Kidney function in early diabetes: the tubular hypothesis of glomerular filtration

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Thomson, Scott C., Volker Vallon, and Roland C. Blantz. Kidney function in early diabetes: the tubular hypothesis of glomerular filtration. Am J Physiol Renal Physiol 286: F8–F15, 2004; 10.1152/ajprenal.00208.2003.—At the onset of diabetes mellitus, the glomerular filtration rate becomes supranormal. Discovery science has identified many abnormalities in the early diabetic kidney that apparently contribute to this phenotype. A serviceable understanding of the early diabetic kidney requires this information to fit together. It is the purpose of this article to present an archetype that explains multiple nuances of kidney function in early diabetes. We refer to this archetype as the “tubular hypothesis of glomerular filtration.” Its basic tenet is that strange effects of diabetes on glomerular filtration stem from primary effects on the proximal tubule or loop of Henle that impact glomerular filtration by feedback through the macula densa. This theory can explain diabetic hyperfiltration, a paradoxical effect of dietary salt on glomerular filtration rate in diabetes, and the renal response to dietary protein and amino acid infusion in diabetes. The discussion centers on the kidney as an integrated system of parts rather than on the specific cellular mechanisms that comprise those parts.

diabetes mellitus is the commonest and fastest growing cause of end-stage renal disease in the developed world (32). The pecuniary impact of this disease and the cost it exacts in human suffering justify the ongoing concerted effort to understand it.

INTRODUCTION TO DIABETES AND THE KIDNEY

We know that diabetes affects the kidney in stages. At the very onset of diabetes, the kidney grows large and the glomerular filtration rate (GFR) becomes supranormal (14). Most recent basic and clinical research have slanted toward sclerosis and kidney failure that occur many years later. However, the original idea that the early hemodynamic phenotype provokes the subsequent demise of a diabetic kidney has not been abandoned (15). Scientific discovery has identified many abnormalities in the early diabetic kidney. Each of these may be viewed as pieces of a puzzle. A serviceable understanding of the early diabetic kidney requires those pieces to fit together. It is the purpose of this article to assemble some of those pieces into an archetype that is serviceable inasmuch as it explains multiple nuances of kidney function in early diabetes. We refer to this archetype as the “tubular hypothesis of glomerular filtration.” It is fashioned around a basic tenet: that strange effects of diabetes on glomerular filtration stem from primary effects on the proximal tubule or loop of Henle that impact glomerular filtration by feedback through the macula densa. This theory can explain diabetic hyperfiltration, a paradoxical effect of dietary salt on GFR in diabetes, and the renal response to dietary protein and amino acid infusion in diabetes. This discussion will focus on control theory and phenomenology and not discuss specific cellular mechanisms except when necessary to illustrate principles. This is not intended to slight the research of those whose discoveries would normally be cited in a review article about kidney function in diabetes. A partial list of those discoveries appears in Table 1. Also, therapeutic concepts related to the tubular hypothesis are presented elsewhere (34) and not discussed here.

PARADIGM FOR CONTROL OF GFR

The Starling forces and capillary surface that determine GFR are directly influenced by various effectors that include nerves, hormones, size and condition of the glomerulus, and tubuloglomerular feedback (TGF) from the macula densa. Physiological effectors of GFR generally function as elements in negative feedback systems that link GFR to some other physiological parameter (Fig. 1). For example, glomerular filtration is linked to extracellular fluid volume (ECF) through multiple parallel feedback loops that respectively incorporate the renal nerves, renin-angiotensin system (RAS), and natriuretic peptides (ANP). Glomerular filtration is linked to the concentration of salt in the tubular fluid that reaches the macula densa (MD[NaCl]) by TGF. GFR and size of the kidney are also linked in a negative feedback arrangement, although how a feedback signal derives from GFR that influences kidney growth remains a mystery.

If an external perturbation is applied to one element of a linear feedback loop, part of the perturbation will be compensated for by feedback around the loop, and the remainder will manifest as a residual error in that element. The efficiency of a negative feedback system is determined by its open-loop gain.

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The open-loop gain is the ratio of the compensated portion of the original disturbance to the residual error. A system that is perfectly efficient has an infinite open-loop gain. A system that buffers half a disturbance has an open-loop gain of unity. When a parameter is protected by multiple feedback loops arranged in parallel, the overall gain of the system for stabilizing that parameter is the sum of the open-loop gains of the individual loops. For the example contained in Fig. 1, the renal nerves, RAS, and ANP will additively compensate for any outside disturbances in ECF.

Feedback loops that are arranged in parallel also compete for control of the system, and the leverage exerted by an individual loop is determined by its own open-loop gain relative to the competition. For example, the feedback loops that link GFR to ECF compete for control of GFR with the loop that links GFR to macula densa salt (Fig. 1). The open-loop gain referable to a disturbance in ECF is directly proportional to the impact of ECF on GFR. However, any change in GFR will alter MD[NaCl], eliciting a TGF response that affects GFR in the opposite direction. Hence, the homeostatic efficiency of the renal nerves, RAS, and ANP system for regulating ECF will decline as the TGF system becomes more efficient.

Moreover, disturbing the ECF will impact the MD[NaCl] in this system, even though the two are not elements of the same feedback loop. In other words, a disturbance in one feedback loop will spill over into all the other loops. A disturbance in ECF will reset MD[NaCl] to a new value. As TGF becomes more efficient, the influence of ECF over MD[NaCl] will shrink. If GFR becomes more sensitive to ECF via the renal nerves, RAS, or ANP, then the impact of ECF on MD[NaCl] will grow larger.

The foregoing example is made without reference to the dynamics of these systems or the known cross talk that occurs between the various components of this system (i.e., direct interactions between renal nerves and RAS, renin suppression by the macula densa, etc.). It also ignores important neurohormonal mechanisms that link ECF to tubular reabsorption. However, it illustrates the point that any parameter linked to GFR by negative feedback will influence all other parameters linked to GFR, even when the parameters are not linked to each other in any other way. Therefore, it is not surprising that almost anything associated with glomerular filtration can appear “abnormal” in diabetes. Looking for the effector that appears most abnormal may not be a good way to establish the primary cause of a change in GFR, because a large effect of diabetes on the value of a parameter may be the result of a primary disturbance or change in the open-loop gain of a parallel feedback loop that does not even contain that parameter.

DEFINING “VASULAR” AND “TUBULAR” EVENTS

Our theory states that the macula densa is the dominant influence over glomerular filtration in early diabetes. One way to test the theory with respect to diabetic hyperfiltration would be to quantify the impact of each putative mediator of glomerular filtration, including MD[NaCl], and rank them. A partial list is shown in Table 1. The list is too long for this approach to be tractable. Instead, we begin by sorting all possible effectors of glomerular filtration into one of two categories. One category contains only the tubular reabsorption-MD[NaCl]-TGF mechanism. The other category contains all other possible effectors, including effectors that remain to be discovered. Any event that alters GFR by way of affecting MD[NaCl] is referred to as a “primary tubular event.” All other events that alter GFR are referred to as “primary vascular events.”

Some examples of primary vascular events include changes in any element contained in the feedback loops that link GFR to ECF in Fig. 1. These might include abnormal sensing of the ECF, abnormal transduction of information about the ECF into a neurohormonal signal, or an altered response to the signal by the renal microvessels. A primary tubular effect is anything, except GFR, that affects reabsorption upstream from the macula densa. GFR affects tubular reabsorption via glomerulotubular balance (GTB). For present purposes, GTB refers to the instantaneous effect of GFR on tubular reabsorption due to kinetic interaction of the tubular fluid with an existing transport machinery. In contrast to GTB, a primary change in tubular reabsorption results from a change in the amount of transport machinery or its functional state. A primary change in tubular reabsorption causes GFR to change through the physiological actions of TGF. A primary vascular effect on GFR causes a secondary change in tubular reabsorption through the physiological actions of GTB (see Fig. 2). Several neurohormonal systems, most notably the renal nerves and RAS, exert both primary tubular and vascular effects.

![Fig. 1. Effectors that influence tubuloglomerular feedback (TGF) of negative feedback loops that link glomerular filtration rate (GFR) to other physiological parameters. ECF, extracellular fluid volume; MD[NaCl], salt concentration of tubular fluid at the macula densa; Nerves, efferent sympathetic renal nerves; RAS, renin-angiotensin system; ANP, atrial natriuretic peptide hormones from the heart; solid lines, proportional effects; dashed lines, inverse effects. A negative feedback loop must contain an odd number of inverse effects.](http://ajprenal.physiology.org/)

**Table 1. Some primary vascular mediators of diabetic hyperfiltration**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal prostaglandins</td>
<td>18</td>
</tr>
<tr>
<td>Natriuretic peptide</td>
<td>18</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>18</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>18</td>
</tr>
<tr>
<td>Ketones</td>
<td>18</td>
</tr>
<tr>
<td>Low insulin</td>
<td>18</td>
</tr>
<tr>
<td>Glucagon</td>
<td>18</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>18</td>
</tr>
<tr>
<td>Kallikrein-kinin</td>
<td>5</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>5</td>
</tr>
<tr>
<td>Dysfunctional Ca^{2+} channels in afferent arteriole</td>
<td>5</td>
</tr>
<tr>
<td>Excess K^{+} channels in afferent arteriole</td>
<td>10</td>
</tr>
<tr>
<td>Impaired electromechanical coupling in the afferent arteriole</td>
<td>4</td>
</tr>
</tbody>
</table>

Most primary vascular mediators are discussed in reference tests or review articles, shown in parentheses.
DIABETIC HYPERFILTRATION AS A PRIMARY TUBULAR EVENT

Because parallel feedback loops compete for control of any parameter(s) they share, GFR must be determined by a balance of forces between primary vascular and primary tubular events. This model accounts for all possible causes of a change in GFR. GFR cannot increase unless there is a dominant primary vasodilatation and/or a dominant primary increase in tubular reabsorption to cause the increase. Because GFR and MD[NaCl] are connected in a feedback loop, no single disturbance can affect GFR without secondarily affecting MD[NaCl] and vice versa. However, primary vascular and tubular events that have the same effect on GFR will have contrary effects on MD[NaCl]. If GFR increases due to a primary vascular effect, then MD[NaCl] must also increase. If GFR increases due to a primary tubular effect, then MD[NaCl] must decrease. Therefore, if one knows how MD[NaCl] is affected during hyperfiltration, then one can ascribe a vascular or tubular cause to hyperfiltration.

Indeed, increased proximal reabsorption has been noted in hyperfiltering patients with early type 1 (16) or type 2 (12) diabetes based on lithium clearances. These and other authors have ignored the macula densa mechanism and posited excessive proximal reabsorption as a cause of systemic volume expansion leading to hemodynamic consequences in diabetes (1). ECF expansion is an essential intermediary if diabetic hyperfiltration is to be explained by this mechanism. However, ECF expansion is not a uniform intermediary if diabetic hyperfiltration is mediated within the juxtaglomerular apparatus.

This approach unmasks a major primary increase in proximal reabsorption in rats with early streptozotocin diabetes (29) (see Fig. 3). For this primary increase in proximal reabsorption to be the dominant cause of glomerular hyperfiltration, the diabetic nephron must operate with MD[NaCl] below normal. In contrast, when a primary vascular event is the dominant cause of hyperfiltration, MD[NaCl] must be above normal. In fact, all published data on the ionic content of the early distal nephron in diabetes list values substantially below normal (20, 23, 33, 35, 37). It is clear that the diabetic kidney meets the requirement for low MD[NaCl] necessary for a primary increase in tubular reabsorption to be the dominant cause of hyperfiltration.

Another requirement of the tubular hypothesis is for the TGF system to respond to the reduced MD[NaCl] by increasing SNGFR. Indeed, the range of the TGF response is preserved in diabetes, although the slope of the response is reduced (29, 33). Also, if hyperfiltration is mediated by a reduced TGF signal, then there should be evidence that TGF is less engaged by the ambient MD[NaCl] in diabetes. The usual way to test for TGF activation is via the proximal-distal (P-D) difference in SNGFR. A greater P-D difference corresponds to greater TGF activation. Technical pitfalls result in a high coefficient of variation in measuring the P-D difference. Nonetheless, we have shown the P-D difference to be small in diabetes (23). In other words, there is upward deviation in the ambient SNGFR along the TGF curve in diabetes, suggesting that the diabetic nephron must operate with MD[NaCl] below normal. In fact, all published data on the ionic content of the early distal nephron in diabetes list values substantially below normal (20, 23, 33, 35, 37). It is clear that the diabetic kidney meets the requirement for low MD[NaCl] necessary for a primary increase in tubular reabsorption to be the dominant cause of hyperfiltration.

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nephron has converted low MD\([\text{NaCl}]\) into hyperfiltration. A hypothetical illustration is provided in Fig. 4.

However, the entire increase in SNGFR cannot be explained by a smaller P-D difference, because SNGFR collected from the proximal tubule also invariably increases in diabetes. As TGF is inoperative during proximal tubular fluid collections, this implies that the TGF curve itself must also shift upward in diabetes. It is a challenge for the tubular hypothesis to account for this upward resetting of the TGF curve. As conventionally defined, TGF confers a specific dependence of SNGFR on MD\([\text{NaCl}]\) from one minute to the next. Changes in SNGFR that are due to TGF are represented by moving from one point to another along a given TGF curve. However, the curve itself may be influenced by events outside of the juxtaglomerular apparatus (JGA). In fact, any primary vascular effect on GFR can be represented by a change in the TGF curve (see Fig. 4). Therefore, the upward shift in the TGF curve in diabetes may represent a primary vascular event mediated by any of the factors listed in Table 1.

When TGF is reset upward by external events such as plasma volume expansion, the operating point migrates downward along to the TGF curve and TGF becomes more activated (27). The same would be expected for any vascular cause of upward resetting. This is contrary to what occurs in diabetes, where the state of TGF activation lessens despite an upward shift in the TGF curve. Therefore, one might conclude that the tubule is the dominant controller of SNGFR with a primary vascular effect as close runner-up and that, under slightly different starting conditions, the roles could be reversed. The tubular hypothesis of glomerular filtration would be much more compelling if TGF resetting were also shown to arise from the tubule.

**TGF Resetting: Tubular or Vascular Event?**

We have defined primary tubular events as being mediated by TGF and have pointed out that any primary vascular effect on GFR can be represented as a resetting of TGF. However, this does not imply that all events that cause TGF to reset are mediated by nerves or circulating hormones, or begin with changes in the renal vessels. An event that occurs in the JGA and causes GFR to change, but is not TGF, fulfills the criteria for a primary vascular event (see Fig. 2). In fact, the JGA does mediate TGF resetting in response to sustained increments in MD\([\text{NaCl}]\). Such resetting normally maintains the operating point of a nephron along the steep portion of the TGF curve (28, 30). A TGF response occurs within seconds whenever there is a change in MD\([\text{NaCl}]\). In contrast, resetting of TGF by MD\([\text{NaCl}]\) begins after 20–30 min. It is likely that those events involved with the initial resetting of TGF are different from those that maintain it hours or days later. Most experimentation in this area has been done using microperfusion or a proximal tubular diuretic to impose a sustained increase in MD\([\text{NaCl}]\) for up to 2 h. Increasing MD\([\text{NaCl}]\) by these maneuvers causes rightward resetting of TGF over 30–60 min (28, 30). In diabetes, however, the stimulus for resetting must come from a decrease in MD\([\text{NaCl}]\) applied for hours or days and must yield an upward resetting of TGF. Data are published in which TGF resetting was tested in response to several hours of increased proximal reabsorption. This was done by first giving a carbonic anhydrase inhibitor to suppress proximal reabsorption for 24 h, then withdrawing the drug to induce the increase in proximal reabsorption relative to the baseline that was established during carbonic anhydrase inhibition. Micropuncture data obtained 8–10 h after withdrawal of the carbonic anhydrase inhibitor revealed hyperfiltration and a clear upward resetting of the TGF curve, notwithstanding that the animals had been in negative fluid balance for the prior 24 h (26). Therefore, resetting of TGF by the JGA can overcome an opposing influence of some magnitude from the ECF and is capable of causing the type of upward TGF resetting seen in early diabetes (see Fig. 4).

The foregoing example demonstrates that a macula densa mechanism for upward TGF resetting is a plausible explanation for what occurs in diabetes, but doesn’t prove it. It would be more convincing to demonstrate that one could prevent TGF resetting by specifically preventing hyperreabsorption, and it would be best to prevent hyperreabsorption by blocking the mechanism that leads to hyperreabsorption in the first place. In theory, proximal reabsorption might be increased in diabetes due to nerves or hormones that impinge directly on the proximal tubule, as a result of increased sodium-glucose cotransport, or because the tubule grows larger overall. It is difficult to use drugs that target the neurohumoral effectors of tubular reabsorption to alter the macula densa control of GFR because these same drugs will have confounding direct effects on the glomerulus. Also, there is no convincing evidence that diabetic hyperreabsorption is directly mediated by overactivity of one hormone or neurotransmitter in the tubule. Acutely blocking sodium-glucose cotransport with phlorizin does reduce proximal reabsorption, increase MD\([\text{NaCl}]\), and eliminate hyperfiltration (37). However, this is akin to activating TGF with a proximal tubular diuretic after TGF is already reset and doesn’t address the role of the tubule in long-term resetting of the TGF curve.

**Growth Is a Tubular Event**

All else being equal, the diabetic proximal tubule should reabsorb more because it is larger. The proximal tubule accounts for most of the increased kidney mass in early diabetes,
and growth of the early diabetic kidney can be attenuated by blocking ornithine decarboxylase (ODC), the rate-limiting enzyme in polyamine biosynthesis (19). ODC is not expressed in the diabetic glomerulus. Therefore, we blocked ODC as a means of examining the primary role of the tubule in hyperfiltration and TGF resetting. Difluoromethyl ornithine (DFMO), the ODC antagonist given during the first 7 days of streptozotocin diabetes, attenuated kidney growth and hyperfiltration in exact proportion. In fact, across groups that included nondiabetic and diabetic animals with and without DFMO, kidney weight predicted 95% of the difference in GFR. Furthermore, DFMO completely prevented both the primary increase in proximal reabsorption and the upward resetting of TGF in diabetes, as assessed by micropuncture. DFMO had no effect on any of these parameters in control animals (29). These findings imply the following sequence of events: diabetes causes the proximal tubule to grow. As the tubule grows, it reabsorbs more, thus causing MD[NaCl] to decline incrementally. As MD[NaCl] declines, GFR increases through the TGF mechanism, while TGF resets upward through a slower macula densa mechanism.

The present discussion is devoted to the consequences of kidney growth rather than its cause. For this purpose, DFMO was a useful tool. We have since identified the distal nephron as the main site of increased ODC expression in early diabetes and confirmed that blocking this pool of ODC prevents hyperplasia of the proximal tubule. These preliminary findings warrant speculation that the distal nephron could exert a paracrine influence on growth of the proximal tubule (6).

**DOES INVOKING THE MACULA DENSIA EXCLUDE A PRIMARY VASCULAR EFFECT?**

Several “defects” in the afferent arteriole have been identified in diabetes that are expected to cause vasoconstriction. Some of these are listed in Table 1. Why doesn’t a residual primary vasodilatory effect of diabetes become apparent when the primary tubular effect is eliminated? It is plausible that the reduced efficiency of electromechanical coupling in the afferent arteriole as reported in diabetes (4) could be part of the mechanism for upward TGF resetting. This hypothesis has not been tested. Another potential explanation is that primary defects in vasmotion are neutralized by strong vasoconstrictor influences that arise via feedback from a deranged systemic milieu in experimental diabetes. If those systemic influences were removed, then the diabetic kidney might hyperfilter independently of the tubular mechanism. One logical way to remove confounding systemic vasoconstrictor influences might be to expand the ECF by feeding a high-salt diet. However, we find that dietary salt has just the opposite effect on hemodynamics in the diabetic kidney.

**THE “SALT PARADOX”**

Any long-term change in salt intake must be matched precisely by a change in salt excretion. For salt excretion to change, there must be a change in GFR and/or tubular reabsorption. Because the normal kidney can adjust salt excretion to accommodate a wide range of dietary intake while GFR remains relatively constant, the tubule must mediate salt balance in most cases. However, it is not surprising that the kidney can respond to a high-salt diet by increasing GFR under some circumstances. For example, hypertensive African-Americans manifest this behavior (17). In contrast, it would be counter-intuitive for GFR to vary inversely with dietary salt. Nonetheless, this salt paradox occurs in diabetes.

The salt paradox was first noted in the form of renal vasodilation and augmented hyperfiltration among rats placed on a low-salt diet for 7 days after several weeks of streptozotocin diabetes (38). The paradox was subsequently confirmed using a high-salt diet in rats with early or established diabetes (36). Renal blood flow and GFR have also been shown to vary inversely with dietary salt in hyperfiltering diabetic patients (13). For good measure, the effect of dietary salt on the renin-angiotensin-aldosterone axis was essentially intact in these subjects.

The salt paradox cannot be explained by any primary vascular mechanism but can be explained in light of the tubular hypothesis, as outlined in Fig. 5. Changes in salt intake are sensed as a disturbance in ECF. In turn, ECF impacts various nerves and hormones that exert primary effects on the glomerulus and tubule. The efficiency of these nerves and hormones can be altered by disease, but their intrinsic character cannot. For example, diabetes may reduce the amount of renal nerve traffic or renin secretion that results from a given decrease in ECF, but diabetes cannot convert norepinephrine or angiotensin II into renal vasodilators. It is also important to note that the primary vascular and tubular limbs of the response to ECF are arranged in parallel. Therefore, it is possible for a disease or condition to simultaneously strengthen the primary tubular response and weaken the primary vascular response that arises from a given disturbance in ECF.

An upward perturbation in ECF will act through the baroreceptors to elicit a primary vasodilation and a primary decrease in tubular reabsorption. If the entire primary decrease in tubular reabsorption occurs downstream from the macula densa, then there will be an upward deviation in MD[NaCl] that results purely from the primary vascular effect, filtered by GTB. In turn, TGF will partially buffer the primary vascular

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**Fig. 5. Control system model for linking GFR to dietary salt by parallel pathways that include primary vascular or primary tubular effects. If the primary tubular effects dominate, GFR will vary inversely with dietary salt. TB salt, total body salt; solid lines, proportional effects; dashed lines, inverse effects. A negative feedback loop must contain an odd number of inverse effects.**
has been tested by micropuncture and confirmations that link glomerular filtration to ECF. This theory applies to SNGFR. Then, dietary salt was shown to exert a strong primary negative impact on proximal reabsorption and a strong positive impact on MD[NaCl] in diabetes. Finally, high salt caused the entire TGF curve to reset downward (reduced SNGFR), but not enough to offset the entire decrease in reabsorption. Therefore, the operating point shifted down along the TGF curve as one would expect for resetting mediated in the JGA (35).

We have observed the salt paradox in diabetic rats of different strains and both sexes in Germany and in the United States. The phenomenon has also been observed in diabetic patients (13). However, from the model (Fig. 5) one can envision circumstances under which the paradox would not be observed. The paradox will occur if, and only if, the primary tubular effect of ECF on GFR outweighs its primary vascular effect. Given the limited range of TGF, the capacity to increase GFR by reducing MD[NaCl] is clearly less than the capacity to reduce GFR through the systemic effects of salt depletion, which, in the extreme case, will result in zero GFR. This likely explains an angiotensin-mediated doubling of renal vascular resistance reported for non-insulin-treated diabetic rats that achieved zero salt excretion on a low-salt diet despite what should have been an ongoing osmotic diuresis (2).

It is not yet known what causes the diabetic proximal tubule to exhibit salt sensitivity. Thus far, we have been unable to implicate angiotensin (Munger KA, unpublished observations) or renal nerves (3) in the salt paradox.

THE TUBULAR HYPOTHESIS, DIETARY PROTEIN, AND VASODILATORY AMINO ACIDS

GFR normally increases during glycine infusion. This phenomenon has been termed “renal functional reserve.” Renal functional reserve is absent in diverse pathophysiological conditions that are united by an apparent tendency for glycine to reduce proximal reabsorption and activate TGF (reviewed in Ref. 9). Protein feeding is another maneuver that normally causes GFR to increase. Protein feeding also increases tubular reabsorption to such an extent that MD[NaCl] declines despite increased GFR (21, 22). Therefore, primary tubular effects contribute to the increase in GFR during glycine infusion and protein feeding. As additional background to the forthcoming argument, the glycine response is absent in some rats and humans with diabetes (8, 24, 25), and a low-protein diet is proposed to normalize glomerular hemodynamics and slow the progression of kidney failure in diabetes (11, 39).

The effects of dietary protein and glycine infusion vis-à-vis the tubular hypothesis of glomerular filtration were recently examined in rats after 1 mo of diabetes (14). Animals were studied before and during glycine infusion. Some were fed a low-protein diet for 1 wk beforehand. TGF activity was inferred from the difference between ambient SNGFR and the midpoint of the TGF curve. Early distal ionic content was used as a surrogate for MD[NaCl]. Data were combined with prior...
information regarding TGF and GTB slopes to mathematically determine the extent to which the effects of glycine and dietary protein on GFR were due to primary vascular or primary tubular events. A low-protein diet was found to normalize MD[NaCl] in diabetes through a primary decrease in tubular reabsorption similar to that predicted for normal rats based on prior work by Seney and Wright (22). SNGFR declined in response, although not to normal. Because the kidney did not shrink to a normal size during 1 wk of a low-protein diet, it is not surprising that normalizing MD[NaCl] failed to completely normalize SNGFR.

During glycine infusion in nondiabetic rats, SNGFR increased while MD[NaCl] remained constant. Lone primary vascular or tubular increases in SNGFR of this magnitude would have caused a substantial change in MD[NaCl]. Because none was observed, the glycine response in normal rats must involve both primary vasodilatation and a primary increase in tubular reabsorption. Eliminating either effect would reduce the glycine response by about half. In diabetes, the primary vascular effect of glycine was minimal, and glycine caused a primary decrease in proximal reabsorption. Prior restriction of dietary protein normalized the primary vascular effect of glycine, but the primary decrease in tubular reabsorption persisted. The renal functional reserve was partially restored. Although the renal functional reserve and the response to dietary protein have been known and studied for decades, little is known of the basic mechanisms. However, it is evident that both vascular and tubular mechanisms must be invoked to describe them. A graphical representation of the above findings and a model to explain them are presented in Figs. 6 and 7. Recent work prompts speculation that NMDA-glycine receptors in the kidney could mediate the glycine response (7) and that dietary protein modulates the expression of these receptors (Munger KA, unpublished observations), although work has not been completed to fully test this hypothesis.

SUMMARY

The factors that influence glomerular filtration may do so by impinging directly on the vasculature or directly on the tubule upstream from the macula densa. Primary tubular effects include TGF and can lead to TGF resetting. Decreased MD[NaCl] is the sine qua non of an increase in GFR mediated through TGF. Upward TGF resetting by the macula densa can be difficult to distinguish from vascular resetting but should yield a smaller P-D difference and lesser MD[NaCl]. In the normal kidney, primary tubular events account for the response to dietary protein and half of the response to glycine infusion, but they are not involved with salt balance. This implies that salt balance is normally mediated downstream from the macula densa. In early diabetes, kidney growth causes a primary increase in proximal reabsorption that is sufficient to classify diabetic hyperfiltration as a primary tubular event. In diabetes, the proximal tubule also assumes a major role in salt balance, leading to a paradoxical effect of dietary salt on GFR. The diabetic tubule retains the ability to increase reabsorption in response to long-term dietary protein, but not in response to acute glycine infusion. The “tubular hypothesis of glomerular filtration” explains at least three kidney function phenotypes in early diabetes.

GRANTS

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REFERENCES


