Vascular Dilatatory Responses to Sodium Nitroprusside (SNP) and α-Adrenergic Antagonism in Female and Male Normal and Diabetic Rats (44433)

BRENDA MARTÍNEZ-NIEVES AND JOSEPH C. DUNBAR[1]

Department of Physiology, Wayne State University, School of Medicine, Detroit, Michigan 48201

Abstract. **Diabetes is associated with impaired vascular dilatatory responses that appear to be influenced by sex as well as diabetic state. Therefore, we hypothesized that vascular and sympathetic control function exhibit a greater deterioration following the induction of diabetes in female than in male rats. We conducted a comparative determination of the effect of sodium nitroprusside (SNP, a nitrous oxide donor) and that of an α_1-adrenergic antagonist, prazosin, on selective vascular flows, mean arterial pressure (MAP), and heart rate (HR), in female and male normal and diabetic rats. Rats were made diabetic using streptozotocin (50 mg/kg, iv) and maintained for 5–6 weeks. Following anesthesia with urethane/α-chloralose, the femoral artery and vein were cannulated for recording and sampling. Flow probes were placed on the iliac, renal, and superior mesenteric arteries. SNP (1, 5, 10, and 20 μg/kg) infusions resulted in a dose-dependent decrease in MAP in normal and diabetic rats. The decrease in MAP in normal males was 37% less at the 20 μg/kg concentration of SNP when compared to normal females. The HR was not significantly changed in response to the hypotensive effect of SNP; however, reflex tachycardia was more prominent in diabetic males. The vascular conductance (flow/MAP) was increased by SNP in normal and diabetic rats in a dose-dependent fashion; however, the responsiveness was decreased in the iliac and superior mesenteric and increased in the renal arteries in diabetics when compared to normals. Diabetic males were 42% and 28% less responsive to SNP in the iliac and superior mesenteric arteries, respectively. On the other hand, diabetic females were 1.5-fold more responsive in the renal artery when compared to normals. Prazosin (4 mg/kg) decreased the MAP in normal and diabetic rats to a comparable degree. Prazosin increased the vascular conductance in all three vascular beds in normal and diabetic rats with the greater increase occurring in the iliac (118%) and superior mesenteric (110%) arteries. We concluded that diabetes is associated with an increased response to NO in the renal vessels and a decreased response in the iliac and superior mesenteric vessels in both females and males. α-Adrenergic tone was greatest in diabetic female and male rats. This study suggests that decreased vascular flow in diabetes is a result of a combination of decreased sensitivity to NO and increased adrenergic tone.** [P.S.E.B.M. 1999, Vol 222]

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[1] To whom requests for reprints should be addressed at Department of Physiology, Wayne State University School of Medicine, 5374 Scott Hall, 540 E. Canfield, Detroit, MI 48201. E-mail: jdunbar@med.wayne.edu

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A major complication of diabetes mellitus is vascular disease that leads to altered peripheral blood flow at the micro- and macrovascular levels, atherosclerosis, hypertension, retinopathy, and chronic ulceration (1–6). Since circulation abnormalities have been implicated in diabetic complications, investigations have focused on the role of the endothelium in the regulation of vascular tone (7). Diabetes is primarily associated with impaired vascular dilatory responses, and these responses appear to be influenced by sex as well as the diabetic state (1–6). Conse-

quently, we propose that vascular and sympathetic control function exhibit a greater deterioration following the induction of diabetes in female than in male rats.

The endothelium production of nitric oxide (NO), a potent vasodilator, plays a regulatory role in the maintenance of blood pressure and the regulation of resting vascular tone in different vascular beds (8–11). NO agonists and antagonists have been useful in characterizing the functional role of NO in regulation of mean arterial pressure (MAP), control of peripheral vascular tone, and endothelial dysfunction in diabetes (11–13).

In addition to the decreased NO production associated with diabetes, endothelial NO-mediated vasodilation may also be impaired in diabetes (14). It has been suggested that this endothelial dysfunction or reduced response to endothelial NO in diabetes contributes to the development of diabetic vascular diseases (8, 14). The first goal of this study was to examine the effect of sex and diabetes on smooth muscle sensitivity to NO as modulated by the administration of SNP, a nitrous oxide donor, in normal and diabetic female and male rats.

Investigations by our laboratories and others have suggested alterations in sympathetic-mediated vascular tone as a cause of diabetic vascular disease (6, 15–17). The enhanced vessel reactivity, especially of the resistance vessels to a specific agonist has been demonstrated (3, 6). Both *in vitro* and *in vivo* studies have demonstrated an increased sensitivity especially to an adrenergic agonist in animals with experimental diabetes and to control levels of circulating catecholamines (11, 18, 19). Consequently, the second goal of this study was to evaluate comparatively the effect of sex and/or diabetes on basal and regional adrenergic tone following the administration of an α_1-adrenergic antagonist.

Materials and Methods

Normal and diabetic female and male, Wistar rats (BW: 250–275 g) were used in our experimental procedures. They were kept in a controlled environment with a 12-hr light cycle and a 23°C room temperature with free access to water and food. Diabetes was induced in normal rats by a single intravenous tail vein injection of 50 mg/kg streptozotocin (STZ) dissolved in sodium citrate (0.1 m*M*, pH 4.5). Five days after the STZ injection, a blood sample was collected to determine hyperglycemia, which was maintained 4–6 weeks post-STZ injection.

On the day of the study and following a 24-hr fast, normal or diabetic rats were anesthetized with urethane (0.5 mg/kg) and α-chloralose (70 mg/kg) and placed on a heating pad to maintain their body temperature. A tracheotomy was performed to diminish respiratory obstructions, and catheters with heparinized saline were placed into the femoral artery and veins. The venous catheter was used for blood sample collection and infusions. The femoral artery cannula was used for cardiovascular recording.

Pulsed-Doppler blood flow transducers (flow probe, Baylor Electronics, Houston, TX) were placed around the iliac, renal, and superior mesenteric arteries. The arterial catheter was connected to a pressure transducer, and the flow probes were connected to a pulsed-Doppler flowmeter (Baylor Electronics).

Female and male normal and diabetic rats were given subsequent bolus injections of increasing concentrations of sodium nitroprusside (SNP; 1, 5, 10, and 20 μg/kg) in 20-min intervals following the establishment of a baseline. On the other hand, prazosin (4 mg/kg) was administered as a single bolus injection 10 min after the establishment of a baseline. Mean arterial pressure (MAP), heart rate (HR), and blood flow (iliac, renal, and superior mesenteric) were monitored continuously.

The Biowindows software program (Modular Instruments, Malvern, PA) and a Micro 5000 signal processing system were used to monitor cardiovascular responses. The Biowindows program records all cardiovascular parameters: mean arterial pressure (MAP), heart rate (HR), and blood flow (Hz Ds units).

Blood samples, 0.2 ml with saline replacement, were collected prior to the study and used for glucose analysis (glucose analyzer; Yellow Springs Instruments Co., Yellow Springs, OH).

The SNP data presented are peak responses following treatments. Prazosin data are averages of 1-min intervals for the reported periods post-treatment. The data were analyzed using two-way ANOVA, *post hoc* analysis where appropriate, and Student's *t* test.

All studies involving the use of animals were conducted in compliance with applicable laws and regulations as well as the principles expressed in the National Institutes of Health, USPHS, *Guide for the Care and Use of Laboratory Animals*, and the studies were conducted on animals that were lawfully acquired. Use of animals was approved by the Wayne State University Animal Care and Use Committee.

Results

The body weight was decreased in females diabetics, and the blood glucose was increased in female and male diabetics when compared to normals. No significant differences were seen in basal MAP between groups. However, diabetic males had a significantly lower basal HR when compared with their corresponding counterpart (Table I). The administration of SNP resulted in a rapid decrease in MAP in normal and diabetic animals in a dose-dependent fashion (Figs. 1A and 2A). Normal males tended to have less of a decrease in MAP with increasing concentrations of SNP when compared to normal females. However, this response was significant only at the 20 μg/kg concentration of SNP (Table II). The HR was increased in normal and diabetic animals (Fig. 1B). All four groups of animals demonstrated a reflexive increase in HR (Figs. 1B and 2B) following SNP treatments. Normal animals tended to have greater increases in HR when compared to diabetic animals and diabetic males had a significantly smaller increase in HR when compared to diabetic females at the lower concentration of SNP, 1 μg/kg (Table II).

Table I. Basal Body Weight, Blood Glucose, Mean Arterial Pressure, and Heart Rate in SNP- and Prazosin-Treated Normal and Diabetic Rats

Group	Body weight (g)	Glucose (mg/dl)	MAP (mm Hg)	HR (beats/min)
Normal female	269 ± 7 (16)	82 ± 4 (16)	70 ± 3 (16)	352 ± 8 (16)
Diabetic female	228 ± 8* (14)	412 ± 37* (14)	65 ± 3 (14)	335 ± 13 (14)
Normal male	290 ± 20 (11)	68 ± 4 (11)	73 ± 3 (11)	372 ± 14 (11)
Diabetic male	258 ± 15 (13)	404 ± 17* (13)	68 ± 2 (13)	325 ± 8* (13)

Note. The values represent the mean ± SEM. *$P < 0.05$ vs. normals, ANOVA. Number in parenthesis = *n*. Basal body weight (g); blood glucose (mg/dl); mean arterial pressure (MAP, mmHg); and heart rate (HR).

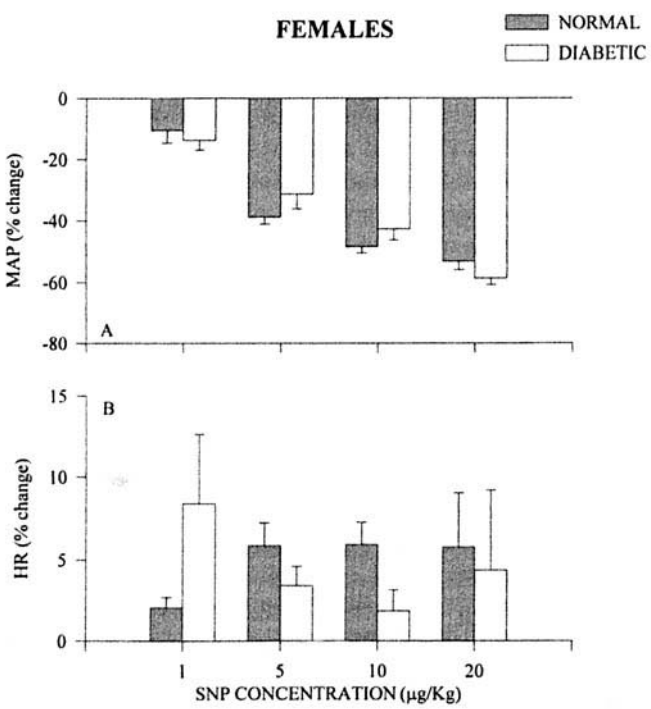

Figure 1. The effect of increasing concentrations of sodium nitroprusside (SNP) on (A) mean arterial pressure (MAP) and (B) heart rate (HR) expressed as percentage change in normal (n = 5, 5, 10, and 5) and diabetic (n = 5, 4, 6, and 2) female rats.

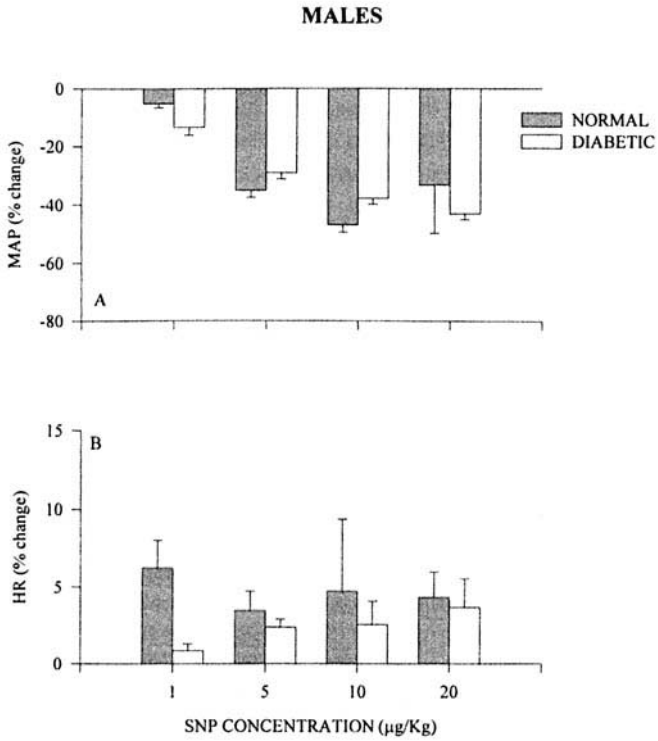

Figure 2. The effect of increasing concentrations of sodium nitroprusside (SNP) on (A) mean arterial pressure (MAP) and (B) heart rate (HR) expressed as percentage change in normal (n = 6) and diabetic (n = 7) male rats.

SNP administration resulted in a dose-dependent increase in conductance (g) in all three vascular beds (Figs. 3 and 4). The dose-dependent response to SNP in the iliac artery (Figs. 3A and 4A) was significantly decreased in the male diabetics but not in the female diabetics. This was particularly true for the 10 μg/kg concentration of SNP when all experimental groups were compared (Table III). The increased iliac conductance in response to SNP was significantly greater in normal males when compared to normal females (Table III). The increased conductance in response to SNP in the superior mesenteric artery (Figs. 3C and 4C) was less in both diabetic females and males. When compared to normals, diabetic males had a greater increase in conductance in response to SNP in superior mesenteric conductance than diabetic females (Table III). On the other hand, the responsiveness to SNP was greater in the renal artery in both diabetic females and males when compared to normals (Figs. 3B and 4B). In addition, when all four experimental groups were considered, diabetic females at the highest concentration of SNP (20 μg/kg) were significantly less responsive than normal females (Table III). The renal conductance had an even greater increase in diabetic males when compared to normals (Fig. 4B). However, diabetic females had a greater increase in conductance in response to SNP highest concentrations (10 and 20 μg/kg) in the renal artery when compared to normals.

α-Adrenergic antagonism using prazosin resulted in a decrease in MAP in normal and diabetic animals (Figs. 5A and 6A). However, in normal males, this decrease in MAP was less when compared to normal females (Table IV). In contrast to females (Fig. 5A), diabetic males had a greater decrease in MAP when compared to their normal counterparts (Table IV) (Fig. 6A). The heart rates were initially decreased after the administration of prazosin, but after approximately 10 min the HR returned toward baseline in all four groups of animals (Figs. 5A and 6A). Nonetheless, the initial decrease in HR was greater in diabetic females when compared to diabetic males (Table IV). However, prazosin had no significant effect on HR.

Table II. Mean Arterial Pressure and Heart Rate Responses to Increasing Concentrations of Sodium Nitroprusside

MAP (% change)				
SNP	Normal		Diabetic	
(μg/kg)	Female	Male	Female	Male
1	−10.42 ± 4.1 (5)	−5.04 ± 1.4 (6)	−13.67 ± 3.2 (5)	−13.23 ± 2.8 (7)
5	−38.87 ± 2.2 (5)	−35.10 ± 2.4 (6)	−31.27 ± 4.9 (4)	−28.95 ± 2.1 (7)
10	−48.36 ± 2.1 (10)	−46.80 ± 2.7 (6)	−42.74 ± 3.6 (5)	−37.55 ± 2.1 (7)
20	−53.11 ± 2.8 (5)	−33.10 ± 17† (6)	−58.57 ± 2.1 (2)	−43.11 ± 2.0 (7)
HR (% change)				
1	2.07 ± 0.6 (5)	6.24 ± 1.7 (6)	8.40 ± 4.2 (5)	0.84 ± 0.5* (7)
5	5.85 ± 1.3 (5)	3.44 ± 1.2 (6)	3.42 ± 1.1 (4)	2.36 ± 0.5 (7)
10	5.92 ± 1.3 (10)	4.72 ± 4.6 (6)	1.87 ± 1.3 (5)	2.52 ± 1.6 (7)
20	5.76 ± 3.2 (5)	4.33 ± 1.6 (6)	4.36 ± 4.84 (2)	3.67 ± 1.9 (7)

Note. The values represent the mean ± SEM. † = $P < 0.01$ vs. normal female.
* = $P < 0.05$ vs. diabetic female, ANOVA. Number in parenthesis = *n*. Mean arterial pressure (MAP); heart rate (HR); and sodium nitroprusside (SNP).

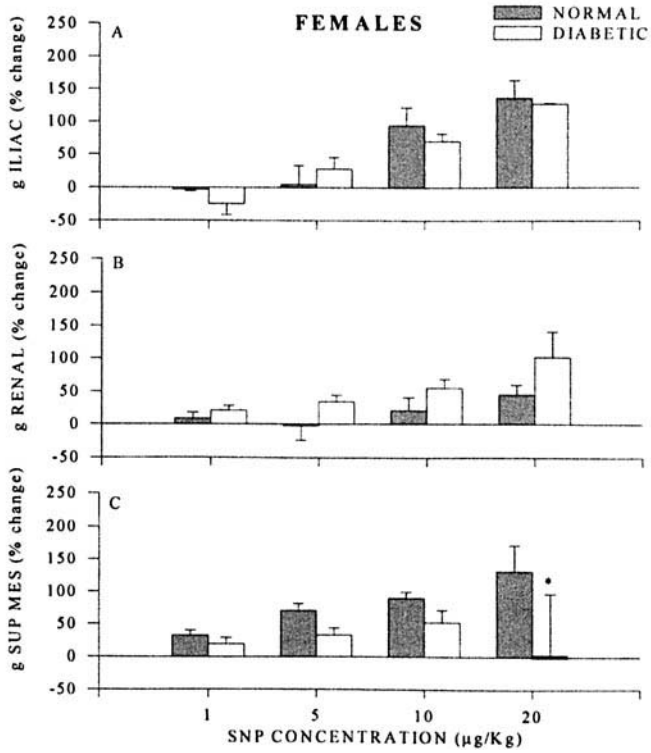

Figure 3. The effect of increasing concentrations of sodium nitroprusside (SNP) on (A) iliac, (B) renal, and (C) superior mesenteric conductance (g) expressed as percentage change in normal ($n = 5$, 5, 10, and 5) and diabetic ($n = 5$, 4, 6, and 2) female rats. *$P < 0.05$ vs. normal female. Two-way ANOVA across concentration group effect normal versus diabetic female g Renal, $P < 0.01$; normal versus diabetic female g SUP MES, $P < 0.001$.

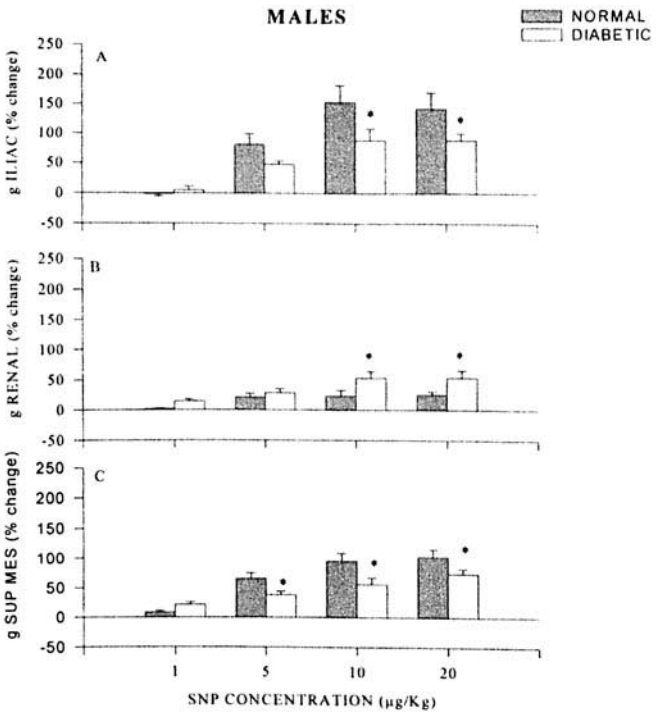

Figure 4. The effect of increasing concentrations of sodium nitroprusside (SNP) on (A) iliac, (B) renal, and (C) superior mesenteric conductance (g) expressed as percentage change in normal ($n = 6$) and diabetic ($n = 7$) male rats. * = $P < 0.05$ vs. normal males. Two-way ANOVA across concentration group effect, normal vs. diabetic male g iliac, $P < 0.05$; normal vs. diabetic male g renal, $P < 0.05$; and normal vs. diabetic male g SUP MES, $P < 0.05$.

The conductance was increased in the three vascular beds in response to prazosin (Figs. 7 and 8). Prazosin increased blood flow in the iliac (Figs. 7A and 8A), renal (Figs. 7B and 8B), and superior mesenteric bed (Figs. 7C and 8C), to a greater extent in diabetic female and male rats (Table V). However, the response to prazosin was less in the renal bed of normals and diabetics (Table V) (Figs. 7B and 8B). Renal conductance in response to prazosin (Table V) was increased to a greater extent in diabetic females when compared to diabetic males and also when compared to normal females (Table V). In addition, renal conductance in diabetic males was significantly increased when compared to normals (Table V). Superior mesenteric conductance was significantly lower in normal males when compared to normal females (Table V). Diabetic females' superior mesenteric conductance was significantly less when compared to normal females (Table V).

Table III. Vascular Conductance Response to Increasing Concentrations of Sodium Nitroprusside in the Iliac, Renal, and Superior Mesenteric Arteries

SNP (μg/kg)	Normal		Diabetic	
	Female	Male	Female	Male
Iliac g (% change)				
1	−2.90 ± 2.3 (5)	−0.80 ± 4 (6)	−24.45 ± 16.9 (5)	5.14 ± 6.6 (7)
5	4.41 ± 27.8 (5)	81.23 ± 18* (6)	27.22 ± 17.5 (4)	47.9 ± 5.6 (7)
10	94.21 ± 28 (10)	152.48 ± 28* (6)	69.58 ± 11.7 (5)	87.63 ± 20† (7)
20	136.39 ± 27.3 (5)	142.0 ± 27 (6)	127.45 ± 1.2 (2)	88.23 ± 11.9 (7)
Renal g (% change)				
1	8.62 ± 9.5 (5)	1.63 ± 1.0 (6)	21.22 ± 7.1 (4)	14.30 ± 3.4 (7)
5	14.79 ± 17.1 (4)	20.88 ± 6.7 (6)	33.5 ± 10.0 (4)	28.58 ± 6.8 (7)
10	20.39 ± 19.3 (10)	23.17 ± 9.2 (6)	54.82 ± 13.5* (5)	53.59 ± 11.2 (7)
20	44.75 ± 15.3 (5)	25.3 ± 5.3 (6)	101.79 ± 39.6* (2)	54.49 ± 11.6 (7)
SUP MES g (% change)				
1	32.39 ± 8.0 (5)	8.11 ± 3.05 (6)	19.28 ± 9.7 (5)	21.37 ± 4.3 (7)
5	71.01 ± 10.7 (5)	65.90 ± 8.8 (6)	32.82 ± 11.4 (4)	38.48 ± 5.9 (7)
10	90.34 ± 9.6 (10)	94.90 ± 13.6 (6)	52.46 ± 18.8 (5)	56.00 ± 10.7 (7)
20	131.55 ± 40.8 (5)	102.14 ± 13.1 (6)	0.288 ± 97* (2)	73.48 ± 8.3‡ (7)

Note. The values represent the mean ± SEM. * = $P < 0.05$ vs. normal female. † = $P < 0.05$ vs. normal male. ‡ = $P < 0.05$ vs. diabetic female, ANOVA. Number in parenthesis = *n*. Vasular conductance (g); sodium nitroprusside (SNP).

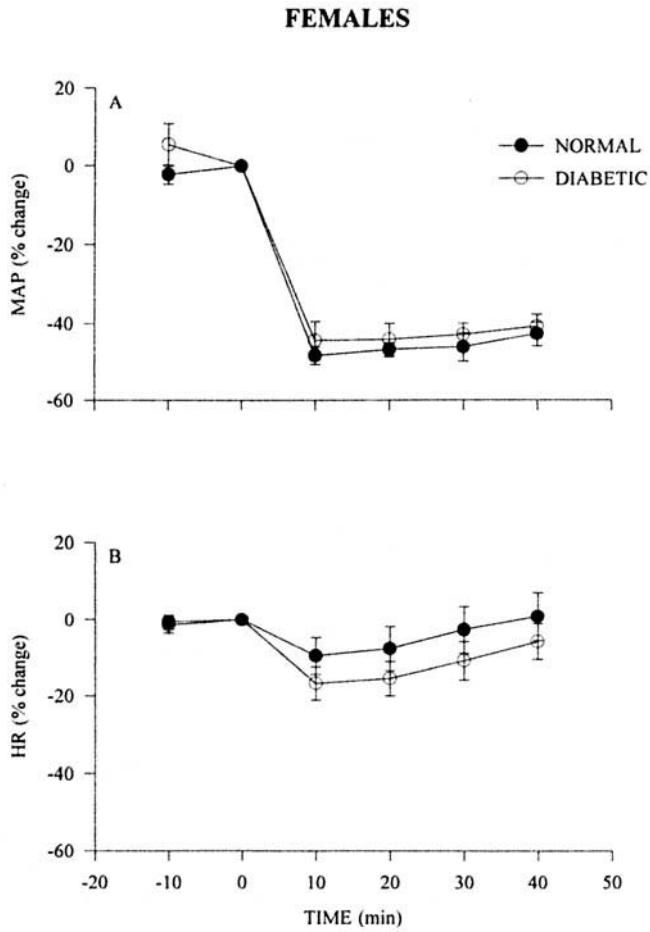

Figure 5. The effect of prazosin (4 mg/kg) on (A) mean arterial pressure (MAP) and (B) heart rate (HR) expressed as percentage change in normal ($n = 6$) and diabetic ($n = 7$) females rats.

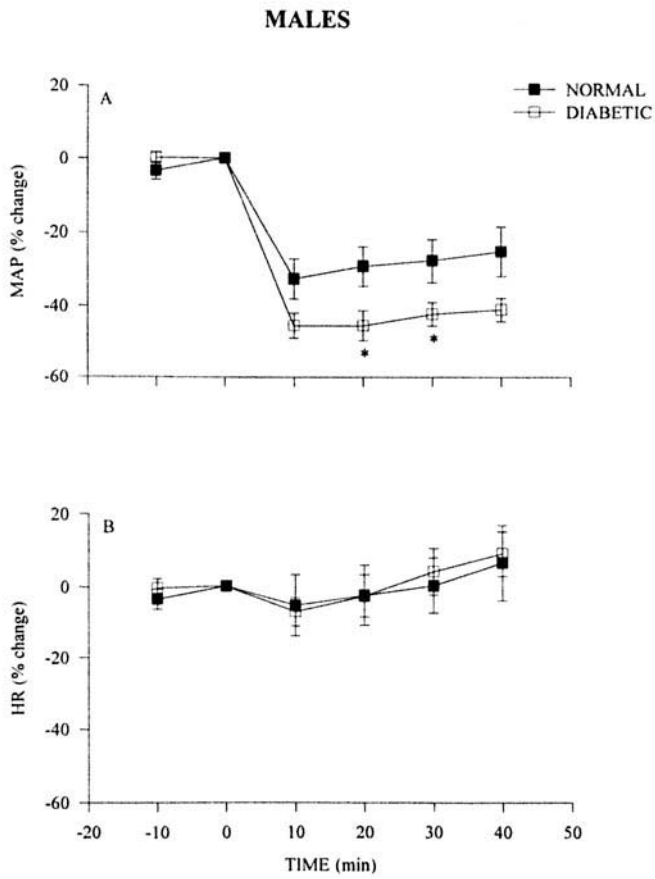

Figure 6. The effect of prazosin (4 mg/kg) on (A) mean arterial pressure (MAP) and (B) heart rate (HR) expressed as percentage change in normal ($n = 5$) and diabetic ($n = 6$) males rats. * = $P < 0.05$ vs. normal male, Student's *t* test. Two-way ANOVA group effect, normal vs. diabetic males MAP, $P < 0.001$.

Table IV. Average Mean Arterial Pressure and Heart Rate Responses to Prazosin

MAP (% change)			
Normal		Diabetic	
Female	Male	Female	Male
−47.16 ± 1.4 (6)	−30.09 ± 3.0* (5)	−43.93 ± 2.2 (7)	−43.90 ± 2.2† (6)
HR (% change)			
−6.57 ± 3.1 (6)	−2.52 ± 4.4 (5)	−14.33 ± 2.6 (7)	−1.47 ± 3.4‡ (6)

Note. The values represent the mean ± SEM. * = $P < 0.001$ vs. normal female. † = $P < 0.001$ vs. normal male. ‡ = $P < 0.01$ vs. diabetic female, ANOVA. Number in parenthesis = *n*. Mean arterial pressure (MAP); heart rate (HR); responses (between 10–30 minutes) to Prazosin (4 mg/kg).

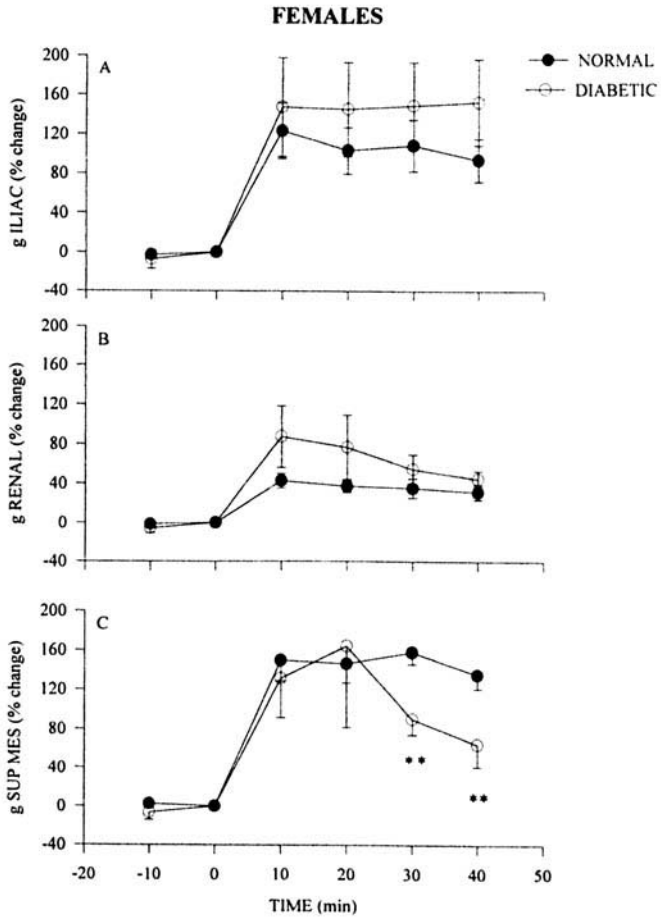

Figure 7. The effect of prazosin (4 mg/kg) on (A) iliac, (B) renal, and (C) superior mesenteric arteries conductance (g) expressed as percentage change in normal ($n = 6$) and diabetic ($n = 7$) female rats. ** = $P < 0.01$ vs. normal female, Student's *t* test. Two-way ANOVA group effect, normal vs. diabetic females g Renal, $P < 0.05$; g SUP MES, $P < 0.001$.

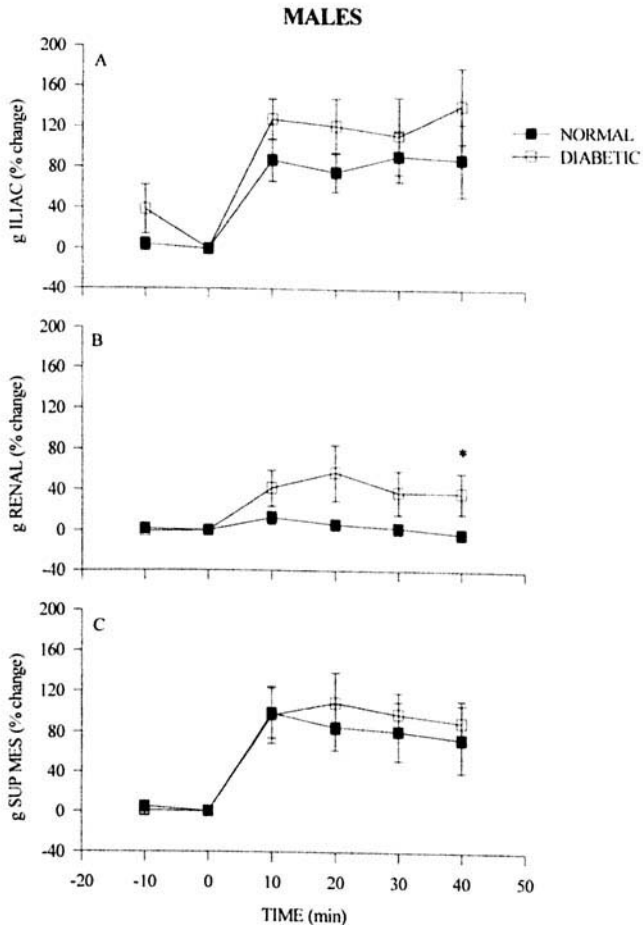

Figure 8. The effect of prazosin (4 mg/kg) on (A) iliac, (B) renal, and (C) superior mesenteric arteries conductance (g) expressed as percentage change in normal ($n = 5$) and diabetic ($n = 6$) male rats. * = $P < 0.05$ vs. normal male, Student's *t* test. Two-way ANOVA group effect, normal vs. diabetic male g Renal, $P < 0.01$.

Discussion

The results presented in this study demonstrate that SNP administration results in a dose-dependent decrease in MAP and decreased peripheral resistance associated with an increased HR in normal and diabetic rats. These findings are consistent with previous observations of systemic administration of SNP (7, 20–22). Since a primary focus of our investigation was to conduct a comparative study, we observed that the sensitivity to SNP-mediated vasodilation was less in diabetic iliac and superior mesenteric arteries when compared to normals (6). This reduced response to SNP was consistent with observations in the human forearm arterial bed and dorsal foot of diabetic patients (7, 14). When a comparison was made based on sex, the diabetic females dilatory response to SNP was significantly less when compared to diabetic males in the iliac and superior mesenteric bed. These results were also consistent with previous observations of sex difference in diabetic patients (23). Two possibilities to the reduced response to SNP in

Table V. Average Iliac, Renal, and Superior Mesenteric Arteries Vascular Conductance Responses to Prazosin

Iliac g (% change)			
Normal		Diabetic	
Female	Male	Female	Male
111.61 ± 14.3 (6)	85.75 ± 11.6 (5)	147.22 ± 26.3 (7)	126.60 ± 15.2 (6)
Renal g (% change)			
38.42 ± 4.3 (6)	6.98 ± 3.2 (5)	73.26 ± 15.3* (7)	42.00 ± 12.2†,‡ (6)
SUP MES g (% change)			
151.78 ± 9.7 (6)	88.21 ± 13.8¶ (5)	103.21 ± 16.2¶ (7)	95.68 ± 15.2 (6)

Note. The values represent the mean ± SEM. * = $P < 0.05$ vs. normal female. † = $P < 0.05$ vs. normal male. ‡ = $P < 0.05$ vs. diabetic female. ¶ = $P < 0.05$ vs. normal female, ANOVA. Number in parenthesis = *n*. Conductance (g); responses (between 10–30 minutes) to Prazosin (4 mg/kg).

diabetes have been suggested: 1) that there is an abnormality/dysfunction in vascular smooth muscle sensitivity to NO in diabetic patients (14); and 2) that endothelial dysfunction is responsible for the decreased responsiveness to SNP (7). Since SNP administration acts at sites distal to endothelial-mediated NO release, our results suggest a decreased sensitivity to NO in our diabetic animals, and this is manifested to a greater extent in skeletal muscle and the splanchnic circulation.

Contrary to what was observed in the blood vessels of the skeletal muscle and the splanchnic vessels, diabetic females and males displayed a significant increased sensitivity in renal response to SNP. These results are also supported by several investigators who have demonstrated that local and systemic infusions of SNP lead to increased renal blood flow, renal vasodilation, and decreased renal vascular resistance (9, 24, 25). Diabetes is independently characterized by abnormal renal hemodynamics, vasodilation, pronounced glomerular hyperfusion, and hyperfiltration (26–28). Therefore, the combination of the two observations suggests that the increased responsiveness to SNP in diabetic animals may add to the abnormal renal hemodynamics and increased responsiveness to SNP in the renal bed.

The administration of the α_1-adrenoceptor antagonist, prazosin, resulted in a decrease in MAP and an increase in regional conductance, both of which are consistent with previous observations (29–31). According to previous studies, the hypotensive response to prazosin is a consequence of the decrease in α-adrenergic-mediated peripheral resistance at the level of vascular smooth muscle (32, 33). The initial bradycardia followed by an increase or return to basal HR observed in all four groups of animals after the administration of prazosin has also been previously documented (34) as well as the diminished reflex tachycardia observed in our female rats (35). Conversely, our normal and diabetic male rats displayed a reflex tachycardia that was consistent with previous studies (10, 34).

Prazosin leads to an increase in vascular conductance/blood flow in the different vascular beds, and our results are in agreement with these observations (31, 36, 37). This response is a reflection of the blockade of the α_1-adrenoceptor-mediated vasoconstrictor tone and the consequent decreased resistance and increased in blood flow (31, 36, 37). The differential responses in different vascular beds are strongly influenced by the distribution of α-receptors, where an increased α-receptor population is associated with an enhanced peripheral blood vessel response, especially in the kidney and the splanchnic circulation (36). In our study, the administration of prazosin resulted in a differential response in blood flow. This was especially so in the iliac and superior mesenteric bed where there was a greater response to the adrenergic blockade than the renal bed in both normal and diabetic animals. A possible explanation for the increased sensitivity to prazosin in the iliac bed may be that the blood flow in skeletal muscle has a greater dependence on adrenergic regulation. Other investigators also support observations that skeletal muscle blood flow is indeed under tonic sympathetic constrictor tone especially at rest (37, 38). Like the skeletal muscle bed, the splanchnic bed also exhibited an increase in conductance following α-adrenergic blockade. This observation is also supported by studies using *in situ* autoperfused superior mesenteric arterial bed from rats, suggesting that α_1-adrenoceptors are strongly represented in this vascular bed (39, 40). On the other hand, the mild response to prazosin in the renal bed when compared to the skeletal muscle and the splanchnic bed is not as easy to reconcile since reports in the literature state that renal vasoconstriction is mainly mediated by α_1-adrenoceptors (40–42). However, investigators have also demonstrated that α_2-adrenoceptors mediate renal vasoconstriction in conscious rats when boluses of norepinephrine are administered into the kidney (43). Nevertheless, the basal vascular tone in the kidney may not be mediated by an α-adrenergic mechanism but mostly by an autoregulatory mechanism by other mediators (15, 44, 45). Therefore, the mild response observed in the renal bed to prazosin when compared to the iliac and superior mesenteric bed may be consistent with the autoregulatory mechanism in the kidney. Another possible mechanism for the increased sensitivity to prazosin in diabetic animals is the upregulation of adrenoreceptors. According to investigators, arteries from diabetic patients, rats, and dogs exhibit an enhanced sensitivity and/or responsive-

ness to norepinephrine and α_1 agonists (46–49). It has also been reported that modified adrenergic receptors may account for sympathetic adrenergic alterations in diabetic patients and rats (50, 51).

In summary, systemic infusions of SNP results in a dose-dependent decreased blood pressure and increased HR in normal and diabetic rats. SNP increased the vascular conductance in normal and diabetic rats in all three vascular beds in a dose-dependent fashion. Diabetes decreased the responsiveness to SNP in the iliac and superior mesenteric vessels and increased the responsiveness in renal vessels. The sex difference is associated with an enhanced responsiveness to NO in the renal vessels of females. Prazosin infusion decreased the MAP in normal and diabetic rats. The α_1-adrenoceptor antagonist increased vascular conductance in all three vascular beds; however, the relative responsiveness to prazosin was greater in the iliac and superior mesenteric arteries when compared to the renal bed. Again, females tended to be more responsive than males in their dilatory response.

We concluded that diabetes leads to a decreased sensitivity to NO in arteries of skeletal muscle and the splanchnic circulation and increased sensitivity in the renal arteries. Males appear to have a generally lower vascular sensitivity to NO when compared to females. The skeletal muscle and the splanchnic circulation are more dependent on α-adrenergic tone when compared to the renal vessels, and this tone is greater in both male and female diabetics.

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