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Glomerular Hyperfiltration and the Salt Paradox in Early Type 1 Diabetes Mellitus: A Tubulo-Centric View

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Abstract. Diabetes mellitus contributes greatly to morbidity, mortality, and overall health care costs. In major part, these outcomes derive from the high incidence of progressive kidney dysfunction in patients with diabetes making diabetic nephropathy a leading cause of end-stage renal disease. A better understanding of the early dysfunctions observed in the diabetic kidney may permit the development of new strategies to prevent diabetic nephropathy. This review proposes a "tubulo-centric" view of glomerular function in early type I diabetes mellitus. The following are particularly discussed (*1*) the *primary* role of an increase in reabsorption by the proximal tubule in early glomerular hyperfiltration, (*2*) the role of sodium-glucose cotransport and tubular growth under these conditions, and (*3*) the *primary* role of reabsorption by the proximal tubule for the paradoxical relationship between dietary salt and glomerular filtration rate. Finally, an outline is presented of potential therapeutic implications for the prevention of diabetic kidney disease.

Diabetes mellitus exacts much human suffering and accounts for an increasing share of health care cost. In major part, this derives from the pool of diabetic patients who develop chronic kidney failure (1). It is therefore urgent to pursue an archetype of the diabetic kidney that ties together those events leading from the onset of diabetes to renal injury with the goal of achieving effective prevention. However, apropos of the Buddhist fable in which blind sages attempt to describe an elephant, diabetes research has compiled detailed descriptions of many elements that comprise the diabetic kidney without proving or disproving any particular theory about how those elements fit together. A growing list of renal phenotypes in diabetes is periodically updated in review articles. These can be roughly classified as pertaining either to renal hemodynamics, kidney growth, or kidney sclerosis. It is the purpose of this article to theorize a bridge between two of these areas, namely between kidney growth and renal hemodynamics via tubular reabsorption. The theory is hardly comprehensive and depends more on classical physiology than pathophysiology. The events we are interested in occur early in diabetes and far in advance of kidney sclerosis. Therefore, it may require an act of faith to assume that piecing these events together will advance the ultimate aim of preventing kidney failure. However, the current strategy of intervening after the onset of albuminuria (*i.e.*, after the onset of sclerosis) may be akin to closing the barn door after the horses are out. To prevent diabetic nephropathy it may prove better to identify and better understand the very early events that initiate the progressive disease.

Before attempting to link kidney growth to hemodynamics, we briefly review the two phenotypes themselves. The hemodynamic phenotype in early diabetes is characterized by glomerular hyperfiltration, which is likely a prerequisite for progressive diabetic nephropathy (2,3). Hyperfiltration does not depend on accumulation of NaCl in the body, because GFR can increase relentlessly in early diabetes, notwithstanding a decline in extracellular volume (4). Glomerular hyperfiltration has been attributed to abnormalities of the glomerulus and preglomerular vessels, although specific mechanisms have not been fully delineated (5,6). Another notable phenotype of the early diabetic kidney is that it grows. This growth phenotype is characterized by impressive enlargement of the kidney through both hyperplasia and hypertrophy, which begin at the very onset of diabetes (7). The proximal tubule accounts for most of the cortical mass to begin with, and the proximal tubule also accounts for the greatest share of growth in diabetes (8,9). On the basis of the principle of mass action, increasing the bulk of the tubule will increase the amount it transports; for present purposes, we consider increased proximal reabsorption to be the main consequence of kidney growth in early diabetes. The timing of kidney growth and glomerular hyperfiltration are such that it is not possible to measure a lag between the two. Therefore, if kidney size and GFR are linked by cause and effect, it will not be possible to establish which is the cause and which is the effect based on the order in which they occur.

Having stated certain characteristics of the growth and hemodynamic phenotypes in early diabetes, we now propose a simple model for uniting them. As the tubule grows, more of the glomerular filtrate is reabsorbed and less reaches the mac-

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ula densa at the end of Henle's loop. This causes GFR to increase through the normal physiologic action of the tubuloglomerular feedback (TGF) system. Simply stated, tubular hypertrophy causes glomerular hyperfiltration via hyper-reabsorption. From here, we proceed with some details of the model and review the data that support this "tubulo-centric" view of glomerular function in the early diabetic kidney. We will address the following: (*1*) evidence that a primary increase in reabsorption by the proximal nephron causes glomerular hyperfiltration; (*2*) the role of ornithine decarboxylase and polyamine synthesis as a factor in diabetic kidney growth leading to hyperfiltration; (*3*) the proximal tubule as initiator of a paradoxical relationship between dietary salt and glomerular filtration in diabetes; (*4*) potential therapeutic implications for the prevention of diabetic kidney disease. Almost all evidence currently available on these issues has been derived from patients and experimental models with type 1 diabetes mellitus. Fewer data have been acquired on the early renal pathophysiology in type 2 diabetes.

Evidence that a Primary Increase in Reabsorption by the Proximal Nephron Causes Glomerular Hyperfiltration

Common sense may suggest that glomerular hyperfiltration implies some defect in microvascular function or an imbalance of hormones impinging directly on the glomerulus. In contrast, we propose a tubulo-centric model in which glomerular hyperfiltration results mainly from *primary* changes in the tubule. Combining the principles of mass action and bulk flow along the tubule, one can predict the qualitative effects that a change in GFR will bring about in tubular reabsorption and distal delivery. This is the principle of glomerulotubular balance (GTB). Operating solely under the influence of GTB, an increase in GFR should always lead to an increase in net reabsorption, along with an increase in distal delivery, and a decrease in fractional reabsorption. Therefore, if fractional reabsorption and GFR happen to change in the same direction, this cannot be explained by GTB alone. In addition to GTB, there must be a change in the number of transporters or in their avidity, *i.e.*, a primary change in tubular reabsorption. Studies in hyperfiltering patients with type 1 diabetes mellitus (10,11) and hyperfiltering rats with streptozotocin (STZ) diabetes (12–16) have confirmed increased fractional reabsorption in the nephron segments upstream from the macula densa where fractional reabsorption should decline if governed solely by GTB. This implies a *primary* increase in tubular reabsorption in hyperfiltering patients and rats with early diabetes. Such a *primary* increase in reabsorption was shown directly for the proximal tubule using micropuncture in STZ diabetic rats. In these experiments, single nephron GFR (SNGFR) was manipulated by perfusing Henle's loop to activate tubuloglomerular feedback. This enabled proximal reabsorption to be established as a function of SNGFR. Using this method to control for the effects of SNGFR, a major *primary* increase in proximal reabsorption was documented for rats with early diabetes (16).

Sodium-Glucose Cotransport and Tubular Growth

What causes the primary increase in proximal tubular reabsorption in early diabetes? On the basis of microperfusion studies in STZ-diabetic rats, Bank and Aynedjian (12) proposed that high glucose in the proximal tubular fluid stimulates sodium absorption through sodium-glucose cotransport. Modeling the effects of sodium linked glucose transport on the active and passive components of proximal reabsorption predicts a positive effect of filtered glucose on net proximal sodium reabsorption up to the point where the filtered load approximately doubles the Tm for glucose (17). Recently, diabetic rat renal cortex was found to contain increased mRNA for the two sodium-glucose cotransporters, SGLT 1 and SGLT 2 (18), which might raise the Tm for glucose. Confirmation of increased SGLT-mediated sodium transport was demonstrated with micropuncture in STZ-diabetic rats with moderate hyperglycemia, by delivering the SGLT inhibitor, phlorizin, directly into the free-flowing early proximal tubule of nephrons with superficial glomeruli. In rats with diabetes, phlorizin elicited a greater decline in absolute and fractional reabsorption up to the early distal tubule (15). These studies support the concept that hyperglycemia causes more glucose to be filtered at the glomerulus which enhances SGLT-mediated reabsorption in the proximal tubule.

As previously stated, the kidney in general, and proximal tubule in particular, grow large from the onset of diabetes (8,9,19). To test whether tubular growth per se contributes to the primary increase in proximal reabsorption in early diabetes mellitus, we used difluoromethylornithine (DFMO), an inhibitor of ornithine decarboxylase (ODC), which had been shown previously to attenuate kidney growth in early STZ-diabetes mellitus (20). We observed that DFMO not only attenuated kidney growth but also eliminated the primary increase in proximal reabsorption in STZ-diabetic rats (16). Earlier, Seyer-Hansen (21) had reported that in early STZ-diabetic rats the glucose reabsorptive rate increased to the same extent as kidney weight. Hence, the primary increase in proximal reabsorption in early diabetes is the combined result of increased sodium-glucose cotransport and growth of the tubule.

Secondary Increase in GFR in Early Diabetes Mellitus and the Role of TGF

The tubuloglomerular feedback (TGF) system senses changes in the concentration of Na^+, Cl^- and K^+ at the luminal macula densa and induces reciprocal changes in SNGFR (22–24). TGF thereby stabilizes electrolyte delivery to the distal tubule which in these nephron segments allows fine adjustment of reabsorption and excretion according to bodily needs. A *primary* increase in proximal reabsorption will reduce the concentration of salt at the macula densa. This will elicit a TGF-dependent increase in SNGFR, which partially compensates for the impact of the original disturbance on macula densa delivery. However, because TGF is imperfect, macula densa salt will remain somewhat reduced. Pollock *et al.* (13) reported that the sodium concentration in early distal tubules of hyperfiltering STZ-diabetic Sprague-Dawley rats is remarkably low (about 30 *versus* 76 mM). We performed similar experiments

in diabetic rats of the Hannover-Wistar-Froemter strain from which it is possible to sample tubular fluid closer to the macula densa. In these studies, respective ambient early distal tubular concentrations of Na^+, Cl^-, and K^+ in nondiabetic rats were 21, 20, and 1.2 mM, respectively. In hyperfiltering diabetic rats of this strain, early distal concentrations of Na^+, Cl^-, and K^+ were reduced by 20 to 28%, indicative of a *primary* increase in upstream reabsorption (15).

The role of tubular reabsorption and a reduced TGF stimulus as antecedents to diabetic hyperfiltration is further supported by the observation that adding phlorizin to the early proximal tubule of diabetic rats caused a decisive reduction in SNGFR in diabetic rats along with a major increase in early distal electrolyte concentration (15). The only reasonable explanation for this combination of findings is that blocking a high rate of sodium-glucose co-transport in the proximal tubule reduced SNGFR by activating TGF (15). Increased reactivity of TGF per se was not likely involved because the incremental slope of the TGF response to any given change in macula densa salt is reduced in STZ-diabetes (14,25). Tubular control of GFR has also been demonstrated in dogs where acute hyperglycemia in dogs caused GFR to increase, but only if TGF was intact (26).

Evidence that increased tubular reabsorption causes diabetic hyperfiltration is also available from hyperfiltering human diabetic patients in whom proximal reabsorption was measured by lithium clearance. In these patients, fractional proximal reabsorption was elevated and positively correlated with GFR (10). Again, on the basis of the principle that GTB cannot explain a positive correlation between GFR and fractional proximal reabsorption, these findings imply a *primary* increase in proximal reabsorption leading to a TGF-mediated increase in GFR.

Finally, intervening with DFMO to reduce early diabetic tubular hypertrophy and hyper-reabsorption also diminished glomerular hyperfiltration in direct proportion to the effect on kidney size (16). Along these lines, each maneuver that succeeds at attenuating kidney growth in diabetes (which may occur with normalization of blood glucose levels by insulin treatment [9,27–28], manipulations of growth hormone signaling, etc.) is expected to also reduce GFR by preventing hyper-reabsorption. Furthermore, glomerular hyperfiltration persists in some diabetic patients even after euglycemia is achieved through aggressive insulin therapy. Established tubular growth reverses only slowly, and complete normalization of kidney size is not achieved in patients even after intensive treatment with insulin supplementation (27–29); therefore, glomerular hyperfiltration may endure in these patients due to persistent tubular enlargement and hyper-reabsorption independent of the average blood glucose level.

The *primary* increase in glucose-dependent tubular reabsorption, in addition to reducing the TGF signal, can lower hydrostatic pressure in Bowman space (P_{BOW}) in diabetes (15). Enhanced reabsorption is expected to reduce P_{BOW} by lowering the flow rate through distal nephron segments where flow resistance is high (30). Furthermore, in early STZ-diabetic rats, tubular growth increases luminal diameter of high flow resistance distal nephron segments (9). Hence, tubular growth might contribute to the decrease in P_{BOW} in diabetes through its effects on tubular reabsorption and tubular diameter. All else remaining equal, this reduction in P_{BOW} could make a small but significant contribution to glomerular hyperfiltration in diabetes (15). Figure 1 integrates the outlined concept of a *primary* role of the proximal tubule for glomerular hyperfiltration in early diabetes mellitus.

The Role of Ornithine Decarboxylase and Polyamine Synthesis in the Growing Diabetic Kidney

We have argued the case for *primary* increases in proximal reabsorption leading to glomerular hyperfiltration in diabetes. What might be the initiating and sustaining factors that contribute to increases in kidney size? Careful studies performed by Rasch and Norgaard (7) suggest that kidney hypertrophy does not account for the entire process. Instead, hypertrophy and hyperplasia are both involved. Another characteristic of the early diabetic kidney is that growth depends, at least in part, on overexpression of the enzyme, ornithine decarboxylase (ODC) (20). ODC converts ornithine to putrescine. This is the rate-limiting step in polyamine synthesis and appears to be a necessary early step for all cell division and for some forms of hypertrophy. Prior knowledge that ODC blockade would mitigate kidney growth in early diabetes proved a useful tool to verify the tubular hypothesis of glomerular hyperfiltraion (16). However, not much is known about the specific affectors or effectors of ODC in diabetes apart from the observation that ODC seems to behave differently in diabetes than in other

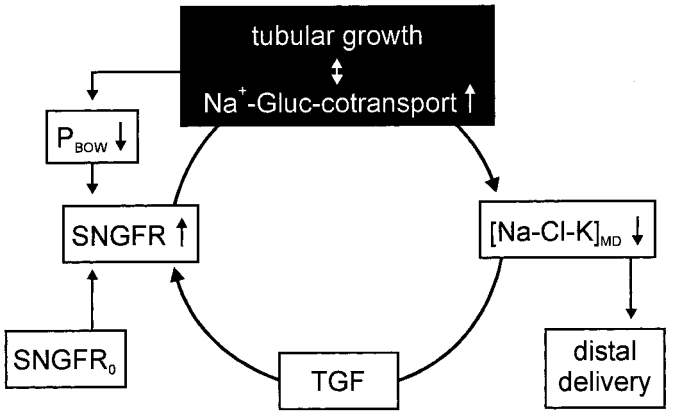

Figure 1. Tubular basis of glomerular hyperfiltration in early diabetes mellitus. Hyperglycemia causes a *primary* increase in proximal tubular reabsorption through enhanced Na^+-glucose (Gluc) cotransport and tubular growth. The enhanced reabsorption rates reduce the TGF signal at the macula densa ($[Na\text{-}Cl\text{-}K]_{MD}$) and via tubuloglomerular feedback (TGF) increase single nephron GFR (SNGFR). Enhanced tubular reabsorption and growth in addition reduce hydrostatic pressure in Bowman space (P_{BOW}), which by increasing effective filtration pressure also increases SNGFR. The resulting increase in SNGFR (i) serves to partly restore the fluid and electrolyte load to the distal nephron, but at the same time (ii) initiates and/or maintains development of diabetic nephropathy. $SNGFR_0$ is the input to SNGFR independent of TGF.

models of rapid kidney growth. For example, ODC activity increases in the remaining kidney after uninephrectomy, but it remains elevated for less than 24 h (31). In contrast, increased ODC activity persists in the STZ-diabetic kidney for several weeks (16,20). The specific mechanisms leading to persistent ODC expression in diabetic kidneys are not known at this time, but the finding is characteristic of this form of kidney growth.

What are the logical avenues to pursue toward understanding kidney growth in diabetes? The potential roles of various growth factors and cell-signaling molecules in diabetic kidney hypertrophy have been reviewed elsewhere (32). However, the earliest change in the local environment of the proximal tubular cell in diabetes is the increase in filtered glucose leading to increased apical entry of sodium and glucose via SGLT. One might imagine glucose and/or sodium in the cell providing some stimulus for the cell to grow. However, by immunostaining, it appears that the increase in ODC expression in early diabetes mainly occurs in the distal nephron (unpublished observation) even though ODC inhibition prevents growth of the proximal tubule. Therefore, polyamines may pass from the distal to proximal tubule in a paracrine fashion. What might signal the distal nephron to express ODC in early diabetes? NaCl delivery to the distal tubule is not increased early in diabetes because of the proximal hyperabsorption; therefore, glucose becomes a logical candidate. Holck and Rasch (33) have shown glycogen accumulation in the distal nephron of diabetic rats that likely correlates with delivery of glucose via the tubular fluid. This is a slower process than ODC expression, but it does verify that large amounts of filtered glucose affects the distal nephron.

In contrast to ODC, arginine decarboxylase (ADC), which converts arginine to agmatine, is less active in early diabetic kidneys (16). Renal ADC and ODC activities are also inversely correlated in the model of contralateral nephrectomy (unpublished observation). Furthermore, agmatine suppresses both ODC expression and polyamine uptake by a variety of mechanisms in numerous cell lines (34), and agmatine-treatment reduced proliferation in the Thy-1 model of proliferative glomerulonephritis (35). Why diabetic kidneys manifest less ADC activity and whether this contributes meaningfully to the increased ODC expression in the particular case of diabetes remains to be determined.

The Salt Paradox in Early Diabetes Mellitus

In addition to causing a high baseline GFR, diabetes also alters the renal hemodynamic response to a variety of stimuli. For example, insulin, which is a renal vasodilator in the normal rat, causes renal vasoconstriction in the diabetic kidney (36). Changes in dietary salt constitute another such stimulus, the renal response to which is abnormal in diabetes. In 1993, we placed male STZ-diabetic rats on a low-salt diet for 7 to 8 d after 6 wk of diabetes. At the time, we were interested in whether the renin-angiotensin system could be activated by reducing salt intake in order to reverse hyperfiltration. To our surprise, the maneuver produced an opposite effect; it further increased renal blood flow, GFR, and kidney weight in diabetic rats, whereas low-NaCl diet did not significantly alter these parameters in nondiabetic controls (37). We extended this observation by demonstrating renal vasoconstriction in response to a high-salt diet among female rats with early (1 wk) or established (4 to 5 wk) STZ-diabetes (38). We have also confirmed the paradoxical effect of dietary salt on SNGFR by micropuncture in male (39) and female (unpublished observation) rats with established STZ-diabetes. In 1997, Miller (40) reported the same phenomenon in young type I diabetic patients who responded to a low-salt diet with renal vasodilation and a rise in GFR (40). This strange salt paradox that pertains to diabetic human and animal subjects may reveal something basic about the main controller of renal function in diabetes, and we offer the following logical argument that the salt paradox is another manifestation of the tubulo-centric nature of renal function in diabetes.

In the long term, salt excretion must always match salt intake. It is clear that the kidney can adjust salt excretion to accommodate a wide range of dietary salt intakes while renal blood flow and GFR remain relatively constant. This implies that the kidney mainly adjusts salt excretion by changing tubular reabsorption, primarily in the distal nephron. However, there are other circumstances where dietary salt significantly influences GFR. One example of this is the hypertensive African-American population in which a high-salt diet causes GFR to increase (41). If all else remains equal, increasing GFR will increase salt excretion. Therefore, it is not surprising that the kidney can invoke an increase in GFR as part of a mechanism to increase salt excretion. However, the negative impact of dietary salt on GFR in diabetes is counterintuitive with regard to salt balance.

Pathophysiology of Salt Paradox in Early Diabetes Mellitus

Salt balance is a central tenet of Arthur Guyton's profound theory of negative feedback with infinite gain (42). From these principles it follows that a change in steady-state salt intake will cause a parallel change in total body salt content, that salt excretion must be proportional to total body salt content, and that salt excretion and total body salt can be represented by elements in a simple negative feedback loop (43). The chain of events leading from total body salt to salt excretion can be broken into several parallel paths, each representing a particular hormone or effector as outlined in a working model for salt balance adapted from the Guyton approach (44), which is illustrated in Figure 2A. Each of these effectors elicits primary vascular effects that influence RBF and GFR and/or primary tubular effects that influence reabsorption independent of GFR. Changes in GFR and tubular reabsorption subsequently converge as the ultimate determinants of salt excretion. The renin-angiotensin system, natriuretic peptides, renal nerves, and pressure natriuresis mechanisms are the major systemic influences that connect salt excretion to changes in total body salt. These influences, however, confer only positive primary vascular effects of dietary salt on RBF and GFR. Altering their efficiency can strengthen this positive effect or reduce it to zero but cannot make it negative. This is made apparent by tracing each of the parallel pathways in Figure 2A which borrows from

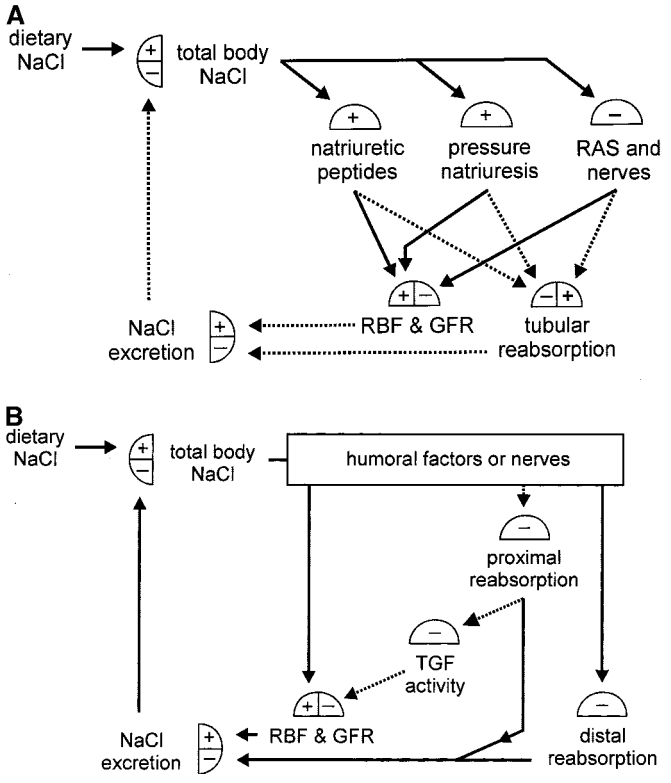

Figure 2. (A) In classical physiology, renal function and total body NaCl are linked by several parallel feedback loops. Paths from dietary NaCl to GFR and renal blood flow (RBF) are highlighted (black arrows). Each highlighted path contains an even number of "−" signs, indicating a positive influence of dietary NaCl on GFR and RBF. Interfering with these processes can alter the strength of this influence, but cannot make it paradoxical. (B) Incorporating TGF provides a pathway whereby dietary NaCl can inversely impact GFR and RBF via a *primary* change in proximal (*i.e.*, upstream to macula densa) reabsorption (note the odd number of − signs along the dotted path). Thus, GFR and RBF are subject to competing influences in response to changes in dietary NaCl. The NaCl paradox arises when TGF prevails.

control theory (45). Hence, the effect of dietary salt on the diabetic kidney presents a paradox that cannot be explained by primary vascular effects of the neurohumoral or pressure natriuresis systems.

Renal salt excretion is determined by filtration and reabsorption; therefore, a negative impact of increased salt intake on GFR is permissible if outweighed by an opposing change in avidity of the tubule for salt. However, our concepts of the renal response to salt associate high-salt intake with suppression of neurohumoral systems, which cause vasoconstriction and enhance tubular reabsorption. No primary vascular effect of the neurohumoral or pressure natriuresis systems is a candidate; therefore, we turn to TGF. As illustrated in Figure 2B, total body salt also connects to GFR by way of the TGF system. Furthermore, on the bases of a potential effect of salt on tubular reabsorption upstream to the macula densa and the normal operation of TGF, this arrangement confers a negative influence of salt content on GFR. Hence, the net effect of salt content on GFR results from a balance of forces between the *primary* vascular changes induced by the neurohumoral-pressure natriuresis systems on the one hand and the *primary* tubular changes upstream to the macula densa affecting GFR through the TGF system on the other hand. The salt paradox will result when the latter system predominates. We therefore predict that TGF must be the dominant force linking GFR to dietary salt in diabetes.

The above conclusion has been confirmed experimentally by micropuncture. Normal rats on various salt intakes were able to manage salt balance with no significant primary effect on reabsorption upstream to the macula densa. Thus, an inverse effect of dietary salt on GFR mediated by TGF did not occur (39). This is appealing from a teleological standpoint. In comparison, we observed a prominent negative impact of dietary salt on reabsorption upstream from the macula densa in STZ-diabetic rats (39). Feeding a high-salt diet to diabetic rats led to a major *primary* decrease in proximal reabsorption (recall that a *primary* change in reabsorption is one which is not attributable to GTB). Furthermore, by measuring concentrations of Na^+, Cl^-, and K^+ in early distal tubular fluid in rats on high-salt and low-salt diet, we confirmed that this primary effect of dietary salt on tubular reabsorption strongly links the TGF signal and the consequent reduction in GFR to dietary salt in diabetes. Thus, the salt paradox in diabetes is explained by a shift in the balance of forces between TGF and the other neurohumoral regulators of glomerular filtration. This occurs because diabetes causes proximal tubular reabsorption to become more sensitive to changes in dietary salt. This results in a strong influence of dietary salt over the TGF signal such that eating more salt leads to greater activation of TGF and vice versa. Obviously, given the limits of TGF, the capacity to increase GFR by reducing distal salt delivery must be less than the capacity to reduce GFR through the systemic influences of salt depletion, which, in the extreme case, will result in zero GFR. Hence, if dietary salt restriction progresses to the point of actual salt depletion, the salt paradox will become inapparent. For example, this should happen when osmotic natriuresis during initiation of diabetes or due to *severe* hyperglycemia causes total body salt to decline below the level where salt normally disappears from the urine (46,47).

The mechanism that makes the diabetic proximal tubule more sensitive to dietary salt remains to be determined. Angiotensin II and renal nerves are the prominent effectors that link proximal reabsorption to the total body salt. Clearance experiments, however, indicate that the enhanced salt-sensitivity of proximal tubular reabsorption is not mediated by renal nerves or angiotensin II acting through angiotensin AT1 receptors, inasmuch as chronic renal denervation (unpublished observation) or chronic treatment with losartan (37) does not prevent the rise in GFR in response to low-sodium diet in STZ-diabetic rats. Furthermore, preliminary micropuncture data do not reveal any particular tendency for dietary salt to affect the ambient influence of angiotensin II over proximal reabsorption in diabetes (unpublished observation).

Is There a Link between Basal Glomerular Hyperfiltration and the Salt Paradox in Early Diabetes Mellitus?

The salt paradox arises in diabetes because the proximal tubule is strikingly sensitive to salt intake, making GFR a "slave" to tubular function. This dovetails with the "tubular hypothesis" of basal diabetic hyperfiltration according to which diabetic hyperfiltration per se results from a primary increase in proximal reabsorption as outlined above. Figure 3 schematically depicts the relationship between salt intake and salt reabsorption in the proximal tubule in early diabetes. According to this relation, the basal tubular hyper-reabsorption (under conditions of so-called normal salt intake) may be interpreted as a consequence of diabetes-induced hypersensitivity of proximal reabsorption to salt intake, where basal hyper-reabsorption and, thus basal glomerular hyperfiltration only occurs in diabetes because normal salt intake is lower than the intake where the relationship in diabetic patients crosses the line of nondiabetic patients. Speculating about a possible common basis for basal glomerular hyperfiltration and the salt paradox, a salt-sensitive transport in the proximal tubule, which, through variation in sodium glucose cotransport, causes secondary changes in tubular growth and GFR could be an attractive mechanism.

Potential Therapeutic Perspectives

The pathophysiologic concept outlined identifies enhanced proximal tubular reabsorption, mediated by increased sodium glucose cotransport and kidney growth as a potential target for the prevention of renal hemodynamic changes in early diabetes, which might avert later damage to the kidney. A high-salt diet may serve to reduce tubular transport proximal to the macula densa and diminish glomerular hyperfiltration in early diabetes. The current dietary recommendation of the American Diabetes Association is to restrict salt intake in diabetic patients (48). Glomerular hyperfiltration is viewed as deleterious; therefore, this relationship of dietary salt and GFR could be clinically relevant. Obviously, a high-salt diet would only benefit a diabetic patient to the extent that the salutary effect of preventing hyperfiltration was not offset by nefarious consequences of sodium-dependent hypertension. The balance of these two effects cannot be predicted a priori, and it may actually be different in type 1 and type 2 diabetes. Clinical research with permanent renal injury as the endpoint will not be a practical way to resolve this issue given the lag time involved, but the problem might be tractable using a surrogate endpoint such as regression of kidney hypertrophy.

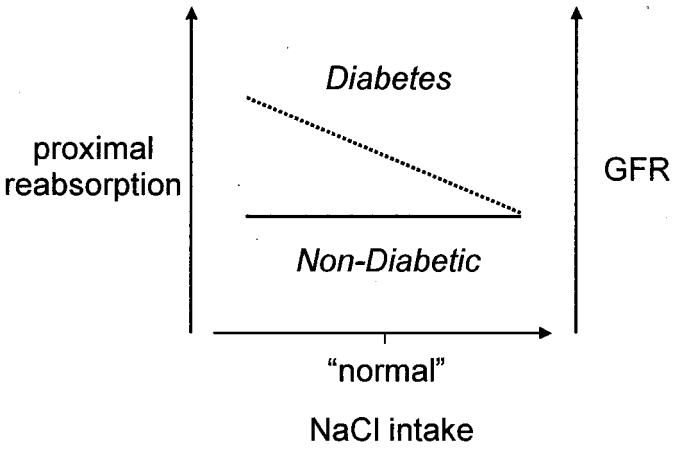

Figure 3. Schematic presentation of the relationship between NaCl intake and reabsorption in the proximal tubule as well as GFR. Is there a link between basal glomerular hyperfiltration and the salt paradox in early diabetes mellitus? See text for further explanation.

Optimal insulin treatment forms the modern basis for preventing of organ damage in diabetes. However, exogenous insulin cannot match the kinetics of a healthy endocrine system. Therefore, all diabetic patients experience episodes of hyperglycemia. It is clear that continuous florid hyperglycemia is not required for diabetic hyperfiltration and kidney growth to occur. Young patients with type I diabetes may hyperfilter while maintaining HbA1C levels that are generally viewed as acceptable (7 to 7.5%; J. Miller, personal communication). However, the smoothing function performed by the HbA1C will mask transient increases in blood glucose, and it may be that intermittent signals in the form of transient elevations in filtered glucose are sufficient to stimulate kidney growth and contribute to sustained glomerular hyperfiltration. Furthermore, patients may be heterogeneous in their capacity to upregulate SGLT and increase proximal tubular reabsorption in response to hyperglycemia, resulting in variable degrees of kidney growth and glomerular hyperfiltration. If glomerular hyperfiltration is a risk factor for diabetic nephropathy, then the diabetic patients at highest risk for diabetic nephropathy are those most susceptible to glucose-induced stimulation of proximal tubular reabsorption and growth. Thus we may learn that genetic polymorphisms affecting sodium-glucose cotransport or glucose-induced proximal tubular growth account for the fact that some patients develop diabetic nephropathy while others do not.

Given that occasional hyperglycemia is unavoidable in patients with diabetes and that this may be sufficient to cause kidney growth with deleterious consequences, the need becomes evident for some treatment which prevents the kidney from sensing and responding to transient increases in filtered glucose. One means to accomplish this might be through the use of SGLT inhibitors to attenuate the immediate effect of blood glucose on proximal reabsorption. The glycosuric effect of inhibiting SGLT, in addition, is expected to lower blood glucose concentrations. Whether prevention of SGLT-mediated transport in early diabetic kidneys is sufficient to prevent the kidney from growing and/or facilitates reversal of established tubular growth remains to be determined. A complete understanding of the mechanisms triggering kidney growth is required, and such knowledge may help identify additional new therapies.

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