Relevance of the Tubuloglomerular Feedback Mechanism in Pathophysiology

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ABSTRACT
The balance between a high filtration rate and high reabsorption rate in the kidney is critical in the maintenance of extracellular fluid volume. One of the mechanisms that maintain this balance is the tubuloglomerular feedback (TGF) mechanism, which operates at the level of the macula densa assessing the load and/or solute concentration coming out of the loop of Henle and controlling this load by adjusting the GFR. This review discusses the potential role of the TGF system with respect to volume homeostasis in various conditions where GFR is maintained, decreased, or increased. In most of the states discussed, the TGF system seems to act appropriately regarding volume control; however, trade-off effects occasionally occur. After acetazolamide administration, during extracellular fluid volume contraction or expansion or acute hyperkalemia, the TGF mechanism responds appropriately with regard to volume balance. After a large reduction of renal mass, the system adjusts to function at a higher level of GFR and distal delivery. In chloride-depletion metabolic alkalosis, glomerulonephritis, diabetes mellitus, and acute renal failure, the adaptation of the TGF system appears to be appropriate with regard to volume control; however, it may lead to trade-off effects, such as maintenance of metabolic alkalosis, glomerular hypertension and sclerosis, or depression of GFR, respectively. Because the TGF mechanism often contributes to compensatory adjustments to or development of disease, it can be appreciated that any in-depth evaluation of the mechanisms responsible for various pathophysiological conditions should include an assessment of the potential role of the TGF mechanism.

Key Words: Renal hemodynamics, tubular reabsorption, autoregulation, hypertension, angiotensin II

The fact that our kidneys have a GFR of 150 to 180 L/day makes us vulnerable to volume depletion and highly dependent on maintaining an equally high tubular reabsorption rate. To achieve homeostatic regulation of extracellular fluid volume (ECFV) and composition, multiple mechanisms maintain a dynamic equilibrium between the filtered load and the reabsorption rate. Some of these mechanisms regulate the glomerular capillary pressure and the plasma flow traversing each glomerulus. By controlling the smooth muscle tone of the renal microvasculature and the glomerular ultrafiltration coefficient, regulation of the GFR can be effected. Homeostatic balance is achieved via mechanisms that maintain the physically determined filtered load at a level appropriate for the metabolically determined reabsorptive capacity of the tubules. The importance of this balance can be appreciated from the simple realization that a disparity of even 5% between filtered load and the reabsorption rate would lead to a net loss of about one third of the total ECFV in 1 day. Obviously, this situation would inevitably lead to vascular collapse.

Several dynamic systems, responding to various stimuli, continuously adjust the filtered load and the rate of tubular reabsorption. In general, adjustments in filtered load occur rapidly, whereas adjustments of tubular transport processes require longer periods of time. In particular, alterations in the cardiovascular system resulting in fluctuations of renal perfusion pressure are quickly compensated for by intrarenal microcirculatory mechanisms that adjust the physical forces governing the GFR. In this review, we will focus on one specific mechanism operating at the single-nephron level. This mechanism depends on signals from the macula densa, which serves the critical function of assessing the load coming out of the ascending loop of Henle into the distal nephron and controlling this load by adjusting the GFR. Indeed, as early as 1957, the Hungarian physiologist László Harsing and his colleagues discussed the vital importance of such a "tubuloglomerular equilibrium"
in regulating distal tubular load during conditions of either osmotically or pharmacologically induced decreases in tubular reabsorption (1,2). On the basis of earlier morphologic observations of Goormaghtigh and others (3-5), it was suggested that along with changes in filling of the distal tubule, "impulses coming from the macula densa play a role in regulation of renal blood flow and glomerular filtration rate." The last three decades have provided unequivocal evidence for the existence of this mechanism, which is now referred to as the tubuloglomerular feedback (TGF) mechanism, and its important role in the normal regulation of GFR and its contribution to sodium homeostasis (6-12).

Numerous studies have been oriented toward the elucidation of the nature of the basic components of this complex system and on the involvement of the TGF mechanism in the induction, maintenance, and/or prevention of pathophysiologic derangements. Although the TGF mechanism has been demonstrated in isolated human kidneys (12), the nature of the phenomenon hinders specific direct studies on the involvement of TGF in human pathophysiology, and as a consequence, TGF-dependent mechanisms have rarely been incorporated into clinical thinking. The perspective of this review, therefore, is to provide a greater appreciation of the clinical relevance of this mechanism by considering how the TGF mechanism participates in pathophysiologic conditions that involve disruption of the forces responsible for glomerular filtration and/or normal tubular reabsorptive function.

DESCRIPTION OF THE SYSTEM

The tight anatomical relationship between the macula densa region of the thick ascending limb of the loop of Henle, the extraglomerular mesangium, the afferent arteriole, and the glomerulus provides the structural foundation for the TGF mechanism (3,5). Under normal conditions, an increase in glomerular filtration results in a net increase in late proximal fluid flow (13). As a consequence of the increased flow into the loop of Henle, early distal chloride concentration (12,14), sodium concentration (15), and osmolality (14) rise. These changes serve as the basis for altered signals to the macula densa cells, which then modify the rate of release of a mediator substance (16) that vasoconstricts the afferent arteriole, decreases glomerular filtration, and restores macula densa flow. Thus, the TGF mechanism, as illustrated in Figure 1, is a classic negative feedback system (9,17). The luminal signal reaching at the macula densa, considered to be the controlled variable, is sensed by the macula densa cells (sensing step). The macula densa transforms this luminal signal and initiates a sequence of cellular events (transmission pathway) that leads to the communi-

Figure 1. Block diagram of the components of the TGF system. Macula densa delivery is controlled by alterations in SNGFR and by glomerulotubular balance, which couples filtered load and proximal tubular reabsorption. The ascending loop of Henle functions to transform changes in tubular flow to changes in the NaCl concentration and in the osmolality of the emerging fluid. These changes in solute concentration serve as a signal to the macula densa cells, which then transmit vasoconstrictor signals to the afferent arteriole.

cation of signals to the afferent arteriole (effector limb). Serially included in the system is glomerulotubular balance, a feed-forward system coupling filtered load to reabsorption rate in an almost linear fashion (13), which also regulates distal delivery (9,18). It should be emphasized that glomerulotubular balance dampens, but does not eliminate, the effect of changes in filtered load on distal delivery. In essence, any disturbance to either GFR or the rate of tubular reabsorption causes changes in macula densa delivery, which in turn, lead to inverse alterations in glomerular filtration and restoration of distal flow.

The exact nature of the signal or signals sensed by the macula densa remains uncertain. Because the intraluminal application of furosemide abolishes the TGF-mediated reduction in single-nephron GFR (SNGFR), the Na⁺, 2 Cl⁻, K⁺-cotransporter has been proposed to be essential for the sensing step (19-21). Some experiments have suggested that tubular fluid chloride concentration or some element linked to transport rate is an important part of the signal (12). However, evidence based on orthograde and retrograde microperfusion experiments indicates that TGF-mediated changes in glomerular function also occur when tubular fluid sodium or chloride concentration is maintained at very low levels. These and other studies have led to the hypothesis that total tubular fluid solute concentration, rather than chloride or sodium concentrations alone, serves as the luminal signal for the initiation of TGF vascular responses (14,16,22). This specific issue becomes relevant when considering certain pathophysiologic states such as metabolic alkalosis. There are also data that suggest the presence of luminal receptors
for other agents that may also activate TGF responses (23-25). The actual mediator that transmits TGF signals from the macula densa cells to the preglomerular microvasculature also remains unclear. Some studies have suggested that purines such as adenosine or ATP may be involved in TGF transmission (25-28). Other candidates include thromboxane or other lipooxygenase or cyclooxygenase metabolites of arachidonic acid (20,23). These complex issues remain uncertain and have been discussed in considerable detail in other reviews (12,16,29). Distinct from the actual mediating pathway, a variety of factors and conditions can modulate the responsiveness of the TGF mechanism. Angiotensin II (ANG II) (6,8,30-34), atrial natriuretic peptide (ANP) (35,36), prostaglandins (20,23,37), and nitric oxide (38) can modulate the operational characteristics of the TGF response. Finally, several studies have indicated that the actual vasoconstriction of the afferent arterioles involves a calcium entry step that can be blocked by calcium channel blockers (39-41).

ASSESSMENT OF THE TGF SYSTEM

The TGF system has been assessed primarily by the use of in utero micropuncture techniques in rats. To estimate the changes in signals arriving at the macula densa, fluid can be collected from early superficial distal tubules and its volume and composition can then be analyzed. Collected tubular fluid can also be used to determine the SNGFR, and when collected from distal tubule segments, the flow to the macula densa is maintained. As a consequence, SNGFR based on distal collections reflects the SNGFR under the regulatory influence of the TGF mechanism. Inactivation of the TGF mechanism can be achieved by inserting an oil or a wax block into a proximal tubular segment and thus preventing flow into the loop of Henle. SNGFR determined from the tubular fluid collected upstream of the block reflects the SNGFR in the absence of flow to the macula densa. This SNGFR, determined from proximal fluid collections, is higher than the normal SNGFR and represents the condition in which the vasoconstrictor influence from the macula densa system on the afferent arteriole is minimal (Figure 2). Thus, one index of TGF activity is the difference between the SNGFR occurring during the normal vasoconstrictive influence of the TGF mechanism (the distally determined SNGFR) and the SNGFR that is unaffected by the vasoconstrictor influence of the TGF mechanism (the proximally determined SNGFR) (6,12,29). The operating point couples spontaneous tubular flow and SNGFR. Alterations that increase or decrease the activity of the TGF mechanism will change the operating point along the TGF function curve.

To assess the responsiveness of the system, that is, the relationship between macula densa delivery (distal delivery) and SNGFR over the full range in which the TGF mechanism can operate, gradual changes in distal delivery and activation of the TGF system can be achieved by microperfusion of the loop of Henle or by perturbation of normal tubular flow (Figure 3). In the case of microperfusion, tubular fluid flow to the macula densa is interrupted by the insertion of either an oil or a wax block into an early proximal tubular segment. Subsequently, the late proximal tubule is perfused with either artificial tubular fluid or previously collected native tubular fluid. Changes in SNGFR, determined from tubular fluid collections proximal to the block, are measured in response to step increases in late proximal perfusion rate, usually in the range of 0 to 40 nL/min in the rat. Under such open-loop conditions, the responses in SNGFR to step changes in late proximal perfusion rate result in a sigmoidal relationship, as shown in Figure 3. An alternative way to determine this relationship is to modulate normal proximal tu-

Figure 2. Illustration of one method frequently used to assess TGF activity. First, tubular fluid collections are obtained from an early distal tubule (left). Tubular fluid flow to the macula densa is maintained, and the TGF mechanism will maintain its vasoconstrictive influence on the preglomerular vasculature. To collect tubular fluid from a late proximal tubule segment (right), an oil block is inserted into the proximal tubule and, thus, flow into the loop of Henle is interrupted. At zero flow to the macula densa, the TGF mechanism has minimal vasoconstrictor effect on the afferent arteriole. The SNGFR determined from this proximal tubular collection will thus exceed the SNGFR obtained from the early distal collection. The difference between the proximally and distally determined SNGFR provides a measure of the activity of the TGF mechanism (6,50).

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Figure 3. TGF responsiveness can be assessed by evaluating SNGFR, Poc, or SFP responses to increases in late proximal perfusion rate. In the resulting sigmoidal relationship, several characteristics defining the TGF function curve can be identified. The threshold (A) is defined as the minimum flow rate that results in a significant decrease in the measured parameter. The flow rate resulting in a half-maximal response is denoted as the turning point (B), and the slope of the curve at the turning point is referred to as sensitivity (C). The maximum response (D) is also used to assess TGF responsiveness.

Bovine fluid flow by the removal or addition of natural tubular fluid, while simultaneously determining SNGFR from early distal tubular fluid collections (42). Alterations in proximal tubular flow in response to perturbations in distal delivery have also been assessed by videometric techniques (43). By these closed-loop approaches, TGF responsiveness can be assessed while the normal feedback loop is left intact.

In the Munich-Wistar strain of rats, which has some glomeruli on the surface of the kidney, glomerular capillary pressure (Poc) can be measured directly by means of a micropipette attached to a servo-null micropressure system. Because Poc is one of the primary determinants of SNGFR, direct measurement of Poc during conditions of normal filtration and reabsorption and during conditions of zero flow to the macula densa allows the assessment of TGF activity. Furthermore, TGF responsiveness can be assessed by measuring Poc during alterations of the flow into the loop of Henle or during modulation of normal proximal tubular flow as mentioned above (44). In most strains of rats, however, superficial glomeruli are not usually found, and thus, indirect methods for assessing glomerular pressure are used. To obtain an index of Poc, the intratubular pressure upstream of the wax block can be used and this pressure is denoted as stop flow pressure (SFP). SFP responses to changes in late proximal microperfusion rate generally follow a response similar to that observed for SNGFR (6, 11, 34, 44, 45). In a few cases, it has been reported that TGF-mediated changes in SNGFR occurred in the absence of changes in SFP or Poc (46).

Several features can be recognized in the sigmoidal relationship between either SNGFR, Poc, or SFP and late proximal perfusion rate (Figure 3) (11). If late proximal perfusion rate is gradually increased from zero, the threshold is defined as the perfusion rate that results in a significant decrease in the measured parameter (A in Figure 3). The perfusion rate causing a half-maximal response is referred to as the turning point (B in Figure 3). The maximum sensitivity is the slope of the relationship at the turning point. Changes in one of these characteristics reflect an overall change in the responsiveness of the TGF system. The maximum response is also frequently used as an index of the overall magnitude of the TGF response. A change in TGF responsiveness implies that there has been a shift in the relationship between distal tubular flow and SNGFR. Furthermore, the attenuation of TGF responsiveness means that, for the same distal flow, the TGF-mediated depression of SNGFR is reduced.

Extrapolation of the knowledge about the TGF mechanism to human pathophysiology has been impeded by the lack of techniques that give reliable information in segmental reabsorption in humans. Despite the limitations of lithium clearance (47), free water clearance, and other techniques that estimate proximal reabsorption rate, these approaches are the only means available to provide indications on reabsorption up to the macula densa in humans. The only parameter that can be monitored directly in humans is GFR. Data on segmental reabsorption during pathophysiologic states and pharmacologic interventions in animals, together with data on GFR and segmental reabsorption obtained by indirect methods in humans, may help to delineate the role of TGF in clinical settings. Further aspects of this review will focus on the possible role of the TGF mechanism in circumstances where GFR is maintained in spite of the pathophysiologic condition and in states where GFR is either decreased or increased as a result of pathophysiologic conditions.

ROLE OF TGF IN REGULATION OF FILTERED LOAD AND CONTRIBUTION TO SODIUM HOMEOSTASIS

Under normal conditions, a change in delivery to the macula densa will be corrected by a compensatory change in GFR mediated by the TGF system. As mentioned above, this rapid feedback maintains distal delivery even during acute external perturbations
such as changes in arterial perfusion pressure. That is, a decrease in filtered load with a subsequent decrease in the signal arriving at the macula densa will lead to a TGF-mediated afferent arteriolar vasodilation and an increase in GFR (Figure 4A, arrow 1), which restores distal delivery. The potency of the TGF mechanism to correct increases in distal delivery with alterations in SNGFR is well illustrated by the administration of carbonic anhydrase inhibitors, such as acetazolamide. The administration of carbonic anhydrase inhibitors is associated with a decrease in proximal tubular reabsorption and depression of GFR (48–50). The decrease in GFR has been attributed to two different mechanisms. One could be physical and not related to TGF in that proximal tubular pressure increases, which reduces net effective filtration pressure (51). The TGF-related mechanism is due to reduced proximal bicarbonate and fluid reabsorption, which leads to an increased delivery of a bicarbonate-rich tubular fluid out of the proximal tubule. This increase in distal solute and electrolyte delivery activates the TGF mechanism, which causes afferent arteriolar vasoconstriction and a fall in SNGFR. Therefore, as a consequence of the normal operation of the TGF mechanism, the diuretic action of acetazolamide is limited (Figure 4B, arrow 1). Thus, it should be recognized that diuretics that exert a substantial action on the proximal tubule may elicit self-limiting responses because of compensatory decreases in GFR mediated by the TGF mechanism, unless the diuretic drug directly influences the renal microvasculature or the TGF mechanism. The latter is the case with the potent diuretic drug furosemide, which decreases reabsorption proximal to the macula densa but, in contrast to acetazolamide, concomitantly reduces TGF responsiveness. Although furosemide causes large increases in distal delivery (19,50,52) due to inhibition of the Na+, 2 Cl−, K⁺-cotransporter in the loop of Henle (53), a TGF-mediated depression of GFR generally does not occur. This has been attributed to concomitant desensitization of the macula densa sensing step, for which the Na+, 2 Cl−, K⁺-cotransporter has been shown to be essential (19–21). Interference with the TGF sensing step decreases TGF responsiveness, so that high distal delivery can occur without the expected decrease in GFR (Figure 4C, arrow 2).

Under several conditions, the TGF system allows alterations in distal delivery, without eliciting compensatory corrections in SNGFR. This requires a shift in the relationship between distal delivery and SNGFR, as the result of some modulatory influence on the TGF mechanism. Such adjustments of TGF responsiveness occur in close association with changes in other mechanisms that control ECFV. With ECFV depletion, proximal tubular reabsorption is enhanced, resulting in lower distal delivery. The intrinsic response of the TGF mechanism would be to decrease its activity, so that SNGFR would increase (Figure 4A, arrow 1) and distal delivery would be restored. However, during ECFV contraction, TGF responsiveness is increased (Figure 4C, arrow 1), so

![Figure 4. Composite figure illustrating the mechanisms by which the TGF mechanism influences SNGFR. Increases in SNGFR (A) can be elicited by both a decrease in distal delivery (arrow 1) and a decrease in TGF responsiveness (arrow 2). Panel B shows the possible mechanisms of the TGF-mediated depression of SNGFR, which can be due to increases in end proximal fluid flow (arrow 1) or an increase in TGF responsiveness (arrow 2). SNGFR can be maintained (C) during a decrease in end proximal fluid flow if accompanied by an increase in TGF responsiveness (arrow 1). Conversely, SNGFR can be held constant if end proximal fluid flow increases but TGF responsiveness is attenuated (arrow 2). A complete shift of the TGF function curve can occur (D), so that it can operate at higher flow rates without losing control over SNGFR.](image-url)
that GFR remains stable, despite a low distal delivery. Several studies now indicate that the increased intrarenal ANG II levels that occur during hypovolemia contribute to an increase in proximal tubular reabsorption (54–57) and concomitantly increase TGF responsiveness (34,45). The enhancement of TGF responsiveness by ANG II, which is distinct from direct vasoconstrictor effects, has been convincingly demonstrated by the systemic (45) and peritubular capillary infusion of ANG II (34). Consistent with these observations, angiotensin-converting enzyme (ACE) inhibitors (30,31) and ANG II receptor antagonists (30,32,33) decrease TGF responsiveness. These synergistic actions of ANG II on proximal reabsorption and TGF responsiveness lead to a situation where GFR remains constant despite a decrease in the signal to the macula densa (Figure 4C, arrow 1) (8,33). The systemic delivery of ANG II can account for the renal effects of ANG II, all of the components of the renin-angiotensin system are locally available (6). The infusion of ANG I solutions into the peritubular capillaries exerts effects similar to those of ANG II (34,54) indicating that the de novo formation of ANG II occurs in the interstitial environment. Thus, intrarenal ANG II, formed independently of the systemic activity of the renin-angiotensin system, may exert important regulatory influences over proximal tubular reabsorption and TGF responsiveness (8,33,34,54).

In contrast to volume depletion, extracellular volume expansion has been shown to depress proximal reabsorption and lead to increased distal delivery (58,59). Normal operation of the TGF mechanism under these conditions would lead to a depression of GFR (Figure 4B, arrow 1), so that distal delivery would be restored. With modest volume expansion that does not elicit marked reductions in the proximal tubular reabsorption rate, the TGF mechanism may not be altered. However, with greater ECFV expansion, the TGF mechanism is reset to allow a high distal delivery and GFR remains stable despite this increased distal delivery. This is accomplished by a decrease in the responsiveness of TGF (Figure 4C, arrow 2). In experimental studies with deoxycorticosterone acetate-induced expansion (58,60–62) and other volume expansion models (45,62,63), the attenuation of TGF responsiveness has indeed been demonstrated. It is well recognized that ECFV expansion leads to suppression of the renin-angiotensin system, and thus, it is likely that the reduced ANG II levels (30,31,45) are responsible for the attenuation of TGF responsiveness. In support of this notion is the observation that during acute volume expansion, the systemic infusion of ANG II restored plasma ANG II concentrations to levels observed in hydropenic animals and restored TGF responsiveness (45). Besides a depression of the activity of the renin-angiotensin system, ECFV expansion causes elevation of ANP levels (64). Although the natriuretic effects of ANP have been primarily localized to the medullary collecting duct (65), proximal reabsorption has also been shown to be directly or indirectly inhibited (66–68). Furthermore, ANP has been shown to attenuate TGF responsiveness (35,36), so that ANP can functionally antagonize ANG II. Consequently, the attenuation of TGF responsiveness by the conditions of ECFV expansion is likely mediated by the combined effects of the reduction in ANG II levels and the elevation of plasma ANP levels.

In cases of ECFV depletion and expansion, appropriate changes in TGF activity and responsiveness allow sustained changes in distal delivery and thereby contribute to the restoration of normal ECFV. However, conditions arise in which TGF responsiveness is inappropriately adjusted, so that pathophysiologic disturbances are maintained or develop. The subsequent sections will analyze the pathophysiologic role of the TGF mechanism in reversing pathophysiologic conditions or the contribution of the TGF mechanism to the maintenance or induction of pathophysiologic states by inappropriate activation and shifts in responsiveness. These aspects are also summarized in Table 1.

THE ROLE OF TGF IN MAINTAINING NORMOFILTRATION

This section considers two examples in which the TGF mechanism allows distal nephron volume and solute delivery to change while GFR is maintained within the normal range. In the condition of acute hyperkalemia, GFR is maintained despite increased distal delivery. This is probably due to the depression of TGF responsiveness, which seems to be homeostatically appropriate, because an increase in distal delivery facilitates distal potassium secretion. In contrast, during the development of hypertension in the two-kidney, one-clip (2K1C) Goldblatt model, GFR in the contralateral kidney is maintained despite a decreased distal delivery. In this case, both proximal tubular reabsorption and TGF responsiveness are enhanced as a result of the synergistic actions of ANG II (7,8,33).

Hyperkalemia and TGF Responsiveness

Acute potassium loading has been associated with decreased volume and electrolyte reabsorption by nephron segments proximal to the macula densa (69–71). Although this increases distal volume and solute delivery, the predicted decrease in GFR due to activation of the TGF system does not occur and GFR is maintained or increased during acute hyperkalemia (70,72–74). These observations during hyperkalemia...
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→ increased salt and volume excretion
→ preservation of ECFV
→ preservation of ECFV
→ facilitate volume excretion
→ promote potassium excretion
→ preservation of ECFV
→ not contributing to correction of CDMA
→ partially counteract impaired glomerular function
→ help to maintain control over SNGFR
→ elevated $P_{oc}$ may contribute to further glomerular damage
→ ECFV preservation
→ appropriate to maintain ECFV control
→ may contribute to glomerular damage
→ appropriate to maintain ECFV control
→ may contribute to glomerular damage
suggest a situation of diminished TGF responsiveness, which allows the maintenance of an increased distal delivery (Figure 4C, arrow 2). Because increases in distal sodium and volume delivery have been demonstrated to promote distal potassium secretion (75,76), the depression of TGF responsiveness would contribute to the restoration of normokalemia. Indirect support for this hypothesis has been provided by studies that have demonstrated the diminished autoregulatory capability of the kidney during acute potassium loading (77). Those authors suggested that potassium might affect the macula densa or the renal microvasculature. Hyperkalemia has been reported to hyperpolarize the smooth muscle cell membrane (78) and increase the activity of Na+, K+-ATPase (79). Both effects can result in a decrease of intracellular Ca2+ (78) and thus vasoconstriction. Furthermore, acute potassium loading may suppress the activity of the renin-angiotensin system (80,81), which would be predicted to reduce intrarenal ANG II levels. A decrease in the activity of the renin-angiotensin system during hyperkalemia would diminish TGF responsiveness and complement the direct vasoconstrictive properties of physiologic hyperkalemia. However, the influence of acute physiologic increases in plasma potassium concentration on TGF responsiveness has not been assessed and was evaluated in recent experiments in our laboratory (82). We observed that acute infusions of different potassium salts increased plasma potassium concentration by 0.7 to 1.6 mmol/L and resulted in an attenuation of TGF responsiveness, as assessed by SFP responses to step increases in late proximal perfusion rate. This attenuation was not due to time-dependent effects or to the concomitant osmotic load, because no attenuation of TGF responsiveness was observed in a time-control group or in a group of rats that received an equimolar NaCl load. Although the specific mechanisms whereby hyperkalemia results in the attenuation of TGF responsiveness remain unclear, the fact that it occurs emphasizes the potential role of TGF in regulating distal delivery and, indirectly, electrolyte handling by the distal nephron.

Hypertension and ANG II Blockers

In hypertension, the kidneys fail to respond to the elevated arterial pressure with a pressure natriuresis sufficient to correct hypertension. Because both glomerulotubular balance and the TGF mechanism allow this condition to persist, both must be reset in a synergistic fashion. This section considers the TGF mechanism in two-kidney one-clip Goldblatt hypertension and in essential hypertension. During the development of hypertension in the 2K1C model, the nonclipped kidney is exposed to high ANG II levels (83-85), which enhance proximal tubular reabsorption and thus reset glomerulotubular balance to a higher level. Although this will lead to a decrease in distal delivery, a TGF-mediated increase in GFR does not occur, because ANG II also increases TGF responsiveness (34), which allows GFR to be maintained at a lower distal delivery. Because of these synergistic actions of ANG II on proximal reabsorption and TGF responsiveness, there are sustained decreases in distal delivery, as depicted in Figure 4C, arrow 1. As a consequence, volume is retained until the elevated blood pressure, together with humoral factors such as ANP, restores glomerulotubular balance and distal delivery to approximately normal levels. Thus, elevated plasma (83,84) and kidney ANG II levels (85) are essential for the initiation and maintenance of hypertension in this model. The administration of ACE inhibitors and ANG II receptor antagonists has been shown to prevent the hypertension (86) and to normalize arterial pressure during established hypertension (31.87-91). Acute ACE inhibitor administration has also been shown to increase GFR and RBF and enhance the sodium excretion of the nonclipped kidney (31,87,88). Furthermore, proximal tubular transport in the nonclipped kidney has been demonstrated to be highly ANG II dependent (89). TGF responsiveness is present during the developmental phase (91) and the maintenance phase of hypertension (31) and is strongly dependent on the presence of ANG II (31,91). After ACE inhibition or ANG II receptor blockade, proximal tubular reabsorption is decreased and TGF responsiveness is diminished (Figure 4C, arrow 2), thereby leading to a state of enhanced distal delivery and sodium excretion (31.33).

The ANG II dependency of arterial pressure in essential hypertension can be appreciated from studies in the spontaneously hypertensive rat, which demonstrate (1) that during the initial phase of the development of hypertension, renin release, PRA, and the sensitivity of the renal vasculature to ANG II are increased (92-94) and (2) that ACE inhibitor administration can prevent the development of hypertension (95). Furthermore, TGF responsiveness has been demonstrated to be enhanced in both the development (96.97) and the maintenance phases of hypertension (96-98). Spontaneously hypertensive rats respond to the administration of ACE inhibitors with an increase in GFR and RBF (92,94). Similar effectiveness of ACE inhibitors in the treatment of essential hypertension in humans further supports a role for the renin-angiotensin system in mediating the altered renal excretory function in essential hypertension.

TGF IN STATES WITH REDUCED GFR

As explained above, both an increase in the macula densa signal (Figure 4B, arrow 1) and an enhance-
ment of TGF responsiveness (Figure 4B, arrow 2) can contribute to a TGF-mediated decrease in GFR. In this section, attention will be focused on the role of the TGF mechanism in three states associated with hypofiltration: chloride depletion metabolic alkalosis (CDMA), glomerulonephritis, and acute renal failure. The involvement of the TGF mechanism in the three states of hypofiltration prevents the organism from further deterioration, but it does not invariably restore a physiologic condition.

The Role of TGF in Metabolic Alkalosis

A depression of GFR has been observed during experimental CDMA in both rats (99,100) and humans (101). Several studies have been undertaken to clarify the pathogenesis of this reduced GFR and to delineate its role in maintaining CDMA. The restoration of GFR by volume expansion with solutions that do not contain chloride does not correct the CDMA (100,102). Furthermore, in DOCA volume expansion, metabolic alkalosis is maintained despite a normal GFR. Studies in humans and animals have shown that the alkalosis can be corrected by chloride repletion, even though volume depletion and reduced GFR are still present (100,101). It is thus considered unlikely that the depression of GFR is essential in maintaining CDMA. Concerning the mechanism leading to the reduced GFR, both an increase in TGF responsiveness (Figure 4B, arrow 2) and an activation of the TGF system (Figure 4B, arrow 1) (99,100) should be considered. Although an increase in TGF responsiveness could be related to the concomitant volume depletion, a reduced GFR could also be demonstrated in alkalotic animals with a normal plasma volume (99). Furthermore, TGF responsiveness, as determined by SFP responses to loop perfusion with artificial tubular fluid, was not perceptibly different in alkalotic animals (99). Thus, an increase in TGF responsiveness related to hypovolemia or the alkalosis seems an unlikely cause of the reduced GFR in CDMA. In contrast, an analysis of early distal tubular fluid composition in normovolemic rats with CDMA and decreased SNGFR demonstrated a nearly twofold increase in tubular fluid osmolality (99), which presumably resulted from the elevated bicarbonate load to the distal nephron, because chloride concentration was actually decreased. In these rats, the proximally derived SNGFR was not different from normal, but the distally derived SNGFR was greatly reduced, indicating that TGF activity was increased.

Collectively, these data suggest that the reduction in GFR in CDMA is due to activation of the TGF mechanism, which occurs as a consequence of the increased tubular fluid solute load. Thus, it appears that in CDMA, the TGF mechanism responds in a homeostatically appropriate manner to prevent a large solute delivery (which in this case consists of bicarbonate) that would saturate the transport mechanisms in the distal nephron and cause even greater fluid and electrolyte loss and subsequently lead to further volume depletion. The condition of CDMA involves coinciding derangements of volume and acid/base balance. Under these circumstances, the kidneys have to choose between the correction of acid/base balance by allowing increased bicarbonate excretion and the preservation of ECFV status by retaining all available electrolytes. Apparently, the TGF mechanism protects the ECFV status and prevents further volume depletion, even if this means maintaining the state of CDMA.

Glomerular Damage by Glomerulonephritis

Most of the information on the renal hemodynamic consequences of immunologic glomerular damage has been obtained from models applying heterologous antiglomerular basement membrane (GBM) antibody and Heymann's nephritis, which uses anti-Fx1A antibodies (103). Whereas the anti-GBM model leads to the development of a similar pattern of glomerular lesions, as described in human glomerular proliferative disease, lesions in Heyman's nephritis resemble those of human membranous nephropathy (103). Despite this morphologic difference, characterization of the renal hemodynamic responses to glomerular injury in these two models has revealed striking similarities. In both the heterologous and autologous phases of anti-GBM antibody nephritis, the glomerular filtration coefficient (Kf) has been shown to be reduced, whereas Poc is consistently increased (104,105). Similar changes have been observed in the anti-Fx1A model 4 months after the induction of the disease, again showing a decreased Kf, increased Poc, and maintenance of SNGFR (106).

These studies suggest that the increase in Poc in glomerulonephritis offsets the decrease in Kf and minimizes the decrease in GFR. The increase in Poc could be mediated by the TGF mechanism in response to a decrease in distal delivery (Figure 4A, arrow 1) or result from a decrease in TGF responsiveness (Figure 4A, arrow 2). A decrease in distal delivery can be anticipated after the reduction of SNGFR caused by the impairment of the glomerular permeability, if glomerulotubular balance is maintained, as has indeed been reported by several investigators (106-108). Under such conditions, the TGF mechanism will restore distal delivery by increasing Poc (Figure 4A, arrow 1). However, as a result of this response, the TGF mechanism uses most of its reserve and the operating point of the system becomes shifted to the insensitive part of the TGF function curve. A decrease in TGF responsiveness could also mediate an increase in Poc (Figure 4A, arrow 2);
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however, this will also lead to impaired control by the TGF mechanism over renal function. ECFV expansion in glomerulonephritis is generally thought to result from an impairment of sodium excretion (107–109). Because of this increase in ECFV, diminished TGF responsiveness was suspected. However, a comparison of unilateral anti-GBM nephritis without alterations in ECFV and bilateral anti-GBM nephritis with concomitant volume expansion revealed similar increases in Poc (108). The functional relationship between late proximal flow and SFP (108) and SNGFR (110) has been demonstrated to be normal, so that decreased TGF responsiveness does not seem to mediate the increase in Poc (108,110).

Interestingly, neither of the two described mechanisms seems to be completely responsible for the increase in Poc. SFP has been demonstrated to be elevated in the absence of distal delivery, suggesting that the afferent vasodilation is not totally due to reduced vasoconstrictor signals from the macula densa (108). The relationship between distal delivery and SNGFR is maintained, but at consistently lower afferent arteriolar resistance (Figure 4D). Apparently, the TGF mechanism adjusts to function at this higher level of Poc (105). Both structural (107) and functional (111) changes affecting the afferent arteriole have been suggested to be responsible for this increase in Poc. Thus, despite these changes in the preglomerular vasculature and the permeability of the glomerular membrane, normal control by the TGF mechanism over glomerular filtration is preserved.

Acute Renal Failure due to Tubular Insufficiency

Although many causes of acute tubular insufficiency have been described (112), a common observation is the major depression of GFR. The mechanism responsible for the almost complete shutdown of glomerular filtration has been the subject of extensive investigation. Tubular obstruction, backleak of filtrate, and vascular events have been identified as potential factors that contribute to the major decrease in GFR. Tubular obstruction has frequently been observed in nephrotoxic and ischemic models of acute renal failure (ARF) in rats, and the resulting increase in tubular pressure would reduce the net driving force for filtration. However, tubular obstruction does not seem to be as extensive in acute tubular insufficiency in humans (113), so that its pathogenetic role in the depression of GFR remains uncertain. Furthermore, the observation of backleak in acute tubular insufficiency is inconsistent, making this factor also an unlikely major cause of the reduced GFR (114). Vascular events have been identified in numerous studies, leading to the notion that functional changes in the renal vasculature are likely contributing substantially to the decrease in GFR in acute tubular insufficiency. Vascular components of ARF that have been recognized are increased activity of the systemic (115) and intrarenal (115,116) renin-angiotensin system, activation of the sympathetic nervous system (116), adenosine-1 receptor-mediated vasoconstriction as a result of increased levels of adenosine (117,118), and increased intracellular calcium levels (119). Several studies have also suggested an important role for the TGF mechanism in mediating the decrease in GFR (120–123).

A confirmed prerequisite for the involvement of the TGF mechanism in acute tubular insufficiency is that the mechanism is still operating (120,122). As mentioned, both a decrease in reabsorption leading to an increase in distal delivery (Figure 4B, arrow 1), and an increase in TGF responsiveness (Figure 4B, arrow 2) can mediate a decrease in SNGFR. A decrease in proximal reabsorption has been demonstrated in several models of acute tubular insufficiency (120,122,124) coincident with an increase in chloride (120,121) and sodium (121,123,125) concentration in early distal tubular fluid, indicating an increased luminal signal to the TGF mechanism. Perfusion of the proximal tubule with furosemide has been demonstrated to prevent a decrease in SNGFR in a single-nephron model of acute tubular injury (122), further indicating the relevance of TGF activation to the hypofiltration in acute tubular insufficiency. Interestingly, it has been demonstrated that TGF-mediated decreases in SNGFR and SFP in response to late proximal perfusion were enhanced if serum samples from patients with ARF were used for the perfusion. This suggests the presence of a substance in the serum from ARF patients that acts to enhance TGF responsiveness (126). However, TGF responsiveness has been reported to be slightly decreased or to be normal in various rat models of ARF (120,127). Taken together, the data suggest that the activation of the TGF mechanism contributes to the hypofiltration in acute tubular insufficiency, even though TGF responsiveness may be slightly reduced. The imbalance caused by acute tubular insufficiency would, if not counterbalanced by a dramatic depression of filtration, inevitably lead to major contraction of the ECFV. The mediatory role of the TGF system in the hypofiltration during acute tubular insufficiency can thus be considered to be a highly appropriate response (123).

The observation that RBF is generally relatively well maintained in acute tubular insufficiency, in contrast to the severely reduced GFR (128), has been recognized as one of the paradoxes of ARF (114). An explanation for the discrepancy between RBF and GFR impairment may be found in differences between nephron populations in ARF (114,117). In the
population of nephrons with functional tubular damage. SNGFR will be low because of the activation of the TGF mechanism, as explained above, and is probably accompanied by a depression of blood flow. In other nephrons, in which the main injury has led to endothelial, capillary, or arteriolar damage to the glomerulus and associated structures, there is a primary damage to the glomerular membrane, a reduction in GFR, and consequently, a reduction of tubular flow to the macula densa. This leads to TGF-mediated decreases in arteriolar resistance, which will partially counteract the increased vascular resistance caused by the injury (128). This will result in the situation in which GFR is only partially restored, but RBF and glomerular pressure are normal or even elevated. This condition totally uses the reserve capacity made possible by the TGF mechanism, and thus, proximal tubular blockade does not elicit any further increases in SNGFR. At the whole-kidney level, the autoregulatory reserve capability has been shown to be exhausted (128). Finally, a variable number of nephrons will be partially or fully obstructed. In these nephrons, SNGFR will approximate zero, as a result of the increased tubular pressure and possible backleak of filtrate, whereas blood flow in these nephrons may be preserved. Because SNGFR will be greatly reduced in all nephron populations and nephron blood flow will be diminished only in the nephron population with tubular insufficiency, whole-kidney GFR may be disproportional decreased compared with RBF (114).

**HYPERFILTRATION: AN AMBIGUOUS CHALLENGE FOR THE TGF SYSTEM**

In response to an influence that increases GFR and consequently increases distal delivery, the TGF mechanism will vasoconstrict the afferent arteriole in an attempt to restore distal delivery (Figure 4B, arrow 1). On the other hand, the TGF mechanism may contribute to hyperfiltration if the distal delivery is chronically diminished (Figure 4A, arrow 1). If TGF responsiveness is chronically attenuated, GFR may increase (Figure 4A, arrow 2), despite a maintained or even increased flow to the macula densa. This section considers the role of the TGF mechanism in two states in which GFR is increased. In diabetes mellitus (129–134), both the possibility that the TGF mechanism contributes to the hyperfiltration and the possibility that the TGF mechanism limits the degree of hyperfiltration are considered. In the single-nephron hyperfiltration that occurs after a substantial reduction in the number of nephrons, the TGF mechanism has to adapt to the requirement that the remaining nephrons increase GFR and distal delivery in order to preserve total renal function. Inappropriate activation of the TGF mechanism could severely limit excretory function in this situation.

**Diabetes Mellitus**

Hyperfiltration associated with insulin-dependent diabetes mellitus (IDDM) has been demonstrated in humans (130–132) and in animal models (133,134). No exclusive causal factor has been demonstrated to explain the hyperfiltration, and multiple phenomena are likely to contribute to its development (130). Studies evaluating the role of the TGF mechanism in contributing to or restricting the hyperfiltration have tried to separate the effects of the diabetic condition from the effects of acute hyperglycemia.

Some support has been obtained to indicate that there is a primary increase in proximal tubular reabsorption related to the enhanced glucose reabsorption. This could result in a decrease in distal delivery and a TGF-mediated afferent vasodilation (Figure 4A, arrow 1). On the basis of lithium clearance data, increased proximal reabsorption has been postulated in the early phase of IDDM in humans (132,135). Furthermore, the in vivo assessment of proximal and loop reabsorption in streptozotocin (STZ) diabetic rats has shown increased reabsorption during hyperfiltration, with decreased early distal sodium concentration 1 wk after the induction of diabetes (133). Several studies have implicated increased Na⁺/H⁺ exchange (136,137), increased Na⁺-K⁺-ATPase activity (138,139), and increased activity of the Na⁺-glucose cotransporter (140). The attenuation of TGF responsiveness could also contribute to hyperfiltration, such that SNGFR could be increased despite a normal (Figure 4A, arrow 2) or even an increased distal delivery (Figure 4C, arrow 2). The attenuation of TGF responsiveness has been shown in STZ-diabetic rats 1 wk after induction (134). In these studies, flow into the loop of Henle was varied by the perfusion of the late proximal tubule with artificial tubular fluid or by the alteration of late proximal tubular flow by the addition or removal of tubular fluid (134). Another study confirmed this attenuation of TGF responsiveness in STZ-diabetic rats 50 days after induction but also indicated the necessity of the presence of glucose and native tubular fluid, because TGF responsiveness was restored when artificial tubular fluid was used (10). These studies support the hypothesis that both a TGF-mediated afferent vasodilation (Figure 4A, arrow 1) and a decrease in feedback responsiveness (Figure 4A, arrow 2) contribute to the hyperfiltration in early diabetes. Similar mechanisms may mediate the hyperfiltration of hyperglycemia in nondiabetic models. Similar to the findings in IDDM, TGF responsiveness in hyperglycemic animals has been demonstrated to be attenuated (141). Furthermore, impaired autoregulation has been observed in dogs during hyperglycemia (142).

Data from other studies in both IDDM and hyperglycemia do not support the hypothesis that a decrease in the macula densa signal, as well as atten-
ulated TGF responsiveness, contributes to the hyperperfusion and hyperfiltration. No changes in proximal tubular reabsorption were observed in diabetic rats 2 to 3 months after induction by STZ (143). Furthermore, the difference between SNGFR determined from proximal and distal tubular fluid collections has been reported to be normal (143) or even increased (133), indicating normal or increased TGF activity. In particular, the latter study suggested that the TGF mechanism limits rather than contributes to the hyperfiltration in IDDM in rats. Nevertheless, the increased activity of the TGF mechanism was not sufficient to reduce SNGFR back to normal (133). Similarly, studies on hyperglycemia have suggested that the TGF mechanism may restrict the hyperfiltration by eliciting afferent arteriolar vasoconstriction in response to an increase in distal delivery. A decrease in proximal tubular reabsorption has been reported during hyperglycemia in both dogs (144) and rats (145).

Thus, some studies support the hypothesis that the TGF mechanism contributes to hyperfiltration in IDDM, whereas other studies indicate that the TGF mechanism limits the hyperfiltration under these conditions. Although the reason for this discrepancy remains unclear, there are several possibilities. First, insulin can influence the tubular transport rate directly (144) and indirectly by inducing hypokalemia (146, 147) and by altering the activity of the renin-angiotensin system (130). Consequently, distal nephron volume delivery and thus the luminal signal to the TGF mechanism could be variably influenced by the prevailing plasma insulin levels. Similarly, modulators of TGF responsiveness, such as ANP (148) and insulin, are also influenced by insulin, and it is possible that variable plasma insulin levels in IDDM result in variable alterations of TGF responsiveness. Second, the chronic nature of the diabetic model could easily induce morphologic changes affecting transport characteristics of the ascending limb of the loop of Henle. The resulting impairment of tubular transport could affect distal delivery, and even the sensing mechanism of the TGF system, if the lesions extend to the macula densa (150).

**Renal Ablation**

After a large reduction in kidney mass, a major challenge is imposed on the remaining nephrons, which leads to acute and chronic adaptations of filtration and reabsorption (151). The remaining nephrons exhibit a marked reduction in fractional proximal reabsorption and restore sodium balance. Assuming normal function of the TGF mechanism, the accompanying increase in distal delivery would elicit TGF-mediated reductions (Figure 4B, arrow 1) in SNGFR. It is recognized, however, that a physiologically more appropriate role for the TGF mechanism is to allow increases in glomerular filtration despite increased distal delivery after substantial reduction of renal mass.

The TGF mechanism can adjust to accept an increase of both SNGFR and distal delivery, by either decreasing responsiveness (Figure 4A, arrow 2) or resetting to a higher operating range (Figure 4D). Only hours after a substantial reduction in renal mass by uninephrectomy in rats, sodium excretion of the remaining kidney is enhanced (151, 152). Although controversy exists as to whether fractional proximal reabsorption is depressed (153, 154) or unchanged (151), an increase in early distal delivery (151, 153, 154) has been shown 12 to 15 h after renal ablation. Interestingly, the SNGFR determined from proximal tubular fluid collections has been shown to be increased (151, 153-155) after renal ablation, indicating that GFR increases independently of the TGF mechanism, because proximal tubular fluid samples are obtained during conditions of zero flow to the macula densa and thus during deactivation of the TGF mechanism. Such a change in proximally determined SNGFR is compatible with resetting of the TGF mechanism to a higher level of filtration. This resetting occurs slowly because the activity of the TGF mechanism, as assessed from differences between proximally and distally determined SNGFR, has been reported to be unchanged immediately after uninephrectomy (151). In addition, TGF responsiveness, as determined from the relationship between late proximal flow and SNGFR, has been shown to be either slightly attenuated (152) or normal (151) in this situation; however, the whole TGF function curve has been shown to be shifted to a higher level (151). Such maintained differences between proximally and distally determined SNGFR and an upward shift of the TGF function curve have also been demonstrated in rats 7 days after % ablation (156). Finally, studies in which TGF activity was assessed several weeks after uninephrectomy and % nephrectomy demonstrated large differences between the SNGFR as determined from both proximal collections and that based on distal tubular fluid collections, suggesting a high activity of the TGF mechanism during renal hypertrophy, even though it was reset to a higher level (155, 157). Indirect support for a high activity of the TGF mechanisms has also been obtained in humans after uninephrectomy (158). From those studies, it seems that the TGF mechanism gradually adjusts to function at a higher SNGFR and a higher distal delivery (Figure 4D) because various growth stimuli induce a structural and functional influence on the glomeruli.

**CONCLUSION**

The TGF mechanism operates at the single-nephron level to maintain distal delivery within the nar-
row limits of the reabsorptive capacity of the distal tubule by adjusting afferent arteriolar tone and filtered load. By making rapid corrections in distal delivery, the mechanism has a critical role in volume control. Changes in distal delivery accompanying many physiologic and pathophysiologic conditions are allowed by adaptations of the TGF mechanism in favor of volume balance or the correction of some other disturbance. Although this response can be regarded as appropriate (Table 1), there are situations where the TGF mechanism allows changes in distal delivery that are unfavorable for volume balance and can therefore be regarded as inappropriate (Table 1).

In this review, we have attempted to discuss the relevance of the TGF mechanism under normal conditions and in some major pathophysiologic states. Analysis of these conditions reveals that, although involvement of the TGF mechanism does not seem apparent at first, the TGF mechanism reacts in a highly appropriate way in order to maintain volume balance under most situations, although potential trade-off effects occur. Consequently, it can be appreciated that any in-depth evaluation of the mechanisms responsible for the development or maintenance of various pathophysiologic conditions should include an assessment of the potential role of the TGF mechanism.

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