle or GI262570 (20 mg/kg/day) for 2 (A), 4 (B), and 10 (C) days. One group of rats was treated with vehicle or GI262570 for 10 days followed by 2 days off the drug (D). Six hours after the last dose (A–C) or at 2:00 PM (D) rats were anesthetized with isoflurane, and blood samples were collected through inferior vena cava. Plasma sodium, potassium, and chloride concentrations were measured. *, p < 0.05 versus vehicle; **, p < 0.01 versus vehicle; and ***, p < 0.0001 versus vehicle (Student’s t test).
Gene Expression. To further explore the role of ENaC in the GI262570-induced plasma volume expansion, we cotreated rats with amiloride at 1 mg/kg q.d. This low dose of amiloride did not prevent the development of GI262570-induced plasma volume expansion (Fig. 5A). On the contrary, rats treated with both GI262570 and amiloride had a greater degree of plasma volume expansion compared with the group treated with GI262570 alone (Fig. 5A). The plasma electrolyte levels taken 2 to 3 h after the administration of amiloride showed a significant decrease in plasma sodium concentration and an increase in plasma potassium concentration (Fig. 5, B and C). This pattern of plasma electrolyte was reversed when the blood samples were taken 6 h after the administration of amiloride. Treatment with both GI262570 and amiloride caused a significant decrease in plasma potassium concentration, even in rats treated with a single dose of amiloride (Fig. 6A). There was no difference in plasma sodium and chloride concentration among the groups (Fig. 6A). In addition, the combined treatment of GI262570 and amiloride also induced an increase in renal ENaC mRNA expression, which was more significant than that of GI262570 alone (Fig. 6B) or of amiloride alone (Fig. 7), although amiloride induced similar changes in plasma electrolytes by itself (Fig. 7).

Discussion

PPARγ is highly expressed in the renal medullary collecting duct with lower expression levels in the renal glomeruli and renal microvasculature (Guan et al., 1997; Yang et al., 1999). This gene distribution pattern suggests that PPARγ may be involved in the fine regulation of electrolytes and water excretion in the distal nephron. In this study, we demonstrate that GI262570, a nonthiazolidinedione PPARγ agonist (Willson et al., 2000), can decrease plasma potassium concentration while increasing the total amount of plasma sodium. These data demonstrate a possible decrease in renal sodium but an increase in renal potassium excretion.

Due to expression patterns of channels and transporters in the kidney, permeability to water, and sensitivity to hormones in different segments of the nephron, each segment

<table>
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<tr>
<th>Genes</th>
<th>2-Day Group</th>
<th>4-Day Group</th>
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<tr>
<td></td>
<td>20 mg/kg/day</td>
<td>2 mg/kg/day</td>
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<tr>
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<tr>
<td>Na,K-ATPase-α</td>
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<td>1.24**</td>
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<td>1.31*</td>
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<tr>
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<tr>
<td>AVP-R2</td>
<td>0.95</td>
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*p < 0.05 versus vehicle; **p < 0.01 versus vehicle.

Fig. 4. GI262570 treatment decreased plasma aldosterone in normal rats. Rats were treated with vehicle or GI262570 for 4 days. Six hours after the last dose rats were anesthetized with isoflurane, and blood samples were collected through inferior vena cava. Plasma aldosterone was determined by EIA. *p < 0.05 versus vehicle (ANOVA).

Fig. 5. The effect of amiloride on GI262570-induced plasma volume expansion. Rats were treated with vehicle or GI262570 (20 mg/kg/day p.o.) for 5 days with or without 1 mg/kg q.d. amiloride. Two hours after the fifth dose, rats were anesthetized with isoflurane and cannulated via one jugular vein. Total plasma volume (A) was then measured using the Evans blue method. Blood samples were taken at the end of the experiment to measure plasma sodium (B) and potassium (C) concentrations. *p < 0.05; **p < 0.01; and ***p < 0.001 (Student's t test).
may handle the reabsorption of electrolytes and water differently (Guyton and Hall, 2000). PPARγ is predominantly expressed in the epithelia of the distal nephron, which is also the only segment that transports sodium and potassium ions in opposite directions. One unique feature of the distal tubule and collecting duct is that they are sensitive to multiple hormones, including aldosterone (Verrey, 2001). Aldosterone acts via MR to enhance the reabsorption of sodium through the principal cells by inducing the expression of genes whose products are involved in sodium transport (Loffing et al., 2001). These genes include ENaC, SGK1, and Na,K-ATPase-α (Naray-Fejes-Toth et al., 1999; Feraille et al., 2003). In addition, aldosterone also stimulates the secretion of potassium from the distal nephron, particularly the distal tubule and the cortical collecting duct principal cells, thus increasing renal potassium excretion (Ganong, 2004). As a consequence, an overactivation of the aldosterone signaling system leads to sodium retention and hypokalemia (Ganong, 2004).
Because sodium retention is always followed by an increase in water reabsorption via the collecting duct, it is rare to see a dramatic change in plasma sodium concentration during hyperaldosteronemia, even though the total body sodium has increased (Ganong, 2004). For all the time points tested in this study, GI262570-treated groups have significantly lower plasma potassium concentrations compared with vehicle control groups (Fig. 2). In some cases, GI262570-treated rats have even higher plasma sodium and chloride concentrations (Figs. 2 and 3). With an increase in plasma volume (Fig. 1), the total amount of sodium will be higher in GI262570-treated rats even if there is no change in its plasma concentration. These changes in plasma electrolytes may suggest an alteration in electrolyte reabsorption and secretion through the distal nephron and a possible activation of the aldosterone signaling pathway in the kidney. However, this is a false hyperaldosteronism because the plasma aldosterone level in GI262570-treated rats was actually lower than that of vehicle controls (Fig. 4).

Aldosterone enhances sodium reabsorption by up-regulating the expression of genes involved in sodium transport (Eaton et al., 2001; Loffing et al., 2001). It is possible that GI262570 may affect the expression and activity of the same group of genes. For example, a recent study suggests that PPARγ agonists could increase the expression of SGK1 in cultured human collecting duct epithelial cells (Hong et al., 2003). We also find an up-regulation of SGK1 mRNA in some GI262570-treated groups (Table 2). Since SGK1 is an early responding gene after aldosterone and serum stimulation and has a rapid mRNA turnover rate (Webster et al., 1993), the timing of sample collection over the course of the in vivo study may cause the variations in results. The role of SGK1 in sodium reabsorption and potassium secretion in distal nephron has been well studied (Chen et al., 1999; Faletti et al., 2002; Palmada et al., 2003; Verrey et al., 2003b). The reabsorption of sodium from the distal nephron principle cells is coordinately regulated by ENaC on the apical and Na,K-ATPase on the basolateral membrane (Eaton et al., 2001). In GI262570-treated rats, there is a significant increase in the mRNA expression of Na,K-ATPase-α (Table 2). Although there is no statistical significance, our data showed a trend of increase in ENaCα mRNA in GI262570-treated groups (Table 2). This spectrum of changes in gene expression is consistent with the hypothesis that GI262570 may increase sodium reabsorption in the distal nephron; however, it is not clear whether GI262570 regulates the expression of Na,K-ATPase and ENaC directly or via other indirect mechanisms, e.g., through the up-regulation of SGK1 (Verrey et al., 2003a), which may also explain why there is no clear time or dose-dependent changes. Meanwhile, an increase in AQPs mRNA expression in the 4-day study may explain the enhanced water reabsorption in GI262570-treated animals. The magnitude of changes in mRNA expression in this study is relatively small (Table 2), which is consistent with moderate changes in electrolytes and the fact that PPARγ agonists only cause mild and slow-onset fluid retention in most cases. Certainly, changes at other levels such as translation, post-translation, and activity may also contribute to the current observation. These possibilities have not been tested in this study.

In clinic, TZD-treated patients with congestive symptoms are often treated with diuretics. In almost all reports, loop diuretics (inhibit Na⁺-K⁺-Cl⁻ symport) and thiazide or thiazide-like diuretics (inhibit Na⁺-Cl⁻ symport) are used (Niemeyer and Janney, 2002; Wang et al., 2002; Kermani and Garg, 2003; Muddaliar et al., 2003; Tang et al., 2003). In most cases, the edema appears to be refractory to diuretics until the TZD therapy is discontinued. Because of the concern of hyperkalemia, K⁺-sparring diuretics are not commonly used in diabetic patients (McNay and Oran, 1970). To confirm the role of ENaC in PPARγ agonist-induced fluid retention, we combined the GI262570 treatment with amiloride, a potent ENaC inhibitor. Since the desire is to block the overactivation, but not the complete effect of ENaC, only a low dose of amiloride is used. Surprisingly, greater fluid retention is observed in amiloride-treated rats compared with the GI262570 monotherapy group (Fig. 5A). Further studies on plasma electrolytes demonstrate that the low-dose amiloride decreases plasma sodium but increases plasma potassium concentration 2 to 3 h after its administration (Fig. 5, B–C). These effects are completely reversed 6 h after the administration of amiloride (Fig. 6A), which suggests a rebound of the ENaC activity. In addition, combinations of amiloride with GI262570 strongly induce the ENaCα mRNA expression (Fig. 6B), but not amiloride or GI262570 monotherapy (Figs. 6B and 7). Although the mechanism is not clear, there may be a synergistic effect of the rebound on sodium reabsorption after amiloride and GI262570 treatment on the transcription of ENaCα.

In addition to aldosterone, other hormones such as insulin and AVP also stimulate sodium reabsorption via ENaC and Na,K-ATPase in the distal nephron (Ecelbarger et al., 2001; Schäfer, 2002; Blazer-Yost et al., 2003). The incidence of edema increases dramatically when TZDs are used in combination with insulin intervention (Hollenberg, 2003). Plasma AVP level is unchanged after GI262570 treatment.

Fig. 8. Potential mechanisms for PPARγ agonist-induced fluid retention.
in rats (data not shown). Further studies are needed to define the role of insulin and AVP in fluid retention associated with PPARγ agonists.

In this study, we focused on the effect of GI262570 on the distal nephron where PPARγ is expressed. Several recent studies also reported the effect of TZDs on renal sodium reabsorption. Song et al. (2004) demonstrated that rosiglitazone increases sodium reabsorption in the proximal nephron based on a decrease in lithium clearance; however, an important fraction of the filtered lithium could be absorbed beyond the early distal tubule in sodium-restricted rats (Fransen et al., 1992). In agreement with our previous results with GI262570 (Yang et al., 2003), Zanchi et al. (2004) demonstrated that pioglitazone had no effect on GFR and results with GI262570 (Yang et al., 2003), Zanchi et al. (2004) suggested that pioglitazone increases sodium reabsorption in the proximal nephron associated with thiazolidinediones. Am J Med 115(Suppl 8A):1115–1155.

The exact mechanism by which GI262570 induces fluid retention is not completely clear but is likely to be multifactorial (Fig. 8). It has been shown that PPARγ agonists such as GI262570 have potent cardiovascular effects, notably a decrease in total peripheral resistance, and an increase in cardiac output with only a slight drop in mean arterial pressure (Callahan et al., 2002; Ryan et al., 2004). The combination of changes in GFR and the expression of sodium transporters in proximal nephron on renal sodium reabsorption. Further comparisons of contributions of proximal and distal nephrons in PPARγ agonist-induced sodium retention are needed in the future.

Address correspondence to: Lihong Chen, Five Moore Drive, Research Triangle Park, NC 27709. E-mail: lihong.chen@gsk.com