2 Altered Renal Microvascular Function in Early Diabetes

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INTRODUCTION

The early stage of type 1 diabetes (T1D) is characterized by glomerular hyperfiltration that arises as the result of preglomerular (primarily afferent arteriolar) vasodilation. Although hyperglycemia is the trigger for this process, the mechanism linking hyperglycemia to reduced afferent arteriolar tone remains an area of active debate. It is well established that diabetic hyperglycemia provokes a condition of oxidative stress in many organs including the kidney. In this chapter, we consider the possible role of oxidative stress in producing a defect in afferent arteriolar electromechanical coupling that involves K^+ channel activation, membrane hyperpolarization, and a consequent decrease in Ca^{2+} influx through voltage-gated channels. As voltage-dependent Ca^{2+} influx is a primary determinant of afferent (but not efferent) arteriolar tone and vasoconstrictor responsiveness, this scenario offers a potential mechanism whereby hyperglycemia results in the preglomerular vasodilation that underlies diabetic hyperfiltration.

TIME-COURSE OF RENAL FUNCTIONAL ALTERATIONS IN T1D

The renal functional complications of T1D are complex and evolve markedly with duration of the disease. The early stage of T1D is characterized by substantial increases in renal blood flow and glomerular filtration rate (GFR). In humans, diabetic hyperfiltration persists for 5–10 yr, before waning to a normal and eventually subnormal GFR. The onset of diabetic nephropathy (DN) is heralded by the appearance of

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microalbuminuria and albuminuria. Advanced DN is characterized by proteinuria, further deterioration of renal function and GFR, glomerulosclerosis, and interstitial fibrosis. This progression is exacerbated by hypertension, underscoring the vascular basis of the process. Maneuvers that limit or prevent development of diabetic hyperfiltration (e.g., by decreasing efferent arteriolar resistance, as provided by angiotensin-converting enzyme (ACE) inhibitors) delay or prevent onset of DN, suggesting that the hyperfiltration occurring early in T1D engenders eventual development of DN.

LOCALIZATION OF THE RENAL MICROVASCULAR DYSREGULATION IN EARLY T1D

Diabetic hyperfiltration is evident not only in humans with T1D, but also in rodent models of T1D. Most experimental studies of renal hemodynamic and glomerular function in diabetes have utilized the streptozotocin (STZ)-treated rat. Renal cross-transplantation studies have established that STZ exerts minimal direct nephrotoxic effects, such that the renal functional changes evident in the STZ rat arise as a consequence of the induction of T1D *(1)*. Within 3 d after STZ injection, renal and glomerular hypertrophy are evident *(2)*, whereas hyperfiltration arises within 1 wk and remains evident for weeks to months (probably dependent on the magnitude of the hyperglycemia). The hyperfiltration can be substantial, as exemplified by our observation of an 80% increase in inulin clearance in Sprague-Dawley rats studied 2 wk after STZ treatment *(3)*. Hence, although there are some limitations in the utility of the STZ rat in studying the processes occurring during advanced DN *(2)*, the STZ rat provides a useful tool for studying the mechanisms underlying diabetic hyperfiltration.

During the 1980s, micropuncture studies in the STZ rat provided the first documentation that diabetic hyperfiltration results from a reduction in preglomerular vascular resistance, with the ultrafiltration coefficient and efferent arteriolar resistance usually unaffected *(4,5)*. This situation increases glomerular plasma flow and capillary hydrostatic pressure, thereby spawning the substantial increase in GFR. The glomerular capillary hypertension in STZ rats is an acutely reversible consequence of insulin deficiency and the resulting hyperglycemia *(4)*. Indeed, acute restoration of euglycemia also restores GFR to normal values in humans with recent onset T1D *(6)*. Hyperfiltration in STZ rats is evident not only at the whole kidney level and in superficial nephrons accessible by standard in vivo micropuncture methods, but also occurs in juxtamedullary nephrons *(3)*. Data obtained through the use of videomicroscopy in concert with the in vitro blood-perfused juxtamedullary nephron technique have confirmed that the increase in GFR can be attributed to a significantly greater afferent arteriolar lumen diameter in STZ kidneys, compared with kidneys from Sham (vehicle-treated) rats, whereas efferent arteriolar diameter is unaffected *(3)*. In addition to the reduced basal arteriolar tone, afferent (but not efferent) arterioles from moderately hyperglycemic STZ rats display attenuated vasoconstrictor responsiveness to norepinephrine *(3)*. Over the course of several studies, we have observed a bell-shaped relationship between blood glucose levels and juxtamedullary afferent arteriolar diameter (Fig. 1). This observation is in accord with previous reports that hyperfiltration occurs in moderately hyperglycemic STZ rats, whereas severe hyperglycemia evokes a reduction in GFR *(5)*.

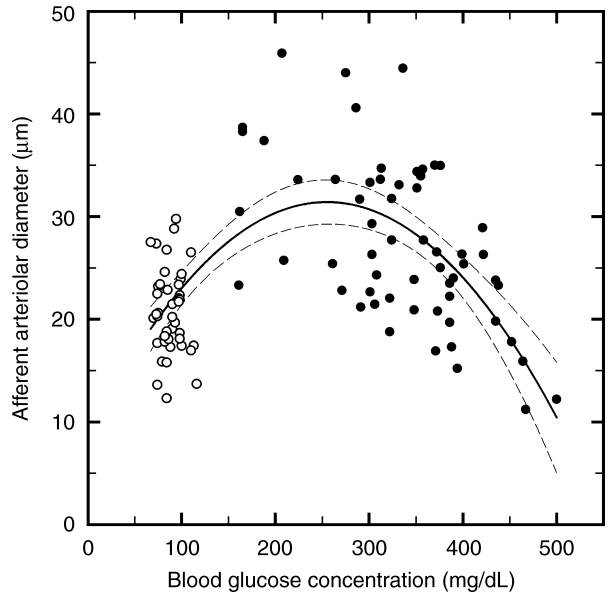

Fig. 1. Relationship between blood glucose concentration and juxtamedullary afferent arteriolar lumen diameter in kidneys from nondiabetic rats (Sham, ○) and rats with STZ-induced T1D (λ). The second-order regression line (solid) with 95% confidence intervals (•) is also provided.

ETIOLOGY OF THE AFFERENT ARTERIOLAR DILATION UNDERLYING DIABETIC HYPERFILTRATION

Results from the Diabetes Control and Complications Trial *(7,8)* established that intensive insulin therapy aimed at near normalization of blood glucose levels reduces the occurrence of microalbuminuria and albuminuria by 39 and 54%, respectively, compared with conventional insulin therapy. These benefits were greatest when intensive therapy was initiated soon after onset of T1D, underscoring the importance of early hyperglycemia-induced processes in leading to development of DN. Whereas it seems likely that hyperglycemia triggers or promotes the development of diabetic hyperfiltration, the events linking hyperglycemia to impaired preglomerular microvascular function in T1D have not been definitively established. Indeed, intensive investigation of many different pathophysiological sequelae proposed to underlie diabetic hyperfiltration (renal prostaglandins, sorbitol, growth hormone, atrial natriuretic peptide, nitric oxide, glucagon, kallikrein–kinin system, the renin–angiotensin system (RAS), etc.) has failed to unveil the undisputed key insult. In this chapter, we consider the possibility that altered electromechanical regulation of vascular smooth muscle tone and renal oxidative stress act in concert to promote the afferent arteriolar dilation underlying diabetic hyperfiltration.

Renal Oxidative Stress in T1D

One widespread consequence of hyperglycemia in T1D is oxidative stress reflecting net accumulation of reactive oxygen species (ROS), which encompass a variety of partially reduced metabolites oxygen. At the forefront of the array of ROS lies superoxide anion ($O_2^{\cdot -}$), which is formed in biological systems as the result of a one-electron reduction

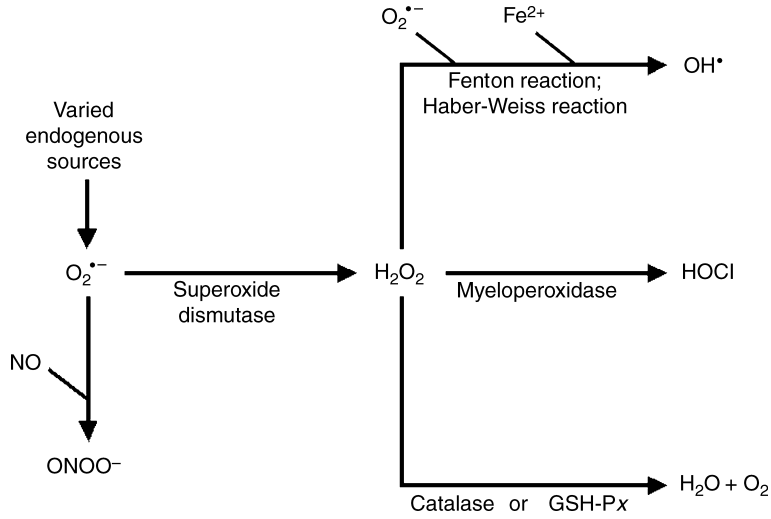

Fig. 2. Cascade of endogenous ROS formation. $O_2^{\bullet-}$, superoxide anion; NO, nitric oxide; $ONOO^-$, peroxynitrite; H_2O_2, hydrogen peroxide; $OH^{\cdot}$, hydroxyl radical; HOCl, hypochlorous acid; GSH-Px, glutathione peroxidase.

of molecular oxygen by oxidases and auto-oxidation processes. As summarized in Fig. 2, $O_2^{\bullet-}$ formation leads to production of several ROS. The initial fate of $O_2^{\bullet-}$ is either dismutation to form hydrogen peroxide (H_2O_2) or reaction with nitric oxide (NO) to form peroxynitrite ($ONOO^-$). Spontaneous dismutation of $O_2^{\bullet-}$ is accelerated more than 30,000-fold by superoxide dismutase (SOD), a reaction that proceeds at approx 60% of the rate of $ONOO^-$ formation *(9)*. Significant amounts of H_2O_2 are produced that, in turn, can be degraded to H_2O and O_2 by antioxidant enzymes. Alternatively, H_2O_2 can serve as a precursor of other damaging substances such as hypochlorous acid (HOCl) and hydroxyl radical ($OH^{\cdot}$).

Whereas net accumulation of one or more ROS can result from excess formation and/or inadequate degradation mechanisms (enzymatic and nonenzymatic scavengers and so on), the initiating event in this cascade is $O_2^{\bullet-}$ production. The cellular sources of $O_2^{\bullet-}$ include the mitochondrial electron transport chain, NAD(P)H oxidase, NO synthase (NOS), xanthine oxidase, cyclooxygenase, and the oxygenated form of cytochrome P450 *(9)*. $O_2^{\bullet-}$ production by the mitochondrial electron transport chain has been proposed to represent a common element that triggers glucose-induced activation of several processes implicated in the vascular complications of T1D *(10,11)*; however, NAD(P)H oxidase and NOS have also been implicated as a sources of excess $O_2^{\bullet-}$ production in T1D *(12,13)*. Activation of one or more of these oxidant pathways during T1D drives an increase in $O_2^{\bullet-}$ formation in the vasculature and in the renal cortex *(14)*. Moreover, compensatory increases in renal antioxidant enzyme activities are evident *(15–17)*. A consequence of accelerated $O_2^{\bullet-}$ production is the formation of $ONOO^-$ and/or H_2O_2. $ONOO^-$ can react with tyrosine residues on proteins, a process presumed to underlie the increase in renal cortical protein tyrosine nitration in T1D *(14,18)*. The possibility of increased renal H_2O_2 production in T1D has received little attention, although this situation can be expected to result from the increases in both $O_2^{\bullet-}$ production and SOD activity *(14)*. In recent preliminary studies, we found that STZ rats exhibit increased urinary H_2O_2 excretion, which could reflect

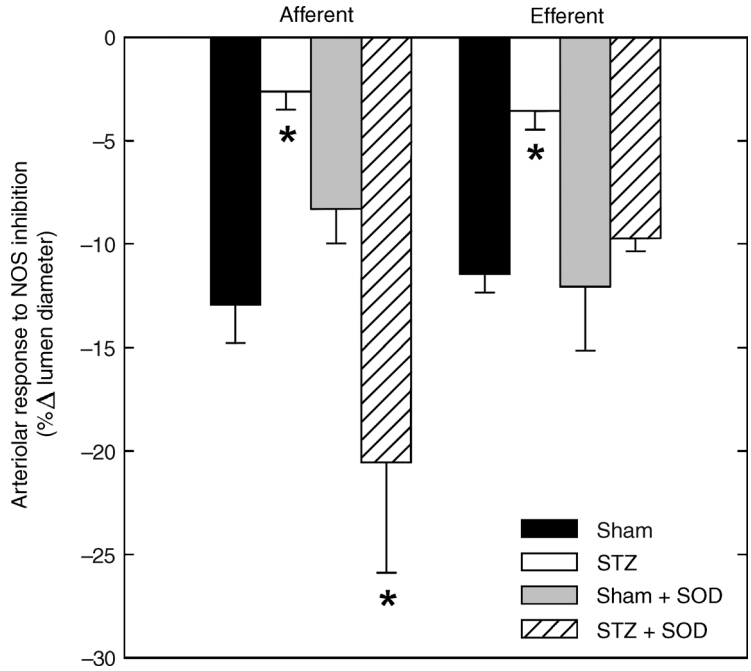

Fig. 3. Suppressed influence of NOS inhibition (100 μ*M* Nitro-L-arginine) on juxtamedullary afferent and efferent arteriolar diameter in STZ kidneys is restored by exogenous SOD (150 U/mL of blood perfusate). $p < 0.05$ vs Sham; $n = 7–10$ arterioles. (Data from Ohishi and Carmines *[27]*.)

net increases in systemic and/or renal H_2O_2 production. H_2O_2 is relatively stable and easily crosses cell membranes; hence, any accumulation of H_2O_2 in the kidney could influence the function of a variety of cell types *(19)*. Alternatively, H_2O_2 could be degraded by catalase or glutathione peroxidase, or it could serve as a substrate for formation of $OH^{\cdot}$ and/or HOCl. Winiarska et al. *(20)* have reported accelerated $OH^{\cdot}$ generation by renal cortical tubules from rabbits with alloxan-induced T1D. Because $OH^{\cdot}$ is highly reactive, it is very short-lived and thus assumed to exert its effects locally. An unexplored possibility is that $OH^{\cdot}$ is produced by (and subsequently influences the function of) the renal microvasculature in T1D. It is also possible that infiltration and activation of leukocytes (the only cells that express myeloperoxidase) leads to HOCl production in the kidney during the early stage of T1D. Indeed, although glomerular infiltration by leukocytes and monocytes/macrophages is evident within 1 wk of STZ injection in rats *(21)*, no attempts have been made to determine if renal HOCl production occurs in diabetes.

Microvascular Impact of Renal Oxidative Stress in T1D

The best-documented vascular consequence of oxidative stress in T1D is a decreased half-life of NO (accelerated degradation as a result of $ONOO^-$ formation). The resulting impairment of agonist-induced NO-dependent relaxation in aorta and other vascular beds is normalized by antioxidant maneuvers *(22–24)*. Agonist-induced endothelium-dependent relaxation is impaired in small intrarenal arteries from STZ rats, apparently as a result of $O_2^{\cdot -}$, $OH^{\cdot}$, and prostaglandin endoperoxide opposition of the effects of NO *(25)*. $O_2^{\cdot -}$-dependent processes are also implicated in impaired endothelium-dependent

relaxation of afferent arterioles isolated from diabetic rabbits *(26)*. As illustrated in Fig. 3, renal arteriolar constrictor responses to NOS inhibition are attenuated in kidneys from STZ rats, but restored by acute exposure to SOD *(27)*. This observation indicates that $O_2^{\cdot-}$ production diminishes the tonic dilator influence of endogenous NO on the renal microvasculature. The $O_2^{\cdot-}$-dependent decrease in NO bioavailability is evident in both afferent and efferent arterioles; thus, it is difficult to envision this phenomenon as contributing to diabetic hyperfiltration. In fact, the decrease in NO bioavailability in early T1D actually increases pre- and postglomerular vascular resistance, rather than producing the selective decline in preglomerular resistance that engenders diabetic hyperfiltration.

$O_2^{\cdot-}$ may also alter renal vascular function via NO-independent mechanisms. In non-renal vascular beds, $O_2^{\cdot-}$ generally promotes vasoconstriction via effects on intracellular Ca^{2+} homeostasis and signaling events *(28–33)*, although a few studies indicate attenuated contractile responsiveness *(34,35)*. $O_2^{\cdot-}$ has also been variably reported to influence K^+ channels and L-type voltage-gated Ca^{2+} channels (VGCCs) (*31,36)*, which are particularly critical to regulation of renal preglomerular microvascular function *(37–39)*. However, no studies have examined the possibility that $O_2^{\cdot-}$ exerts an NO-independent influence on the renal vasculature.

Systemic infusion of $ONOO^-$ evokes renal, hindquarter and mesenteric vasodilation possibly via a mechanism involving ATP-sensitive K^+ channels (K_{ATP} channels) *(40,41)*. $ONOO^-$ also dilates cerebral arterioles by activating K_{ATP} channels *(35)*. In contrast, $ONOO^-$ contracts rat cerebral artery *(42,43)* and diminishes currents through voltage-sensitive K^+ channels (K_v channels), as well as reducing the dilator influence of these channels in rat small coronary arteries *(44)*. This phenomenon may result from nitration of tyrosine residues in the pore-forming α-subunit of the K_v channel *(44)*. As $ONOO^-$ appears to activate K_{ATP} channels and inhibit K_v channels in vascular smooth muscle, the resulting change in vascular tone may reflect the relative prominence of these channel subtypes in a particular vascular bed. It is intriguing note that K_{ATP} channels have increased functional impact on afferent arteriolar function in T1D (*see* pp. 30–31), thus raising the possibility that this phenomenon might arise via a $ONOO^-$-dependent mechanism.

A survey of literature concerning the vasoactive effects of H_2O_2 yields a mixed bag of constrictor *(31,45)* and dilator effects *(46–48)*. In some cases, contraction is evident at low concentrations with higher concentrations provoking a transient contractile response followed by a sustained dilation *(49,50)*. Most studies indicating vasodilator responses to H_2O_2 have implicated increased K^+ channel activity in the response *(49,51–53)*. Renal medullary interstitial infusion of H_2O_2 decreases medullary blood flow *(54)*; however, our preliminary data unveiled a concentration-dependent, NOS-independent afferent arteriolar dilator response to H_2O_2 *(55)*. Although we do not know if this phenomenon is endothelium dependent or if it reflects vasoactive effects of H_2O_2 metabolism products ($OH^{\cdot}$ and HOCl), this observation suggests that increased H_2O_2 production in the renal cortex during T1D might contribute to the afferent arteriolar dilation and hyperfiltration.

Little information exists concerning the potential renal vascular effects of $OH^{\cdot}$, except for one report indicating that $OH^{\cdot}$ contributes to impaired endothelium-dependent dilation of small intrarenal arteries from STZ rats *(25)*. A similar effect of $OH^{\cdot}$ has been described in the basilar artery of STZ rats *(56)*. Thus, it appears likely that $OH^{\cdot}$ impairs NO-dependent dilator events, possibly by oxidizing NO *(57)*.

However, conflicting reports regarding the effects of $OH^{\cdot}$ on vascular tone include a vasodilator impact on cerebral arterioles *(58)*, but an endothelium-independent constrictor influence on rat aorta *(59)*.

Among the ROS, the vasoactive effects of HOCl are the most poorly characterized. HOCl increases vascular resistance in the perfused rat liver *(60)*. In isolated pulmonary arteries from sheep, HOCl produces vasoconstriction under resting force and vasodilation when the pulmonary arteries are precontracted *(61)*. HOCl also appears capable of impairing NO-dependent vasodilation *(62,63)*. Moreover, a recent report indicates that exposure of rat aortic rings to 20 m*M* glucose for 5 h sensitizes the vessel to myeloperoxidase-induced endothelial dysfunction *(64)*, an observation that underscores the potential for a vascular effect of HOCl if even only modest renal leukocyte infiltration/activation occurs during the early stage of T1D. However, nothing is known about the effects of HOCl on renal hemodynamics, even in inflammatory states in which increased renal myeloperoxidase activity and HOCl-oxidized protein have been documented *(65–67)*. It is interesting to note that immunosuppressant/anti-inflammatory therapy is beneficial in preventing glomerular injury in uninephrectomized STZ rats (which display accelerated development of diabetic nephropathy), although this phenomenon appeared to arise independent of the hemodynamic changes associated with diabetic hyperfiltration *(68)*.

In addition to direct effects on the renal vasculature, ROS production in T1D may elicit tubuloglomerular feedback-dependent alterations in afferent arteriolar tone. A complex interaction exists between $O_2^{\cdot -}$ and NO in determining tubuloglomerular feedback regulation of afferent arteriolar tone *(69)*. Moreover, ROS can influence Na^+ transport by various segments of the nephron. For example, in the medullary thick ascending limb, $O_2^{\cdot -}$ increases net NaCl reabsorption, $ONOO^-$ inhibits Na^+-K^+-ATPase activity, and H_2O_2 has no effect on Na^+ transport *(70)*. The possibility that HOCl and $OH^{\cdot}$ might influence renal Na^+ transport has not been explored. The pluripotential effects of the various ROS on Na^+ transport might change solute delivery to the macula densa, thereby indirectly altering afferent arteriolar resistance. Obviously, this phenomenon could represent a mechanism through which ROS influence the magnitude of diabetic hyperfiltration.

Summary of the Potential Role of Oxidative Stress in Diabetic Hyperfiltration

Oxidative stress in T1D is implicated in multiple complications of the disease, including diabetic nephropathy, which has its origin in dysregulation of renal preglomerular microvascular tone. Intense investigative effort has established several pathways through which ROS production results from hyperglycemia. However, it is not clear which renal cells produce excess ROS in T1D, nor is it clear which ROS predominates in the kidney (and in the renal microvasculature) under these conditions. Even less well understood are the functional effects of the various ROS—information that is critical for understanding the mechanisms through which these substances contribute to the deleterious effects of T1D. Each ROS has the potential to influence renal microvascular tone via direct effects on the resident vascular smooth muscle cells, through effects on NO bioavailability (as documented for $O_2^{\cdot -}$), or indirectly via effects on tubular transport that evoke tubuloglomerular feedback-mediated vascular responses. Any or all of these events can be expected to influence the magnitude of diabetic hyperfiltration.

Disrupted Electromechanical Regulation of Preglomerular Microvascular Resistance in STZ-Induced T1D

Basal tone and contractile responsiveness of the preglomerular microvasculature are highly dependent on Ca^{2+} influx through voltage-gated channels, whereas efferent arteriolar function seems much less reliant on this process *(37)*. Accordingly, alterations in electromechanical coupling events would have a functional impact on a variety of processes in the preglomerular microvasculature, with little impact on the efferent arteriole *(71)*. In light of the fact that multiple aspects of afferent arteriolar function are impaired in T1D, with relative preservation of efferent arteriolar function, we have proposed that T1D provokes a functional defect in electromechanical regulation of afferent arteriolar function.

Functional Impairment of Afferent Arteriolar Voltage-Gated Ca^{2+} Channels in T1D

Bank and colleagues *(72)* first suggested that insulinopenia in T1D might impair Ca^{2+} movement through VGCCs in the renal vasculature. Subsequently, Williams and Schrier *(73)* found that cultured rat aortic vascular smooth muscle cells exposed to high extracellular glucose concentrations for 12 h exhibited suppressed voltage-sensitive and agonist-induced [$^{45}Ca^{2+}$] uptake responses. In recent preliminary studies, we confirmed that culture of renal preglomerular microvascular smooth muscle cells for 3–5 d in high-glucose media significantly impaired $[Ca^{2+}]_i$ responses to depolarization *(74)*. These observations link hyperglycemia with depressed VGCC activation. We have reported attenuation of afferent arteriolar contractile responses to BAY K 8644 (a dihydropyridine activator of L-type VGCCs) in kidneys from STZ rats. Moreover, the EC_{50} for KCl-induced afferent arteriolar contraction was 40% greater in STZ kidneys than in kidneys from Sham rats *(75)*. We also found that afferent arterioles from STZ rats isolated and studied in media containing 20 m*M* glucose exhibited blunted $[Ca^{2+}]_i$ responses to K^+-induced depolarization (Fig. 4) *(75)*. Although afferent arterioles from Sham rats were unaffected by bath glucose concentration, $[Ca^{2+}]_i$ responsiveness to depolarization in arterioles from STZ rats was restored within 10 min of exposure to normal bath glucose values. The rapid reversibility of this phenomenon is reminiscent of the ability of acute restoration of euglycemia to normalize GFR in STZ rats, as noted earlier *(4)*, and also makes it unlikely that a decrease in VGCC expression in afferent arteriolar smooth muscle cells is responsible. Rather, these observations suggest that hyperglycemia in T1D provokes altered regulation of afferent arteriolar VGCCs, probably representing a diminished sensitivity to membrane potential. This phenomenon can be expected to result in reduced responses to a variety of stimuli that normally rely on depolarization-dependent Ca^{2+} influx to evoke increases in preglomerular vascular resistance—including autoregulatory and tubuloglomerular feedback responses, as well as contractile responses to AngII, vasopressin, norepinephrine, and other agonists *(37,76–78)*. Accordingly, the impaired afferent arteriolar responsiveness to depolarization in T1D should promote afferent arteriolar dilation and diabetic hyperfiltration *(71)*.

Exaggerated Impact of ATP-Sensitive K^+ Channels on Afferent Arteriolar Tone in T1D

Studies from our laboratory have also explored the possibility that K^+ channel regulation of afferent arteriolar function is altered in T1D. In particular, we have focused on

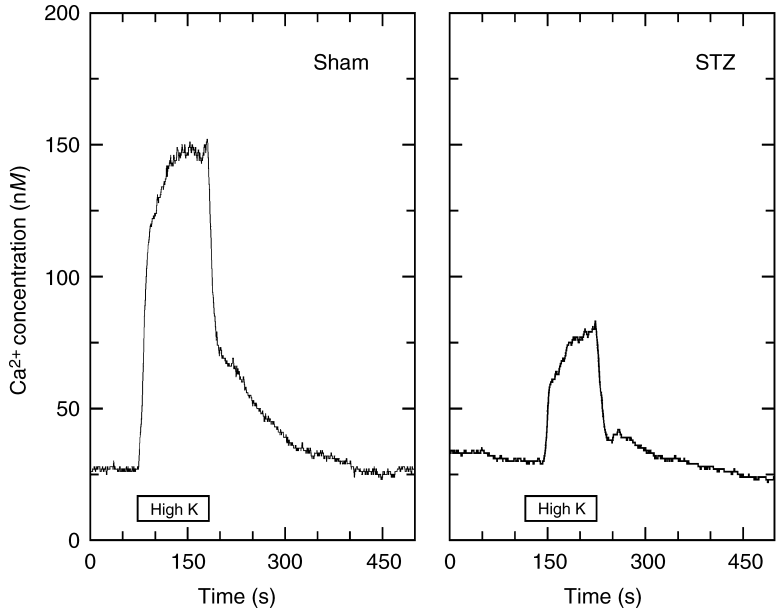

Fig. 4. Typical $[Ca^{2+}]_i$ responses to depolarization (40 m*M* K^+ bath) of isolated afferent arterioles from Sham and STZ rats. (Data from Carmines et al. *[75]*.)

the K_{ATP} channel *(79)*, the activation of which may reflect the cellular metabolic state. Several studies have provided functional evidence of K_{ATP} channel expression in the renal microcirculation *(80–83)*. We confirmed that potassium channel openers (pinacidil or PCO-400; both specific for K_{ATP}) evoke concentration-dependent afferent arteriolar dilation in kidneys from nondiabetic rats (Fig. 5), indicating the functional expression of K_{ATP} channels; however, the normal afferent arteriole is minimally responsive to glibenclamide (a sulfonylurea K_{ATP} inhibitor). Thus, the normal afferent arteriole possesses a recruitable pool of K_{ATP} channels having a low open probability in the absence of pharmagological activators and in the presence of physiologic intracellular ATP levels. In contrast, afferent arterioles from STZ rats contracted significantly in response to glibenclamide (Fig. 5), indicating the emergence of a K_{ATP} channel-dependent component of afferent arteriolar tone in T1D. Indeed, as the afferent arteriole is typically vasodilated in the hyperfiltering kidney of the STZ rat, glibenclamide-induced contraction of these vessels restored arteriolar diameter to values that did not differ significantly from arterioles in Sham kidneys *(79)*. Afferent arterioles from STZ rats also exhibited an exaggerated vasodilator response to pinacidil and PCO-400, consistent with an increased functional expression of K_{ATP} channels and/or an enhanced impact of these channels on membrane potential (and hence arteriolar tone). As opening of K_{ATP} channels promotes afferent arteriolar dilation, this phenomenon can be expected to contribute to the etiology of diabetic hyperfiltration *(71)*.

Summary of the Potential Role of Impaired Afferent Arteriolar Electromechanical Coupling in Diabetic Hyperfiltration

Increased functional availability and basal activation of K_{ATP} channels in T1D should result in dysregulation of membrane potential (favoring hyperpolarization). Moreover, this situation should be exacerbated by impaired VGCC responsiveness

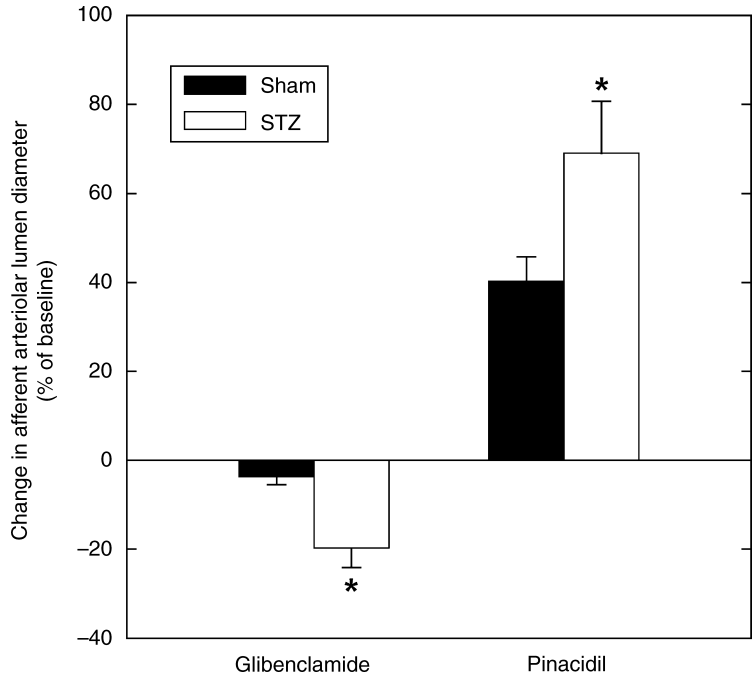

Fig. 5. Impact of K_{ATP} channels on juxtamedullary afferent arteriolar lumen diameter in kidneys from Sham and STZ rats. Responses to 100 μM glibenclamide (K_{ATP} blocker) and 100 μM pinacidil (K_{ATP} opener) are illustrated. $p < 0.05$ vs Sham; $n = 7–9$ arterioles. (Data from Ikenaga et al. *[79]*.)

to membrane depolarization. These synergistic effects of T1D on K_{ATP} channels and VGCCs would tend to diminish afferent arteriolar responsiveness to myriad constrictor stimuli, thus promoting the characteristic afferent arteriolar dilation that evokes diabetic hyperfiltration. However, the events that underlie altered electromechanical coupling in the preglomerular microvasculature during T1D have not been elucidated.

Could Oxidative Stress in T1D Underlie the Alterations in Afferent Arteriolar Electromechanical Coupling?

In considering the potential roles of renal oxidative stress and impaired afferent arteriolar electromechanical coupling in the etiology of diabetic hyperfiltration, it is intriguing to note a potential link between these phenomena. Indeed, many of the direct vasoactive effects of ROS arise via changes in K^+ channels that regulate membrane potential or Ca^{2+} channels that respond to changes in membrane potential. These channels play prominent roles in the electromechanical regulation of afferent arteriolar tone (and are much less prominent in the efferent arteriole). Thus, as illustrated in Fig. 6, it is conceivable that renal oxidative stress in T1D might activate K^+ channels (perhaps the K_{ATP} channel) in afferent arteriolar smooth muscle cells, resulting in hyperpolarization and diminished Ca^{2+} influx through VGCCs, thus engendering afferent arteriolar dilation and hyperfiltration. These events may occur in parallel with effects of ROS that reduce NO bioavailability (tempering hyperfiltration) and/or ROS-stimulated changes in tubular transport that evoke tubuloglomerular feedback-dependent responses (which could either favor or blunt hyperfiltration). This complex scenario of factors impacting the magnitude of diabetic hyperglycemia awaits validation through detailed experimental scrutiny.

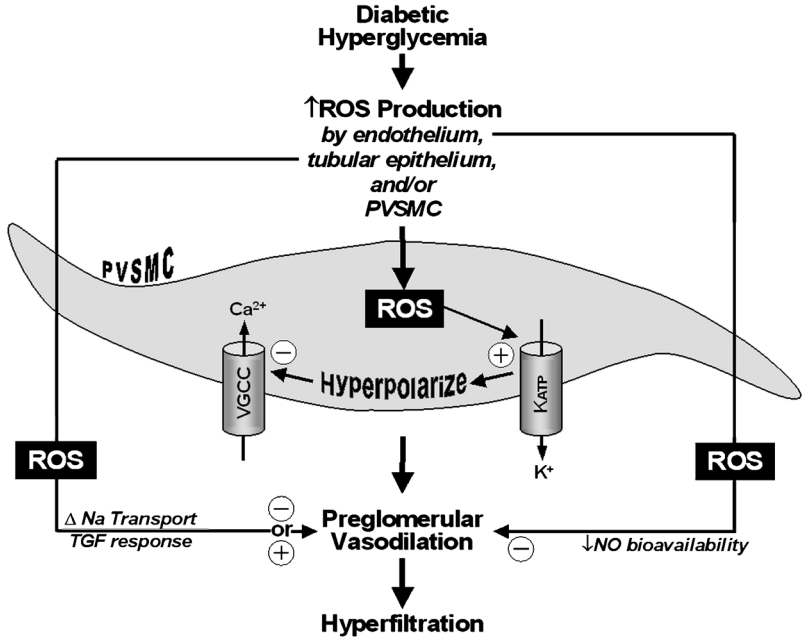

Fig. 6. Putative means through which renal oxidative stress in T1D might evoke hyperfiltration by impairing electromechanical coupling in preglomerular microvascular smooth muscle cells (PVSMCs). Also indicated are the potential indirect effects of ROS on afferent arteriolar function arising via reduced NO bioavailability and tubuloglomerular feedback.

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