Effects of ascorbic acid on impaired vascular reactivity in aortas isolated from age-matched hypertensive and diabetic rats

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Received 16 February 2006; received in revised form 28 April 2006; accepted 2 May 2006

Abstract

Impaired vascular reactivity is a hallmark of several cardiovascular diseases that include hypertension and diabetes. This study compared the changes in vascular reactivity in age-matched experimental hypertension and diabetes, and, subsequently, tested whether these changes could be affected directly by ascorbic acid (10 μM). Endothelium-derived nitric oxide (NO) modulation of ascorbic acid effects was also investigated. All the experiments were performed in the presence of a cyclooxygenase inhibitor, indomethacin (10 μM). Results showed that the endothelium-dependent and -independent relaxations induced by acetylcholine (ACh) and sodium nitroprusside (SNP), respectively, were blunted to a similar extent in isolated aortic rings from age-matched spontaneously hypertensive (SHR) (Rmax: ACh=72.83±1.86%, SNP=96.6±1.90%) and diabetic (Rmax: ACh=64.09±5.14%, SNP=95.84±1.41%) rats compared with aortic rings of normal rats (Rmax: ACh=89%, SNP=104.0±1.0%). The α1-receptor-mediated contractions induced by phenylephrine (PE) were augmented in diabetic (Cmax =148.8±9.0%) rat aortic rings compared to both normal (Cmax =127±6.9%) and SHR (Cmax =118±4.5%) aortic rings. Ascorbic acid pretreatment was without any significant effects on the vascular responses to ACh, SNP and PE in aortic rings from normal rats. Ascorbic acid significantly improved ACh-induced relaxations in SHR (Rmax =89.09±2.82%) aortic rings to a level similar to that observed in normal aortic rings, but this enhancement in ACh-induced relaxations was only partial in diabetic aortic rings. Ascorbic acid lacked any effects on SNP-induced relaxations in both SHR and diabetic aortic rings. Ascorbic acid markedly attenuated contractions induced by PE in aortic rings from both SHR (Cmax =92.9±6.68%) and diabetic (Cmax =116.9±9.4%) rats. Additionally, following inhibition of nitric oxide synthesis with L-NAME, ascorbic acid attenuated PE-induced contractions in all aortic ring types studied. These results suggest that (1) vascular hyper-responsiveness to α1-receptor agonists in diabetic arteries is independent of endothelial nitric oxide dysfunction; (2) ascorbic acid directly modulates contractile responses of hypertensive and diabetic rat aortas, likely through mechanisms in part independent of preservation of endothelium-derived nitric oxide.

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Keywords: Ascorbic acid; Diabetes; Endothelium; Hypertension; Nitric oxide; Vascular reactivity

1. Introduction

The endothelium maintains vascular homeostasis through the release of a number of regulatory substances; among which nitric oxide (NO) is most important (Furchgott and Vanhoutte, 1989; Gewaltig and Kojda, 2002). The bioactivity of endothelium-derived NO is impaired in cardiovascular disease conditions including hypertension and diabetes (Gewaltig and Kojda, 2002; Endemann and Schiffirin, 2004). Vascular production of superoxide anions and its reactive oxygen intermediates such as hydrogen peroxide are increased in hypertension and diabetes (Gewaltig and Kojda, 2002; Endemann and Schiffirin, 2004). Superoxide anions would incapacitate the NO, exacerbate local oxidative stress and ultimately leads to alterations in the vascular tone. Several studies have documented reduced endothelium-mediated vasodilatation to vasodilators, such as acetylcholine, and enhanced vasoconstrictions to adrenergic receptor agonists, such as norepinephrine, in hypertensive and diabetic vessels when compared with physiological vessels (Ting et al., 1996; Dresner et al., 1997; Taddei et al., 1998; Nascimento et al., 2003). However, some evidence suggests that the hyper-responsiveness of diabetic vessels to receptor agonists was independent of endothelial–nitric oxide dysfunction, and it...
has been proposed that such a defect may depend on superoxide-mediated direct alterations in vascular smooth muscle (Chang et al., 1993a; Weber and Macleod, 1997).

Ascorbic acid (vitamin C) is the main water-soluble antioxidant in human plasma (Frei et al., 1990). Several studies have demonstrated that ascorbic acid improves endothelium-dependent vasodilatation in hypertension and diabetes, and it has been proposed that such effects may be due to scavenging of superoxide anions and its reactive oxygen intermediates (Ting et al., 1996; Taddei et al., 1998; Akpaffiong and Taylor, 1998). However, a considerable number of studies also have demonstrated lack of vascular effects of ascorbic acid in diabetes (May, 2000; Darko et al., 2002). In addition, one study found that ascorbic acid modulates venous tone independent of putative endothelium-derived NO (Grossmann et al., 2001). Recent studies indicate that oral doses of ascorbic acid lower systolic and mean arterial blood pressure in hypertension and diabetes (Ceriello et al., 1991; Vasdev et al., 2002; Mullan et al., 2002). Indeed, ascorbic acid has been shown to exert vasodilatation in isolated hypertensive rat aortas, achieved via preservation of NO (Akpaffiong and Taylor, 1998).

The present study was planned to evaluate the changes in vascular reactivity in age-matched experimental hypertension and diabetes, and, subsequently, to test whether these changes could be directly modulated by ascorbic acid. In addition, endothelium-derived NO modulation of ascorbic acid effects was also studied. Endothelium-dependent and -independent relaxations induced by acetylcholine (ACh) and sodium nitroprusside (SNP), respectively, and α₁-receptor-mediated contractions induced by phenylephrine (PE) were tested in aortic rings isolated from age-matched spontaneously hypertensive rats (SHR), streptozotocin-induced diabetic Wistar–Kyoto (WKY) rats and their age-matched normal WKY rats in the presence and absence of ascorbic acid using isolated tissue bath experiments.

2. Materials and methods

2.1. Drugs and chemicals

The following drugs were used: l-ascorbic acid, phenylephrine–HCl, indomethacin, acetylcholine chloride, streptozotocin, Nω-nitro-l-arginine methyl ester (Sigma Chemical Co., St. Louis, MO., USA), sodium nitroprusside and Krebs salts (BDH Limited and BDH Laboratory Supplies, Poole, England). Except for indomethacin, all the other drug solutions were prepared fresh on the day of experiment by dissolving weighed amounts of respective drugs in distilled water. Indomethacin (10 mM) stock solution was prepared in 0.5% w/v sodium carbonate. The final concentrations were prepared by serial dilutions with distilled water.

2.2. Experimental animals

Male Wistar–Kyoto (WKY) and spontaneously hypertensive (SHR) rats, aged about 12–13 weeks, were used in this study. All the experimental procedures were performed in accordance with guidelines issued by the University of Malaya Animal Experimentation Ethics Committee. The rats were maintained under controlled room conditions (temperature: 22±2 °C, humidity 30–40%) and had free access to food and water. Diabetes was induced in one group of WKY rats by a single dose (75 mg/kg of body weight, i.p.) of streptozotocin (STZ) dissolved in cold normal saline. Plasmatic glycemia was examined 3 days after diabetes induction and the rats were considered as diabetics only if their blood glucose level exceeds 17 mmol/l. All the rats were then maintained at the specified conditions for 8 weeks prior to being sacrificed.

2.3. Vascular ring preparation and pharmacological studies

The rats were anaesthetized with pentobarbital (60 mg/kg, i. p.). The descending thoracic aorta was excised by midline incision, cleaned of fat and connective tissues, with care taken not to stretch the vessel excessively or to disturb the luminal surface of the rings, to ensure the integrity of the endothelium. The aorta was then cut into small rings (3–5 mm in width) and suspended between two wire stirrups in a jacketed organ bath containing 5 ml of normal Krebs physiological solution (KPS) of the following composition (mM): NaCl 118.2, KCl 4.7, CaCl₂-H₂O 2.5, KH₂PO₄ 1.2, MgCl₂ 1.2, glucose 11.7, NaHCO₃ 25.0 and EDTA 0.026. The bathing solution was bubbled continuously with a mixture of 95% oxygen and 5% carbon dioxide at 37 °C. The rings were then progressively stretched to an optimal tension of 1 g and allowed to equilibrate for 45 min. During this period, the bathing solution was replaced every 15 min and, if needed, the resting tension was readjusted to 1 g. Following the equilibration period, the aortic rings were allowed to achieve maximal tension by repeated exposure (each for 5 min) to isotonic potassium chloride solution (high K⁺, 80 mM). After washout of the responses to high K⁺, the rest of the experimental protocol was performed in the presence of indomethacin, which was added to the tissue bathing solution to prevent the possible influence of prostaglandins. The cumulative relaxation responses to ACh (0.1 nM–10 μM) and SNP (10 pM–1 μM) were recorded in PE (1 μM) pre-contracted aortic rings in the presence and absence (control) of ascorbic acid (10 μM), which was added to bathing solution 20 min prior to PE stimulation. In another set of aortic rings, the cumulative concentration–response curves for PE (0.1 nM–10 μM) were recorded in the presence and absence (control) of ascorbic acid (10 μM) and/or Nω-nitro-l-arginine methyl ester (L-NAME, 10 μM), in the tissue bathing medium. Ascorbic acid concentration of 10 μM in this study was selected based on previous investigations showing that in vitro incubation with antioxidants (at concentrations ≥ 1 μM) improved impaired endothelium-dependent relaxations in hypertensive or diabetic vessels (Akpaffiong and Taylor, 1998; Nascimento et al., 2003).

2.4. Data analysis

The concentrations mentioned in text or in figures represent the final bath concentrations of respective compounds.
Relaxation responses to cumulative concentrations of ACh and SNP were calculated as percentage inhibition of PE-induced peak contraction. Concentration-dependent contractile responses to PE were recorded as percentage of the maximal contraction obtained with high K+. All results are given as mean ± standard error of mean (S.E.M.). The concentration–response curves for each experimental condition was plotted (Prism version 2.0, Graph Pad software, USA) and from it was deduced pEC_{50} (negative logarithm of median effective concentration) and the maximum agonist-induced relaxation (R_{max}) or contraction (C_{max}) response values. The observed differences were analyzed for statistical significance using unpaired Student’s t-test and one factor ANOVA (Prism version 2.0, Graph Pad software, USA). In all the cases, a value of p<0.05 was considered statistically significant.

3. Results

3.1. ACh- and SNP-induced relaxations

ACh (Fig. 1) and SNP (Fig. 2) concentration-dependently relaxed PE pre-contracted aortic rings from various groups of rats studied. The relaxant effect of ACh at maximal concentration (10 μM) tested was significantly reduced in aortic rings from SHR and diabetic rats compared with aortic rings from normal rats (Table 1). Pretreatment with ascorbic acid did not modify the vasodilator responses to ACh in aortic rings from normal rats. Ascorbic acid normalized the vasodilator effect of the highest concentration of ACh in SHR aortic rings, but only partially enhanced in diabetic rat aortic rings. Besides, endothelium-independent vasodilatation to the highest concentration of SNP (1 μM) was significantly reduced in aortic rings from both SHR and diabetic rats compared with that attained in normal rat aortic rings (Table 1). Ascorbic acid had no effect on the vasodilator responses to SNP in aortic rings from either group of rats studied.

3.2. PE-induced contractions

Cumulative addition of PE elicited a concentration-dependent contraction in all aortic ring types studied (Fig. 3). The vasoconstriction of PE at the highest concentration tested (10 μM) was significantly augmented in diabetic rat aortic rings, but remains similar in SHR aortic rings, compared with aortic rings taken from normal rats (Table 2). Ascorbic acid had no effect on vasoconstrictor responses of PE in aortic rings of normal rats. However, ascorbic acid markedly decreased the vasoconstriction of aortic rings of SHR (−26%) and diabetic (−32%) rats to the highest concentration of PE.

To ascertain the involvement of endothelium-derived NO in the effects of ascorbic acid, we examined the effects of ascorbic acid on PE-induced vasoconstriction in aortic rings incubated with L-NAME, a nitric oxide synthase (NOS) inhibitor (Fig. 4). Presence of L-NAME significantly increased
the vasoconstriction of the highest concentration of PE (10 μM) in different aortic ring types utilized. However, the vasoconstriction of PE was significantly lesser in SHR aortic rings, but remains similar in diabetic rat aortic rings, compared with normal rat aortic rings (Table 2). Ascorbic acid markedly reduced the vasoconstrictor responses of the highest concentration of PE in SHR, diabetic as well as normal rat aortic rings. The magnitude of this reduction in SHR (−21%) as well as diabetic (−36%) rat aortic rings was essentially similar to that observed in respective aortic rings in the absence of L-NAME.

4. Discussion

In this study, we evaluated the changes in vascular reactivity in aortic rings isolated from age-matched hypertensive and diabetic rats and, subsequently, tested whether these changes could be directly affected by ascorbic acid. The major observations were that, compared with normal rat aortic rings, endothelium-dependent and -independent relaxations induced by ACh and SNP, respectively, were blunted in both SHR and diabetic rat aortic rings whereas α₁-receptor agonist-induced contractions induced by PE were augmented in aortic rings from diabetic rats. Pretreatment with ascorbic acid (10 μmol l⁻¹) improved ACh-induced relaxations in SHR aortic rings to a level similar to that observed in normal aortic rings, but there was only partial improvement in the diabetic aortic rings. Ascorbic acid attenuated PE-induced contractions in both SHR and diabetic rats incubated with and without L-NAME. Ascorbic acid attenuation of PE-induced contractions was also observed in normal rat aortic rings incubated with L-NAME.

The present data agrees with previous observations showing that hypertensive and diabetic blood vessels displayed an impairment of endothelium-dependent and -independent vasodilatations (Craven et al., 1994; Ting et al., 1996; Taddei et al., 1998; Kagota et al., 2001). However, to the best of our knowledge, in the present study, we have demonstrated for the first time that the extent of impairment was of a similar magnitude in aortic rings isolated from age-matched SHR and STZ-induced diabetic rats. These alterations could involve a decreased bioavailability of endothelium-derived nitric oxide either due to decreased synthesis from endothelium or an increased incapacitation of nitric oxide by superoxide anions and its reactive oxygen intermediates, and/or decreased responsiveness of the vascular smooth muscle to relaxation by nitric oxide (Craven et al., 1994; Ting et al., 1996; Taddei et al., 1998; Kagota et al., 2001). In this study,

Table 1

<table>
<thead>
<tr>
<th>Rats</th>
<th>Treatment group</th>
<th>Acetylcholine (ACh)</th>
<th>Sodium nitroprusside (SNP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum relaxation (%)</td>
<td>pEC₅₀</td>
<td>Maximum relaxation (%)</td>
</tr>
<tr>
<td>Normal Control</td>
<td>89.70±3.31</td>
<td>7.70±0.17</td>
<td>104.0±1.0</td>
</tr>
<tr>
<td>AA</td>
<td>89.60±6.13</td>
<td>7.55±0.15</td>
<td>101.9±4.41</td>
</tr>
<tr>
<td>SHR Control</td>
<td>72.83±1.86</td>
<td>7.27±0.09</td>
<td>96.6±1.90</td>
</tr>
<tr>
<td>AA</td>
<td>89.09±2.82</td>
<td>7.19±0.09</td>
<td>98.37±1.37</td>
</tr>
<tr>
<td>Diabetic</td>
<td>64.09±5.14</td>
<td>6.91±0.16</td>
<td>95.84±1.41</td>
</tr>
<tr>
<td>AA</td>
<td>66.86±2.15</td>
<td>7.32±0.06</td>
<td>98.73±2.84</td>
</tr>
</tbody>
</table>

*p<0.05 versus corresponding normal aortic rings; **p<0.05 versus corresponding control tissues.

Table 2

<table>
<thead>
<tr>
<th>Rats</th>
<th>Treatment group</th>
<th>Phenylephrine (PE)</th>
<th>pEC₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum contraction (%)</td>
<td>pEC₅₀</td>
<td></td>
</tr>
<tr>
<td>Normal Control</td>
<td>127.6±6.90</td>
<td>7.07±0.11</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>119.8±8.59</td>
<td>7.13±0.12</td>
<td></td>
</tr>
<tr>
<td>SHR Control</td>
<td>118.5±4.50</td>
<td>7.29±0.11</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>92.9±6.68**</td>
<td>7.03±0.12</td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>148.8±9.0*</td>
<td>7.17±0.12</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>116.9±9.4**</td>
<td>7.01±0.12</td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>176.9±10.4***</td>
<td>7.25±0.11</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>141.8±9.73***</td>
<td>7.60±0.18</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05 versus control normal aortic rings, **p<0.05 versus corresponding control aortic rings, ***p<0.05 versus corresponding L-NAME incubated control aortic rings.

Fig. 3. α₁-Adrenergic receptor-mediated contractions induced by phenylephrine (PE) in control- or ascorbic acid (AA, 10 μM)-pretreated aortic rings isolated from (A) normal and (B) spontaneously hypertensive (SHR) or streptozotocin (STZ)-induced diabetic rats. Symbols represent mean±S.E.M. (n=8 or 9). *p<0.05 versus corresponding normal aortic rings; **p<0.05 versus corresponding control tissues.
we found that pretreatment with ascorbic acid normalized ACh-induced relaxations in SHR rings and partially enhanced in diabetic rat aortic rings whereas had no effect on vasodilatation to exogenous nitric oxide donor SNP in both aortic rings types. We also found that ascorbic acid did not affect ACh-induced relaxations in normal rat aortic rings, where the production of superoxide anions has been thought to be too little to alter the bioavailability of endothelium-derived nitric oxide. Taken together, these findings suggest that enhancement of vascular response to ACh by ascorbic acid may involve protecting nitric oxide from inactivation by superoxide anions. This view is consistent with previous observations showing that the beneficial effects of ascorbic acid on endothelium-dependent vasodilatation may be related to the scavenging of oxygen free radicals (Akpffiong and Taylor, 1998; Taddei et al., 1998). It is notable that, in diabetes, very high physiological concentrations of ascorbic acid are required to prevent the superoxide anions from scavenging the nitric oxide (Jackson et al., 1998; Price et al., 2001). It is because endothelial cells exposed to high glucose concentration inhibit ascorbic acid transport and/or uptake into the endothelial cells (Kapeghian and Verlangieri, 1984; Malo and Wilson, 2000; Price et al., 2001). It is also demonstrated that impaired ascorbic acid–glutathione pathway in hyperglycemic conditions can contribute to lack of effects of ascorbic acid in diabetes (May, 2000). Therefore, it seems reasonable to speculate that the concentration of ascorbic acid used in this study is not sufficient to scavenge intracellular superoxide anions in diabetic rat aortic rings, as was evidenced by only partial enhancement in vascular responses to ACh.

PE-induced vasoconstriction was augmented in diabetic rings whereas contractions in SHR aortic rings were comparable to those observed in normal untreated rings. Inhibition of nitric oxide synthesis with L-NAME potentiated the vascular response to PE to a similar extent in both normal and diabetic rat aortic rings. It has previously been reported that \( \alpha_1 \)-receptor-mediated vasoconstrictions can be modulated by nitric oxide released by the activation of adrenergic receptors on endothelial cell membrane (Godfraind et al., 1985; Lembo et al., 2000). An alternative explanation is that basal release (tonic) of nitric oxide is involved in regulation of vascular tone and a phasic release of nitric oxide modulates the vascular responses evoked by PE. Taking these reports into consideration, the present findings provide novel evidence that the phasic nitric oxide component involved in the PE vasoconstriction is defective in diabetic rat aortic rings. Contrary, the finding that, despite similar attenuation in ACh-induced vasodilatations, PE-induced contraction was only augmented in diabetic rat aortic rings tend to extend support to the previous studies showing that endothelial–nitric oxide dysfunction was not involved in hyper-responsiveness of diabetic vessels to adrenoceptor agonists (Chang et al., 1993a; Weber and Macleod, 1997). The present results showed that ascorbic acid treatment reduced with the same magnitude the vascular response to PE in SHR and diabetic rat aortic rings. We also found that ascorbic acid attenuation of PE-induced contractions was intact in both SHR and diabetic rat aortic rings incubated with L-NAME, although PE-induced contractions remained similar to the respective control rings. Interestingly, these observations were similar to that observed in our recent investigations, which demonstrated that flavonoid antioxidant quercetin attenuated PE-induced contractions in aortas isolated from both SHR and diabetic rats, and treatment with L-NAME reversed the contractions to PE to the levels similar to that observed in control aortic rings (Ajay et al., 2006b; Ajay et al., 2006a). These results clearly indicate that ascorbic acid attenuation of PE-induced contractions in SHR and diabetic rat aortic rings may be related to mechanisms in addition to or other than to the preservation of endothelium-derived nitric oxide. Previous studies have demonstrated that ascorbic acid promotes the production of prostacyclin from the endothelium (Beetens et al., 1986; Toivanen, 1987). The present study, however, involved the use of indomethacin, a cyclooxygenase inhibitor, in the organ chamber through out the experiments, making such possibility unlikely. These observations are consistent with a previous study showing that the ascorbic acid-induced vasodilatation results from mechanisms independent of eNOS-mediated nitric oxide synthesis as well as cyclooxygenase products (Grossmann et al., 2001). It is also reported that in isolated aortic rings ascorbic acid modulates receptor- and potential-operated calcium channels (Chang et al., 1993b) and inhibits \( \alpha \)-adrenergic receptor binding (Jones and Bylund, 1986). In

![Graph A](image1.png)

**Fig. 4.** \( \alpha_1 \)-Adrenergic receptor-mediated contractions induced by phenylephrine (PE) in control- or ascorbic acid (AA, 10 \( \mu \)M)-pretreated aortic rings isolated from (A) normal and (B) spontaneously hypertensive (SHR) or streptozotocin (STZ)-induced diabetic rats in the presence of endothelial nitric oxide synthase inhibitor, Nω-nitro-l-arginine methyl ester (l-NAME, 10 \( \mu \)M). Symbols represent ± S.E.M. (\( n=8 \) or 9). *\( p<0.05 \) versus corresponding control aortic rings.
addition, ascorbic acid has been shown to induce vasodilatation in human veins via activation of vascular smooth muscle potassium channels through cyclic GMP (Grossmann et al., 2001). However, since the attenuation by ascorbic acid of PE-induced contractions in aortic rings from normal rats was not observed in this study, such possibilities appear unlikely.

The present experiments showed that ascorbic acid significantly reversed the enhanced PE-induced contractions in l-NAME treated aortic rings from normal rats. Since the attenuation by ascorbic acid of the PE-induced contraction in rings from normal rats was not observed in the absence of l-NAME, it is proposed that the effects of ascorbic acid would be much more pronounced when the bioavailability of endothelium-derived nitric oxide is impaired. Production of superoxide anions in physiological vessels are increased in the presence of eNOS inhibitors (Sekiguchi et al., 2004). In addition, it is demonstrated that α₁-receptor-mediated vasoconstriction is the result of a direct action on vascular smooth muscle and an indirect vasoconstriction action through release of oxygen free radicals (Lembo et al., 2000). It is also reported that superoxide anions and its reactive oxygen intermediates could directly mediate vascular hyper-responsiveness to α₁-receptor agonists in diabetic blood vessels, achieved via changes in vascular smooth muscle sensitivity to receptor agonists and/or increased intracellular calcium levels (Chang et al., 1993a; Weber and Macleod, 1997; Pieper et al., 1997). Taking these reports into consideration, it is possible that attenuation of PE vascular response may be related to ascorbic acid scavenging of superoxide anions produced extracellularly in vascular smooth muscle cells or secondary to release from endothelial cells. This hypothesis was consistent with the previous observations showing that ascorbic acid can act intracellularly in endothelial cells or extracellularly at the interspatial gap between endothelial and vascular smooth muscle cells (Akpaффiong and Taylor, 1998).

The real time measurement of various free radicals in tissue bath solutions might be useful in clarifying these assumptions.

In conclusion, the present study suggests that in age-matched experimental hypertension and diabetes, the endothelium-dependent and -independent vasodilatations were reduced similarly whereas the agonist-induced vasoconstriction was only augmented in diabetes. Ascorbic acid in a concentration of 10 μmol l⁻¹ attenuated α₁-adrenergic receptor-mediated vasoconstrictions in both hypertensive and diabetic rat aortas, likely through mechanisms in part independent of preservation of nitric oxide. Further studies are warranted to characterize the precise mechanisms involved in the effects of ascorbic acid on α₁-adrenergic receptor-mediated vasoconstrictions in hypertensive and diabetic arteries.

Acknowledgements

This study was supported by an IRPA grant (No. 06-02-03-6020) from Ministry of Science, Technology and Innovation, Malaysia.

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