Erectile dysfunction in the type II diabetic db/db mouse: impaired venoocclusion with altered cavernosal vasoreactivity and matrix

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Luttrell IP, Swee M, Starcher B, Parks WC, Chitaley K. Erectile dysfunction in the type II diabetic db/db mouse: impaired venoocclusion with altered cavernosal vasoreactivity and matrix. Am J Physiol Heart Circ Physiol 294: H2204–H2211, 2008. First published March 7, 2008; doi:10.1152/ajpheart.00027.2008.—The number of men with type II diabetes-associated erectile dysfunction (ED) continues to grow rapidly; however, the majority of basic science studies has examined mechanisms of ED in animal models of type I diabetes. In this study, we first establish an in vivo mouse model of type II diabetic ED using the leptin receptor mutated db/db and wild-type control BKS mouse. Furthermore, we hypothesized that dual mechanical impairments contribute to the impaired erectile function in the type II diabetic mouse, altered vasoreactivity, and venoocclusive disorder. In vivo erectile function was measured as intracavernosal pressure (ICP) normalized to mean arterial pressure (MAP) following electrical stimulation of the cavernosal nerve. Venoocclusion was assessed by the maintenance of elevated in vivo ICP following intracorporal saline infusion. Vasoreactivity of isolated cavernous in response to contractile and dilatory stimulation was examined in vitro by myography. Collagen and elastin content were evaluated by quantification of hydroxyproline and desmosine, respectively, as well as by quantitative PCR and histological analysis of isolated cavernousum. Erectile function was significantly decreased in db/db vs. BKS mice in a manner consistent with impairments in venoocclusive ability and decreased inflow. Heightened vasoconstruction and attenuated dilation in cavernousum of db/db vs. BKS mice suggest an overall lowered relaxation ability and thus impaired filling of the cavernosal spaces. A decrease in desmosine and hydroxyproline as well as lowered mRNA levels for tropoelastin, fibrillin-1, and α1(I) collagen were detected. These vasoreactive and sinusoidal matrix alterations may alter tissue compliance dispensability, preventing the normal expansion necessary for erection.

matrix; elastin; collagen; penis

IN TYPE II DIABETIC patients, erectile dysfunction (ED) is associated with risk factors such as neuropathy, vascular disease, smoking, and poor lifestyle conditions such as inactivity and obesity, which are components of the metabolic syndrome (1, 8). Although many studies have examined ED associated with type I diabetes, few studies have examined underlying mechanisms of decreased erectile function in animal models of type II diabetes.

The penile circulation is unique in that it is composed of arterioles that supply a network of collagenous sinusoidal cavities lined with endothelial and smooth muscle cells. During sexual arousal or nocturnal tumescence, the synthesis of nitric oxide (NO) by the neuronal NO synthase, located in non-adrenergic/noncholinergic nerves, initiates cavernosal smooth muscle relaxation (2, 3). The dilation of the cavernosal arteriolar and sinusoidal smooth muscle permits increased penile blood flow or shear flow, resulting in further production of NO by endothelial cell nitric oxide synthase (eNOS) to maintain filling and expansion of the erectile tissue (4). The outer layer of the corpus cavernosum, the tunica albuginea, is rich in elastic fibers and has the capacity to expand in response to the force of blood pressure, resulting in an increased length and diameter of the penis. However, the expandability of the tunica is finite, and, ultimately, the initial rise in intracavernosal pressure (ICP) along with the opposing force of the tunica albuginea activates a mechanical occlusion or “sandwiching” of the venous outflow. Thus the combined inflow of blood following penile arteriole and sinusoidal dilation, as well as subsequent venoocclusion, result in maintained elevation of ICP and erection.

To date, no studies have demonstrated in vivo ED in an animal model of type II diabetes nor established vasoreactivity changes in a type II diabetic mouse. In this study, we first establish impaired in vivo erectile function in the leptin receptor-mutated db/db mouse, an established model of type II diabetes (21). Furthermore, we demonstrate dual impairments that contribute to the diminished erectile function in the type II diabetic mouse. Our data suggest that db/db mice have a venoocclusive disorder that stems from a lack of tissue filling due to both altered vasoreactivity consistent with impaired cavernosal relaxant ability as well as impairments in tissue dispensability resulting from altered deposition of fibrillar collagen and elastin.

MATERIALS AND METHODS

Mice. BKS.Cg-m +/+ Lepr<sup>db</sup>/J (db/db) mice have a spontaneous Lepr<sup>db</sup> mutation. db/db mice develop hyperinsulinemia, hyperglycemia and obesity by 1–2 mo of age. Aged-matched, C57BS/KJ mice were used as controls (BKS). Male mice (2–3 mo of age; Harlan) were housed in a temperature-controlled room with a 12:12-h light-dark cycle and maintained with access to food and water ad libitum. All procedures were conducted with the approval of the Institutional Animal Care and Use Committee of the University of Washington and in accordance with National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. Blood glucose was checked via tail stick with a freestyle glucose monitor to verify the presence of hyperglycemia (defined in our study as ≥300 mg/dl) in the db/db mice.

In vivo assessment of erectile function. ICP in response to electrical stimulation of the cavernosal nerve was assessed in db/db and BKS...
mice as described (14). Briefly, anesthesia was induced with 4% isoflurane in 10% O2. To monitor and calculate mean arterial blood pressure (MAP), the left carotid artery was cannulated with a stretched down PE-10 tubing cannula tied in with 6-0 silk suture and fitted to a heparinized saline-filled pressure transducer (Kent Scientific) with PE-50 tubing. The left cavernosal nerve was accessed via a midline incision and stimulated with a bipolar platinum electrode (in-house design; Grass S48K nerve stimulator, and stimulus isolation unit SIU5; Grass Telefactor) at 20 Hz, 0.2 ms, and 2 V for 60 s to confirm placement of the cannula and electrode. ICP changes were then monitored in response to 1-, 2-, 5-, 10-, and 20-Hz stimulations for 1 min every 3 min. ICP and arterial pressure were converted from analog to digital signals and transmitted to a data-acquisition program (Hem 3.2; Notocord). The erectile response was calculated using the area under the curve (AUC, in mmHg) for ICP during the 1-min stimulation period (∆ICP). This value was divided by the AUC for the calculated MAP during the same 1-min stimulation (∆ICP/MAP). The maximum ICP response was also recorded and normalized to MAP at the time of maximum ICP.

**Venoocclusive function.** The cavernosal nerve was first electrically stimulated (20 Hz, 2 V) as described above, and the response returned to baseline. The cavernous was then further primed by infusion of saline at a rate of 2 ml/min, which generally elicited a sharp rise in ICP (~250 mmHg), and infusion then halted. For the experimental protocol, the infusion rate was restarted at 0.4–0.6 ml/min. In the BKS mouse, this resulted in a controlled increase in ICP lasting up to 10 s. In all BKS animals used for this experiment, a rate of 0.4–0.6 ml/min resulted in a pressure increase of 250–300 mmHg, at which point the infusion was stopped and ICP was monitored until it returned to baseline. Attempts to achieve a similar response in the db/db mice failed using infusion rates of 0.4–0.6 ml/min. An infusion rate of 1.2 ml/min was required in the db/db mice to elicit an ICP response comparable to BKS mice (250–300 mmHg). When 250–300 mmHg ICP were reached in the db/db mice, infusion was stopped, and pressure was monitored until its return to baseline values. Both the AUC for the ICP response as well as time were measured and recorded from the point of infusion cessation to the return of ICP to baseline.

**In vitro measurement of cavernosal vasoreactivity.** Before collection of tissue, mice were weighed, and blood glucose was checked. Following anesthetization with Isoflurane at 4% in O2, penises were excised at the level of the shaft after removal of the urethra and the sections to EFS was performed in the presence of phenylephrine at 3 μM for 10 min. Relaxation of penile sections to EFS was monitored during the delivery of increasing frequencies of EFS (for 45 s at 2 ms and 10 V every 5 min) at 0.31, 0.62, 1.25, 2.5, 5.0, 10.0, 20.0, 30.0, 50.0, and 100 Hz. Concentration-dependent contraction to phenylephrine (1 nM-100 μM) in half-log increments were evaluated in some tissues. EFS-induced relaxation experiments were performed after 30 min of incubation with bretylium tosylate, a norepinephrine reuptake inhibitor (Sigma), at 30 μM and precontraction with phenylephrine at 3 μM for 10 min. Relaxation of penile sections to EFS was monitored during the delivery of increasing frequencies of EFS (for 45 s at 2 ms and 10 V every 5 min) at 0.31, 0.62, 1.25, 2.5, 5.0, 10.0, 20.0, and 30.0 Hz. Penile relaxation to acetylcholine was monitored (after 10 min of precontraction with phenylephrine at 3 μM) with the delivery of increasing half-log doses every 5 min starting at 1 nM and ending with 10 μM. Force generation was monitored with an ADInstruments PowerLab 8/30 and interpreted by Chart 5.5.4 for Windows (ADInstruments).

**Assessment of elastin and collagen.** To quantify the levels of elastin and collagen, desmosine/isodesmosine and hydroxyproline content in mouse cavernous were measured as described (12, 19). Briefly, cavernous isolated from each animal was homogenized in PBS, 6 N HCl was added, and the samples were hydrolyzed at 110°C for 24 h. Desmosine/isodesmosine content was measured in hydrolyzed samples using a competitive radioimmunoassay. Hydroxyproline was assessed in remaining hydrolyzed samples. Cooled samples were mixed with citrate-acetate buffer (5% citric acid, 1.2% glacial acetic acid, 7.25% sodium acetate, and 3.4% sodium hydroxide) and chloroform-T solution (1.4% chloramine-T, 10% n-propanol, and 80% citrate-acetate buffer) in a 96-well plate, and the lysates were incubated at room temperature. Ehrlich’s solution (2.5 g p-dimethylaminobenzaldehyde added to 9.3 ml of n-propanol and 3.9 ml of 70% perchloric acid) was added to each well, and the plates were incubated (16°C, 18 min). The absorbance of each sample was measured at 550 nm. Standard curves were generated for each experiment using a known concentration of reagent hydroxyproline. Results were expressed as micrograms of hydroxyproline contained in each mouse penis.

**Quantitative PCR.** RNA was isolated from cavernous using a modified Trizol/Qiagen Hybird protocol [Qiagen RNasea Mini Kit (Invitrogen)]. Primers and TaqMan probes (FAM dye-labeled) for mouse tropoelastin, fibrillin-1, α1(I)-collagen, and hypoxanthine guanine phosphoribosyl (HPRT; Applied Biosystems, Foster City, CA) were added to cDNA synthesized from 3 μg total RNA with a High-Capacity cDNA Archive kit (Applied Biosystems), and product amplification was measured with an ABI HT7990 Fast Real-Time PCR System. The threshold cycle (Ct) for the endogenous control HPRT ranged from 26.06 to 27.73. The ΔCt was the difference between the Ct for the specific cDNAs and the Ct for HPRT in each sample. The ΔΔCt was the average ΔCt for db/db minus the average ΔCt of BKS. The data are expressed as relative quantification, which is the degree of change, and calculated as 2^-ΔΔCt.

**Histology.** Transcardiac perfusion with 4% paraformaldehyde was performed, and cavernous was excised. Masson’s trichrome staining was performed on 10-μm sections. To highlight elastic fibers, the cavernous was distilled with intracavernosal injection of 8% paraformaldehyde via a 30-G needle attached directly to a 3-ml syringe. The infusion of paraformaldehyde distended the penis while simultaneously fixing it in an engorged state. Sections (8 μm) were stained with either modified Hart’s, Verhoeff van Giesen, or Gomori’s aldehyde fuchsin stains. Images were captured using a Leitz DM RB microscope at ×4 and ×10 magnification with an Image Pro system and Spot Insight digital camera.

**Statistics.** Statistical significance between db/db and BKS groups for myography and in vivo studies was determined by ANOVA with repeated measures followed by t-test for planned comparisons between groups for each dose. Time to cessation and AUC for ICP during venoocclusion experiments were compared using Mann-Whitney nonparametric analysis. Blood glucose, body and penile weights, desmosine/isodesmosine, and hydroxyproline levels as well as real-
time PCR were compared by Student’s $t$-test. For all experiments, $P < 0.05$ denoted statistical significance.

**RESULTS**

**Glucose levels and body and penile weight in diabetic mice.** *db/db* mice displayed significantly increased blood glucose compared with BKS mice (in mg/dl: $482.7 \pm 11.6$ vs. $193.0 \pm 18.0$, respectively, $P < 0.05$, $t$-test). Body weights were also elevated in the *db/db* vs. BKS mice (in g: $56.2 \pm 1.2$ vs. $27.5 \pm 0.4$, respectively, $P < 0.05$). Penile weights for *db/db* mice were less than that of BKS mice (mg: $3.5 \pm 0.23$ vs. $6.0 \pm 0.25$, respectively, $P < 0.05$, $t$-test).

**In vivo erectile function.** *db/db* mice exhibited a significantly diminished in vivo erectile response following electrical stimulation of the cavernosal nerve (Fig. 1). This impairment was characterized by a decrease in the AUC of the ICP/MAP response at all frequencies of electric stimulation in the *db/db* mouse (Fig. 1A). However, the maximum ICP/MAP response was not altered at the higher frequencies but was significantly decreased only at 5 Hz in the *db/db* mouse because of the lack of response at this frequency of nerve stimulation in many mice from this group (Fig. 1, B and C). The time to reach maximal ICP in BKS mice vs. *db/db* mice (at the 20-Hz stimulus) was $46 \pm 5$ vs. $28 \pm 8$ s, respectively ($P < 0.05$, $n = 5$/group).

These data indicate that, compared with BKS mice, *db/db* mice have both an inability to maintain high pressures following cavernosal nerve stimulation and an increased time to initiate an elevation in ICP/MAP.

**Venoocclusive function.** In all BKS mice used in our studies, infusion of saline at a rate of 0.4–0.6 ml/min resulted in a

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**Fig. 1.** Differential in vivo assessment of area under the curve (AUC) and maximum intracavernosal pressure (ICP)/mean arterial pressure (MAP). A: there was a significant decrease in the AUC ICP-to-MAP ratio in *db/db* vs. BKS mice following electrical stimulation of the cavernosal nerve. B: at the higher frequencies, the maximum ICP/MAP response was not significantly different in *db/db* vs. BKS mice. The significant attenuation in maximum ICP/MAP at 5 Hz in the *db/db* mice was due to an overall right shift in sensitivity to the increasing frequencies and the lack of pressure increase to 5 Hz stimulus in some *db/db* mice. C: representative tracings of the ICP response to electrical stimulation of the cavernosal nerve in *db/db* and BKS mice; $n = 6$ /group. Significant interactions were determined by repeated-measures ANOVA, with $t$-test for planned comparisons at each dose ($*P < 0.05$).
pressure of 250–300 mmHg. At this level, infusion was stopped, and ICP was monitored until this parameter returned to baseline. Elevated ICP sufficient for erection was maintained even after the cessation of intracavernosal saline infusion in the BKS mice (Fig. 2A). The duration of elevated ICP was >100 s in the BKS mice (Table 1). Attempts to achieve an elevated ICP response in the db/db mice using an infusion rate of 0.4–0.6 ml/min failed, presumably because of resistance to inflow in the db/db cavernosum. However, an infusion rate of 1.2 ml/min elicited an ICP response comparable to BKS mice (250–300 mmHg). Following achievement of 250–300 mmHg ICP in db/db mice, the infusion was ceased, and ICP returned to baseline in a sharp, rapid manner, taking <30 s in each mouse (Table 1). These observations suggest that db/db mice also have an inability to maintain cavernous filling. The greater ability to maintain ICP after stopping saline infusion in the BKS vs. db/db mice is also reflected by increased ICP AUC values from the time of infusion cessation to the return of ICP to baseline (Table 1).

In vitro vasoreactivity. EFS-induced (Fig. 3A) and phenylephrine-induced contraction (Fig. 3B) of isolated cavernosum were significantly elevated in tissue from db/db vs. BKS mice. Together these data indicate increased smooth muscle contractile signaling, as opposed to a potential reduction in sympathetic nerve terminals alone. In the presence of bretylium tosylate, a norepinephrine reuptake inhibitor, precontracted cavernosum relaxed to increasing frequencies of EFS. EFS-induced relaxation was significantly decreased in cavernosum from db/db vs. BKS mice (Fig. 3C). Endothelium-dependent relaxation to acetylcholine was also significantly impaired in cavernosum from db/db vs. BKS mice (Fig. 3D).

Collagen content and morphology. The impaired hemodynamic properties of db/db cavernosum suggest altered tissue structure. To test this idea, we assessed the deposition of the extracellular matrix components known to be critical for vascular wall integrity and function. Quantification of cavernosal collagen by measurement of tissue hydroxyproline content demonstrated a significantly lower amount of collagen in penis from db/db vs. BKS mice (Fig. 4A). Quantitative PCR revealed a significant decrease in expression of α1(I) mRNA, which codes for the principal chain of type I collagen in the db/db cavernosum compared with BKS tissue (Fig. 4B). Masson’s trichrome staining indicated a qualitative decrease in overall collagen content in cavernosal cross sections from db/db vs. BKS mice, which was seen widespread throughout the cavernosum, in both the sinusoidal trabecular structures as well as the outer tunica albuginea (Fig. 4C).

Elastin content. Desmosine/isodesmosine are covalently cross-linked lysine products found only in mature elastic fibers and are a reliable quantitative measure of the elastin content of a tissue (17). The desmosine/isodesmosine content per cavernosum was significantly reduced in db/db vs. BKS mice (Fig. 5A). Quantitative PCR also demonstrated significantly lowered expression of tropoelastin mRNA, the elastin precursor, and fibrillin-1, the scaffold protein upon which tropoelastin is deposited and cross linked, in db/db vs. BKS cavernosum (Fig. 5B). Histological analysis of cavernosal cross sections from distended, fixed tissue by modified Hart’s, Verhoeff van Gieson, and Gomori’s aldehyde fuchsin staining demonstrated the presence of elastin fibrils dispersed throughout the sinusoidal regions, as well as in the outer tunica albuginea layer (data not shown). However, no overt differences in deposited elastin were seen between cavernosum from db/db vs. BKS mice.

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<th>db/db</th>
<th>BKS</th>
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<tr>
<td>Time to detumescence, s</td>
<td>741±371</td>
<td>29±4*</td>
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<tr>
<td>ICP (AUC)</td>
<td>122,779±56,447</td>
<td>2,627±690*</td>
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Values are means ± SE; n = 4 mice/group. AUC, area under the curve; ICP, intracavernosal pressure. *P < 0.05 Mann-Whitney nonparametric test.
In this study, we establish for the first time that a mouse model of type II diabetes exhibits decreased in vivo erectile responses. Our data also suggest that both altered vasoreactivity and impaired venoocclusive function underlie the attenuated erectile function. The net attenuation in vasodilator capacity may translate to insufficient or delayed inflow of blood to the cavernosum, as well as inadequate filling of corporal spaces required for activation of the venoocclusive mechanism. Venoocclusive dysfunction may also result from the significant alteration in collagen and elastin, which is necessary for penile dispensability and the maintained rigidity characteristic of erection, in cavernosum from db/db mice.

The impaired erectile function observed following electrical stimulation of the cavernosal nerve in db/db mice was marked by both an inability to maintain a sustained elevation in ICP/MAP following each stimulus (Fig. 1) as well as increased time to achieve maximum pressures (Fig. 1C). Maximum ICP/MAP was achieved to a similar level in db/db vs. BKS mice; however, AUC measurements revealed the inability to sustain the higher pressures in the diabetic mice (Fig. 1A and C). This impairment, along with the increased time to achieve maximum ICP/MAP after electrical stimulation of the cavernous, may involve an inability to limit the outflow of blood from the cavernous, resulting in a venous leak.

Indeed, additional experiments designed to assess venoocclusive function demonstrate a rapid decrease in ICP upon cessation of saline infusion in the cavernosum in db/db mice, whereas BKS mice exhibited a slow, steady decrease in ICP upon cessation of the saline infusion (Fig. 2). The maintenance of ICP in the BKS mice after cessation of inflow indicates the activation of passive mechanisms to prevent cavernous outflow, namely the venoocclusive mechanism. This finding is consistent with a report by Kovanecz et al. (11) in a type II diabetic rat model. Venoocclusion could be comprised of compression of subtunical veins by elongation or by cavernosal tissue and direct effects of the tunica albuginea. The characteristics of improper venous occlusion and ED in the db/db mouse appear to have multifaceted origins.

Vasoreactivity changes have been described in cavernosum from animal models of type I diabetes (14, 16). The most predominant dysfunction in the type II diabetic, db/db, cavernosum was a greatly heightened contractile response to EFS, which is driven by activation of sympathetic nerve terminals or direct adrenergic receptor stimulation (Fig. 3A). The phenylephrine response is also significantly potentiated in cavernosum from db/db vs. BKS mice; however, not to the extent of the responses to EFS-induced contraction. EFS-induced contraction in our study was examined in the presence of a nitric oxide synthase inhibitor to block neuronal nitric oxide synthase-mediated effects. The response to phenylephrine in the presence of this inhibitor is indeed similar to that of EFS (data not shown). The study by Carneiro et al. (5) reported no change in phenylephrine-induced contraction but an increase in EFS-mediated contraction in db/db mice. In our study, we normalized the phenylephrine response to the tissue weight of each cavernosal strip, since cavernosum...
Fig. 4. Decreased collagen content in cavernosum from db/db vs. BKS mice. A: hydroxyproline content was significantly lower in db/db vs. BKS cavernosum; n = 4/group. B: quantitative PCR revealed a significant decrease in expression of α1(I)-collagen mRNA, normalized to hypoxanthine guanine phosphoribosyl (HPRT), in cavernosum from db/db vs. BKS mice; n = 3/group, with each n representing RNA isolated from 3 different pooled cavernosum. C: Masson’s trichrome staining (4× and 10×) of cavernosal tissue cross sections revealed a strikingly different morphology between db/db and BKS mice. Note the increase in sinusoidal space corresponding to decreases in collagen staining in the db/db tissue, as well as the lesser amounts of collagen toward the outer tunica albuginea. Arrowhead, dorsal vein; long arrow, dorsal artery; thick arrow, dorsal nerves. (Urethra is absent in sections.) Sections are from n = 2/group, with 3 stained sections/cavernosum. For A and B, *p < 0.05, t-test.
...matrix changes that prevent the normal expansive capacity likely contributed to the inability to rapidly achieve and maintain elevated ICP in the 

The delayed pressure increases seen in the ICP/MAP tracings (Fig. 1C) are consistent with the notion of impaired or slowed cavernosal vasodilation and thus inadequate sinusoidal filling. Furthermore, poor relaxant capacity of the cavernosum may also contribute to insufficiencies in blood-mediated volume increases in the cavernosum, resulting in inadequate sinusoidal distension that is required for venoocclusion. However, the most direct mechanism underlying the venoocclusive dysfunction in the 

Both collagen and elastin content were dysregulated in cavernosum from 

Parasympathetic and eNOS-mediated relaxation was also significantly impaired in cavernosum from 

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from 

was far less in mass than that from 

This was done to be certain changes in force were not due solely to changes in tissue size.

The mechanism for vasoreactive changes and alterations in collagen and elastin in the penis of type II diabetic mice is unclear. The profile of in vivo dysfunction and vasoreactive changes in the differs from that seen in models of type I diabetic ED. We recently detected in vivo ED in a mouse model of type I diabetes; however, unlike the data from the type II mouse in this study, the type I diabetic mouse displayed decreased maximum ICP/MAP and a reduced AUC (14). Furthermore, in this study, the mouse cavernosum displays a large hypercontractile sensitivity that is not established type I diabetic dysfunction. Furthermore, although dilatory dysfunction exists in cavernosum from both type I and type II diabetic mice, the extent of parasympathetic impairment in our model was modest compared with reports in type I diabetic models (14). These discrepancies suggest that hyperglycemia alone is not the driving force for alterations underlying ED in diabetes, and it is more likely that the disease origins are multifactorial and may stem from the commonality of hyperglycemia as well as additional alterations such as hyperinsulinemia or hyperlipidemia observed in the type II diabetic model. Hyperglycemia has indeed been linked to the modification of eNOS (7, 15), resulting in enzyme impairment that may affect both type I and type II diabetic dilatory capacity. Glycation of both collagen and elastin has been reported (22), but it is unclear how this event may affect the stability of matrix components in the penis.
The venoocclusive mechanism is dependent on sufficient increases in blood flow to fill and distend the cavernosum, resulting in mechanical occlusion of the venous outflow. The net impaired dilatory ability of the cavernosum may be a factor contributing to the inability to achieve venoocclusion, in addition to the dysregulation of penile collagen and elastin deposition. It is most likely that the mechanism underlying impaired venoocclusion and ED in the db/db mouse is multifaceted.

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GRANTS

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