Neuronal NOS contributes to biphasic autoregulatory response during enhanced TGF activity

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Ichihara, Atsuhiro, and L. Gabriel Navar. Neuronal NOS contributes to biphasic autoregulatory response during enhanced TGF activity. Am. J. Physiol. 277 (Renal Physiol. 46): F113–F120, 1999.—To assess the afferent arteriolar autoregulatory response during increased activity of the tubuloglomerular feedback (TGF) mechanism and to delineate the contribution of neuronal nitric oxide synthase (nNOS) to this response, afferent arteriolar diameter responses to changes in renal perfusion pressure (RPP) were monitored in vitro using the blood-perfused rat juxtamedullary nephron preparation. At RPP of 100 mmHg, basal afferent arteriolar diameter averaged 21.1 ± 1.4 μm (n = 9). The initial and sustained constriction responses of afferent arterioles to a 60-mmHg increase in RPP averaged 14.8 ± 1.4% and 13.3 ± 1.3%, respectively. Acetazolamide treatment, which enhances TGF responsiveness by increasing distal nephron volume delivery, significantly decreased basal afferent arteriolar diameter by 8.2 ± 0.5% and enhanced the initial response (25.5 ± 2.3%) to a 60-mmHg increase in RPP but did not alter the sustained response (14.3 ± 1.5%). In another series of experiments, nNOS inhibition with 10 μM S-methyl-L-thiocitrulline (L-SMTC) significantly decreased afferent arteriolar diameter from 20.3 ± 1.3 to 18.3 ± 1.1 μm (n = 7) and enhanced both the initial (34.3 ± 3.5%) and sustained constriction responses (27.6 ± 2.9%) to a 60-mmHg increase in RPP. Treatment with acetazolamide further enhanced both initial (56.4 ± 3.0%) and sustained responses (54.6 ± 2.7%). Interruption of distal delivery by transection of the loops of Henle prevented the enhanced responses to increases in RPP elicited with either acetazolamide or L-SMTC. These results indicate that nNOS contributes to the counteracting resetting process of biphasic afferent arteriolar constriction responses to increases in RPP through a TGF-dependent mechanism.

afferent arterioles; renal microcirculation; neuronal nitric oxide synthase; macula densa; acetazolamide; tubuloglomerular feedback

THE TUBULOGLOMERULAR FEEDBACK (TGF) mechanism and the myogenic mechanism are recognized as the main mechanisms responsible for the intrarenal vascular resistance adjustments that occur in response to changes in renal perfusion pressure (RPP) (17). Studies using the juxtamedullary nephron preparation have demonstrated that elimination of the TGF mechanism with furosemide, papillectomy, (19, 22), or placing an oil block in the macula densa segment (16) results in significant impairment of the autoregulation-mediated adjustments in afferent arteriolar diameter in response to arterial pressure alterations. These findings indicate that the afferent arteriolar diameter responses to changes in RPP are mediated, at least in part, through the TGF mechanism and that decreases or interruption of distal flow diminishes autoregulatory efficiency. However, afferent arteriolar autoregulatory responses during increased activity of the TGF mechanism have received less attention (20).

Recent studies have demonstrated that nitric oxide (NO) derived from activation of neuronal nitric oxide synthase (nNOS) exerts a counteracting modulatory influence on TGF-mediated afferent arteriolar constriction (10, 23). Because the TGF mechanism contributes to afferent arteriolar autoregulation (16, 19, 22), nNOS may also exert a counteracting modulatory influence on the afferent arteriolar diameter autoregulatory responses to changes in RPP.

For the present study, we hypothesized that increased activation of the TGF mechanism caused by increased distal volume and salt delivery significantly enhances the afferent arteriolar autoregulatory responses to increases in RPP but that nNOS contributes to a counteracting modulation of the enhanced autoregulatory responses during increased activity of the TGF mechanism. To test the hypothesis, the “initial” and “sustained” responses of the arterial pressure-induced changes in afferent arteriolar diameter were delineated. The initial response is defined as the maximum decrease in afferent arteriolar diameter after an increase in perfusion pressure and involves delayed counteracting vasoconstrictor responses to increases in perfusion pressure. The sustained response is defined as the average change in the final 2 min during an increase in perfusion pressure and involves delayed counteracting vasoconstrictor responses to increases in perfusion pressure. The sustained response was assessed under conditions of normal and increased activity of the TGF mechanism. This assessment was also performed during selective nNOS inhibition with 10 μM S-methyl-L-thiocitrulline (L-SMTC) (5, 10). To increase the activity of the TGF mechanism, kidneys were treated with the carbonic anhydrase inhibitor, acetazolamide, which inhibits net proximal tubular reabsorption rate and thus increases volume and salt delivery to the macula densa cells (14, 18).

METHODS
Assessment of Afferent Arteriolar Diameter

The experiments were performed in accordance with the guidelines and practices established by the Tulane University Animal Care and Use Committee. Afferent arteriolar diameter was assessed in vitro using the blood-perfused juxtamedullary nephron technique combined with videomicroscopy, as previously described (3, 4). Each experiment used two male Sprague-Dawley rats (Charles River Labs, Wilmington, MA), weighing 350–400 g, with one rat serving as the blood donor.
was pressurized with a 95% O2-5% CO2 gas mixture. Reconstituted blood was passed through a 5-µm nylon mesh and the second rat as the kidney donor. Rats had free access to water and standard rat chow (Ralston-Purina, St. Louis, MO) prior to the experiments. Rats were anesthetized with pentobarbital sodium (50 mg/kg ip), and a cannula was inserted into the left carotid artery of the blood donor. Donor blood was collected into a heparinized (500 U) syringe via the carotid arterial cannula and centrifuged to separate the plasma and cellular fractions. Theuffy coat was removed and discarded. Plasma oncotic pressure was adjusted to 18 mmHg by the addition of bovine serum albumin (Sigma Chemical, St. Louis, MO). After sequential passage of the plasma through 5- and 0.22-µm filters (Gelman Sciences, Ann Arbor, MI), erythrocytes were added to achieve a hematocrit of 33%. This reconstituted blood was passed through a 5-µm nylon mesh and thereafter stirred continuously in a closed reservoir that was pressurized with a 95% O2-5% CO2 gas mixture.

The right kidney of the kidney donor was perfused through a cannula inserted into the superior mesenteric artery and advanced into the right renal artery. The perfusat was a Tyrode's solution (pH 7.4) containing 5.1% bovine serum albumin, and a mixture of L-amino acids as previously described (3). The kidney was excised and sectioned longitudinally, retaining the papilla intact with the perfused dorsal two-thirds of the organ. The papilla was reflected to expose the pelvic mucosa and tissue covering the inner cortical surface. Overlying tissue was removed to expose the tubules, glomeruli, and related vasculature of the juxtamedullary nephrons. The arterial supply of the exposed microvasculature was isolated by ligating the larger branches of the renal artery with fine suture (nylon black monofilament, 10-0; Vanguard Surgical System, Houston, TX).

After the dissection was completed, the Tyrode's perfusate was replaced with the reconstituted blood. Perfusion pressure was monitored by a pressure cannula centered in the tip of the perfusion cannula. RPP was regulated by adjusting the rate of gas inflow into the blood reservoir and initially set at 100 mmHg. The inner cortical surface of the kidney was continuously superfused with a warmed (37°C) Tyrode's solution containing 1% bovine serum albumin.

The tissue was transilluminated on the fixed stage of a Leitz Laborlux-12 microscope (Midland, Canada), equipped with a water-immersion objective (x40, Zeiss). Video images of the microvessels were transferred by a Newvicon camera (model NC-67M; Dage-MTI, Michigan City, IN) through an image enhancer (model MFJ-1452; MFJ Enterprises, Starkville, MS) to a video monitor (Conrac Display Systems, Covina, CA). The video signal was recorded on videotape for later analysis (Super VHS videocassette recorder; Panasonic, Secaucus, NJ). Afferent arteriolar inside diameter was measured at 12-s intervals using a calibrated digital image-sharpening monitor (Instrumentation for Physiology and Medicine, San Diego, CA). Measurement sites along the microvasculature were selected to achieve the maximum clarity of the vascular walls at a location as close to the glomerulus as possible. A 10-min equilibration period was allowed before the initiation of each experimental protocol. The initial and sustained vasoconstrictor responses to increases in perfusion pressure were assessed. The maximum afferent arteriolar vasoconstriction during the first minute and the average change in diameter during the second and third minute following the increases in RPP were utilized for statistical analyses of initial and sustained responses, respectively.

Experimental Protocols

Time control study of afferent arteriolar response to increases in RPP. Afferent arteriolar diameters were assessed during increases in RPP in a stepwise manner from 100 to 130 and 160 mmHg. This assessment was repeated three times to determine the reproducibility of afferent arteriolar responses to repeated increases in RPP and to determine the diameter recovery responses upon return of perfusion pressure to control levels.

Afferent arteriolar responses to increases in RPP during enhanced TGF activity. Afferent arteriolar autoregulatory responses were examined by increasing RPP in a stepwise manner from 100 to 130 and 160 mmHg. After restoration of RPP to 100 mmHg and recovery of afferent arteriolar diameter, 10 mM acetazolamide (Sigma Chemical) was added to the blood perfusate to increase distal nephron sodium and volume delivery. After a 5- to 10-min stabilization, the responses to increases in RPP during acetazolamide treatment were determined. Acetazolamide inhibits proximal tubular reabsorption and thus increases distal volume and sodium chloride/bicarbonate delivery (14, 18). We have previously demonstrated that this dose of acetazolamide leads to enhanced TGF constrictor signals, which decrease afferent arteriolar diameter (9, 10).

Effects of nNOS inhibition on afferent arteriolar responses to increases in RPP during enhanced TGF activity. The afferent arteriolar responses to increases in RPP from 100 to 130 and 160 mmHg were determined under control conditions, during superfusion of the selective nNOS inhibitor, L-SMTC (Alexis, San Diego, CA) alone and combined with acetazolamide treatment. After the control assessment of afferent arteriolar responses to increases in RPP, the superfusate was changed to one containing 10 µM L-SMTC. We have previously shown that 10 µM L-SMTC does not influence acetylcholine-induced vasodilation of juxtamedullary afferent or efferent arterioles, which can be blocked by nonspecific NOS inhibition (10). After a 5-min stabilization period, the afferent arteriolar responses to increases in RPP were determined during L-SMTC treatment. After restoration of RPP to control levels and recovery of afferent arteriolar diameter, acetazolamide was added to the blood perfusate to achieve a 10 mM concentration, and the afferent arteriolar responses to increases in RPP were again determined during superfusion of L-SMTC.

Effects of norepinephrine-induced vasoconstriction on afferent arteriolar responses to increases in RPP. To examine whether increased constrictor tone alone was responsible for the enhanced afferent arteriolar reactivity to increases in RPP, afferent arteriolar responses to increases in RPP from 100 to 130 and 160 mmHg were assessed before and during superfusion of 250 nM norepinephrine (Levophed bitartrate; Sanofi Winthrop Pharmaceuticals, New York, NY) which elicited similar degrees of vasoconstriction as L-SMTC plus acetazolamide treatment.

Effects of L-SMTC and acetazolamide treatment on afferent arteriolar responses to increases in RPP in papillectomized kidneys. The juxtamedullary nephrons give rise to long loops of Henle that extend into the papilla before looping back to the macula densa segment (4). As described previously (9, 10, 19, 22), acute papillectomy was performed after the initial 5-min control period to interrupt the flow of tubular fluid to the macula densa segment and thus minimize TGF-dependent vasoconstrictor influences on the afferent arteriole. After a 10-min stabilization period, the afferent arteriolar responses to increases in RPP from 100 to 130 and 160 mmHg were determined in papillectomized kidneys under control conditions, during L-SMTC treatment alone, and in combination with acetazolamide treatment.
Statistical Analysis

Analyses of changes in afferent arteriolar diameters with increases in RPP and treatments were performed using the one-way analysis of variance for repeated measures combined with Newman-Keuls post hoc test. Differences in afferent arteriolar responses to increases in RPP between treatment groups were determined using the two-way analysis of variance for repeated measures combined with Newman-Keuls post hoc test. A probability value of \( P < 0.05 \) was considered statistically significant. Data are presented as the means ± SE.

**RESULTS**

**Time Control Study of Afferent Arteriolar Responses to Increases in RPP**

Figure 1 illustrates the time course of the repeated afferent arteriolar responses to increases in RPP elicited in the absence of any other interventions. In this series, afferent arteriolar diameters were measured 89.5 ± 4.9 µm upstream from the glomerulus and averaged 23.1 ± 1.4 µm (n = 5). As illustrated in Fig. 2, initial and sustained values of the first vasoconstrictor responses to 130 mmHg averaged 15.2 ± 2.5% and 10.4 ± 1.9%, respectively, and were similar to those in the second (11.9 ± 2.5% and 7.5 ± 2.1%, respectively) and the third trials (16.0 ± 1.7% and 13.0 ± 0.6%, respectively). Initial and sustained values of the vasoconstrictor responses to 160 mmHg averaged 20.7 ± 1.6% and 17.5 ± 2.0%, respectively, and were not different from those in the second (22.3 ± 0.9% and 19.4 ± 1.9%, respectively) and the third trials (23.7 ± 1.4% and 20.1 ± 1.7%, respectively).

**Afferent Arteriolar Responses to Increases in RPP During Enhanced TGF Activity**

Figure 3 demonstrates the time course of afferent arteriolar responses to increases in RPP before and during addition of acetazolamide to the blood perfusate. In this series of experiments, afferent arteriolar diameters were measured at a site 78.6 ± 5.8 µm upstream from the glomerulus and averaged 21.1 ± 1.4 µm (n = 9). Addition of acetazolamide significantly decreased afferent arteriolar diameter to 19.4 ± 1.3 µm and enhanced the initial responses to increases in RPP but did not change the sustained responses.

As summarized in Fig. 4, the maximum decreases in afferent arteriolar diameters (initial responses) to 130 and 160 mmHg averaged 10.2 ± 0.3% and 14.8 ± 1.4%, respectively, under control conditions. In the presence of acetazolamide, the initial responses to 130 and 160 mmHg averaged 17.6 ± 2.4% and 25.5 ± 2.3%, respectively, and were significantly greater than the control responses. However, sustained changes in afferent arte-
riolar diameters to 130 and 160 mmHg averaged 8.9 ± 1.5% and 13.3 ± 1.3%, respectively, under control 
conditions. During addition of acetazolamide, the sus-
tained constrictor responses to 130 and 160 mmHg 
averaged 8.1 ± 1.4% and 14.3 ± 1.5%, respectively, and 
were similar to control responses.

Effects of nNOS Inhibition on Afferent Arteriolar 
Responses to Increases in RPP During Enhanced 
TGF Activity

Figure 5 depicts the time course of afferent arteriolar 
responses to increases in RPP under control conditions, 
during nNOS inhibition with 10 µM L-SMTC, and 
during combined treatment with L-SMTC and acetazol-
amide. In this series of experiments, afferent arteriolar 
diameters were measured at sites averaging 80.7 ± 3.8 
µm upstream from the glomerulus, and average control 
diameters were 20.3 ± 1.3 µm (n = 7). L-SMTC 
treatment significantly decreased afferent arteriolar 
diameter to 18.3 ± 1.1 µm and enhanced constrictor 
responses to increases in RPP. In the presence of 
L-SMTC, acetazolamide treatment further decreased 
afferent arteriolar diameters to 14.6 ± 0.9 µm and 
enhanced the afferent arteriolar constrictor responses 
to increases in RPP.

As demonstrated in Fig. 6, initial afferent arteriolar 
constrictor responses to 130 and 160 mmHg averaged 
13.5 ± 2.9% and 20.4 ± 3.3%, respectively, under 
control conditions. During superfusion with L-SMTC, 
the initial afferent arteriolar constrictor responses averaged 24.1 ± 4.4% and 34.4 ± 3.5%, respectively, and 
were significantly greater than control responses. Dur-
ing L-SMTC plus acetazolamide treatment, the initial 
afferent arteriolar constrictor responses averaged 36.8 ± 
5.2% and 56.4 ± 3.0%, respectively, and were signifi-

Fig. 5. Time course of afferent arteriolar responses to increases in 
RPP under control conditions, during superfusion with 10 µM 
S-methyl-l-thiocitrulline (L-SMTC), and during L-SMTC treatment 
combined with addition of 10 mM acetazolamide (ACZ) to the blood 
perfusate. Experiments were performed using 7 arterioles.

Fig. 6. Initial (A) and sustained (B) responses of pressure-induced 
afferent arteriolar constriction under control conditions (○), during 
superfusion of 10 µM L-SMTC (△), and during L-SMTC treatment 
combined with addition of 10 mM acetazolamide to the blood perfus-
ate (●). Data are presented as percent changes from the diameter at a 
RPP of 100 mmHg. *P < 0.05 vs. 100 mmHg. †P < 0.05 vs. control response. §P < 0.05 for L-SMTC vs. L-SMTC + acetazolamide.
cantly greater than the responses during L-SMTC treatment alone. Sustained afferent arteriolar constrictor responses to 130 and 160 mmHg averaged 9.1 ± 1.8% and 15.4 ± 2.8%, respectively, under control conditions. During superfusion of L-SMTC, the sustained afferent arteriolar constrictor responses averaged 17.9 ± 2.8% and 27.6 ± 2.9%, respectively, and were significantly greater than control responses. During L-SMTC plus acetazolamide treatment, the sustained values of afferent arteriolar constrictor responses averaged 27.6 ± 3.5% and 54.6 ± 2.7%, respectively, and were significantly greater than responses obtained during L-SMTC treatment alone.

Effects of Norepinephrine-Induced Vasoconstriction on Afferent Arteriolar Responses to Increases in RPP

As shown in Fig. 7, norepinephrine treatment (250 nM) significantly decreased afferent arteriolar diameter (measured at a site 81.7 ± 4.4 µm upstream from the glomerulus) from 20.4 ± 1.4 to 15.4 ± 1.2 µm (n = 6). The decrease in diameter in response to this dose of norepinephrine averaged 24.6 ± 2.1% and was not different from that caused by L-SMTC plus acetazolamide treatment (28.7 ± 1.1%). Figure 8 depicts that, in the presence of norepinephrine, the initial and sustained afferent arteriolar constrictor responses to 130 and 160 mmHg were similar to those observed under control conditions. Thus preconstriction with norepinephrine did not lead to an enhanced reactivity of the arterioles to increases in RPP.

Effects of L-SMTC and Acetazolamide Treatment on Afferent Arteriolar Responses to Increases in RPP in Papillectomized Kidneys

Figure 9 shows the time course of afferent arteriolar responses to increases in RPP under control conditions, during L-SMTC treatment alone, and during L-SMTC + acetazolamide treatment in papillectomized kidneys. In this series of experiments, afferent arteriolar diameters were measured at a site 81.3 ± 3.6 µm upstream from the glomerulus, and control diameters were 20.9 ± 0.9 µm (n = 6). In papillectomized kidneys, increases in RPP to 160 mmHg significantly decreased afferent arteriolar diameters by 15.9 ± 2.0% and 10.7 ± 0.7% at the initial and sustained periods, respectively. Although the initial constrictor responses were similar to those observed in papilla-intact kidneys (18.5 ± 1.3%, n = 27), the sustained responses were significantly lower compared with the papilla-intact kidneys (16.0 ± 1.2%). As demonstrated in Fig. 10, L-SMTC...
alone or l-SMTC plus acetazolamide treatment did not alter afferent arteriolar diameter and did not modulate initial or sustained afferent arteriolar responses to increases in RPP.

**DISCUSSION**

Impaired autoregulatory responses to alterations in RPP after interruption of the TGF mechanism have been observed at the levels of whole kidney (8, 13, 17), single nephron (20, 21), and individual afferent arterioles (16, 19, 22). However, there is less information regarding autoregulatory responses to alterations in RPP during increased activity of the TGF mechanism.

Impaired autoregulatory responses to alterations in RPP after interruption of the TGF mechanism have been observed at the levels of whole kidney (8, 13, 17), single nephron (20, 21), and individual afferent arterioles (16, 19, 22). However, there is less information regarding autoregulatory responses to alterations in RPP during increased activity of the TGF mechanism. Schnermann and Briggs (20) demonstrated that the autoregulation efficiency of glomerular pressure in response to alterations in RPP was enhanced by stimulation of the TGF mechanism by maintaining an increased flow through the loop of Henle, indicating an intimate modulatory interaction between the TGF mechanism and the other components responsible for autoregulation, such as the myogenic mechanism. However, there is less information regarding autoregulatory responses to alterations in RPP during increased activity of the TGF mechanism.

In our control studies, we observed biphasic afferent arteriolar constrictor responses to increases in RPP with an immediate vasoconstriction (initial response) that was followed by a modest waning (sustained response). During increased distal nephron delivery elicited pharmacologically by acetazolamide treatment, the initial responses to increases in RPP were enhanced, but the sustained responses were similar to those observed during control conditions, leading to much greater differences between the initial and sustained responses. The enhancement of the initial response by acetazolamide treatment was prevented in kidneys with interruption of distal nephron volume and sodium chloride delivery to the macula densa segment caused by transection of the loops of Henle. These results indicate that increased activity of the TGF mechanism enhances an early vasoconstrictor mechanism mediating the afferent arteriolar autoregulatory responses to increases in RPP. In addition, during selective nNOS inhibition with L-SMTC, acetazolamide treatment enhanced the sustained as well as the initial responses to increases in RPP, and neither enhancement was present in papillectomized kidneys. These results suggest that NO derived from nNOS contributes to the delayed counteracting vasodilator response that is part of the biphasic autoregulation-mediated changes in afferent arteriolar diameter occurring during increases in RPP, and that this effect is a TGF-dependent mechanism.

During nNOS inhibition with L-SMTC, both the initial and sustained afferent arteriolar constrictor responses to elevations in RPP were significantly greater than those observed under control conditions, but again the initial responses were only slightly greater than the sustained responses. These results indicate that, under normal conditions, basal activity of nNOS provides a vasodilator influence on both the initial and sustained afferent arteriolar autoregulatory responses to increases in RPP. During increased distal nephron volume and salt delivery, nNOS inhibition greatly enhanced the sustained, but not the initial, afferent arteriolar constriction in response to an increase in perfusion pressure. These results indicate that, during increased activity of the TGF mechanism, increased activity of nNOS appears to influence predominantly the sustained afferent arteriolar autoregulatory responses.

In papillectomized kidneys with interruption of the TGF mechanism, the sustained constrictor responses of afferent arterioles to increases in RPP were attenuated compared with those observed in control kidneys. However, the initial constrictor responses were similar to those observed in control kidneys. These results indicate that the TGF mechanism contributes primarily to the sustained afferent arteriolar autoregulatory responses during normal or subnormal distal nephron volume and sodium chloride delivery. During enhanced TGF activity caused by increased distal nephron volume and salt delivery, the TGF mechanism contributes more to the initial afferent arteriolar autoregulatory responses. These results suggest that the quantitative contributions of the TGF and myogenic mechanisms to the overall autoregulatory related changes in afferent arteriolar diameter differ depending on the distal nephron volume and salt delivery.

Consistent with previous studies (9, 10, 22), L-SMTC treatment alone and L-SMTC plus acetazolamide treat-
ment significantly decreased afferent arteriolar diameters, and papillectomy led to increases in afferent arteriolar diameters. Therefore, the resting vascular wall tension may constitute an important determinant of the magnitude of afferent arteriolar autoregulatory responses to increases in RPP. However, norepinephrine treatment, which constricted afferent arterioles to the same degree as L-SMTC plus acetazolamide treatment, did not enhance the initial or sustained afferent arteriolar constrictor responses to increases in RPP.

The role of NO in modulating afferent arteriolar responses to alterations in perfusion pressure has remained uncertain. In isolated and microperfused rabbit afferent arterioles (12) and in juxtamedullary afferent arterioles of in vivo hydronephrotic kidneys (7), nonselective NOS inhibition enhanced the afferent arteriolar constrictor response to alterations in perfusion pressure. In contrast, in vivo studies demonstrated that renal blood flow autoregulation is well preserved during nonselective NOS inhibition, although basal blood flow is decreased (1, 2, 15). In addition, in the artificial fluid-perfused juxtamedullary nephron preparations (11) and hydronephrotic kidneys (6), nonselective NOS inhibition did not alter the afferent arteriolar constrictor responses to increases in RPP. In the present study, we demonstrated that selective nNOS inhibition significantly enhances the initial and sustained afferent arteriolar constrictor responses to alterations in RPP in the blood-perfused juxtamedullary nephrons. Importantly, nNOS-derived NO contributes to the modulation of afferent arteriolar responses to changes in RPP only when the TGF mechanism is intact or has increased activity.

In conclusion, in afferent arterioles of juxtamedullary nephrons, nNOS contributes to the counteracting resetting resetting process of the biphasic afferent arteriolar constrictor responses to increases in RPP, but only when the intensity of the TGF mechanism is maintained and distal tubular flow is preserved. This nNOS-dependent modulation also partially compensates the enhanced constrictor responses to increases in RPP during increased TGF activity caused by increased distal tubular flow, contributing to a complex but balanced regulation of afferent arteriolar resistance.

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