Connecting Tubule Glomerular Feedback in Hypertension

Hong Wang, Martin A. D’Ambrosio, Jeffrey L. Garvin, Yilin Ren, Oscar A. Carretero

Abstract—In Dahl salt-sensitive rats (Dahl SS), glomerular capillary pressure increases in response to high salt intake and this is accompanied by significant glomerular injury compared with spontaneously hypertensive rats with similar blood pressure. Glomerular capillary pressure is controlled mainly by afferent arteriolar resistance, which is regulated by the vasoconstrictor tubule glomerular feedback (TGF) and the vasodilator connecting TGF (CTGF). We hypothesized that Dahl SS have a decreased TGF response and enhanced TGF resetting compared with spontaneously hypertensive rats, and that these differences are attributable in part to an increase in CTGF. In vivo, using micropuncture we measured stop-flow pressure (a surrogate of glomerular capillary pressure). TGF was calculated as the maximal decrease in stop-flow pressure caused by increasing nephron perfusion, TGF resetting as the attenuation in TGF induced by high salt diet, and CTGF as the difference in TGF response before and during CTGF inhibition with benzamil. Compared with spontaneously hypertensive rats, Dahl SS had (1) lower TGF responses in normal (6.6±0.1 versus 11.0±0.2 mm Hg; P<0.001) and high-salt diets (3.3±0.1 versus 10.1±0.3 mm Hg; P<0.001), (2) greater TGF resetting (3.3±0.1 versus 1.0±0.3 mm Hg; P<0.001), and (3) greater CTGF (3.4±0.4 versus 1.2±0.1 mm Hg; P<0.001). We conclude that Dahl SS have lower TGF and greater CTGF than spontaneously hypertensive rats, and that CTGF antagonizes TGF. Furthermore, CTGF is enhanced by a high-salt diet and contributes significantly to TGF resetting. Our findings may explain in part the increase in vasodilatation, glomerular capillary pressure, and glomerular damage in SS hypertension during high salt intake. (Hypertension. 2013;62:00-00.) • Online Data Supplement

Key Words: benzamil ■ CTGF ■ Dahl salt-sensitive rats ■ rats, inbred SHR ■ TGF

There is evidence that in hypertension, glomerular capillary pressure (Pgc) greatly influences the progression of renal nephrosclerosis.1,2 In blacks with salt-sensitive hypertension, high salt intake causes an abnormal renal hemodynamic response and an increase in estimated Pgc.3 In Dahl salt-sensitive rats (Dahl SS), Pgc increases in response to high salt intake and this is accompanied by significantly greater glomerular injury compared with spontaneously hypertensive rats (SHR) with similar blood pressure.4–6 Pgc is controlled by both afferent arteriolar (Af-Art) and efferent arteriolar resistance. Af-Art resistance is regulated by mechanisms similar to other arterioles, including sympathetic nerve activity, angiotensin II, nitric oxide, eicosanoids, and myogenic response. In addition, Af-Art resistance is also regulated by 2 intrinsic renal autoregulatory mechanisms, namely tubule glomerular feedback (TGF) and connecting TGF (CTGF). TGF is initiated by increases in NaCl in the macula densa and causes Af-Art constriction, whereas CTGF is initiated by increases in NaCl in the connecting tubule and causes Af-Art dilatation7 (Figure 1). CTGF is initiated by Na entry via the epithelial Na channel (ENaC) in the connecting tubule and is blocked by the ENaC inhibitor benzamil. CTGF is mediated by prostaglandin E2 and epoxygenesatrienoic acids (EETs).8–11

During high salt intake, if TGF were to remain unchanged, it would cause a decrease in Pgc and glomerular filtration attributable to enhanced distal delivery of NaCl and thus a decrease in renal natriuretic response to high salt intake. However, this does not occur because TGF resets, so that a greater amount of NaCl is required to elicit the same vasoconstriction.12 In addition to high salt, TGF resetting occurs in response to physiological and pathophysiological conditions such as volume expansion, diabetes mellitus, and unilateral nephrectomy.13–16 The mechanisms that mediate TGF resetting are not completely understood.

In vivo NaCl in the lumen of the distal nephron regulates Af-Art resistance via the combined effect of TGF and CTGF.10 Thus, the observation that TGF is attenuated or reset in certain conditions could reflect an increase in CTGF that counteracts TGF. In fact, we have recently reported that CTGF partly mediates acute TGF resetting induced by sustained perfusion of single nephrons at the high end of the physiological tubular flow range.17 The roles of TGF resetting and CTGF in hypertensive rats have not been well characterized. Here we studied for the first time the role of CTGF in the regulation of Pgc and salt-induced TGF resetting in Dahl SS and SHR. We hypothesized

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that Dahl SS have a decreased TGF response and enhanced TGF resetting compared with SHR, and that these differences are attributable in part to an increase in CTGF. To test this hypothesis, we used Dahl SS, Dahl salt-resistant rats (Dahl SR), SHR, and Wistar Kyoto rats (WKY) that were fed a normal or high-salt diet and performed micropuncture of individual nephrons to measure stop-flow pressure ($P_{SF}$; a surrogate of $P_{GF}$). TGF was calculated as the decrease in $P_{SF}$ caused by increasing nephron perfusion.

**Methods**

Male Dahl SS, Dahl SR, SHR, and WKY weighing 307.9±2.6 g were fed either a normal (0.23% NaCl) or high-salt diet (4% NaCl) for 2 weeks. In micropuncture experiments in vivo, 2 consecutive $P_{SF}$ curves were performed. In half of the experiments, the ENaC blocker benzamil was added during the second $P_{SF}$ curve to inhibit CTGF. TGF was calculated as the maximal decrease in $P_{SF}$ caused by increasing nephron perfusion, TGF resetting as the attenuation in TGF induced by high-salt diet, and CTGF as the difference in TGF response before and during CTGF inhibition with benzamil. An expanded Methods is available in the online-only Data Supplement.

**Results**

**Dahl SS and Dahl SR Fed Normal Salt Diet: TGF Response and Role of CTGF**

Dahl SS (black circles) had an attenuated TGF response compared with Dahl SR (white circles). These differences reached statistical significance when the tubules were perfused at a rate of $≥20$ nL/min (Figure 2). In rats fed a normal salt diet, blocking CTGF potentiated the TGF response in both Dahl SR and Dahl SS (Figure 3A and 3B). Although this potentiation was somewhat greater in Dahl SS, it was not of statistical significance (Figure 3C). In time control experiments, we confirmed that 2 consecutive TGF responses were reproducible in Dahl SR and Dahl SS with no time effect (Figure S1A and S1B in the online-only Data Supplement).

**SHR and WKY Fed Normal Salt Diet: TGF Response and Role of CTGF**

SHR (black circles) had a greater TGF response compared with WKY (white circles). These differences reached statistical significance when the tubules were perfused at a rate of $≥20$ nL/min (Figure 4A). These data were normalized to baseline $P_{SF}$ because basal pressure was significantly higher in the SHR (see absolute numbers in Figure 4B). Inhibition of CTGF with benzamil potentiated TGF response in WKY when the tubules were perfused at a rate of $≥30$ nL/min (Figure 5A). However, in SHR, inhibition of CTGF did not potentiate the TGF response (Figure 5B), suggesting that SHR fed a normal salt diet have little or no CTGF. WKY tended to have greater CTGF than SHR ($P<0.01$ for the overall ANOVA group comparison). When CTGF in SHR was compared with that of WKY at each individual flow rate, $P$ values were <0.05 at 30 and 40 nL/min; however, these differences did not reach statistical significance after adjustment for multiple comparisons (Figure 5C). In time control experiments, we confirmed that 2 consecutive TGF responses were reproducible in WKY and SHR with no time effect (Figure S2A and S2B).

**Dahl SS and Dahl SR: TGF Resetting Induced by High-Salt Diet (2 Weeks), Role of CTGF in TGF Resetting**

When the rats were fed a high-salt diet (4% NaCl), TGF responses were attenuated in both Dahl SR and Dahl SS.

**Figure 1.** Schematic representation of tubule glomerular feedback (TGF) and connecting TGF (CTGF). The macula densa triggers TGF when Na is reabsorbed via the Na/K/2Cl cotransporter type 2 (NKCC2), by releasing ATP, which is broken down to adenosine, which in turn causes constriction of the afferent arteriolar (Af-Art). The connecting tubule triggers CTGF when Na is reabsorbed via the epithelial sodium channel (ENaC), by releasing epoxyeicosatrienoic acids (EETs) and prostaglandin E$_2$ (PGE$_2$), which cause dilation of the Af-Art. DCT indicates distal convoluted tubule; and PT, proximal tubule.

**Figure 2.** Tubule glomerular feedback (TGF) response in Dahl salt-resistant rats (Dahl SR) and Dahl salt-sensitive rats (Dahl SS) fed normal salt diet (NSD). TGF induced by increased perfusion rates in the late proximal tubule in Dahl SR (○) and Dahl SS (●) on NSD. When the tubules were perfused at 20, 30, and 40 nL/min, TGF was significantly attenuated in Dahl SS. **$P<0.01$, ***$P<0.001$, Dahl SR vs Dahl SS.
These differences reached statistical significance when the tubules were perfused at 30 and 40 nL/min (Figure 6A and 6B). However, the resetting was greater in Dahl SS than in Dahl SR (Figure 6C). Inhibition of CTGF with benzamil in Dahl SR and Dahl SS fed a high-salt diet led to a potentiation of TGF responses when the tubules were perfused at 30 and 40 nL/min (Figure 7A and 7B). An interstrain comparison showed that when fed a high-salt diet Dahl SS had a greater CTGF response than Dahl SR (Figure 7C). In Dahl SS, the percentage of resetting attributable to CTGF was 53%, whereas in Dahl SR, it was only 21% (Figure S3).

**SHR and WKY: TGF Resetting Induced by High-Salt Diet (2 Weeks), Role of CTGF in TGF Resetting**

When WKY were fed a high-salt diet, TGF responses were attenuated; these differences reached statistical significance when the tubules were perfused at 30 and 40 nL/min (Figure 8A). When SHR were fed a high-salt diet, there was a small decrease in TGF response, but it did not reach statistical significance (Figure 8B). Resetting was significantly greater in WKY than in SHR (Figure 8C). Inhibition of CTGF with benzamil in WKY and SHR fed a high-salt diet led to potentiation of TGF responses when the tubules were perfused at 30 and 40 nL/min (Figure 9A and 9B). An interstrain comparison showed that when fed a high-salt diet the CTGF response was greater in WKY than in SHR (Figure 9C).

**Dahl SS and SHR on Normal and High-Salt Diet: Comparison of TGF Response, TGF Resetting, and Role of CTGF**

Dahl SS on a normal salt diet had a significantly lower TGF response than SHR on normal salt diet (Figure 10; white
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TGF resetting induced by high salt intake was significantly greater in Dahl SS than in SHR (3.3±0.1 versus 1.0±0.3 mmHg; \( P < 0.001 \); Figure 10; \( \Delta \) between white and black circles versus \( \Delta \) between white and black triangles). Inhibition of CTGF with benzamil potentiated the TGF response in WKY (A) but not in SHR (B). C, SHR (closed bars) tended to have a smaller CTGF response compared with WKY (open bars). \( P < 0.01 \) for the overall comparison between strains (ANOVA) and \( P < 0.05 \) at the 30 and 40 nL/min perfusion rates, but not statistically significant after adjustment for multiple comparisons.

These data suggest that TGF responses are much lower in Dahl SS than in SHR, and that TGF resetting and the role of CTGF are more pronounced in Dahl SS than in SHR.

Discussion

In humans, susceptibility to hypertension-induced renal damage varies, with blacks at high risk. Blacks often have SS hypertension, and high salt intake causes an abnormal renal hemodynamic response and an increase in estimated \( P_{GC} \).
Thus, their enhanced susceptibility to renal damage may be related to the increased $P_{GC}$ associated with salt sensitivity, as salt sensitivity in humans predicts higher microalbuminuria in the short term and higher mortality on long-term follow-up studies.21

In animal models, there is substantial evidence that in hypertension $P_{GC}$ greatly influences the progression of renal nephrosclerosis.1,2,4,22 It is well known that at similar levels of systemic hypertension Dahl SS but not SHR develop glomerular injury. Furthermore, these differences in glomerular pathology occur because Dahl SS but not SHR develop glomerular hypertension.4 In SHR, $P_{GC}$ in cortical nephrons is normal in spite of severe systemic hypertension because of a marked increase in preglomerular arteriolar resistance.5 Thus, glomeruli of SHR are protected from systemic hypertension. On the other hand, hypertensive Dahl SS display increased glomerular blood flow and $P_{GC}$ as a result of decreased preglomerular arteriolar resistance.6 The present study is the first to explore whether
differences in glomerular hemodynamics between these strains may be attributable to differences in CTGF.

TGF responses in Dahl rats have not been well characterized. Wilcox and Welch reported that Dahl SS fed a low-salt diet had an attenuated TGF response compared with Sprague-Dawley rats. On the other hand, Karlsen et al. found no differences in TGF between Dahl SS and Sprague-Dawley rats. We have previously shown that Sprague-Dawley rats have CTGF, that CTGF antagonizes TGF, and that CTGF at least partially mediates TGF resetting induced acutely by volume expansion. In the current work, we have not included Sprague-Dawley rats; rather, we have compared the Dahl SS with its genetic control and with SHR (to contrast these 2 models of hypertension). We believe our current work will help clarify the TGF response in Dahl rats, as well as provide the first studies of CTGF in hypertension. In our study, Dahl SS had an attenuated TGF response compared with Dahl SR on both normal and high-salt diets.
high-salt diets. Dahl SS fed a high-salt diet had greater TGF resetting and greater CTGF than in Dahl SR. In Dahl SS, inhibition of CTGF decreased TGF resetting by 53%, whereas in Dahl SR, it did so by only 21%. Collectively, these results suggest that in Dahl SS fed a high-salt diet CTGF is increased, leading to higher $P_{GS}$ and $P_{GC}$. In this way, higher CTGF may participate in the development of nephrosclerosis. In this study, we used $P_{GS}$ as a surrogate for $P_{GC}$ because Dahl SS do not have superficial glomeruli that can be directly punctured to measure $P_{GC}$.25

In contrast to Dahl SS, we found that SHR fed a normal salt diet had a much greater TGF response than WKY or Dahl SS and that TGF resetting induced by high salt intake was minimal or nonexistent, consistent with previous reports.26,27 Furthermore, in SHR, antagonism of CTGF to the TGF response and its contribution to TGF resetting were also minimal, indicating that a diminished CTGF may at least partially explain the enhancement in TGF and reduced TGF resetting. These data suggest that a decrease in CTGF in SHR increases preglomerular vascular resistance and helps maintain a normal $P_{GC}$, thus preventing renal damage, in stark contrast to Dahl SS.

Our findings in WKY also expand our understanding of the role of CTGF in TGF resetting in normotensive rats. We previously reported that CTGF partly mediates TGF resetting in normotensive Sprague–Dawley rats induced acutely by sustained perfusion of the nephron at a high flow rate for 30 minutes.17 Here we found for the first time that CTGF also partly mediates TGF resetting that was induced chronically by high salt intake >2 weeks. However, CTGF does not completely explain the enhancement in TGF and reduced TGF resetting. Therefore, decreased levels of EETs, which partly mediate CTGF, could explain the decrease in CTGF in SHR.

The mechanism by which CTGF is enhanced in Dahl SS remains unknown, but may relate to the fact that CTGF is initiated by Na transport in the CNT via ENaC. In spite of their high blood pressure and low serum aldosterone levels, Dahl SS fed a high-salt diet had increased ENaC mRNA, protein, and sodium transport compared with Dahl SR.28–33 Furthermore, Pavlov et al.14 recently measured ENaC single-channel activity by patch clamp studies in split-open cortical-collecting ducts and found higher ENaC activity in Dahl SS on a high-salt diet compared with either a normal diet or with Dahl SR. In addition, CTGF is mediated by prostaglandin E1, and EETs.9,11

In Dahl SS, high salt intake increases renal cortical COX-2 expression35 and urinary prostaglandin E2 excretion.36 Thus, it is possible that in Dahl SS increased ENaC and prostaglandin E2 may cause enhanced CTGF, enhanced $P_{GC}$, and enhanced glomerulomer damage. Conversely, attenuation of CTGF in SHR may be attributable to decreased EETs, because soluble epoxide hydrolase, the enzyme that metabolizes EETs, is increased in the kidney in this strain.37 Therefore, decreased levels of EETs, which partly mediate CTGF, could explain the decrease in CTGF in SHR.

In summary, our studies provide direct evidence that a high-salt diet causes TGF resetting, and that CTGF mediates TGF resetting induced by a high-salt diet, at least in part. Hypertensive Dahl SS have lower TGF compared with either SHR or Dahl SR, and because of an increased TGF resetting in Dahl SS, these differences become exaggerated on a high-salt diet. These differences are attributable in part to a greater CTGF in Dahl SS fed a normal salt diet, as well as greater enhancement of CTGF by a high-salt diet. Our findings may help explain the excessive increase in $P_{GC}$ and glomerular damage observed in SS hypertension.

**Perspectives**

An increase in CTGF may explain the higher glomerular pressure and renal damage in SS hypertensive individuals, such as blacks, the elderly, and the diabetic. ENaC-blocking drugs (potassium-sparing diuretics), by blocking CTGF and decreasing glomerular perfusion pressure, could be useful in preventing hypertensive nephrosclerosis. Our studies may also help explain the beneficial effects seen with mineralocorticoid receptor blockers and suggest new targets for prevention of renal damage.

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**Disclosures**

None.

**References**

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Novelty and Significance

What Is New?

- Connecting tubule glomerular feedback (CTGF) is a novel mechanism of regulation ofafferent arteriole resistance.
- We show that CTGF is responsible for part of the TGF resetting induced by chronic high salt intake.
- In salt-sensitive hypertension, CTGF is augmented and explains >50% of TGF resetting.

What Is Relevant?

- In the United States, more than one fourth of adults diagnosed with hypertension have moderate to severe chronic kidney disease, and hypertension is the second leading cause of end-stage renal disease. In the last 2 decades, the incidence of hypertension-induced end-stage renal disease has nearly doubled, even as control of hypertension increased from 24% to 50%. Despite adequate blood pressure control, renal function declines more often in individuals with salt-sensitive hypertension, including blacks, the elderly, and people with diabetes mellitus, all of whom are more susceptible to developing hypertensive renal damage. The cause of this enhanced susceptibility is related to the increased glomerular capillary pressure associated with salt sensitivity, as salt sensitivity in humans predicts higher microalbuminuria in the short term and higher mortality on long-term follow-up studies.

Summary

Our study shows that CTGF, which is a novel mechanism of regulation of afferent arteriole resistance, is responsible for >50% of the increase in glomerular capillary pressure in salt-sensitive hypertension. Understanding the mechanism that increases glomerular capillary pressure in salt-sensitive hypertension may lead to both prevention and better treatment of renal disease in salt-sensitive hypertension.
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SUPPLEMENTARY ONLINE MATERIAL

Connecting tubule glomerular feedback (CTGF) in Hypertension

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Short title: CTGF and hypertension
Expanded Methods section

All experiments were approved by the Henry Ford Health System Institutional Animal Care and Use Committee (IACUC) and were conducted in accord with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. Male Dahl SS, Dahl SR, SHR, and WKY weighing 307.9 ± 2.6 g were fed either a normal (0.23% NaCl) or high salt diet (4% NaCl) for two weeks. Then they were anesthetized with thiobutabarbitral (125 mg/kg body weight, intraperitoneal). Body temperature was maintained at 37.5°C using a feedback-controlled, heated surgical table. A tracheostomy was performed with PE-240 tubing to facilitate spontaneous breathing. The right jugular vein and left femoral artery were catheterized with PE-10 tubing; the jugular vein for infusion of 0.9% NaCl at a rate of 1.5 ml/h, and the femoral artery for continuous monitoring of blood pressure. The left kidney was approached through a flank incision, freed of adherent fat and connective tissue, and placed in a Lucite cup designed to hold a rat kidney. It was then bathed in saline and immobilized by surrounding it loosely with saline-soaked cotton. The bladder was emptied at the start of the experiment by direct puncture and aspiration of the bladder contents through the abdominal opening. After a 30- to 45-min equilibration period, proximal tubules were identified by injecting phosphate buffer (pH 7.4) containing 7% of a green dye made from FD&C yellow #5, FD&C yellow #6, and FD&C blue #1 in a random proximal segment using a glass pipette (OD 6–8 μm at the tip). A nephron was used when at least three downstream proximal segments were identified, indicating an early proximal puncture site. An early proximal tubule was blocked with grease approximately 420 μm in length (Type T Medium Temperature Vacuum Grease; Apiezon). A perfusion pipette (OD 8–10 μm) attached to a nanoliter infusion pump was inserted into the last superficial proximal segment to perfuse the loop of Henle and distal nephron with a solution containing (in mmol/L): 140 NaCl, 10 HEPES, 1 CaCO3, 0.5 K2HPO4, 4 KHCO3, 1.2 MgSO4, 5.5 glucose, 0.5 Na acetate, 0.5 Na lactate, and 0.5% of the above mentioned green dye (pH 7.4). To measure stop-flow pressure (Psf), a pressure pipette (OD 3–4 μm) attached to a micropressure system (model 900A; World Precision Instruments, Sarasota, FL) was inserted into an early proximal segment. To generate a TGF response curve, the late proximal perfusion rate was increased from 0 to 10, 20, 30, and 40 nL/min while measuring Psf. Each perfusion rate was maintained for 1–5 min as required to observe a stable Psf. Next, either the ENaC inhibitor benzamil (1 μM, Sigma-Aldrich, St Louis, MO) or vehicle (time control) was added to the perfusion fluid and a second Psf curve was generated.

Ninety-six rats were used, 24 from each of the following strains: Dahl SS, Dahl SR, SHR, and WKY. Half of the rats were fed 0.23% NaCl diet, the other half 4% NaCl diet. All animals underwent micropuncture as described above. Data from the first (vehicle) Psf curve was used for comparisons of TGF responses between different strains, comparisons of TGF responses between the two diets on a given strain, as well as for comparisons of TGF resetting between strains, thus the n for these measurements was 12 rats per strain per diet. The second Psf curve was generated in the presence of benzamil added to the lumen of the tubule in half of the rats, while the other half of rats served as time controls with only vehicle in the lumen of the nephron. Because only data from the benzamil experiments was used to calculate CTGF, the n in our CTGF measurements was 6 rats per strain per diet.
TGF was calculated as the decrease in $P_{SF}$ caused by increasing nephron perfusion, i.e. $\Delta P_{SF} = (P_{SF} \text{ at 0 nL/min perfusion rate}) - (P_{SF} \text{ at 40 nL/min perfusion rate})$.

TGF resetting was calculated as the attenuation in TGF induced by high salt diet, i.e. $\text{TGF resetting} = (\Delta P_{SF} \text{ in normal salt diet}) - (\Delta P_{SF} \text{ in high salt diet})$.

CTGF was calculated as the difference between the TGF response before and during CTGF inhibition with benzamil, i.e. $\text{CTGF} = (\Delta P_{SF} \text{ benzamil}) - (\Delta P_{SF} \text{ vehicle})$.

**Statistics**

Data are expressed as mean ± SE. Student’s paired $t$-test was used to compare $P_{SF}$ for each flow rate between the control and experimental flow-response curves. Hochberg’s step-up procedure was used to adjust the $P$-values for multiple comparisons so that the family-wise type I error rate, predefined as 0.05, was controlled.
Figure S1A. TGF response in Dahl SR fed normal salt diet, time control. TGF induced by increased perfusion rates in the late proximal tubule in Dahl SR two consecutive times. The first (●) and second (○) curves were not significantly different. TGF response was stable and reproducible.
Figure S1B. TGF response in Dahl SS fed normal salt diet, time control. TGF induced by increased perfusion rates in the late proximal tubule in Dahl SS two consecutive times. The first (●) and second (O) curves were not significantly different. TGF response was stable and reproducible.
Figure S2A. TGF response in WKY fed normal salt diet, time control. TGF induced by increased perfusion rates in the late proximal tubule in WKY two consecutive times. The first (●) and second (O) curves were not significantly different. TGF response was stable and reproducible.
Figure S2B. TGF response in SHR fed normal salt diet, time control. TGF induced by increased perfusion rates in the late proximal tubule in SHR two consecutive times. The first (●) and second (○) curves were not significantly different. TGF response was stable and reproducible.
Figure S3. Role of CTGF in TGF resetting in Dahl SR and Dahl SS: Open bars represent TGF resetting in the presence of CTGF, i.e., (Δ$P_{SF}$ in normal salt diet, vehicle) - (Δ$P_{SF}$ in high salt diet, vehicle); closed bars represent TGF resetting in the absence of CTGF, i.e., (ΔPSF in normal salt diet, benzamil) - (ΔPSF in high salt diet, benzamil). ***P < 0.001, with CTGF vs. without CTGF. CTGF participates in TGF resetting in both strains, but to a greater extent in Dahl SS.