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Role of the sympathetic and renin angiotensin systems in the glucose-induced increase of blood pressure in rats

Santiago Villafaña, Fengyang Huang, Enrique Hong*

Departamento de Farmacobiología, CINVESTAV-I.P.N., Calzada de los tenorios 235, Col. Granjas Coapa, Deleg. Tlalpan, México, D.F., C.P. 14330, Mexico

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Abstract

The pressor effect induced by acute hyperglycemia is not well understood, therefore, it was of interest to study the effect of intravenous glucose infusion on the mean arterial pressure of anesthetized Wistar rats. Animals received glucose (100 mg/kg/min, i.v.), mannitol or saline during 30 min, but only glucose increased the mean arterial pressure (about 40 mm Hg), plasma glucose, insulin and nitric oxide (NO). Pretreatment with reserpine or indorenate (a central antihypertensive) inhibited completely the pressor effect of glucose. Reserpine also decreased the plasma NO levels. Pretreatment with ramipril or with streptozotocin decreased the late phase of the glucose-induced pressor response and the NO levels, the latter treatment also abolishes insulin plasma concentrations. The present results suggest that the pressor effect induced by glucose has an early phase due to an increase of efferent sympathetic discharges and a delayed phase produced by the activation of the renin angiotensin system.

Keywords: Blood pressure; Glucose; Insulin; Renin angiotensin system; Sympathetic nervous system; Vasodilation

1. Introduction

Hypertension occurs more frequently among diabetic patients than in the general population (Epstein and Sowers, 1992; Fuller, 1985). In diabetes type 1 (insulin dependent), hypertension has been related with renal abnormalities (Krolewski et al., 1998; Elliott et al., 2001; Hinderliter and Runge, 2001; Jandeleit-Dahm and Cooper, 2002), while in diabetes type 2 (noninsulin dependent), it has been related with the metabolic syndrome, also known as X syndrome, characterized by insulin resistance, dyslipidemia, hypertension and coronary artery disease (Hinderliter and Runge, 2001; Jandeleit-Dahm and Cooper, 2002; Reaven, 1995). Study of the acute hyperglycemia has not been extensively studied, despite the fact that hyperglycemia is found in any diabetic patient. On the other hand, obesity is characterized by repeated hyperglycemia (observed after meals), and this condition is also related to hypertension (Cubeddu and Hoffmann, 2002). Furthermore, obesity in children is also accompanied by hypertension in an increasing number of patients (Sorof and Daniels, 2002). It has been reported that hyperglycemia can affect vascular relaxations (Tesfamariam et al., 1991; Beckman et al., 2001; Williams et al., 1998), probably by the accumulation of sorbitol and *myo*-inositol depletion (Tesfamariam et al., 1992), the production of free radicals (Tesfamariam and Cohen, 1992), or by the activation of protein kinase C (Tesfamariam et al., 1991). In addition, hyperglycemia has been reported to stimulate the sympathetic nervous systems (Tomita et al., 1989; Routh, 2002), maybe by activating neurons in the hypothalamus (Routh, 2002), and this activation leads to increased norepinephrine release (Tomita et al., 1989). These reports suggest that hyperglycemia may participate in the development of hypertension. For these reasons, in the present study, we aimed to examine whether the acute hyperglycemic state can increase the arterial blood pressure and to evaluate the mechanisms involved in the phenomenon. Since multiple reports describe that NO can

* Corresponding author. Tel.: +52 55 5061 2864; fax: +52 55 5061 2863.
E-mail address: ehong@mail.cinvestav.mx (E. Hong).

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be modified by many endogenous substances, it was decided to measure the plasma NO_x at the end of experiments.

2. Materials and methods

2.1. Preparation of animals

Male Wistar rats (10–12 weeks) were maintained on a 12-h light–dark cycle and provided with access to standard rat Purina Chow and tap water ad libitum for at least 1 week before being assigned to experimental protocols. All procedures were in accordance with institutional guidelines from the animal care committee. Animals were deprived of food overnight before the experiments (but allowed to drink water ad libitum).

2.2. In vivo experiments

Rats were anesthetized with sodium pentobarbital (40 mg/kg, i.p.). Catheters were inserted into the jugular veins for the administration of antihypertensive agents and for intravenous glucose infusion by a pump, and the right carotid artery for monitoring arterial blood pressure throughout the experiment. Mean arterial blood pressure was recorded by means of a P23 Gould transducer connected to a 7P Grass Polygraph. Body temperature was maintained at 37 °C by a heating lamp during all the experiments.

A group of rats was dosed with reserpine (5 mg/kg, i.p.) 24 h before the experiments. None of the reserpine-treated rats need to be excluded from the study based on a large pressor response to tyramine (mean arterial pressure increased: 13 ± 2 vs. 57 ± 4 mm Hg, $P<0.05$, in reserpinized and control rats, respectively).

Streptozotocin (60 mg/kg, i.p.) was injected to rats 48 h before the experiments. Efficacy was determined by the level of blood glucose (5.08 ± 0.124 and 15.16 ± 1.10 mM before and after streptozotocin, respectively, $P<0.05$).

2.3. Organ bath experiments

Wistar rats were sacrificed, and the descending thoracic aorta was rapidly removed and placed in Krebs's solution of the following composition (mM): NaCl 118, KCl 4.8, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25, glucose 11.7 and EDTA 0.026. Aortas were cut in rings (of 3 mm length), and they were suspended from strain gauges for measurement of isometric force. Tension was measured by means of a BIOPAC Systems attached to a computer. The tissue was bathed in Krebs solution at 37 °C (pH 7.4) and continually gassed with 95% O_2:5% CO_2. The initial tension was 4 g. The tissue was repeatedly washed and allowed to stabilize over 2 h, while responses to phenylephrine (10^{-7} M) were obtained every 30 min until they become uniform. Aortic rings were then contracted with phenylephrine (10^{-6} M) and exposed to log increments of acetylcholine (10^{-9} to 10^{-5} M) or diazoxide (10^{-7} to 10^{-4} M); after that, aortic rings were then incubated with normal (11.7 mM) or elevated glucose (46.8 mM) for 30 min and contracted with phenylephrine (10^{-6} M) and exposed to log increments concentrations of acetylcholine (10^{-9} to 10^{-5} M) or diazoxide (10^{-7} to 10^{-4} M).

2.4. Determination of plasma glucose, insulin and NO_x

Blood samples were taken by venopucture of the tail for the determination of glucose (Bayer, Glucometer Elite) before glucose infusion and by cardiac punction for glucose, insulin and NO_x (NO_2+NO_3) evaluation after the glucose infusion. Blood samples were centrifuged at 4000 rpm for 15 min. Plasma samples for insulin (DRG diagnostic) determinations were frozen (−70 °C) until assayed by enzyme-linked immunosorbent assay (ELISA); NO_x was determined by the Griess reagent (Green et al., 1982), and glucose, by SERA-PAK Plus Glucose (Bayer).

2.5. Protocols

2.5.1. Protocol 1

The effect of glucose infusion on the arterial pressure in anesthetized rats was studied. The glucose infusion (100 mg/kg/min) during 30 min was compared with saline (0.2 ml/kg/min) or mannitol (100 mg/kg/min) since both glucose and mannitol posses the same osmolality (Yasuhara et al., 1982). Both glucose and mannitol were given in a volume of 0.2 ml/kg/min. At the end of the experiment, blood samples were collected for glucose, insulin and NO_x determinations. All subsequent experiments were compared with the same group of glucose.

2.5.2. Protocol 2

This protocol involved the study of different antihypertensive agents on the effect of glucose infusion. We analyzed the effect of indorenate (5 mg/kg, i.v.) and ramipril (2.5 mg/kg, i.v.) on the arterial blood pressure. These antihypertensive agents were administrated 30 min before the glucose infusion. At the end of experiment, blood samples were collected for glucose, insulin and NO_x.

2.5.3. Protocol 3

The participation of sympathetic nervous system and insulin on the effect of the glucose infusion was studied in this protocol. Reserpine (5 mg/kg, i.p.) and streptozotocin (60 mg/kg, i.p.) were administrated at 24 and 48 h before the experiment, respectively. We analyzed the effect of 30-min infusion of glucose on blood pressure in reserpinized or streptozotocin-treated rats. At the end of the experiment, blood samples were collected for glucose, insulin and NO_x determinations.

2.5.4. Protocol 4

This protocol studied the effect of glucose on aortic rings relaxations. Aortic rings from Wistar rats were incubated

Table 1
Mean blood pressure and glucose plasma levels before glucose administration

	Mean blood pressure (mm Hg)	Glucose (mM)
Protocol 1		
Saline	114.58±4.98	5.46±0.35
Glucose	106.67±4.22	5.03±0.35
Mannitol	105.71±2.77	5.34±0.19
Protocol 2		
Glucose	106.67±4.22	5.03±0.35
Indorenate	119.17±9.32	5.50±0.12
Ramipril	63.06±3.14*	5.49±0.21
Protocol 3		
Glucose	106.67±4.22	5.03±0.35
Reserpine	77.08±3.19*	4.84±0.32
Streptozotocin	109.64±5.13	15.16±1.11*

Data are given as mean±S.E.M. All groups have n=6. Control values in protocol 1 correspond to saline and to glucose in protocols 2 and 3.
* P<0.05 vs. control.

with different concentrations of glucose (11.7 and 46.8 mM) for 30 min; rings were contracted with phenylephrine (10^{-6} M), and the relaxation to log increments concentrations of acetylcholine (10^{-9} to 10^{-5} M) or diazoxide (10^{-7} to 10^{-4} M) were assessed. Two groups of rings were incubated only with the diazoxide vehicle and involved as controls in the presence of normal and high glucose.

2.6. Drugs

Reserpine was from Fluka, and phenylephrine were from RBI; ramipril was from Hoechst, and indorenate from CINVESTAV-IPN. Streptozotocin, acetylcholine, tyramine and diazoxide were from Sigma. Diazoxide (2.3 mg) was dissolved in 0.3 ml of NaOH (0.1 N) and then diluted with saline.

2.7. Statistical analysis

All data are presented as the mean±S.E.M.; the statistical evaluation of the data was made using Dunnett's test or Student's test, according to that was needed. P values <0.05 were regarded as significant.

3. Results

3.1. Effects of the infusion of glucose on the arterial pressure in anaesthetized rats

Mean blood pressure and glucose plasma levels before the glucose or mannitol were not significantly different from that of the control rats that received saline (Table 1). Saline and mannitol did not exhibit an effect on mean

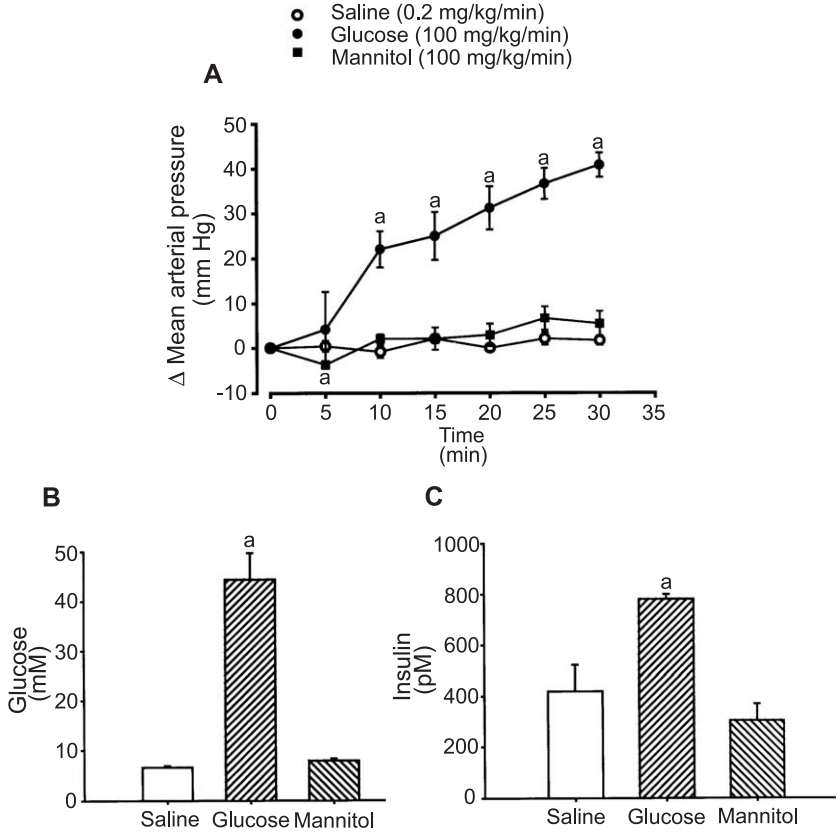

Fig. 1. Effects of the i.v. infusion of glucose to anaesthetized rats. Effect on (A) mean arterial pressure, (B) plasma glucose and (C) plasma insulin. Data are given as mean±S.E.M. All groups have n=6. [a]P<0.05 vs. control (saline).

Table 2
NO_x plasma levels at the end of experiments

	NO_x (μM)
Protocol 1	
Saline	27.98±2.68
Glucose	36.86±2.69*
Mannitol	26.99±4.21
Protocol 2	
Glucose	36.86±2.69
Indorenate+glucose	35.74±3.43
Ramipril+glucose	13.07±2.31*
Protocol 3	
Glucose	36.86±2.69
Reserpine+glucose	24.01±4.71*
Streptozotocin+glucose	15.30±1.12*

Data are given as mean±S.E.M. All groups have n=6. Control values in protocol 1 correspond to saline and to glucose in protocols 2 and 3.
* P<0.05 vs. control.

arterial pressure, while glucose infusion increased the mean arterial pressure by 40 mm Hg (significantly different vs. saline, Fig. 1A). The baseline values of blood glucose were not significantly different among these groups (saline, mannitol or glucose were 5.46±0.35, 5.34±0.19 and 5.03±0.34 mM, respectively). After the 30-min glucose infusion, blood glucose increased markedly (44.38±5.34 mM), while saline and mannitol exhibited smaller effects on blood glucose levels (6.60±0.29 and 7.36±0.44 mM, respectively; Fig. 1B). The glucose infusion increased significantly the plasma insulin level (781.26±19.14 pM) when compared with saline or mannitol infusion (419.34±102.66 and 304.50±66.12 pM, respectively; Fig. 1C). The values of NO_x were significantly higher after glucose infusion than after saline or mannitol (Table 2).

3.2. Study of different antihypertensive agents on the effect of glucose infusion

Mean blood pressure before glucose administration was lower in animals pretreated with ramipril than in those receiving only glucose or indorenate (Table 1).The increase of mean arterial pressure induced by glucose infusion was abolished by indorenate and was blocked partially by ramipril (Fig. 2A). Rats pretreated with reserpine or ramipril have a mean blood pressure of 77.08±3.19 and 63.06±3.14 mm Hg, respectively, while the control group that received saline had 114.58±4.98 mm Hg. However, indorenate had 119.17±9.32 mm Hg, which was not different from the control group. The baseline values of blood glucose before antihypertensive agents were not

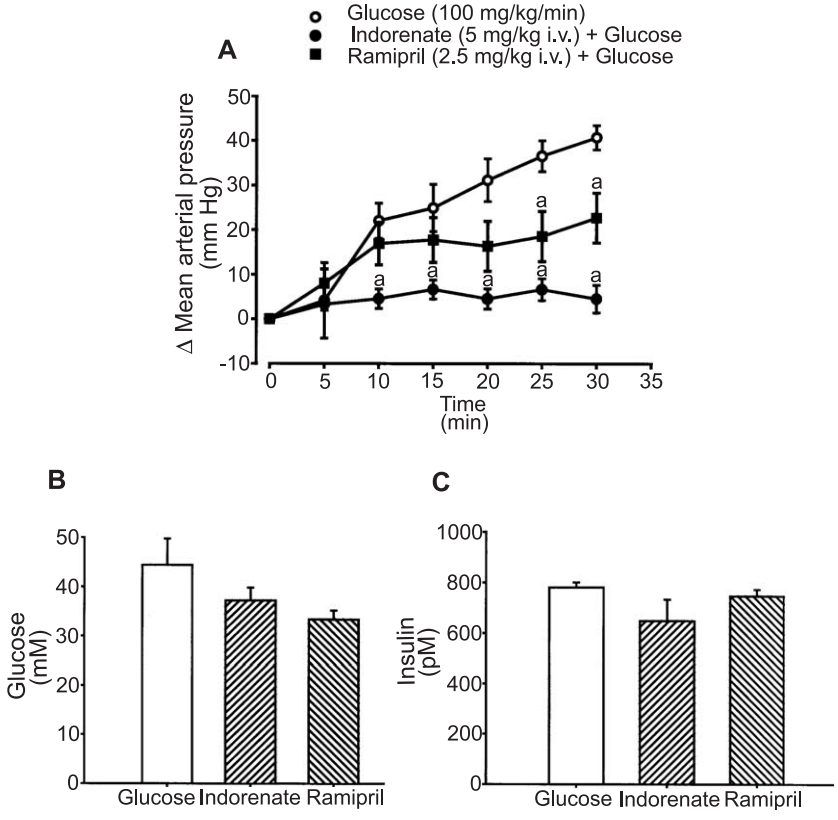

Fig. 2. Effects of different antihypertensive agents on the glucose infusion. Effect on (A) mean arterial pressure, (B) plasma glucose and (C) plasma insulin. Data are given as mean±S.E.M. All groups have n=6. [a]P<0.05 vs. control (glucose).

different between the groups (glucose, indorenate and ramipril were 5.03±0.34, 5.48±0.11, 5.42±0.20 mM, respectively). After antihypertensive drugs, glucose values were not significantly different among these groups (glucose, indorenate or ramipril were 5.03±0.34, 4.94±0.44 and 5.23±0.36 mM, respectively). The blood glucose levels after 30 min of glucose infusion in rats treated with indorenate and ramipril were 37.17±2.64 and 33.33±1.82 mM, respectively, and they were not significantly different when compared with the glucose infusion (44.38±5.34 mM; Fig. 2B). The levels of insulin also increased after glucose infusion; indorenate and ramipril exhibited no effect on the glucose-induced hyperinsulinemia. The levels of insulin in rats with glucose, indorenate and ramipril were 781.26±19.14, 647.28±85.26 and 746.46±26.1 pM, respectively (Fig. 2C). The plasma NO_x increased after glucose infusion; indorenate did not change it, but ramipril decreased the NO_x level when compared with glucose infusion (Table 2).

3.3. Participation of sympathetic nervous system and insulin on the effect of the glucose infusion

Mean blood pressure was significantly lower in reserpinized rats than in those pretreated with streptozotocin or the group that received only glucose, while plasma glucose before the glucose infusion was much greater in the group pretreated with streptozotocin (Table 1). The increase in mean arterial pressure induced by glucose infusion was totally abolished in reserpinized rats, but it was only partially blocked in streptozotocin-treated rats (Fig. 3A). After the 30 min of glucose infusion, the blood glucose in reserpinized rats (38.44±3.85 mM) and streptozotocin-treated groups (55.14±0.47 mM) was not significantly different when compared with the glucose infusion (44.38±5.34 mM; Fig. 3B). Insulin concentration did not change in reserpinized rats (760.38±15.66 pM) versus the glucose group (781.26±19.14 pM); however, in streptozotocin-treated rats (67.86±40.02 pM), it was significantly lower (Fig. 3C). The plasma NO_x increased after glucose infusion, but reserpine and streptozotocin decreased the NO_x levels (Table 2).

3.4. The effect of glucose on aortic rings relaxation

Aortic rings were precontracted with phenylephrine and relaxed by acetylcholine or diazoxide. Rings were incubated in Krebs's solution with regular amounts of glucose or with a four times higher concentration. Glucose did not change significantly the vascular relaxations induced by either acetylcholine (Fig. 4A) or diazoxide (Fig. 4B). The high

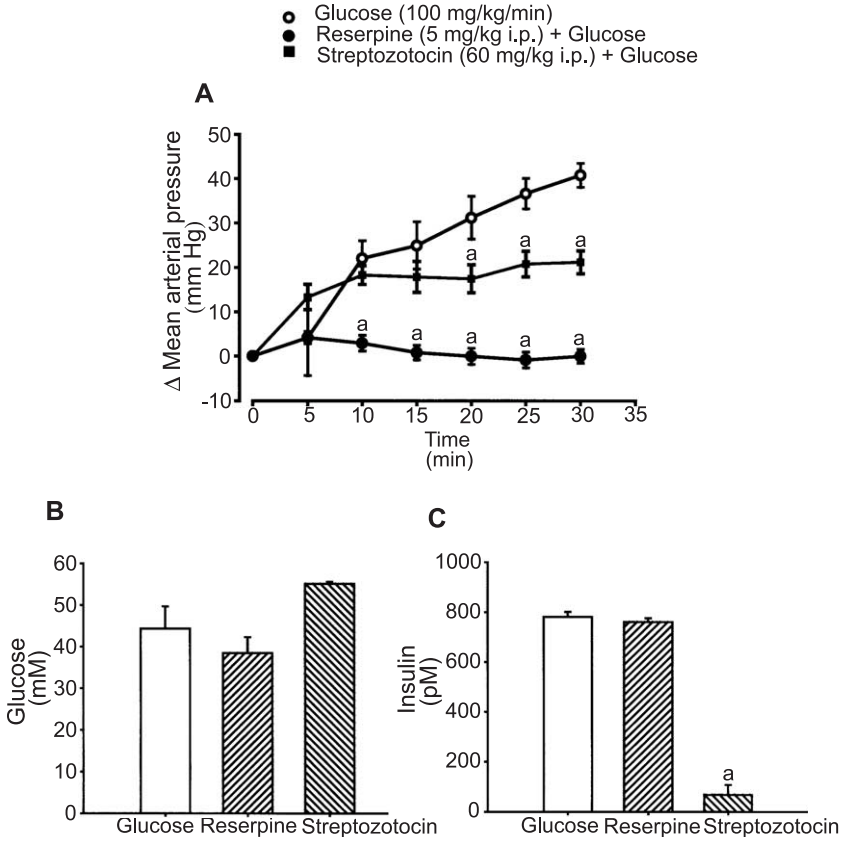

Fig. 3. Effect of pretreatment of animals with reserpine or streptozotocin on the glucose infusion effect. Effect on (A) mean arterial pressure, (B) plasma glucose and (C) plasma insulin. Data are given as mean±S.E.M. All groups have n=6. [a]P<0.05 vs. control (glucose).

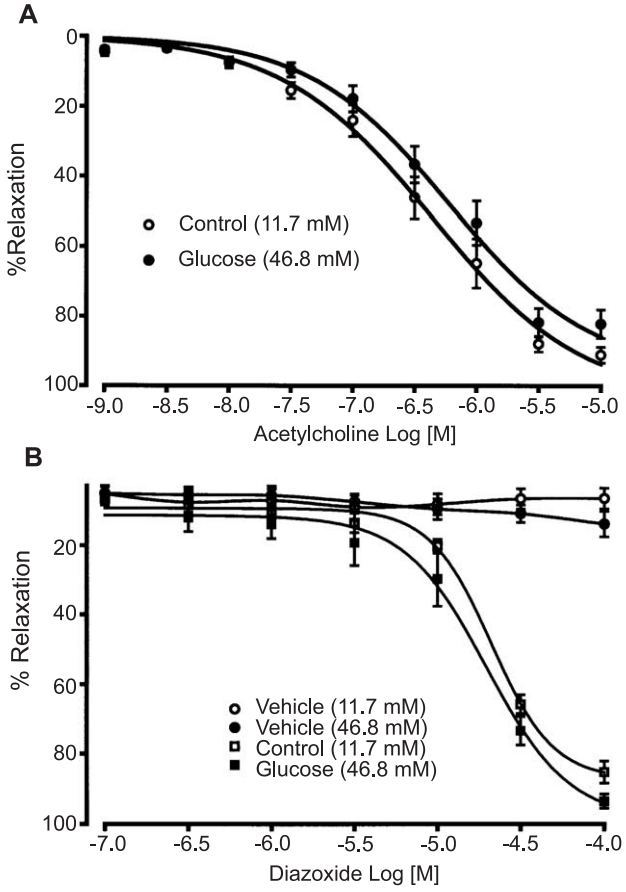

Fig. 4. Effect of glucose on vascular relaxation induced by (A) acetylcholine or (B) diazoxide in isolated rat aortic rings precontracted with phenyleprine, incubated with normal Krebs solution or in Krebs with fourfold glucose concentration. Two groups of rings that contained only the diazoxide vehicle were incubated as controls with the two glucose concentration. Data are given as mean±S.E.M. All groups have n=6. [a]P<0.05 vs. control.

glucose concentration did not affect the rings incubated with the diazoxide solvent.

4. Discussion

This study showed a substantial increase in blood pressure after glucose infusion; the pressor effect of glucose was not due to changes in volume or osmolality, since neither mannitol nor saline exhibited a pressor effect. The dose of glucose used was high; however, the blood glucose levels obtained after the glucose infusion were not much different from those reported in diabetic patients (Kitabchi et al., 2001) or from those obtained in rats after 10–12 weeks of streptozotocin treatment (Makino and Kamata, 2000; Walter et al., 2000). Mean blood pressure before glucose administration was significantly lower in ramipril- and reserpine-treated groups than in the control groups that received saline. However, indorenate did not show a significant change in mean blood pressure before glucose administration. The glucose-induced pressor effect seems to be in intimate relation with the sympathetic nervous system, since indorenate and reserpine abolished this effect. Indorenate is an agonist of the 5-HT_{1A} receptors (Hong et al., 1983; Safdy et al., 1982; Benitez-King et al., 1991), and the activation of these receptors produces a fall in blood pressure (McCall and Clement, 1994; Ramage, 2001) by the inhibition of sympathetic nerve firing (McCall and Clement, 1994). Reserpine depletes the central and peripheral catecholamines and produces sympathetic dysfunction (Weber et al., 1990; Oates, 1996). Although mean blood pressure just before glucose administration was lower in the case of ramipril and reserpine, only the second inhibited completely the glucose pressor effect. On the other hand, indorenate, which did not cause any mean blood pressure decrease before glucose administration, also inhibited the glucose-induced pressor response. Therefore, the present study suggests that the sympathetic activity is necessary for the glucose-induced pressor effect; this is in agreement with some reports, which showed that the acute hyperglycemia can induce sympathoexcitation (Giugliano et al., 1997; Hoffman et al., 1999). Furthermore, the administration of glucose to healthy volunteers was followed by a significant increase of blood pressure and plasma norepinephrine concentrations (Giugliano et al., 1997). Our results showed that renin angiotensin system is also involved in the pressor effect of glucose, since ramipril, which inhibits the conversion from Ang I to Ang II to produce its antihypertensive properties (Schölkens et al., 1984; Unger et al., 1984), partially blocked this effect. The finding that ramipril did not modify the initial increase of the glucose-induced pressor response, but affected the latter phase of the response, could be explained by an initial component due to the sympathetic nervous system and a delayed component due to the activation of the renin angiotensin system. This is in agreement with previous studies describing that the sympathetic nervous system can stimulate renin release (Saxena, 1992; Cody, 1997). The results suggest that the glucose-induced pressor effect is initially produced by the activation of sympathetic nervous system, and in a latter stage, the renin angiotensin system is also involved, as a consequence of the sympathetic discharge leading to renin release (Saxena, 1992; Cody, 1997).

Hyperinsulinemia has been related with elevated blood pressure (Keen et al., 1996; Brands et al., 1991; Zavaroni et al., 1989). To analyze whether the glucose-induced pressor effect is mediated by insulin, the model type I of diabetes was used. It showed that the pressor effect induced by glucose was significantly lower than that observed in control rats, this suggests that the glucose-induced pressor effect is due to both hyperglycemia and hyperinsulinemia. This is consistent with previous reports describing that both a poor glycemic control (Brands and Hopkins, 1996) and hyperinsulinemia can raise blood pressure (Keen et al., 1996; Brands et al., 1991; Zavaroni et al., 1989); additionally, insulin is able to stimulate the renin-angiotensin system

(Fang and Huang, 1998), therefore, the response elicited by glucose in the streptozotocin-pretreated animals could be mainly due to sympathetic stimulation. Glucose has been reported to decrease vascular relaxation (Tesfamariam et al., 1991; Beckman et al., 2001; Williams et al., 1998; Pieper et al., 1995), probably by the accumulation of sorbitol and *myo*-inositol depletion (Tesfamariam et al., 1992), the production of free radicals (Tesfamariam and Cohen, 1992), or by activating protein kinase C (Tesfamariam et al., 1991). However, our study showed that relaxations to acetylcholine and diazoxide were unchanged when incubated with a fourfold higher concentration of glucose. It might be due to the short incubation time with glucose (30 min) because a much larger incubation time, as 6 or 7 h, has been reported to decrease such relaxations (Tesfamariam et al., 1991; Beckman et al., 2001; Pieper et al., 1995). This study suggests that neither the endothelium-dependent relaxation to acetylcholine nor the vascular smooth muscle relaxation elicited by diazoxide was impaired. Our work demonstrated that glucose could increase the release or production of NO_x. It is known that NO_x can be increased by a variety of endogenous substances, including insulin (Han et al., 1995; Mather et al., 2001), catecholamines (Bruck et al., 2001; Huang et al., 2003) and angiotensin II (Boulanger et al., 1995; Pueyo et al., 1998; Gossmann et al., 2000). It seems that this effect is also regulated by insulin, since the level of NO_x was decreased in diabetic rats. Other researchers also reported that insulin produces nitric oxide release in the vasculature through insulin receptors (Han et al., 1995; Mather et al., 2001). The finding that the plasma NO_x level did not increase in reserpinized animals is probably due to the intense catecholamines depletion, since catecholamines increase the release of NO (Bruck et al., 2001; Huang et al., 2003). However, the possibility that being the NO_x basal levels of very low magnitude opens another possibility that, maybe, there was some increment induced by the glucose administration, but it was not noticed because reserpinized animals had a much smaller starting point. In addition to this, reserpine probably decreases eNOS and nNOS activity (through catecholamines depletion) not only in peripheral tissue, but also in the central nervous system. The involvement of iNOS does not seem likely, since the minimal time required for increment of iNOS gene expression by glucose is 2 h (Ceriello et al., 2002). The lack of effect of indorenate on plasma NO_x could be explained in terms of a decrease of sympathetic impulses coming from the central nervous system, but without impairment of either the adrenergic nerve ending or the adrenal medulla. Ramipril diminished the amount of NO, which could be due to the decrement of Angiotensin II, since this endogenous peptide increases nitric oxide release (Boulanger et al., 1995; Pueyo et al., 1998; Gossmann et al., 2000).

In summary, our results showed that acute hyperglycemia can increase blood pressure, probably by the stimulation of the sympathetic nervous system, initially, and latter, by the activation of the renin angiotensin system. Our study suggests that the acute hyperglycemia may play a significant role in the development of hypertension. Extrapolation of these data to the clinical situation may suggest that hyperglycemia could be a relevant factor in the development of hypertension in both diabetes mellitus and obesity, where hyperglycemia is significantly increased in postprandial situations, especially after eating a large meal.

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