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Vascular reactivity to vasopressin during diabetes: gender and regional differences

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Abstract

The isometric response to vasopressin of 2-mm-long segments of basilar, coronary, renal and tail arteries from male and female, control (normoglycemic) and streptozotocin-induced diabetic rats was studied. Vasopressin (10^{-12}–3×10^{-8} M) produced arterial concentration-dependent contraction, with a lower potency in coronary arteries from female than from male rats, and was similar for both genders in basilar, renal and tail arteries. This contraction was reduced by diabetes in basilar and coronary arteries, increased in renal arteries, and not modified in tail arteries, in both genders. Inhibition of nitric oxide synthesis with N^{W}-nitro-L-arginine methyl ester (L-NAME, 10^{-4} M) increased the contraction to vasopressin in coronary arteries from control female and diabetic female rats; as well as in renal arteries from control male and control female rats, but not in any other experimental group. Inhibition of cyclooxygenase with meclofenamate (10^{-5} M) reduced the contraction to vasopressin in basilar arteries from diabetic female rats and in renal arteries from diabetic male rats, but not in any other experimental group. These results suggest that the response to vasopressin (a) has lower potency in female coronary arteries due to higher nitric oxide production; (b) is reduced by diabetes in basilar and coronary arteries from both genders, by mechanisms independent of nitric oxide and prostanoids; and (c) is increased by diabetes in renal arteries due to reduced production of nitric oxide in females, and to both reduced production of nitric oxide and increased production of prostanoids in males. Therefore, the effects of diabetes on vascular reactivity to vasopressin may differ between vascular beds, and the mechanisms underlay these effects may be distinct between genders.

Keywords: Cerebral artery; Coronary artery; Renal artery; Tail artery; Nitric oxide (NO); Prostanoid

1. Introduction

Cardiovascular abnormalities are some of the most serious complications of diabetes mellitus (Nathan, 1993). For this reason, the vascular reactivity to vasoactive agents during this disease has been the subject of intensive investigation (Tomlinson et al., 1992). One aspect of this subject is the study of diabetic vascular alterations in males and females. It is known that cardiovascular diseases in the general, non-diabetic population are more frequent in men than in premenopausal women (Douglas, 1997; Hayward et al., 2000), and this has been related to the protective effects of ovarian hormones (Mendelsohn and Karas, 1999). However, diabetes may produce a relatively greater impairment in the female cardiovascular system, so the difference between men and women regarding cardiovascular diseases disappears in the diabetic patients (Farmer and Gotto, 1997). In agreement with this notion, it has been found that diabetes reduces in females but not in males the relaxation to acetylcholine of rat basilar artery (Mayhan et al., 2002) and rat aorta (Pinna et al., 2001), and the relaxation of human leg circulation to metacholine (Steinberg et al., 2000). However, for other vascular stimuli diabetes may produce a greater affectation of blood vessels from males, as diabetes reduces the vasodilatation to a nitric oxide donor in iliac arteries of male but not of female rats (Martínez-Nieves and Dunbar, 1999), and diabetes increases the contraction to prostanoids in the pulmonary circulation of male but not of female rats (Russ and Tobin, 1998).

Knowledge of vascular reactivity to vasopressin during diabetes could be of interest as this peptide may be of relevance for diabetic cardiovascular pathophysiology. Osmoregulation is disturbed during diabetes, and it has been reported that the plasmatic levels of vasopressin are

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consistently elevated during this disease, both in rats with experimental diabetes (Brooks et al., 1989) and in diabetic patients (Vokes et al., 1987), and it has been suggested that these elevated levels of vasopressin may be relevant for the regulation of arterial blood pressure during diabetes (see Tomlinson et al., 1992). Studies about the effects of diabetes on vascular response to vasopressin report contradictory results as the effect of this hormone on arterial blood pressure following ganglion blockade is reduced in diabetic rats (Hebden et al., 1987), and the vasoconstrictor effect of vasopressin is reduced in kidney vasculature (Sarubbi et al., 1989; Loichot et al., 2001) and in the cutaneous circulation (Lawrence and Brain, 1992) of diabetic rats, but this effect is not modified by diabetes in basilar (Mayhan, 1998; Van Buren et al., 1998) and mesenteric arteries (Van Buren et al., 1998). These discrepancies may be due to the experimental procedures and the types of vessels used in these studies. Both the effects of diabetes (Hill and Larkins, 1989) and the response to vasopressin (García-Villalón et al., 1996) may differ markedly between vascular beds. Also, the role of nitric oxide in the vascular effects of vasopressin may differ between vascular beds (García-Villalón et al., 1996), and the liberation of nitric oxide seems to be altered during diabetes (Pieper, 1998). Regarding gender differences, the vascular effects of vasopressin may be different in male and female animals (Laycock and Whitehead, 1995), and both higher (Crofton et al., 1988, Wang et al., 1997) and lower (Altura, 1975; Stallone et al., 1991; Stallone, 1993) maximal responses in males compared to females have been reported. These differences may depend on the vascular bed examined and the experimental procedure (i.e., in vivo or in vitro) used. A previous study from our laboratory has shown that vasopressin has a potentiating effect on the sympathetic contraction of rat tail arteries, that this potentiation is higher in arteries from males compared to females, and that diabetes abolishes this gender difference (Sanz et al., 2001). However, the interaction of gender and diabetes on the response to vasopressin in other vascular beds has not been studied, to our knowledge.

The aim of the present study was to analyse the effects of diabetes on the response to vasopressin in various blood vessels from male and female animals, as well as the role of nitric oxide and prostanoids in these effects. This was performed using four types of arteries (basilar, coronary, renal and tail) from male and female, control (normoglycemic) and diabetic rats. Diabetes was induced by injection of streptozotocin, a model of experimental diabetes frequently used (Öztürk et al., 1996).

2. Materials and methods

A total of 44 male and 28 female Sprague–Dawley rats, weighting 250–350 g at the beginning of the study, were used. This investigation conforms with the principles expressed in the National Institutes of Health, Guide for the Care and Use of Laboratory Animals, and has been approved by the institutional ethics committee. In one group of male and female rats, diabetes was induced by intraperitoneal injection of streptozotocin (60 mg/kg, dissolved in citrate buffer pH 4.5), and a second group of age-matched control rats received only the vehicle. All rats were housed in cages and allowed free access to food and water. The concentration of glucose in plasma was determined from a drop of blood from the tail using Glucostix reactive strips (Bayer Diagnostics). Glucose determination was performed before and 2 days after streptozotocin injection, and again on the day of the experiment. In the female rats, the stage of the estrous cycle in the day of the experiment was determined by microscopic examination of vaginal smears. As no differences were found in the vascular responses from animals in the different days of the cycle, the results from all female animals were pooled.

Six weeks after streptozotocin or vehicle injection, the rats were killed by pentobarbitone overdose (200 mg/kg) followed by exanguination, and the following arteries were carefully dissected: basilar, anterior interventricular coronary, renal and ventral caudal (tail). The arteries were placed in cold isotonic saline solution, cut in 2-mm-long segments, and each segment was prepared for isometric tension recording in a 4-ml organ bath at 37 °C, containing modified Krebs–Henseleit solution with the following composition (mmol): NaCl, 115; KCl, 4.6; KH_2PO_4, 1.2; $MgSO_4$, 1.2; $CaCl_2$, 2.5; $NaHCO_3$, 25; glucose, 11. The solution was equilibrated with 95% oxygen and 5% carbon dioxide to give a pH of 7.3–7.4. Briefly, the method consists of passing through the lumen of the vascular segment two fine tungsten wires, which were 75 μm in diameter for basilar and coronary arteries, and 100 μm for renal and tail arteries, and were fixed by both ends to prevent bending during contraction of the vascular segments. One wire is fixed to the organ bath wall, while the other is connected to a strain gauge for isometric tension recording, thus permitting the application of passive tension in a plane perpendicular to the long axis of the vascular cylinder. The recording system included a Universal Transducing Cell UC3 (Statham Instruments), a Statham Microscale Accessory UL5 (Statham Instruments) and a Beckman Type RS Recorder (model R-411, Beckman Instruments). An optimal passive

Table 1
Body weight and glycemia in male and female rats, 6 weeks after induction of diabetes by streptozotocin and in normoglycemic controls

	Weight (g)	Glycemia (mg/100 ml)
Males		
Normoglycemic	490±13	91±4 (20)
Diabetic	289±12[a]	337±10[a] (24)
Females		
Normoglycemic	245±6[b]	95±4 (15)
Diabetic	185±9[a,b]	357±15[a] (13)

Values are means±S.E.M. Number of animals in parenthesis.
[a] Significantly different from normoglycemic animals of the same gender ($P<0.01$).
[b] Significantly different from males ($P<0.01$).

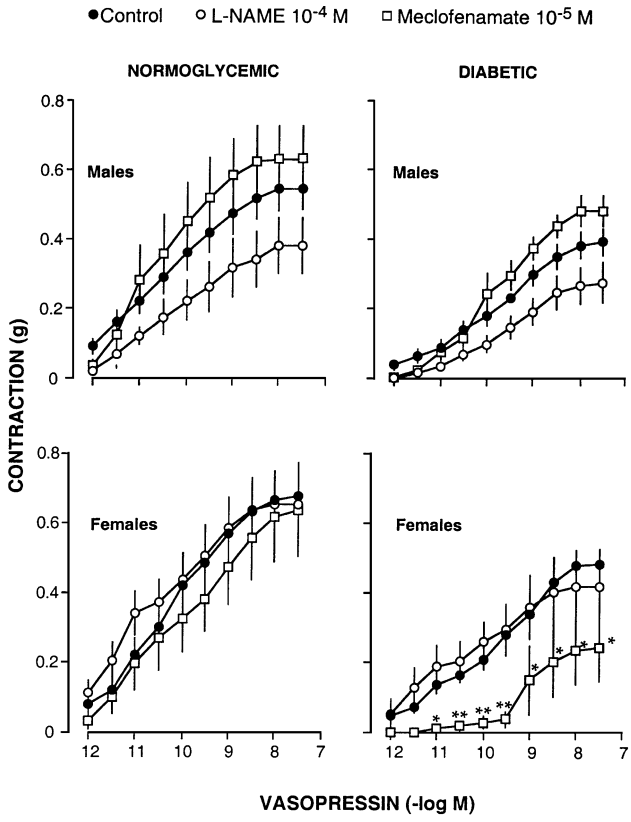

Fig. 1. Contraction to vasopressin (10^{-12}–3×10^{-8} M) of basilar arteries from normoglycemic (left panels) or from diabetic (right panels), male (upper panels) or female (lower panels) rats, in control conditions, in the presence of L-NAME (10^{-4} M) or in the presence of meclofenamate (10^{-5} M). Values are means±S.E.M. *, **: Statistically significant compared to control (*P<0.05; **P<0.01).

tension, which was 0.25 g for basilar and coronary arteries and 0.75 g for renal and tail arteries, was applied to the vascular segments, and then they were allowed to equilibrate for 60–90 min. These optimal tensions were determined in preliminary experiments, by stretching the segments to different passive tensions and recording the contraction to 5-hydroxytryptamine (10^{-5} M).

Cumulative concentration–response curves to arginine–vasopressin (10^{-12}–3×10^{-8} M) were recorded in basilar, coronary, renal and tail arteries from male and female, control and diabetic rats. This was performed in these arteries under control conditions and in the presence of the inhibitor of nitric oxide synthesis N^{W}-nitro-L-arginine methyl ester (L-NAME, 10^{-4} M) or the cyclooxygenase inhibitor meclofenamate (10^{-5} M). These inhibitors were added to the bath 20 min before beginning to test the vasopressin effect.

The values of the contraction to vasopressin are shown in absolute values, and these data are expressed as means±S.E.M. EC_{50} values for the concentration–response curves for vasopressin were calculated as the concentration producing 50% of the maximal effect by geometric interpolation, and are expressed as pD_2 ($-\log EC_{50}$). Data from male and female, control and diabetic rats were compared by two-way analysis of variance (ANOVA), followed by Newman–Keuls' test to determine which comparisons were statistically significant. Data obtained in the presence of L-NAME or meclofenamate were evaluated by one-way ANOVA, followed by Dunnett's test to compare each experimental condition with its control. P<0.05 was considered significant.

Drugs used included the following: L-NAME; [Arg^8]-vasopressin acetate, and meclofenamate (2[1,6-Dichloro-3-methylphenyl-amino]benzoic acid, sodium salt); obtained from Sigma. All drugs were dissolved in distilled water and further diluted in isotonic NaCl.

3. Results

Six weeks after treatment with streptozotocin, male and female rats showed higher glycemia values (P<0.01) and lower body weight (P<0.01) than age-matched control rats (Table 1). Body weight was higher in male than in female,

Table 2
pD_2 values and maximal contraction (E_{max}) to vasopressin in basilar arteries from male and female rats, 6 weeks after induction of diabetes by streptozotocin and in normoglycemic controls, in the absence (control) and in the presence of L-NAME (10^{-4} M) or meclofenamate (10^{-5} M)

	Control		L-NAME		Meclofenamate	
	pD_2	E_{max} (g)	pD_2	E_{max} (g)	pD_2	E_{max} (g)
Males						
Normoglycemic	10.48±0.14	0.58±0.05 (26)	9.93±0.19	0.38±0.08 (6)	10.32±0.27	0.62±0.10 (6)
Diabetic	9.87±0.12[a]	0.40±0.03[a] (26)	9.69±0.16	0.26±0.06 (7)	9.75±0.18	0.48±0.04 (6)
Females						
Normoglycemic	10.57±0.16	0.67±0.07 (15)	10.78±0.25[b]	0.65±0.09 (9)	10.00±0.37	0.64±0.13 (6)
Diabetic	9.91±0.19[c]	0.48±0.04 (12)	10.62±0.28	0.42±0.1 (5)	8.70±0.15[a,d,e]	0.24±0.10[f] (7)

Values are means±S.E.M. Number of segments in parenthesis.
[a] Significantly different from normoglycemic animals of the same gender (P<0.01).
[b] Significantly different from males (P<0.05).
[c] Significantly different from normoglycemic animals of the same gender (P<0.05).
[d] Significantly different from males (P<0.01).
[e] Significantly different from control (P<0.01).
[f] Significantly different from control (P<0.05).

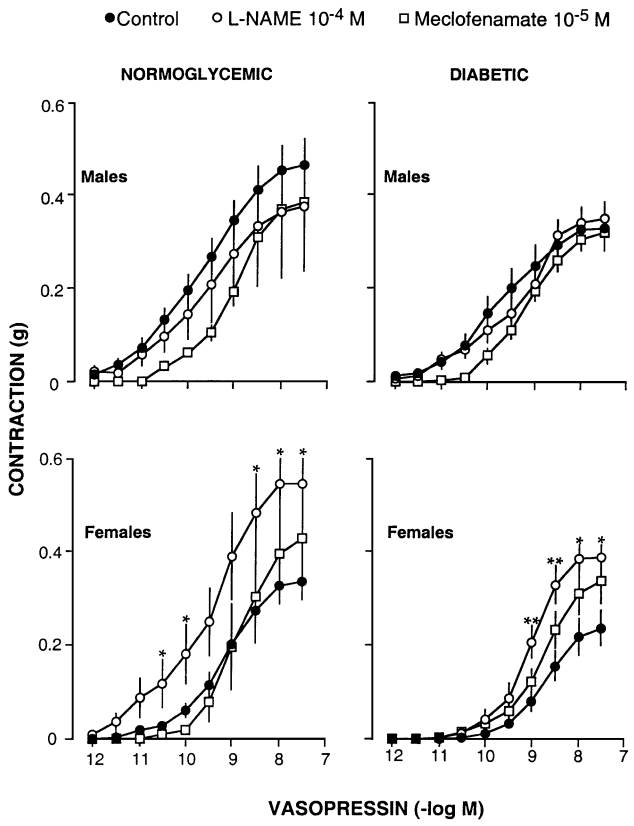

Fig. 2. Contraction to vasopressin (10^{-12}–3×10^{-8} M) of coronary arteries from normoglycemic (left panels) or from diabetic (right panels), male (upper panels) or female (lower panels) rats, in control conditions, in the presence of L-NAME (10^{-4} M) or in the presence of meclofenamate (10^{-5} M). Values are means±S.E.M. *, **: Statistically significant compared to control (*P<0.05; **P<0.01).

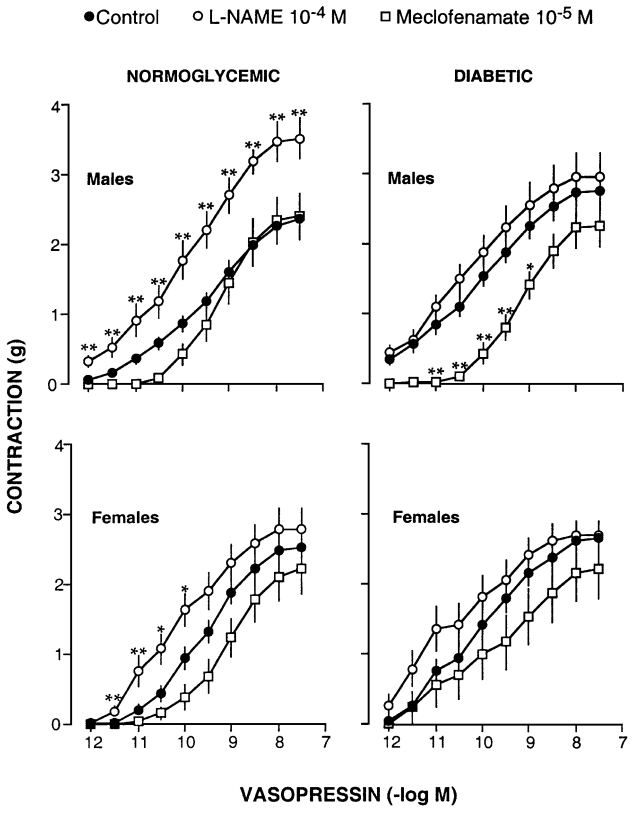

Fig. 3. Contraction to vasopressin (10^{-12}–3×10^{-8} M) of renal arteries from normoglycemic (left panels) or from diabetic (right panels), male (upper panels) or female (lower panels) rats, in control conditions, in the presence of L-NAME (10^{-4} M) or in the presence of meclofenamate (10^{-5} M). Values are means±S.E.M. *, **: Statistically significant compared to control (*P<0.05; **P<0.01).

control and diabetic rats (P<0.01), but glycemia values in control rats, or in streptozotocin-treated rats, were similar in the corresponding male and female animals (Table 1).

Basilar arteries upon stretch developed spontaneous, intrinsic tone in most cases (about 75% of the arterial segments), which was not different in those from control male (0.33±0.04 g) and female (0.47±0.05 g) rats, or in those from diabetic male (0.34±0.06 g) and female (0.43±0.06 g) rats. Coronary, renal and tail arteries did not develop intrinsic tone upon stretch in any case.

Vasopressin (10^{-12}–3×10^{-8} M) produced concentration-dependent contraction in all types of arteries studied. In the arteries from normoglycemic rats, the order of sensitivity for males was: basilar (P<0.01)>coronary=renal (P<0.01)>tail

Table 3
pD_2 values and maximal contraction (E_{max}) to vasopressin in coronary arteries from male and female rats, 6 weeks after induction of diabetes by streptozotocin and in normoglycemic controls, in the absence (control) and in the presence of L-NAME (10^{-4} M) or meclofenamate (10^{-5} M)

	Control		L-NAME		Meclofenamate	
	pD_2	E_{max} (g)	pD_2	E_{max} (g)	pD_2	E_{max} (g)
Males						
Normoglycemic	9.63±0.12	0.44±0.05 (27)	9.53±0.29	0.37±0.14 (7)	9.00±0.06	0.38±0.05 (6)
Diabetic	9.51±0.11	0.29±0.04[a] (22)	9.30±0.24	0.35±0.03 (5)	9.19±0.13	0.32±0.01 (7)
Females						
Normoglycemic	9.22±0.10[b]	0.34±0.04 (15)	9.44±0.20	0.55±0.09[c] (9)	9.00±0.14	0.43±0.10 (6)
Diabetic	8.70±0.12[a,d]	0.24±0.04 (13)	9.06±0.11	0.39±0.03[c] (6)	8.77±0.07 [d]	0.34±0.05 (7)

Values are means±S.E.M. Number of segments in parenthesis.
[a] Significantly different from normoglycemic animals of the same gender (P<0.05).
[b] Significantly different from males (P<0.05).
[c] Significantly different from control (P<0.05).
[d] Significantly different from males (P<0.01).

Table 4
pD_2 values and maximal contraction (E_{max}) to vasopressin in renal arteries from male and female rats, 6 weeks after induction of diabetes by streptozotocin and in normoglycemic controls, in the absence (control) and in the presence of L-NAME (10^{-4} M) or meclofenamate (10^{-5} M)

	Control		L-NAME		Meclofenamate	
	pD_2	E_{max} (g)	pD_2	E_{max} (g)	pD_2	E_{max} (g)
Males						
Normoglycemic	9.50±0.08	2.32±0.14 (31)	10.07±0.22[a]	3.49±0.29[a] (7)	9.19±0.13	2.38±0.33 (7)
Diabetic	10.13±0.11[b]	2.73±0.17 (30)	10.50±0.27	2.95±0.34 (8)	9.24±0.05 [a]	2.26±0.31 (7)
Females						
Normoglycemic	9.60±0.11	2.51±0.17 (15)	10.21±0.16[a]	2.77±0.30 (9)	9.08±0.15	2.22±0.36 (6)
Diabetic	10.10±0.16[c]	2.66±0.17 (13)	10.69±0.30	2.68±0.23 (6)	9.59±0.35	2.21±0.41 (7)

Values are means±S.E.M. Number of segments in parenthesis.

[a] Significantly different from control ($P<0.01$).
[b] Significantly different from normoglycemic animals of the same gender ($P<0.01$).
[c] Significantly different from normoglycemic animals of the same gender ($P<0.05$).

arteries, and for females was: basilar ($P<0.01$)>renal ($P< 0.05$)>coronary=tail arteries (Tables 2, 3, 4 and 5), and the order of the maximal contraction for males was: tail ($P< 0.01$)>renal ($P<0.01$)>basilar=coronary arteries, and for females was: tail ($P<0.01$)>renal ($P<0.01$)>basilar ($P<0.05$)>coronary (Tables 2, 3, 4 and 5).

In basilar arteries, the sensitivity and maximal response to vasopressin was similar in both genders. In these arteries, the sensitivity ($P<0.01$) and the maximal effect ($P<0.01$) to vasopressin was reduced by diabetes in male rats, and only the sensitivity was reduced ($P<0.05$) by diabetes in female rats (Fig. 1 and Table 2). Treatment with L-NAME did not modify the response to this peptide in basilar arteries from any experimental group (Fig. 1 and Table 2). Treatment with meclofenamate reduced the sensitivity and maximal effect of basilar arteries from diabetic female rats, but meclofenamate did not modify the response to vasopressin in any other experimental group, control female, control male or diabetic male rats (Fig. 1 and Table 2).

In coronary arteries, the sensitivity to vasopressin was lower ($P<0.05$) in those from female than in those from male rats (Fig. 2 and Table 3), both in control and diabetic animals. On the other hand, the maximal effect of vasopressin was reduced by diabetes in males ($P<0.05$), and the sensitivity was reduced by diabetes in females ($P<0.05$). L-NAME treatment increased similarly the sensitivity to vasopressin ($P<0.05$) in coronary arteries from control female and from diabetic female rats, but L-NAME did not modify the response of coronary arteries from control male or diabetic male rats (Fig. 2 and Table 3). Meclofenamate did not modify the response of coronary arteries to vasopressin in any experimental group (Fig. 2 and Table 3).

In renal arteries, the response to vasopressin was not different when compared between arteries from male and female rats, but diabetes increased the sensitivity of this response in rats of both genders (Fig. 3 and Table 4). L-NAME increased the sensitivity of renal arteries from control female rats, and both the sensitivity and maximal effect of renal arteries from control male rats. This inhibitor of nitric oxide synthesis, however, did not modify the response to vasopressin in renal arteries from diabetic male and diabetic female animals (Fig. 3 and Table 4). Meclofenamate increased ($P<0.01$) the sensitivity to vasopressin in arteries from diabetic male rats, but meclofenamate did not modify the contraction to vasopressin in the other experimental groups, control male, control female or diabetic female rats (Fig. 3 and Table 4).

In tail arteries, the contraction to vasopressin was similar in male and female rats, and this contraction was not modified in diabetic rats of both genders, neither by treatment with L-NAME or meclofenamate in any experimental group (Table 5).

Table 5
pD_2 values and maximal contraction (E_{max}) to vasopressin in caudal arteries from male and female rats, 6 weeks after induction of diabetes by streptozotocin and in normoglycemic controls, in the absence (control) and in the presence of L-NAME (10^{-4} M) or meclofenamate (10^{-5} M)

	Control		L-NAME		Meclofenamate	
	pD_2	E_{max} (g)	pD_2	E_{max} (g)	pD_2	E_{max} (g)
Males						
Normoglycemic	8.98±0.05	2.87±0.13 (32)	8.83±0.08	3.34±0.21 (9)	9.21±0.10	3.49±0.44 (7)
Diabetic	9.04±0.09	2.82±0.13 (31)	8.74±0.15	3.10±0.23 (8)	9.05±0.09	2.85±0.14 (8)
Females						
Normoglycemic	9.08±0.07	3.25±0.19 (15)	9.19±0.11	3.75±0.22 (9)	9.20±0.20	2.98±0.30 (6)
Diabetic	8.89±0.06	2.87±0.21 (13)	8.94±0.07	3.03±0.19 (6)	8.86±0.06	2.73±0.37 (7)

Values are means±S.E.M. Number of segments in parenthesis.

4. Discussion

The results of the present study suggest that diabetes may affect the vascular response to vasopressin in some vascular beds, but not in others, as we have found that diabetes reduced this response in basilar and coronary arteries, increased it in renal arteries, and did not modify it in tail arteries. The rats treated with streptozotocin showed elevated glycemia values, which are in the range of the hyperglycemia which may be observed in diabetic patients. This model also reproduces some features of clinical Type I diabetes, such as reduction of body weight. This weight loss was severe in our study, and this reduction may be involved in the vascular alterations observed in this condition. However, the changes found in this study in the vascular response to vasopressin were not observed with a different vasoconstrictor (the thromboxane analog U46619, Sanz et al., in press), suggesting that these changes are not due to unspecific arterial damage by the experimental conditions.

We have found that the contraction to vasopressin had a lower potency in coronary arteries from females than in coronary arteries from males, and this difference may be due to the higher production of nitric oxide in those arteries from females, as the contraction to vasopressin was increased by inhibition of nitric oxide synthase in coronary arteries from female, but not in those from male rats. There are abundant reports in literature showing reduced vasoconstriction to stimuli other than vasopressin in different vascular beds due to increased nitric oxide production in blood vessels from females (see Hayward et al., 2000), and this has been related to the facilitating action of female sexual hormones on nitric oxide synthesis (Kauser and Rubanyi, 1997). However, in the case of vasopressin conflicting results have been reported, as in vitro increased maximal contraction to this peptide due to lower nitric oxide production has been found in aorta (Stallone et al., 1991; Stallone, 1993) and mesenteric arteries (Altura, 1975; Stallone, 1995) from female compared to those from male rats, and on the contrary, the in vivo increase in arterial pressure, and in renal and mesenteric vascular resistance after vasopressin injection was higher in males than in females (Wang et al., 1997). These discrepancies may be related to the response to vasopressin may vary between vascular beds and between genders, to the different role of nitric oxide in this response between vascular regions, as well as to the experimental procedure used. Interestingly, the incidence of cardiovascular diseases is lower in premenopausal women than in men (Douglas, 1997), and this difference may be related to a higher production of nitric oxide and/or lower vasoconstriction in the coronary vascular bed in premenopausal females, as suggested by our results. We have not found differences in the response to vasopressin between arteries obtained in different stages of the estrous cycle, as it has been also observed by others in an in vitro study (Stallone et al., 1991). Varying responsiveness to vasopressin during the estrous cycle, however, has been observed in vivo (Crofton et al., 1988). This discrepancy is probably related to the fact that arteries in vivo are exposed to varying hormonal levels during the different stages of the estrous cycle, whereas in vitro the arteries are not exposed to sexual hormones.

The effects of diabetes on the vascular reactivity to vasopressin also may differ between vascular beds. Diabetes reduced this response in basilar and coronary arteries, and increased it in renal arteries. The particular manner of this effect may also vary; for example, in coronary arteries from males diabetes reduced the maximal effect of vasopressin, whereas in females diabetes reduced the sensitivity to vasopressin. This latter difference may be related to the degree of affectation by diabetes in the different cases, or to the importance of receptor reserve in these arteries. The impairment of the response to vasopressin by diabetes found in basilar and coronary arteries in our study is not probably related to changes in the release of nitric oxide. L-NAME did not modify the response of basilar arteries in any experimental group, nor in coronary arteries from control and normoglycemic males, and although L-NAME increased the response of coronary arteries from females, this increase was similar in control and diabetic animals. Prostanoids production also may not be related to the impairment induced by diabetes on vasopressin effects, because these effects were not modified by meclofenamate in coronary arteries in any case, nor in basilar arteries from control male and diabetic male rats, nor in basilar arteries from control female rats. In basilar arteries from diabetic female rats, meclofenamate reduced the contraction to vasopressin, suggesting that in diabetic females the production of vasoconstrictor prostanoids in these particular arteries may increase during stimulation with vasopressin, however this increase in vasoconstrictor prostanoids cannot explain the lower potency in arteries from diabetic animals. As the reduction in the contraction of basilar and coronary arteries during diabetes is probably not related to changes in nitric oxide or prostanoid release, it may be hypothesized that this reduction may be due to changes in sensitivity and/or number of vasopressin receptors in vascular smooth muscle.

Our results in basilar arteries contrast with those of Mayhan (1998) and Van Buren et al. (1998), who did not find alterations in the response of these arteries to vasopressin during diabetes. The discrepancy with the results of Mayhan (1998) may be related to the different experimental procedure used (measurement of arterial diameter in vivo vs. isometric contraction recording in vitro) or the duration of diabetes (3–4 months vs. 6 weeks). More difficult is to explain the difference with the study of Van Buren et al. (1998), which used in vitro tension recording and a range of diabetes duration which included that used in the present study (4–40 weeks vs. 6 weeks). This difference could be related to the rat strain used, which was Wistar in the study of Van Buren et al., (1998) and Sprague–Dawley in ours.

However, other studies have found reduced in vivo response to vasopressin during diabetes in the cutaneous circulation (Lawrence and Brain, 1992) or in the arterial pressor response to this peptide (Hebden et al., 1987).

The results observed in renal arteries differ from those found in the other vascular beds studied in our work, as the contraction to vasopressin was increased in these arteries from diabetic rats. L-NAME increased the response to vasopressin in renal arteries from control male and female rats, but it did not modify this response in renal arteries from diabetic rats, suggesting that nitric oxide release, and thus its modulatory role may be reduced during diabetes in both genders. Release of constrictor prostanoids may be increased in renal arteries of males, but not of females, during diabetes, as meclofenamate inhibited the contraction to vasopressin in renal arteries of diabetic male rats but it did not modify this response in renal arteries of control male rats. Therefore, our results suggest that reduced nitric oxide production in females, and both reduced nitric oxide and increased prostanoids release in males, may contribute to the augmented contraction to vasopressin observed in renal arteries during diabetes. In agreement with this, impaired production of nitric oxide during diabetes seems to underlay the increased contraction of rat mesenteric arteries (Taylor et al., 1992) or rat aorta (Pinna et al., 2001) to noradrenaline, and of rat aorta to phenylephrine (Chang and Stevens, 1992), and production of thromboxane A_2 may be involved in the increased response to noradrenaline observed in femoral vascular bed of diabetic dogs (Koltai et al., 1990). Moreover, it has been reported that increased production of constrictor prostanoids may reduce the relaxation to acetylcholine in cerebral (Mayhan et al., 1991), renal (Dai et al., 1993), and mesenteric (Heygate et al., 1995) arteries from diabetic rats. In line with these observations, it has been suggested that hyperglycemia may stimulate prostanoid production (Tesfamariam et al., 1990).

In summary, the present results suggest that diabetes may alter the responsiveness of some vascular beds (e.g., basilar, coronary and renal) but not that of others (e.g., tail arteries) to vasopressin, and that the characteristics and mechanisms of this alteration may show regional and gender differences. During diabetes, the response of basilar and coronary arteries to vasopressin may be decreased by a mechanism not related to nitric oxide or prostanoids, and the response of renal arteries to this peptide may be increased by reduced production of nitric oxide in females, and by both reduced production of nitric oxide and increased production of prostanoids in males.

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