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Primary kidney growth and its consequences at the onset of diabetes mellitus*

Review Article

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Summary. Diabetes mellitus is a primary contributor to progressive kidney dysfunction leading to end-stage renal disease (ESRD). In the early phase of diabetes, prior to the onset of further complications, both kidney size and glomerular filtration rate (GFR) increase. Glomerular hyperfiltration is considered a risk factor for downstream complications and progression to ESRD. Abnormalities in vascular control have been purported to account for the glomerular hyperfiltration in early diabetes. In this review we discuss a *tubulo-centric* concept in which tubular growth and subsequent hyper-reabsorption contribute to the onset of glomerular hyperfiltration that demarks the early stage of diabetes. Kidney growth, in this concept, is no longer relegated to a compensatory response to hyperfiltration, but rather plays a *primary* and *active* role in its genesis and progression. As such, components of kidney growth, such as the polyamines, may provide a means of early detection of diabetic kidney dysfunction and more effective therapeutic intervention.

Keywords: Type-1 diabetes – Hyperfiltration – Tubuloglomerular feedback – Kidney – Polyamines – Hypertrophy

Introduction

Diabetic nephropathy is a primary cause of end-stage renal disease (ESRD), yet the mechanisms responsible for the onset and progression of this disease have not been fully resolved. Diabetes mellitus affects the kidney in stages. At the very onset of diabetes, the kidney grows large and the glomerular filtration rate (GFR) becomes supranormal (Mogensen, 1971; Rasch and Norgaard, 1983). Tubulointerstitial fibrosis and kidney failure occur many years later. Damage from glomerular hyperfiltration in the early stage of the disease is a central tenet for the later downstream complications that eventually culminate in ESRD (O'Bryan and Hostetter, 1997). The contemporary management of patients with diabetes is aimed toward slowing the progression to kidney failure after the onset of albuminuria or proteinuria. However, at this advanced stage even the strictest regiment cannot entirely eradicate disease progression. Identifying and understanding the very early events in the diabetic kidney could prove beneficial for earlier diagnosis and more effectual therapeutic intervention and management.

In patients and in experimental animal models, the early phenotype of renal growth and glomerular hyperfiltration provokes or accelerates the subsequent demise of a diabetic kidney (Mogensen, 1986; O'Bryan and Hostetter, 1997; Wolf and Ziyadeh, 1999). Although kidney growth and increased GFR are considered associated at the advent of the disease, it becomes a chicken and egg conundrum, i.e., which came first? Or more specifically, which is the cause and which the effect? Due to the very close temporal profile of these two phenomena, this has been a difficult question to address.

Early glomerular hyperfiltration could be the result of glomerular vascular abnormalities leading to renal vasodilation. Renal vasodilation leads to hyperfiltration with eventual damage to the kidney. In this scenario

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hyperglycemia-induced hyperfiltration is thought to cause a *compensatory* growth response of the kidney, principally in the proximal tubules. Logical conjecture from this concept would view the resultant, compensatory tubule growth and increase in reabsorption capacity as a response to a greater tubular load in order to prevent urinary salt and fluid losses.

In contrast, we propose a *tubulo-centric* concept in which diabetes-induced growth and hyperreabsorption of the proximal tubules *actively* and *primarily* contribute to glomerular hyperfiltration (Thomson et al., 2001, 2004; Vallon et al., 1999, 2003, 2005). The tubulo-centric concept involves the tubuloglomerular feedback (TGF) system. According to this concept primary tubular events (changes in tubular reabsorption, i.e. changes in re-uptake of salt and fluid from the tubular lumen back into the plasma) affect via the normal physiologic operation of the TGF system the GFR of the same nephron, as will be discussed in more detail below. Diabetes does not just affect the glomerular vasculature, but also affects the tubules. Examining how diabetes affects the tubule and the interaction between the tubule and the glomerulus will aid in understanding the pathophysiology of renal hemodynamics in early diabetes and possibly the later development of diabetic nephropathy.

Kidney function and regulation by tubuloglomerular feedback (TGF)

The function of the kidney is well known to remove metabolic waste products from the blood and excrete them in the urine. The kidney is also vital in maintaining the body's water and inorganic ion balance and thus contributes to blood pressure regulation.

The functional unit of the kidney, the single nephron, shows a particular organization: blood is filtered in the glomerulus and the filtrate passed to a tubular system along which by reabsorption and secretion the final composition of the urine is established. The tubule will eventually again make contact with its own glomerulus (Fig. 1). The structures that comprise this tubulo-glomerular contact site, aptly termed the juxtaglomerular apparatus, significantly contribute to the fine coordination between glomerular filtration and tubular reabsorption through the mechanism of tubuloglomerular feedback, or TGF. The TGF mechanism refers to a series of events whereby changes in the Na^+, Cl^- and K^+ concentrations in the distal tubular fluid are sensed by the macula densa cells of the juxtaglomerular apparatus. The macula densa then induces *inverse* changes in GFR. For example, a reduction in proximal reabsorption would elicit a higher salt load to the macula densa, which would then signal for a reduction in the GFR of that nephron. Likewise, a decrease in salt load to the macula densa would result in an increase in single nephron GFR (Fig. 1). Thus, a feedback loop exists within each nephron to regulate its own filtration rate in response to the salt concentration sensed by the macula densa. In this way the TGF mechanism maintains the fluid and electrolyte delivery to the further distal nephron segments within certain limits. This facilitates the fine adjustments in reabsorption or secretion in these nephron segments under the control of hormones such as aldosterone and vasopressin. Thus, the TGF mechanism helps to coordinate glomerular filtration rate and tubular reabsorption of fluid and electrolytes. The importance of this coordination may be appreciated from the fact that a disparity of as little as 5% between glomerular filtration and subsequent reabsorption would lead to a net urinary loss of about one third of total extracellular fluid volume in one day, a situation which inevitably would lead to vascular collapse.

In summary, the TGF mechanism serves to establish an appropriate balance between tubular reabsorption upstream from the macula densa and GFR (Vallon, 2003).

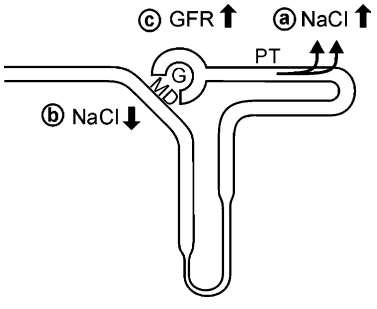

Fig. 1. Early kidney growth and glomerular hyperfiltration in diabetes. *a* Diabetes *primarily* increases the size of the proximal tubules and thus salt reabsorption at this site. *b* This reduces the salt delivered to the macula densa, and *c* via TGF increases single nephron GFR, and thus contributes to diabetes-induced glomerular hyperfiltration. *G* Glomerulus; *PT* proximal tubule; *MD* macula densa (adapted from Vallon, 2003)

The tubular hypothesis of glomerular hyperfiltration in early diabetes

There is now convincing evidence for a *primary* increase of fluid and electrolyte reabsorption in nephron segments upstream of the macula densa, including the proximal tubule, in rats with streptozotocin (STZ)-induced experimental Type 1 diabetes (Bank and Aynedjian, 1990; Thomson et al., 2001; Vallon et al., 1995, 1999, 2003) as well as in early Type 1 diabetes in humans (Brochner-Mortensen et al., 1984; Hannedouche et al., 1990; Vervoort et al., 2005). We consider this rise in reabsorption *primary*, as it

is not just the consequence of glomerular hyperfiltration. By that we mean that not only is the absolute proximal reabsorption (APR) of salt increased in diabetes, but the fractional proximal reabsorption (FPR), or the APR normalized for GFR, is also increased. This indicates a *primary*, hyperfiltration-independent increase in proximal salt reabsorption in early diabetes.

The aberrant reabsorption of salt up-stream of the macula densa results in reduced salt at the salt-sensing macula densa cells in early diabetes (Vallon et al., 1999). The macula densa cells at the tubulo-glomerular contact site, in turn, signal for an increase in filtration rate. This contributes to the glomerular hyperfiltration observed in early diabetes, which serves to normalize the salt load to the distal nephron (Fig. 1). In this concept, the increase in tubular salt transport, which contributes to hyperfiltration, is the combined result of tubular growth and increased Na^+/glucose cotransport (as a consequence of the hyperglycemia) (Thomson et al., 2001; Vallon et al., 1999, 2003). In this review we will address the growth component.

The kidney growth response in early diabetes mellitus

With regard to total volume, early growth of the diabetic kidney is attributed primarily to the proximal tubule, where a period of hyperplasia precedes diabetic hypertrophy (Huang and Preisig, 2000). DNA synthesis is increased in the proximal tubules of STZ-induced diabetes, peaking at day 2, with hyperplasia and hypertrophy contributing an equal extent to kidney growth (Rasch and Norgaard, 1983). This is in accord with in vitro studies where high glucose treatment of a glomerular mesangial cell line stimulates a biphasic early cell proliferation (24 to 48 h) and a later growth inhibitory phase (72 to 96 h) (Wolf et al., 1992). The early proliferative phase is associated with increased expression of the immediate early genes c-myc and egr-1 and increased proliferating nuclear cell antigen, whereas the later antiproliferative phase is attributed to the bioactivation of endogenous transforming growth factor beta (TGF-β). STZ-induced diabetes in rats also stimulates growth factor expression and early mesangial proliferation observed at day 3, with increased TGF-β expression at 14 and 30 days (Young et al., 1995).

Growth factor induction

Numerous growth factors are associated with the early onset of diabetes, including insulin-like growth factor (IGF-1), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and diacylglycerol (DAG). All of these factors induce ornithine decarboxylase (ODC) activity (Bianchi et al., 2002; Higaki et al., 1993; Hovis et al., 1986; Huber and Poulin, 1996; Olanrewaju et al., 1992; Schulze-Lohoff et al., 1991; Torring et al., 1997). ODC is the first and rate-limiting enzyme of polyamine biosynthesis. Polyamines are required components for hyperplasia and most likely also for hypertrophy in the early diabetic kidney (Deng et al., 2003; Pedersen et al., 1992; Thomson et al., 2001). Also in the heart, overexpression of ODC markedly increases α-adrenergic induced hypertrophy (Shantz et al., 2001). Initial ODC induction occurs as a mid-G1 phase event, with polyamine transport also increasing in cell cycle progression.

Phosphoinositide 3-kinase/Akt (Pi3K/Akt)

Activation of the phosphoinositide 3-kinase (PI3K)/Akt (Kimball et al., 1999; Shantz, 2004) and protein kinase C (PKC) pathways (Hovis et al., 1986; Hsieh and Verma, 1988; Jetten et al., 1985), both important mediators for the progression of diabetes, can affect ODC activity. Activation of the PI3K/Akt pathway brings about a complex and coordinated series of events with resultant anti-apoptotic, yet pro-growth, survival, protein translation, cell cycle entry, and angiogenic effects (Fig. 2).

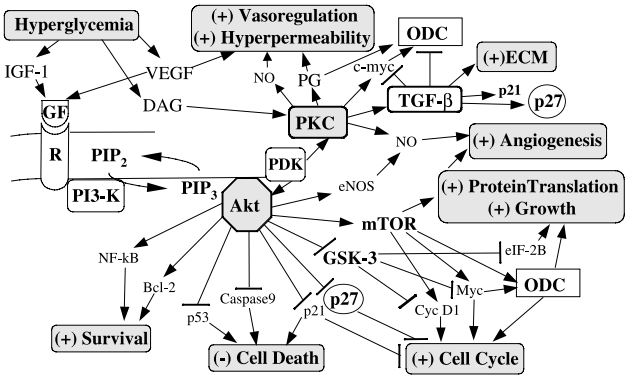

Fig. 2. PI3K/Akt and PKC pathways in the early diabetic kidney. Recruitment and activation of Akt is central to a coordinated series of anti-death, pro-growth pathways. Early induction of growth factors in diabetes, such as VEGF, will via PKC activation enforce the Akt pro-growth pathway, including induction of ODC. The latter is of primary importance for the early growth of the diabetic kidney. PKC induction of TGF-β may institute the later anti-proliferative, pro-fibrotic effects. Arrows represent stimulatory, and bars inhibitory, effects. *GF* Growth factor (e.g., IGF-1, VEGF); *R* receptor; *PG* prostaglandins; *ECM* extracellular matrix; *Cyt* cytokines

VEGF, induced in both the STZ-model (Type 1) (Cooper et al., 1999; Senthil et al., 2003) and the db/db mouse model (Type 2) of diabetes (Senthil et al., 2003), increases protein synthesis in renal epithelial cells utilizing the PI3K/Akt pathway to mediate its hypertrophic effects (Senthil et al., 2003). As such, ODC would be a downstream effector of VEGF (Lan et al., 2000). The use of neutralizing antibodies to VEGF suppresses hypertrophy in a high protein diet model (Schrijvers et al., 2002), and improved a number of renal parameters in both the STZ-induced (de Vriese et al., 2001) and db/db mouse (Flyvbjerg et al., 2002) models of diabetes.

IGF-1 may be the most studied mediator of the early growth phase in diabetes, and like VEGF the effects of IGF-1 are attributed principally to the PI3K/Akt pathways (Fig. 2). There are numerous examples of IGF-1 administration increasing ODC activity, and of ODC inhibition blocking the mitogenic effects of IGF-1 (Glikman et al., 1990; Mattsson et al., 1990; Olanrewaju et al., 1992; Torring et al., 1997; Widmer et al., 1985). In vitro, IGF-1 overexpression in NIH/3T3 cells increases ODC activity (Kato et al., 1993), whereas a functional mutation in the IGF-1 receptor prevents IGF-1 induction of ODC activity (Kato et al., 1994). IGF-1 also increases the half-life of ODC activity (Huber and Poulin, 1996). In vivo, temporal induction of IGF-1 correlates with induction of ODC activity (Hayakawa et al., 1996). Also at the onset of STZ diabetes, the rapid yet transient induction of IGF-1 (Fervenza et al., 1997; Price et al., 1997) temporally correlates with renal ODC expression and activity (Deng et al., 2003; Pedersen et al., 1992; Thomson et al., 2001), induction of intracellular polyamines in the kidney cortex (Deng et al., 2003), and the proliferative phase (Figs. 2 and 3). Together these studies establish a strong link between diabetes induced growth factor expression and ODC activation in early diabetes.

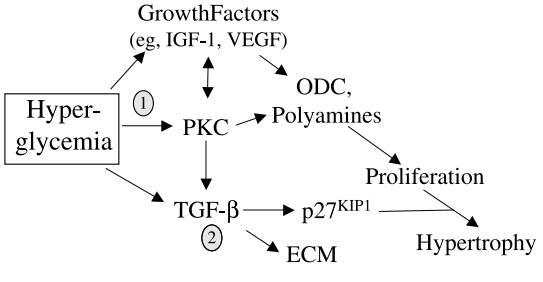

Fig. 3. Simplified sequence of early diabetic kidney growth. *1* Hyperglycemia induction of growth factors leads to early proliferation. *2* TGF-β/$p27^{KIP1}$ induction in diabetes occurs within a few days of onset. $p27^{KIP1}$ mediates a G1 arrest that initiates the switch from hyperplasia to hypertrophy. TGF-β also suppresses ODC activity and induces the formation of extracellular matrix (ECM) and fibrosis

Protein kinase C (PKC)

One important signal transduction pathway that has been attributed to promoting diabetic kidney growth involves PKC (Derubertis and Craven, 1994; Ishii et al., 1998) (Fig. 2). PKC activation can produce a myriad of consequences in diabetes including a mitogen-induced early proliferation phase (Brownlee, 2001). Pharmacological inhibition of PKC-beta was found to ameliorate diabetes-induced parameters including glomerular hyperfiltration, albuminuria, mesangial expansion and structural injury (Ishii et al., 1996; Kelly et al., 2003; Kikkawa et al., 2003; Koya et al., 1997, 2000; Tuttle and Anderson, 2003). These studies form the basis for the current evaluation of a PKC-beta inhibitor to prevent diabetic nephropathy in clinical trials. Notably, expression of PKC-beta 1 was localized to the proximal tubule of the rat (Pfaff et al., 1999) and its membrane-associated expression (activation) was further upregulated at this site in response to STZ diabetes in rats (Pfaff and Vallon, 2002). Whether this activation contributes to kidney growth and increased proximal reabsorption in early diabetes remains unknown, but it is sensitive to angiotensin-converting-enzyme inhibitors, which currently are the primary drugs used to prevent or treat diabetic nephropathy (Pfaff and Vallon, 2002). One of the downstream effectors of PKC activation is an increase in the activity of ODC (Fischer et al., 1993; Hsieh et al., 1989), likely by induction of immediate early genes c-myc, c-jun and c-fos (Bello-Fernandez and Cleveland, 1992; Bianchi et al., 2002; Hickok et al., 1990; Kaneto et al., 2002; Messina et al., 1992; Wen et al., 1989; Zhang et al., 1993) (Fig. 2). PKC-induced ODC activation can trigger the proliferation phase in the early diabetic kidney (Fig. 3). Later temporal activation of TGF-β can blunt this mitogenic response (see below).

Switching from hyperplasia to hypertrophy: role of TGF-β

The diabetic kidney switches from hyperplastic to hypertrophic growth very early in the course of hyperglycemia, e.g. at around day 4 in the STZ model (Huang and Preisig, 2000), which matches the time frame of hyperplasia we observed using 5-bromodeoxyuridine (BrdU) incorporation (Deng et al., 2003), an indicator of cell cycle progression. TGF-β is an important mediator of this switch in diabetes. High glucose administered to primary tubule cells from TGF-β $-/-$ mice exhibited reduced fibronectin production, an increased rate of proliferation relative to isolated cells from wild type littermates, and no hypertrophy (Chen et al., 2004). The progression of fibrosis in diabetes

is an essential factor attributed, in large part, to TGF-β. TGF-β can arrest cells in the G1 phase of the cell cycle by induction of the cyclin dependent kinase inhibitor (CKI) $p27^{KIP1}$ (p27) (Kamesaki et al., 1998). It is this G1 arrest that switches kidney hyperplastic growth to the hypertrophic phenotype observed in diabetes. Thus, p27 is a key factor in glucose-mediated hypertrophy (Fig. 3) (Monkawa et al., 2002; Wolf et al., 2001).

Temporal activation of ODC in the diabetic kidney?

Together the above data implicate ODC as a required mediator linking early diabetic growth factors with a growth response. ODC is one of the most highly regulated, yet short-lived, eukaryotic enzymes. It is responsive to growth factors, and is a proto-oncogene significantly elevated in tumors (Scalabrino and Ferioli, 1981, 1982). However, aside from transformed cells where activity is maintained at high levels for long periods, ODC activation lasts for hours to days, not weeks, months or years.

STZ-induced diabetes increases ODC activity several fold in the kidney (Levine et al., 1980; Pedersen et al., 1993; Sochor and McLean, 1980; Thomson et al., 2001), liver (Levine et al., 1978), and intestine (Parekh et al., 1998, 1999; Younoszai and Parekh, 1993), with maximum induction at 24 hours. DFMO, an inhibitor of ODC, suppresses hypertrophy and hyperplasia, and in jejunal mucosal enterocytes results in hypoplasia. By 7 days after STZ administration some reports demonstrate a continued elevation in renal ODC activity (Pedersen et al., 1993; Thomson et al., 2001), and others report that levels drop to below control by 3 or 4 weeks (Levine et al., 1980; Sochor and McLean, 1980). A temporal activation of ODC activity may be attributed to temporal changes in the local growth factor/mitogenic content. For example, IGF-1 induction is transient, with levels peaking at day 3 and normalizing by day 7 (Fervenza et al., 1997; Hayakawa et al., 1996).

Active ODC is a homodimer containing a cysteine within the active site at the dimer interface (Coleman et al., 1994). Nitrosylation of this cysteine by nitric oxide inhibits enzyme activity (Satriano et al., 1999). This process is readily reversible, depending upon the oxidative state of the cell (Satriano et al., 1999). High glutathione levels, typical of *unstressed* cells would reverse this inhibition, whereas low glutathione levels under conditions of *oxidative stress* (potential including the diabetic kidney) would promote and maintain ODC nitrosylation (Satriano, 2003) and thus ODC inhibition.

The continued hypertrophy observed later in diabetes may be more a consequence of decreased proteolysis than cell cycle arrest (Franch, 2002), and may also not be dependent upon growth factor/PI3K/Akt induction (Franch et al., 2002). Microarray analysis demonstrated no significant increase in ODC mRNA in patients with established diabetic nephropathy compared to that of control patients, supporting ODC as a mediator that may be limited to the early stage of diabetic growth (personal communication, Dr. D. Schlondorff, Munich, Germany).

The growth component of diabetes-induced hyperfiltration

Polyamines are required components of growth and cellular proliferation. ODC mRNA and protein expression are increased as a very early response to the onset of diabetes (Thomson et al., 2001). To determine the impact of the growth component on diabetes-induced glomerular hyperfiltration, pharmacological inhibition of ODC by the selective inhibitor difluoromethylornithine (DFMO) was utilized. DFMO prevented the early renal increase in BrdU positive cells and reduced kidney growth in early STZ diabetic rats (Pedersen et al., 1993; Thomson et al., 2001). The decrease in kidney growth observed in the diabetic rats administered DFMO correlates with a decrease in glomerular hyperfiltration (Fig. 4) (Thomson et al., 2001). This illustrates the impact of tubular growth on kidney function in response to STZ. Interestingly, the abnormal increases in absolute and fractional proximal reabsorption observed in diabetes are also markedly decreased with

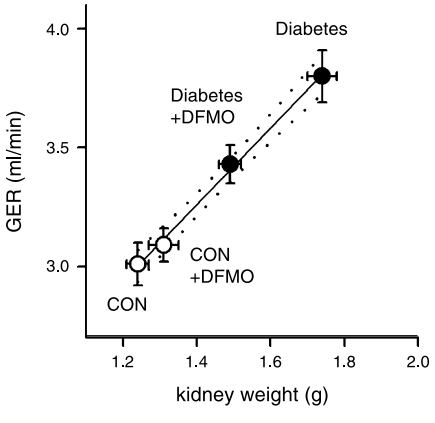

Fig. 4. Inhibiting kidney growth lowers GFR in early diabetic rats. Kidney growth is suppressed in 7-day STZ-diabetic rats by administration of the ODC inhibitor, DFMO. GFR vs. kidney weight is illustrated in control (CON) and 7-day diabetic rats ± DFMO. GFR is for two kidneys. Kidney weight is wet-weight of left kidney. Dashed lines are 95% confidence intervals for linear regression. $r^2 = 0.996$. (adapted from Thomson et al., 2001)

DFMO treatment, demonstrating a reduction of proximal tubule salt hyperreabsorption with suppression of tubular growth (Thomson et al., 2001).

That suppression of the initial phase of kidney growth affects outcome is also supported by experiments with VEGF neutralizing antibodies. VEGF neutralizing antibodies suppress the initial diabetic growth phase, improve renal parameters and diminish disease progression, including hypertrophy mediated by decreased protein degradation (de Vriese et al., 2001; Flyvbjerg et al., 2002; Schrijvers et al., 2002).

Is this early growth alone sufficient to mediate the hyperfiltration and downstream complications observed in diabetes? Other models of kidney growth, which do not lead to renal failure, imply a more complicated system is in effect in diabetes. Additional factors may come into play in diabetes that induce a particular form of growth or that induce detrimental effects in combination with growth to explain this disparity. One of these factors may be the induction of TGF-β. Other related factors include the induction of oxidative stress and of apoptosis. Together these appear to be important aspects in the progression of the early hypertrophic processes to the late, irreversible changes in the kidney observed in diabetes. Wolf and Ziyadeh (1999) note: ''It is debatable whether or not these (early) hypertrophic processes (in diabetes mellitus) will inevitably lead to irreversible fibrotic changes in humans, but experimental animal models provide ample evidence that this may indeed be the case''. In experimental animal models growth always precedes glomerulosclerosis (O'Bryan and Hostetter, 1997). Moreover and besides the outlined effects on tubular reabsorption and hyperfiltration, reducing early growth in diabetes could diminish the oxidative response leaving the cells with higher protective thiol pools and less susceptible to progressive oxidative effects (Wassef et al., 2004).

Optimal insulin treatment forms the modern basis for preventing 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 kidney growth and hyperfiltration to occur. Patients may be heterogeneous in their response to hyperglycemia with regard to kidney growth, and thus in tubular hyperreabsorption, and as a consequence, in 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 growth inducing aberrant reabsorption. Thus, we may learn that genetic polymorphisms affecting diabetes-induced kidney growth account for the fact that some patients develop diabetic nephropathy while others do not.

Conclusion

Defining the network of responses set in motion at the onset of diabetes is useful in understanding potential mechanisms that may be employed to disable or avert this disease in patient populations. We hypothesize that early tubule growth contributes to the generation of a renal phenotype in response to the diabetic environment, which is pivotal to the commitment towards early glomerular hyperfiltration and the progression of kidney disease. In this hypothesis kidney growth is not just a compensatory response to diabetic glomerular hyperfiltration, but rather is a primary contributing factor to the latter, and thus to the progression towards tubular and glomerular damage. Kidney growth then becomes a parameter that could be targeted to modulate disease progression. Suppressing growth via inhibition of ODC activity decreases glomerular hyperfiltration in diabetic rats thus demonstrating the utility, and future prospects, of addressing the growth phase of this disease. Polyamine transport may also be critical for diabetic kidney outcome, but perhaps due to the scarcity of such selective inhibitors, the efficacy of such a treatment has not yet been evaluated in this disease. Furthermore, as ODC activity appears delimited to the early stage of the disease, high renal ODC activity may be a marker of the onset of diabetic nephropathy, prior to albuminuria. This may apply not only to Type 1 diabetes, but to Type 2 diabetes as well. Thus, a better understanding of the early pathogenesis of the diabetic kidney, such as the polyamine dependent growth phase discussed herein, could offer the opportunity for earlier diagnosis and therapeutic intervention.

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