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Physiologic adaptations of the tubuloglomerular feedback system

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The maintenance of volume homeostasis is sufficiently important to mammalian terrestrial life that a large amount of evolutionary energy has been expended in the development of multiple control systems, each involved in regulating the volume and composition of internal body fluids. The kidney, which participates in most of these systems, has evolved physiologic attributes which enhance the efficiency of volume regulation. Perhaps the most fundamental of these attributes is a close coordination between the processes of glomerular filtration and tubular reabsorption. Such coordination is required to prevent the amplification of small fluctuations in glomerular filtration rate into large fluctuations in total body salt and water content.

It was first suggested by Homer Smith that reabsorption of fluid from the nephron should increase as the delivery of tubular fluid into that segment increases [1]. When applied to the proximal tubule, this principle of flow-dependent transport has come to be referred to as "glomerulotubular balance" [2, 3]. Glomerulotubular balance depends upon intrinsic properties of the proximal nephron including the affinities and densities of various solute transporters and the differential permeabilities of the nephron to various solutes and water, and upon the transepithelial concentration gradients of these solutes [4–6]. By definition, glomerulotubular balance describes the functional dependence of tubular reabsorption on glomerular filtration rate independently of other neuro-humoral effectors of tubular transport. However, since glomerulotubular balance is a substrate-driven process, it cannot accomplish an increment in proximal tubular reabsorption which exceeds an increment in delivered load. Therefore, in the absence of effectors other than glomerulotubular balance the volume of fluid entering the distal nephron must be a monotonically increasing function of GFR [7].

How then, may the kidney avert an unintentional diuresis should the hemodynamic forces favoring glomerular filtration combine to overwhelm the reabsorptive capacity of the nephron? In 1937 Goormaghtigh suggested that the juxtaglomerular apparatus might participate in the maintenance of volume homeostasis by generating some sort of signal in response to changes in the composition of distal tubular fluid [8]. The peculiar anatomic arrangement of the nephron would facilitate transmission of this signal to the upstream glomerulus and lead to alterations in the physiologic determinants of glomerular filtration. This hypothesis has been refined over the past three decades as substantial experimental data have accrued to support the existence of an operational system of tubuloglomerular feedback (TGF) [9]. Contemporary models of the TGF system, by analogy to negative feedback-driven control systems in engineering control theory, divide the system into three component processes [10]. The first of these components is a parameter which the system is designed to regulate, in this case, the rate at which tubular fluid transits the late proximal nephron or V_{LP}. The second component includes the macula densa and surrounding interstitium which serve to detect differences between the current value of V_{LP} and some internal set-point, and translate this information into an output command. The third component, or effector limb, of the TGF system is constituted by the contractile glomerular mesangium and glomerular arterioles which respond to the aforementioned output command by altering nephron filtration rate (SNGFR) to keep V_{LP} in line with the system's internal set-point. When TGF is allowed to function as a closed-loop system [7], as is the case in vivo, its presence is, by nature, undetectable. However, when late proximal flow is uncoupled from nephron filtration by artificial microperfusion of the late proximal tubule, a dependence of SNGFR on V_{LP} can be defined [11]. This relationship is referred to as the "TGF function", or "gain" of the TGF system [7, 10]. This TGF function specifies a continuum of points in the V_{LP}-SNGFR plane at which the nephron may operate. The actual operating point of the system exists at the point in this plane where the TGF and glomerulotubular balance functions intersect (Fig. 1).

The TGF function may vary in response to the changing needs of the organism, both with regard to volume homeostasis and renal function. The altering of TGF under conditions of pregnancy, loss of renal mass, and a variety of other pathophysiologic conditions suggests that the juxtaglomerular apparatus is involved in events pertinent not merely to volume regulation but to overall renal growth and function.

Internephron interaction and TGF

Most studies of the TGF system have employed in vivo micropuncture in experiments designed to assess the TGF response within individual nephrons [11–14]. The techniques employed in such experiments as originally developed by Schnermann et al [11, 12] involve isolation of the proximal from

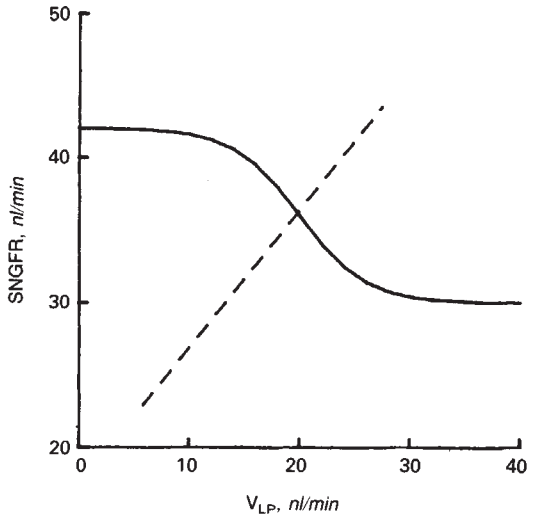

Fig. 1. *Tubuloglomerular feedback (TGF, ——) and glomerulotubular balance (GTB, ---) functions superimposed.* Late proximal flow rate (V_{LP}) and nephron filtration rate (SNGFR) serve as independent variables for the TGF and GTB functions, respectively. Since the conditions of both relationships must hold, the operating point of the nephron occurs at the intersection of the TGF and GTB functions.

distal nephrons and perfusion of the macula densa with various solutions via micropipettes placed in the late proximal or early distal tubules, while monitoring changes in SNGFR or the glomerular capillary pressure of the same nephron. In this single-nephron model of TGF, 30 to 60% decrements in SNGFR have been recorded as V_{LP} is varied between physiologic extremes [9–14].

Studies intended to evoke a TGF response in the entire kidney have, by necessity, been less direct. Prior to the routine availability of micropuncture, Harsing et al noted that suppression of proximal tubular reabsorption with a carbonic anhydrase inhibitor would result in a reduction in GFR despite replacement of diuretic losses [15]. He postulated that this occurrence could be accounted for by the action of a system of tubuloglomerular feedback. We have employed systemic infusions of the carbonic anhydrase inhibitor, benzolamide, in conjunction with micropuncture measurements, and have observed reductions in SNGFR which result in a more efficient restoration of V_{LP} to baseline values than would be predicted on the basis of TGF profiles derived from single nephron perfusion studies [16, 17]. These data suggest that the aggregate response to a simultaneous activation of TGF in all nephrons within a kidney is greater than the sum of the responses if each nephron were activated separately. In other words, near its operating point, the slope of the TGF profile for an individual nephron must be greater when the same change in V_{LP} is applied to all nephrons rather than to the index nephron alone.

Current understanding of the TGF system, therefore, has come to involve inter- as well as intranephron interactions. The concept of internephron feedback interactions has been advanced by reports of oscillatory patterns of proximal tubular hydrostatic pressure attributable to TGF which could be altered by manipulating V_{LP} in adjacent nephrons [18]. Recently, Källskog and Marsh have provided further evidence of internephron communication vis-a-vis TGF [19]. These investigators were able to advance a thin catheter through the arterial vasculature of the rat to the level of the cortical radial artery and thereby identify a number of nephrons supplied by the same cortical radial artery. Next, they perfused the late proximal tubule of an index nephron by micropuncture and recorded changes in glomerular capillary pressure by the stop-flow technique (P_{SF}) in adjacent nephrons. A "TGF" response, as manifested by a reduction in P_{SF}, was observed in nephrons adjacent to the index nephron, but only if those nephrons were supplied by the same cortical radial artery. This suggests upstream propagation of the TGF response from the vascular pole of the index glomerulus to its cortical radial artery, thereby increasing the preglomerular vascular resistance of other nephrons supplied by that terminal arterial vessel. Whether this propagation occurs electrically via gap junctions, by myogenic reflex, or by another form of internephron communication remains to be determined.

A whole-kidney TGF response has also been implicated in the mechanism whereby GFR declines in a variety of pathophysiologic models. In acute renal failure induced by systemic injection of uranyl nitrate, we found GFR to be reduced due to a decline in glomerular ultrafiltration coefficient, or LpA [20]. If animals also received captopril, or were studied after 2.5% plasma volume expansion, the effects of uranyl nitrate on SNGFR and LpA were no longer observed [21]. Uranyl nitrate administration also resulted in histologic evidence of damage to renal tubules and a loss of tubular integrity as manifested by an inability to retain inulin within the tubular space, effects which were not altered by captopril or plasma volume expansion. Nephron obstruction was not observed in this model. While not providing rigorous proof that TGF is responsible for the effects of uranyl nitrate on GFR, these studies did demonstrate that a functional reduction in GFR could occur in the setting of a structural injury to the tubule and that these glomerular and tubular events could be dissociated by maneuvers which are known to diminish the activity of the TGF system. A modified form of this model was recently examined in which we were able to induce "acute renal failure" at the single nephron level by microperfusion of the early proximal tubule with uranyl nitrate [22]. Presumably, this technique spared the glomerulus from any direct toxic exposure. Within five minutes of uranyl nitrate infusion into the early proximal tubule, reabsorption of fluid from the proximal tubule was reduced and SNGFR declined by 20 to 35%, providing further circumstantial evidence that the glomerular hemodynamic effects of uranyl nitrate may be mediated by TGF.

Transduction of the TGF signal

Goormaghtigh originally argued, based on anatomic grounds, that the sensing element of the TGF system resides in the macula densa [8]. This notion has never met with serious challenge and, in fact, now rests on solid experimental footing. Antegrade and retrograde microperfusion studies performed in vivo have isolated the sensing element to that portion of the nephron between the late proximal and early distal tubules [11, 12]. Ex vivo perfusion of short nephron segments, which include the macula densa attached to a glomerulus, have provided information regarding physiological properties of the macula densa. Epithelial cells of the macula densa region appear to have certain characteristics in common with cells of

the thick ascending limb of Henle's loop, including furosemide inhibitable transport of NaCl [23]. However, the actual rates of sodium and chloride transport by the macula densa may be somewhat less than those observed in the thick ascending limb, while the macula densa segment possesses a much greater hydraulic permeability than does the water-impermeable ascending limb [24]. Architecturally, the macula densa region of the nephron varies from the remainder of the ascending limb in several respects, notable among which is the presence of a fluid-containing cleft separating the basolateral macula densa from the extra-glomerular mesangium [25]. This cleft is located such that its fluid content is not in direct communication with capillaries or lymphatics. Therefore, although rigorous proof of its origin remains to be provided, the fluid within this cleft most likely derives from transport and diffusion of salt and water across the macula densa. Current theory, supported by some experimental evidence, suggests that the ionic constituency of the fluid within this space varies in response to changes in sodium and chloride concentration and osmolarity of tubular fluid transiting the nephron at the level of the macula densa. When measured in *Necturus* by Persson and Marsh, the chloride concentration in the basolateral space adjacent to the macula densa exceeded that in plasma by several-fold [26]. Furthermore, the volume occupied by the basolateral space diminishes after administration of furosemide or in the setting of hyperglycemia, conditions which are associated with inhibition of transepithelial transport in that segment of the nephron [25, 27]. Based on assumptions that, relative to the transepithelial route, other paths of communication with the basolateral space are of greater impedance, and that the local balance of osmotic and hydrostatic pressures favors the movement of water from tubule to interstitium, Rich and Moore have theorized that the chloride concentration of fluid within this space should vary directly with the rate of epithelial chloride transport and tubular fluid osmolarity, and inversely with the hydraulic permeability of the macula densa [28]. This model predicts that fluctuations in chloride concentration will increase in amplitude when translated by the macula densa from tubule to interstitium. It also reconciles prior controversy between those favoring the chloride ion vs. those favoring tubular fluid osmolarity as the afferent stimulus to TGF [29, 30].

Discussion of the ionic content of fluid within the basolateral space adjoining the macula densa has assumed increased importance in light of certain in vitro findings of Kurokawa and associates [31]. These investigators have provided a link between extracellular chloride concentration and the response of cultured rat mesangial cells to angiotensin II (Ang II). Since hemodynamic conditions leading to activation of TGF (that is, volume expansion with elevated GFR) are contrary to those (volume depletion, hypotension, etc.) which cause stimulation of the renin-angiotensin system, Ang II is unlikely to be the primary effector for TGF. Nonetheless, a modicum of Ang II must be present in order to elicit a TGF response. This peptide binds to specific receptors on the surface of mesangial cells, leading to the liberation of Ca^{++} from intracellular stores and, subsequently, to cell contraction [32]. This cell contraction hypothetically represents the in vitro correlate to the end-organ TGF response. Kurokawa has demonstrated that the response of mesangial cells to Ang II (or ADH), as assessed by calcium transients, production of IP_3, or cell contraction, diminishes as

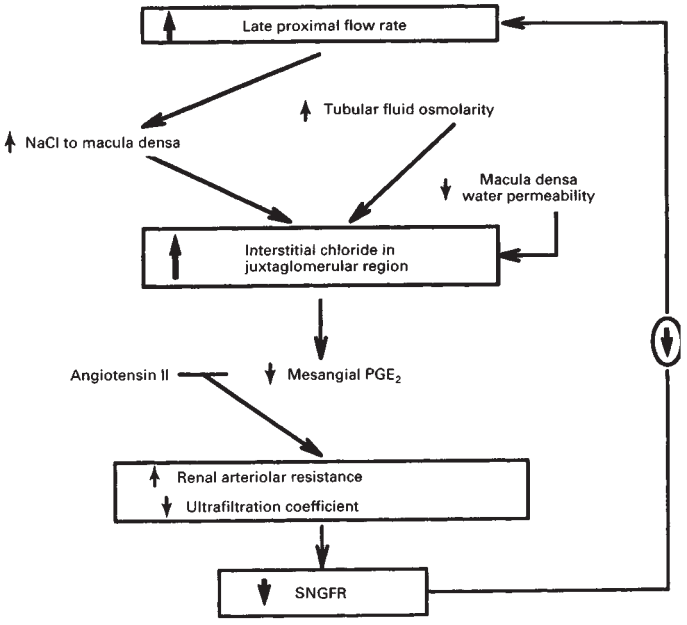

Fig. 2. *Putative tubuloglomerular feedback transduction pathway.*

extracellular chloride is isosmotically replaced with the impermeant anion, methanesulfonate [31]. Additionally, prostaglandin E_2, a physiologic antagonist of the glomerular hemodynamic effects of Ang II, is synthesized by mesangial cells in increasing amounts as the extracellular chloride concentration is reduced. Finally, inhibition of prostaglandin synthesis with indomethacin, eliminates the effects of extracellular chloride on the response to Ang II. These findings are consistent with a model whereby changes in chloride concentration within the mesangial interstitium effect the TGF response by modulating the synthesis of PGE_2 against a tonic background of Ang II (Fig. 2).

Altering the sensitivity of the TGF system

A TGF function is defined as the measurable dependence of SNGFR (or P_G) on late proximal flow. This response, as outlined above, is a net result of interactions between multiple physiochemical processes. Therefore, events which alter any of these processes would be expected to alter the gain of the TGF system. It has been observed that TGF profiles vary predictably with physiologic circumstance, and information is now coming to light which allows correlation of these phenomenological observations with changes in cell function. Several examples follow:

Volume expansion causes the TGF profile to shift upwards and to the right and diminishes the maximum amount by which SNGFR declines as V_{LP} is increased from zero to infinity [33]. This permits a higher SNGFR at any given V_{LP}, and causes a (Fig. 3) lesser decrement in SNGFR for any given increase in V_{LP}. Teleologically, the TGF system, which exists to avert inordinate volume losses, becomes less sensitive under such conditions where a given volume loss would be best tolerated. The mechanism whereby volume expansion leads to desensitization of the TGF system probably involves suppression of the renin-angiotensin system. TGF, as mentioned above, is not directly mediated by Ang II, although Ang II must be present in

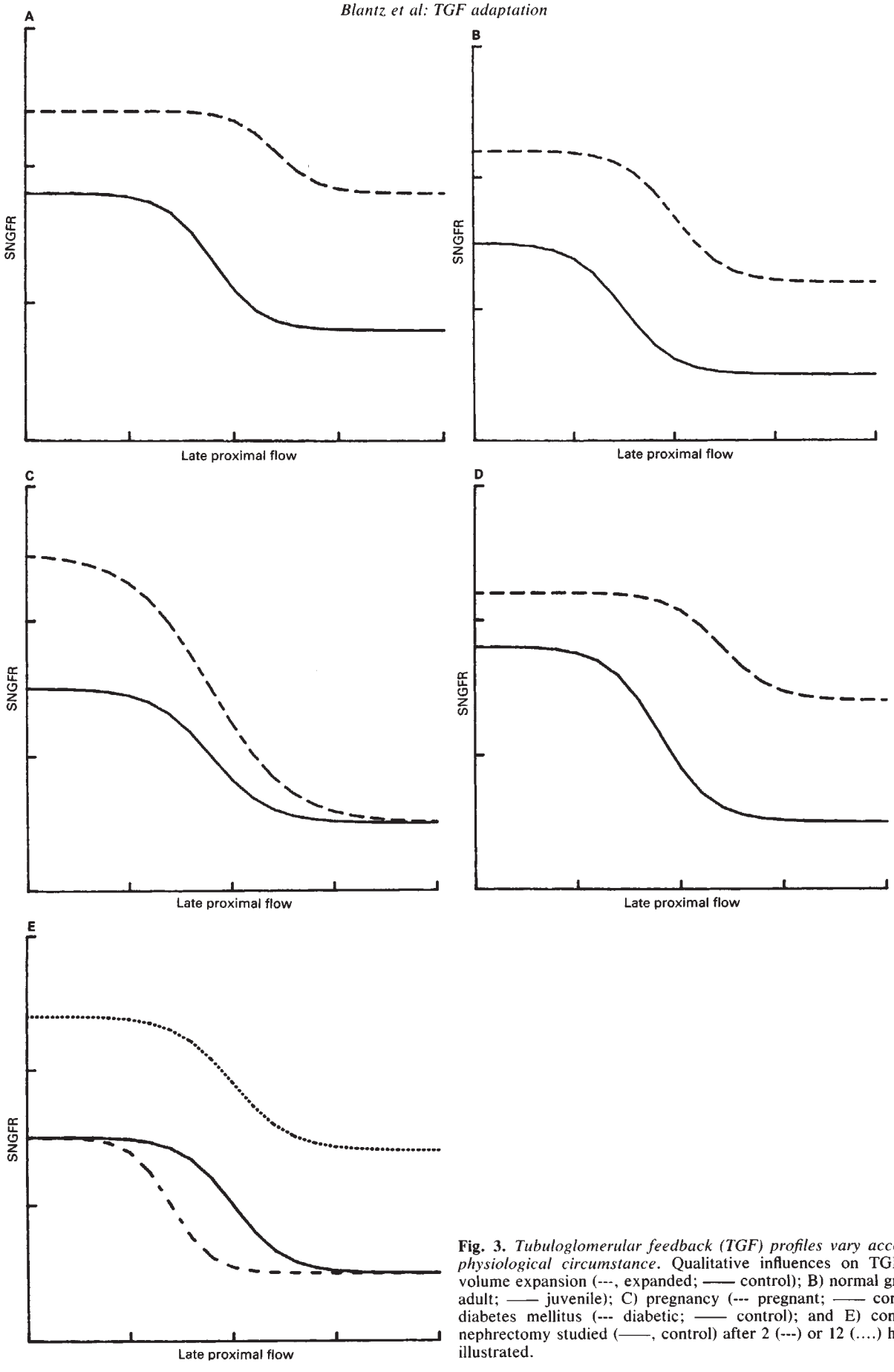

Fig. 3. *Tubuloglomerular feedback (TGF) profiles vary according to physiological circumstance.* Qualitative influences on TGF of: A) volume expansion (---, expanded; —— control); B) normal growth (--- adult; —— juvenile); C) pregnancy (--- pregnant; —— control); D) diabetes mellitus (--- diabetic; —— control); and E) contralateral nephrectomy studied (——, control) after 2 (---) or 12 (....) hours, are illustrated.

order to elicit a TGF response [34, 35]. If TGF occurs as the activity of the vasodilatory PGE_2 is modulated against a background of Ang II-dependent tonic vasoconstriction, then suppression of endogenous Ang II would blunt the response to fluctuations in PGE_2. Plasma volume expansion, which suppresses the renin-angiotensin system, may alter the TGF profile by that means. Other evidence has recently been made available to suggest that prolonged elevation of the afferent stimulus to TGF itself might lead to the desensitization of TGF associated with volume expansion. Volume expansion diminishes the intensity of a number of stimuli to proximal tubular reabsorption, thereby increasing the fraction of a filtered load which transits the tubule at the level of the macula densa. If such a shift in the glomerulotubular balance function were to occur instantaneously, causing it to intersect the TGF function at a lower SNGFR, then a new operating point would be defined with an elevated V_{LP} and depressed SNGFR. Skött and Briggs have recently found, however, that perfusion of isolated nephron segments including macula densa and attached glomeruli results in suppression of renin release from a glomerulus as its macula densa is perfused at increasing rates [36]. Therefore, a prolonged change in late proximal flow may modulate the TGF profile via effects on the renin-angiotensin system. In this regard, a change in V_{LP} may induce conflicting alterations in the various paracrine processes which integrate to cause a TGF response. A TGF response which depends upon the duration as well as the magnitude of an applied stimulus may reflect variability among the frequency responses of different competing subsystems. For instance, it may be that the intrarenal renin-angiotensin system is relatively insensitive to "high frequency" fluctuations in V_{LP} as generally employed in experiments designed to measure TGF.

Another important example of TGF adaptation involves the response to normal (Fig. 3B) growth. As an animal grows and kidney size increases, the TGF profile is translated upward and to the right while the maximum response [SNGFR(∞)-SNGFR(0)] remains intact [37]. The mechanism accounting for the adaptation of TGF during growth is unknown, but it seems unlikely that coincidental increases in the size of glomerular and tubular structures alone could be responsible. Although experimental evidence is not yet available to support such hypotheses, it seems more likely either that a primary growth-related increase in proximal tubular reabsorption elicits changes in the TGF profile allowing SNGFR to rise, or that a primary shift of the TGF profile and increase in SNGFR elicits growth in the tubule and an increase in reabsorptive capacity.

An example of transient adaptation of the TGF profile in the absence of (Fig. 3C) significant hypertrophy is provided by pregnancy [38]. Although kidney weight increases during pregnancy, the increase is primarily due to increased content of water and not to true hypertrophy. However, in the rat at mid-gestation, GFR is elevated by 30 to 40% over the prepregnancy value to which it returns post-partum. During the time that GFR is elevated the TGF profile is altered such that there is an upward shift of SNGFR over the lower range of V_{LP}, with the curve becoming superimposable on that of a nonpregnant animal at higher values of V_{LP}. The cellular processes mediating this effect of pregnancy on TGF are not understood.

TGF activity is also altered in certain pathophysiologic states. Glomerular hyperfiltration and increased kidney size are characteristic findings in Type I diabetes mellitus in humans and in experimental diabetes in the rat. In recent studies of the streptozotocin-induced diabetic rat, micropuncture studies performed 50 days after the establishment of diabetes have documented abnormal TGF profiles, notable for a diminished maximum response of SNGFR to late-proximal perfusion [39] (Fig. 3D). Rasch and Holck have recently reported the presence of heavy glycogen deposits within the thick ascending limb of Henle's loop in the diabetic rat [40]. The existence of these lesions, which bear morphologic resemblance to the Armani-Ebstein lesion, suggests a possible pathologic correlate to functional abnormalities in loop reabsorption associated with diabetes. If abnormal ascending-limb transport persists a distance to involve the macula densa, then the transmission of a TGF stimulus could be interrupted. This line of reasoning gains further credibility from the additional finding that diabetes is associated with a collapse of the basolateral space which separates the macula densa from the extra-glomerular mesangium. Since the content of this space arises via transepithelial transport across the macula densa, the collapse of the space implies either an interruption of transport or osmotically-induced water flow into the lumen and concomitantly, a breakdown of the TGF pathway.

The hypothesis that a structural lesion in the macula densa could desensitize the TGF system by inhibiting transport does not immediately reconcile with additional findings linking the suppression of TGF in diabetic animals to some constituent of tubular fluid [39]. The above experiments, in which suppression of TGF was associated with collapse of the space surrounding the macula densa, were performed using a perfusate which consisted of native tubular fluid, harvested from the same diabetic rat. When experiments were repeated using glucose-free artificial tubular fluid, TGF activity was restored. Furthermore, loop of Henle reabsorption, which was depressed in the diabetic rat perfused with native tubular fluid, returned toward normal when the loop was perfused with artificial tubular fluid. Interestingly, when the loop of Henle was perfused with artificial tubular fluid, not only were TGF and loop reabsorption restored, but the basolateral space adjacent to the macula densa of the perfused nephron was no longer collapsed.

The most obvious difference between native and artificial perfusates was the presence, in the former, of osmotically active glucose. It seems unlikely that the amount of glucose present would exert an osmotic pressure sufficient to overwhelm that of the NaCl normally transported across the macula densa and thereby obliterate the basolateral space entirely. In fact, one would expect that the addition of a small amount of an impermeant osmol to the tubular fluid should enhance TGF by causing the chloride concentration in the basolateral space to increase. It is also unlikely that the presence of glucose in the tubular perfusate results in a lesser chloride concentration of fluid reaching the macula densa, since the administration of osmotic diuretics have been shown to result in increased concentrations of sodium in fluid sampled from early distal nephrons [11]. It seems more likely that native tubular fluid actually inhibits epithelial transport across the macula densa in the diabetic rat. Artificial perfusates containing glucose are being employed in ongoing studies in the diabetic rat to ascertain whether the presence versus absence of glucose is sufficient to account for dependence of TGF on the type of perfusate [13].

Another pathophysiologic condition with effects on TGF and upon which interest has been focused is the loss of renal mass.

The adaptive response of an organism to the loss of renal mass involves: 1) an elevated blood pressure; 2) glomerular hemodynamic alterations; and 3) induction of growth factors leading to hypertrophy of remaining renal structures and elaboration of byproduct matrix materials. The signals which elicit these responses have not been well defined. However, since the net volume excreted by an individual nephron may be supplemented by diminishing fractional reabsorption in a way which does not require any increase in metabolic machinery, it is reasonable to suppose that the compensatory hypertrophy of remaining nephrons following acute loss of functioning renal tissue is directed toward an increase in reabsorptive, rather than excretory, capacity. Our teleologic understanding of the role of the TGF system similarly involves the kidney's need to avoid presenting the nephron with a filtered load which exceeds its reabsorptive capacity. With this parallel in mind, we have begun to investigate the response of the TGF system to unilateral nephrectomy (Fig. 3E).

Six to twelve hours following unilateral nephrectomy, GFR in the remaining kidney begins to increase. In order to study the events which antecede any increase in GFR, TGF profiles were probed two to four hours after removal of the contralateral kidney [41].

At this early stage, TGF was activated in that the operating point was shifted downward on the TGF profile and SNGFR measured in distal tubules was slightly lower than the two kidney control values. Loop of Henle reabsorption was not decreased in this setting, such that this alteration in TGF activity could not be attributed to an increase in the fraction of perfusate reaching the macula densa. There was a quantitative leftward shift in the turning point as well, but the value for the turning point was not statistically different when submitted to a rigorous curve-fitting analysis. The increase in urinary excretion of NaCl and water observed at two hours did not require either suppression of TGF or an increase in SNGFR [42].

Twelve hours after unilateral nephrectomy, TGF profiles in the remaining kidney were shifted upward relative to pre-nephrectomy curves, with SNGFR at low perfusion rates increased by 25% over those observed in the pre-nephrectomy state. In order for this adaptation to have occurred, events must have transpired in the period between four and twelve hours after nephrectomy which allowed flow past the macula densa to increase without eliciting a reduction in SNGFR. It is of interest that the magnitude of the functional increase in SNGFR which occurs within one day following contralateral nephrectomy can be modified by maneuvers that are known to modify TGF activity. When given acutely, benzolamide, by inhibition of proximal reabsorption, will summon a TGF response leading to a reduction in SNGFR [16]. However, when administered continuously for 18 hours after unilateral nephrectomy, benzolamide appears permissive for a greater adaptation of TGF activity and a greater increase in SNGFR than nephrectomy alone [43].

Speculative roles for the macula densa-juxtaglomerular system

Faced with a loss of functioning renal mass, the kidney responds by signalling for an increase in SNGFR and an augmentation of reabsorptive capacity among the remaining nephrons. In order to maintain interim control of systemic volume, these two responses must be coordinated in time. Since the juxtaglomerular apparatus is strategically situated to provide a link between glomerular and tubular events, it is not unreasonable to suspect that this same portion of the nephron which is responsible for mediating control of the determinants of SNGFR via TGF, is involved in regulating the synthesis of the cellular machinery required for tubular function. In other words, the above-described alteration of the TGF system which occurs in the aftermath of unilateral nephrectomy should occur coincident with the elaboration of whatever growth factors are required to induce hypertrophy within the tubule [44]. Since certain of the growth factors which are capable of acting on proximal tubular cells are actually synthesized in more distal segments of the nephron and in glomerular cells [45, 46], elaboration of these factors followed by transport to more proximal sites of action may constitute a feedback mechanism to govern growth in the proximal tubule. Although such a notion remains wanting for supporting experimental evidence, anatomic relationships could allow for convective movement of growth-promoting substances from the early distal tubule to the proximal nephron if they were to pass by way of the macula densa and glomerulus.

Summary

Knowledge of the existence of a tubuloglomerular feedback system has been available for many years. Only recently, however, have tenable hypotheses and supporting experimental data become available which have served to provide details regarding the complex inner workings of this system. The facility for examining this integrated physiologic network has derived, in large part, from the routine ability to perform in vivo micropuncture. We anticipate that further advances in this field will hinge on the development of additional experimental techniques to allow cellular biologic aspects of the system to be closely monitored in situ.

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