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European Journal of Pharmacology 471 (2003) 35–40
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Role of K^+ channels in the coronary and renal vascular reactivity to vasopressin in diabetic rats

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Received 30 January 2003; received in revised form 29 April 2003; accepted 6 May 2003

Abstract

To study the role of K^+ channels in the coronary and renal vascular response to vasopressin during diabetes mellitus, and whether there are gender differences in this role, we have examined the isometric response to this peptide of 2-mm-long arterial segments from male and female, normoglycemic and streptozotocin-induced diabetic rats. Vasopressin (10^{-12}–3×10^{-8} M) produced arterial concentration-dependent contraction, and during normoglycemia, this contraction was lower in coronary arteries from female than from male rats, and it was similar in renal arteries from both genders. This contraction was reduced by diabetes in coronary arteries, and increased in renal arteries, from both genders. The blocker of Ca^{2+}-sensitive K^+ channels charybdotoxin (10^{-7} M) increased the contraction to vasopressin in coronary arteries of diabetic females, but not in the other cases (diabetic males and normoglycemic females or males). This blocker also increased the contraction to vasopressin in renal arteries from diabetic, but not in those from normoglycemic female rats, and also increased it in a higher magnitude in arteries from diabetic than in those from normoglycemic male rats. The blocker of ATP-sensitive K^+ channels glybenclamide (10^{-5} M) or the scavenger of superoxide radicals superoxide dismutase (100 U/ml) did not modify the contraction to vasopressin in any experimental group. These results suggest that diabetes activates the modulatory role of K^+ channels in the coronary and renal vasoconstriction to vasopressin, but it alters in a different way the vasoconstriction to vasopressin in these two types of arteries. The effects of diabetes on this vasoconstriction are not related to increased release of superoxide radicals.

Keywords: Diabetes; Vasopressin; Gender; Renal artery; Coronary artery; K^+ channel

1. Introduction

There is increasing evidence that the alterations induced by diabetes mellitus in the vascular system may show gender differences. It is known that cardiovascular diseases in the general, nondiabetic population are less frequent in premenopausal women than in men (Douglas, 1997; Hayward et al., 2000), and this has been related to the protective effects of ovarian hormones in premenopausal females (Mendelsohn and Karas, 1999). However, diabetes may produce a relatively greater impairment in the cardiovascular system of premenopausal females, so the difference between men and women regarding cardiovascular disease disappears in the diabetic patients (Farmer and Gotto, 1997).

Previous studies from our laboratory suggest that these gender differences in the effects of diabetes on the vascular system may occur with regard to the vascular response to vasopressin. We have observed that the contraction to vasopressin may be modified by diabetes, as this response was reduced in pial and coronary arteries, and increased in renal arteries, from diabetic rats (García-Villalón et al., 2003), and that subthreshold concentrations of vasopressin increased the sympathetic contraction of rat tail arteries, and the mechanism of this modulating effect may be modified in arteries from diabetic female rats (Sanz et al., 2001). In these studies, we found that these alterations were related, in part, to changes in the effects of nitric oxide and prostanoids during diabetes. Vasopressin may be of relevance for diabetic cardiovascular pathophysiology, as osmoregulation is disturbed during diabetes, and it has been reported that the plasmatic levels of vasopressin are consistently elevated during this disease, both in rats with experimental diabetes (Brooks et al., 1989) and in diabetic patients (Vokes et al.,

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doi:10.1016/S0014-2999(03)01815-6

1987), and the vascular response to this peptide may be reduced in diabetic rats (Hebden et al., 1987; Sarubbi et al., 1989; Lawrence and Brain, 1992).

Other mechanism, in addition to nitric oxide and prostanoids, that may modulate vascular responses during diabetes is the activation of K^+ channels. Mainly, Ca^{2+}-sensitive K^+ channels and ATP-sensitive K^+ channels may be involved in modulating the vascular response (Brayden, 2002), although other subtypes may also be involved in some cases. As the effects of K^+ channels may be modified during diabetes (Sobey, 2001), this mechanism might be involved in the changes of the vasopressin response in this condition. One possible mechanism through which diabetes may affect K^+ channel function is the production of superoxide radicals (Liu and Gutterman, 2002b), which is markedly increased during diabetes (West, 2000). Superoxide radicals may impair channel function, although this impairment may be dependent of the subtype of K^+ channel (Liu and Gutterman, 2002a).

Therefore, the aim of this work was to extend previous studies by analyzing whether the changes in the vascular response to vasopressin during diabetes, and the gender differences in these changes, could be related to alterations in the function of K^+ channels, or to the action of superoxide radicals. To this, the contraction to vasopressin was recorded in coronary and renal arteries from control (normoglycemic) and diabetic, male and female rats, and the effects of Ca^{2+}-sensitive and ATP-sensitive K^+ channel blockers and of a superoxide scavenger on this response were analyzed. Diabetes was induced by injection of streptozotocin, a model of experimental diabetes frequently used (Öztürk et al., 1996).

2. Methods

Male (47) and female (49) Sprague–Dawley rats, weighting 250–350 g at the beginning of the study, were used. This investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). 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 anterior interventricular coronary and the renal arteries were carefully dissected. 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 (millimolar): 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 coronary arteries, and 100 μm for renal, 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). Changes in isometric force were recorded on a Macintosh computer by use of Chart v 3.6/s software and a MacLab/8e data acquisition system (ADInstruments). An optimal passive tension, which was 0.25 g for coronary and 0.75 g for renal 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 coronary and renal arteries from male and female, normoglycemic (control) and diabetic rats. This was performed in arteries nontreated and treated with the blocker of Ca^{2+}-sensitive K^+ channels charybdotoxin (10^{-7} M), the blocker of ATP-sensitive K^+ channels glybenclamide (10^{-5} M), or with the superoxide scavenger superoxide dismutase (100 U/ml). These substances 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. Data from male and female, normoglycemic (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 the charybdotoxin, glybenclamide and superoxide dismutase 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. To test whether the effects of the blockers were different in normoglycemia and in diabetes, a two-way ANOVA was performed.

Drugs used were charybdotoxin, glybenclamide (Glyburide), superoxide dismutase from horseradish, and Arg-vasopressin acetate salt (all from Sigma). All drugs except

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

	Weight (g)	Glycemia (mg/100 ml)	
Males			
Normoglycemic	396 ± 18	90 ± 4	(20)
Diabetic	289 ± 12[a]	449 ± 19[a]	(27)
Females			
Normoglycemic	260 ± 4[b]	87 ± 4	(26)
Diabetic	190 ± 7[a,b]	434 ± 21[a]	(23)

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

glybenclamide were dissolved in distilled water and further diluted in isotonic NaCl. Glybenclamide was dissolved in dimethylsulphoxide and further diluted in isotonic NaCl, and the same volume of the vehicle was added to the control segments.

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, 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).

Vasopressin (10^{-12}–3×10^{-8} M) produced concentration-dependent contraction in both coronary and renal arteries. In coronary arteries, the maximal contraction to vasopressin was lower in the arteries from normoglycemic females than in those from normoglycemic males, and it was reduced by diabetes both in male and female animals. Charybdotoxin increased the maximal contraction in coronary arteries from diabetic females, but not in coronary arteries from diabetic males, or from normoglycemic males and females (Fig. 1). However, two-way ANOVA analysis could not find difference between the effects of charybdotoxin in diabetic males and females.

In renal arteries, the contraction to vasopressin was similar in normoglycemic males and females, and diabetes increased the sensitivity of this contraction in both males and females (EC_{50} 1.6×10^{-10} vs. 4×10^{-10} in males and 8.5×10^{-11} vs. 2.5×10^{-10} in females; $P<0.05$). Charybdotoxin increased the maximal contraction in renal arteries from normoglycemic males, and the sensitivity in renal arteries from diabetic males (EC_{50} 3.1×10^{-11} M vs. 1.6×10^{-10} M; $P<0.01$) (Fig. 2). Although charybdotoxin increased the

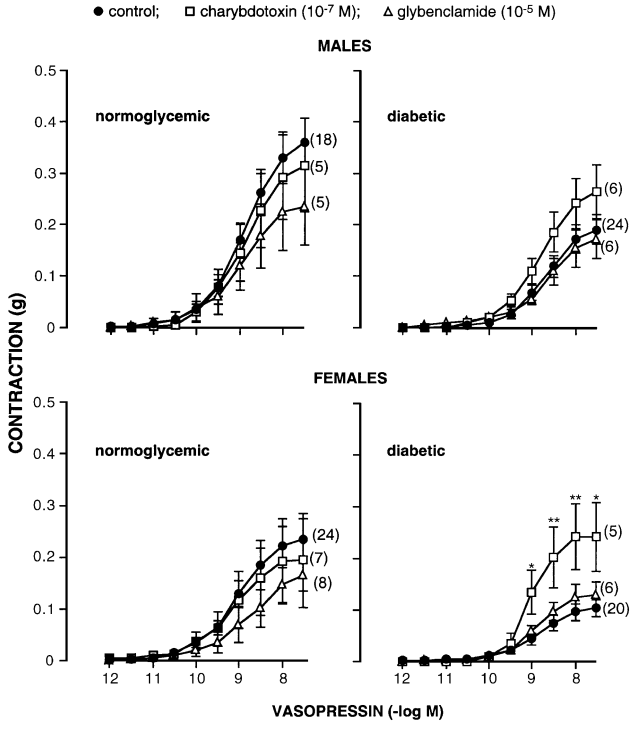

Fig. 1. Contraction to vasopressin (10^{-12}–3×10^{-8} M) of coronary arteries from normoglycemic (left panels) or from diabetic (right panels), male (upper panels) or female (lower panels) rats, in arteries nontreated and treated with charybdotoxin (10^{-7} M), or glybenclamide (10^{-5} M). In parenthesis is the number of animals. Values are means ± S.E.M. Statistically significant compared to nontreated (*$P<0.05$; **$P<0.01$).

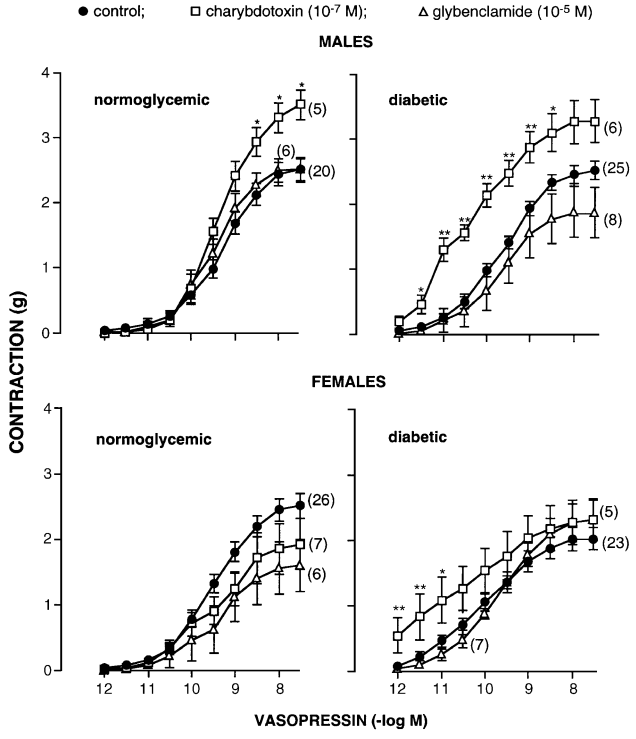

Fig. 2. Contraction to vasopressin (10^{-12}–3×10^{-8} M) of renal arteries from normoglycemic (left panels) or from diabetic (right panels), male (upper panels) or female (lower panels) rats, in arteries nontreated and treated with charybdotoxin (10^{-7} M) or glybenclamide (10^{-5} M). In parenthesis is the number of animals. Values are means ± S.E.M. Statistically significant compared to nontreated (*$P<0.05$; **$P<0.01$).

response in renal arteries from both diabetic and normoglycemic male rats, the increments were higher in diabetic than in normoglycemic animals, and two-way ANOVA indicated significant interaction between diabetes and charybdotoxin factors ($P < 0.05$). Charydotoxin also increased the response to low concentrations (10^{-12}–10^{-11} M) of vasopressin in renal arteries from diabetic females, without modifying significatively the EC_{50} or the maximal effect, and this blocker did not modify the contraction of renal arteries from normoglycemic females (Fig. 2).

Glybenclamide (Figs. 1 and 2) or superoxide dismutase (not shown) did not modify the contraction to vasopressin of coronary and renal arteries from normoglycemic or diabetic, male and female rats.

4. Discussion

The present work extends a previous study from our laboratory showing that the contraction to vasopressin of pial, coronary and renal arteries of the rat is modified by diabetes (García-Villalón et al., 2003). This study showed that the effects of diabetes on these arteries could be mediated, in part, by changes in the release or the effects of nitric oxide and/or prostanoids. The present study suggests that K^+ channels also may be involved in these effects.

In the present study, we have found that: (1) during normoglycemia, the contraction of coronary arteries to vasopressin is lower in females than in males, and that of renal arteries is similar in both genders, and (2) that the contraction of coronary arteries to vasopressin is reduced during diabetes in both males and females, and that of renal arteries is increased in both genders. This agrees with, and confirms, the results observed in a previous study from our laboratory (García-Villalón et al., 2003). The reduction of the contraction to vasopressin in coronary arteries was not dependent on nitric oxide or prostanoids, and it was hypothesized that this impaired contraction might be due to desensitization of vasopressin receptors in vascular smooth muscle (García-Villalón et al., 2003). The present results suggest that K^+ channels may be involved in diabetes-induced reduction of the response of coronary arteries to vasopressin. Charybdotoxin increased the contraction to vasopressin in coronary arteries from diabetic females, and thus charybdotoxin reverted the inhibitory effect of diabetes on the response of these arteries to vasopressin. This suggests that the impairment in the contraction of coronary arteries to vasopressin induced by diabetes on females may be due, at least in part, to increased activation and/or effects of K^+ channels during this condition. In coronary arteries from diabetic male rats, charybdotoxin tended to increase the contraction to vasopressin, but this increment was not statistically significant. However, two-way ANOVA analysis did not found a significant interaction between gender and charybdotoxin in coronary arteries, therefore we cannot conclude whether there is a difference between genders regarding the effects of K^+ channels during diabetes.

In the case of renal arteries, K^+ channels may be involved in the contraction to vasopressin during normoglycemia in males but not in females, as charybdotoxin increased this contraction only in renal arteries on males. This potentiating effect of charybdotoxin found in normoglycemic males was accentuated in diabetic males, suggesting that diabetes enhances the probable modulating role of K^+ channels in the renal vasoconstriction to vasopressin present in normoglycemic males. Charybdotoxin also increased the response to vasopressin in renal arteries from diabetic females, whereas this inhibitor did not affect this response in normoglycemic females. This suggests that K^+ channels may be involved in the renal vasoconstriction to vasopressin in females during diabetes but not during normoglycemia. Therefore, K^+ channels may be involved in the coronary vasoconstriction to vasopressin during normoglycemia in males but not in females, and during diabetes in both genders. As diabetes alone, and charybdotoxin during diabetes increased the renal vasoconstriction to vasopressin in males and females, this increased contraction by diabetes is not due to the enhanced modulatory role of K^+ channels in this vasoconstriction. Indeed, charybdotoxin treatment increased the differences in the contraction to vasopressin between renal arteries from diabetic and normoglycemic rats, therefore it is suggested that diabetes increases the contraction of renal arteries by other mechanisms (e.g., changes in the release of nitric oxide or prostanoids, (García-Villalón et al., 2003)), and K^+ channels activation may attenuate the increased response of renal arteries to vasopressin during diabetes.

K^+ channels produce relaxation or reduce the contraction of blood vessels by inducing hyperpolarization of vascular smooth muscle cells, and reducing the concentration of cytoplasmatic Ca^{2+} (Jackson, 2000). The present results with charybdotoxin suggest that the modulation of the contraction to vasopressin by K^+ channels is increased by diabetes in coronary arteries from females, and in renal arteries from both genders. Regarding the subtype of K^+ channel involved, it is probably the high conductance, Ca^{2+}-sensitive one, which is blocked by charybdotoxin, and not the ATP-sensitive subtype, as glybenclamide did not modify the contraction to vasopressin in any experimental group studied.

The increased activity of K^+ channels during diabetes found in the present study might be due to changes in the release of mediators which activate or inhibit K^+ channels, such as endothelium-derived hyperpolarizing factor (EDHF), and/or 20-hydroxyeicosatetraenoic acid (20-HETE), or to diabetes which affects directly K^+ channels to increase their activity. There is evidence that activation of the ATP-sensitive subtype of K^+ channels is

increased during the early stage of diabetes (Kersten et al., 1995; Ikenaga et al., 2000) and attenuated at a later stage (Kamata et al., 1989; Bouchard et al., 1999; Mayhan, 1994; Glocker and Quast, 1997, Zimmermann et al., 1997), but the effect of diabetes on the Ca^{2+}-dependent, charybdotoxin-sensitive K^+ channel has been less studied. These latter channels are unaltered in tail artery smooth muscle cells from diabetic rats (Wang et al., 2001), but their activity is increased by elevated glucose concentration in cultured bovine retinal pericytes (Berweck et al., 1994), and this may agree with the present results. Superoxide radicals are increased during diabetes, and although these radicals activate Ca^{2+}-sensitive K^+ channels (Liu and Gutterman, 2002b), this is not probably the mechanism of increased activity of these channels reported in the present study, as the superoxide scavenger superoxide dismutase did not modify the coronary and renal vasoconstriction to vasopressin during diabetes as occurred during normoglycemia. It has been suggested (Liu and Gutterman, 2002b) that Ca^{2+}-sensitive K^+ channels are relatively unaffected by oxidative stress, in contrast with other subtypes of K^+ channels (e.g., ATP-sensitive) that may be impaired in this condition, and thus these Ca^{2+}-sensitive K^+ channels may play a compensatory vasodilator role in diseases such as diabetes, hypercholesterolemia or hypertension, in which oxidative stress is increased and nitric oxide-mediated relaxation is reduced.

Summarizing, the present results suggest that: (a) diabetes reduces the coronary vasoconstriction to vasopressin in females by increasing the modulatory role of K^+ channels in this vasoconstriction; (b) diabetes increases the renal vasoconstriction to vasopressin in both genders, and increases the inhibitory role of K^+ channels, thus attenuating the increased vasoconstriction. Therefore, diabetes may provoke different effects in the coronary and renal vasoconstriction to vasopressin, but it might induce similar effects on the modulatory role of K^+ channels in this vasoconstriction. The different effects induced by diabetes on the response of coronary and renal vessels to vasopressin would be mainly related to mechanisms different from K^+ channels, such as nitric oxide or prostanoids (García-Villalón et al., 2003).

Acknowledgements

The authors are grateful to Mrs. M.E. Martínez and H. Fernández-Lomana for technical assistance. This work was supported, in part, by DGICYT (SAF 99.0004), FIS (99/0224) and CAM (08.4/0003/1998).

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