Simultaneous renal hypertension and type 2 diabetes exacerbate vascular endothelial dysfunction in rats

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Summary

Despite the high rate of occurrence of both diabetes and hypertension in humans, the cardiovascular effects of the two conditions have not been investigated when they occur simultaneously. Thus this study examined the vascular effects of simultaneous type 2 diabetes and renal hypertension on endothelial function. Serum malondialdehyde and systolic blood pressure (SBP) were measured, glucose tolerance test (GTT) was performed, and concentration-response to phenylephrine (PE) in the absence and presence of nitro-arginine methyl ester (l-NAME), acetylcholine and sodium nitroprusside were conducted on aortic rings from diabetic control, type 2 diabetes, sham-operated, renal hypertensive, and simultaneous type 2 diabetes plus hypertension rats respectively. Hypertension, diabetes, and simultaneous diabetes and hypertension were associated with either increased or decreased maximal responses ($E_{\text{max}}$) of PE dependent on in the presence or absence of l-NAME. There was also increased serum malondialdehyde and decreased $E_{\text{max}}$ of acetylcholine. Thus simultaneous hypertension and diabetes caused a greater decrease in $E_{\text{max}}$ of acetylcholine compared to that seen with either diabetes or hypertension alone higher than that seen in hypertension. The blood glucose during GTT was lower than that seen in diabetes groups. Thus simultaneous type 2 diabetes and the SBP was renal hypertension is associated with improved glucose tolerance, but with further deterioration of endothelial dysfunction compared with either condition alone.

Keywords
renal hypertension, type 2 diabetes, vascular function

Diabetes mellitus and hypertension often occur simultaneously. About 58% of subjects had hypertension at the time that they were diagnosed as having diabetes mellitus (Chen et al. 2011). In addition, 87.2% of African-American subjects with obesity and high-blood pressure exhibited insulin-resistance (Campbell et al. 2004). There is a general agreement that coexistence of diabetes and hypertension is associated with a higher cardiovascular risk and mortality in humans (Endemann et al. 2004; Colivicchi et al. 2008) and animal models (Hendriks et al. 1993; Ballo et al. 2010).

Diabetes, either in human or animals, is associated with a number of changes in the cardiovascular system. Animal models of diabetes are associated with the impairment of endothelium-dependent relaxation (Matsumoto et al. 2007), unchanged endothelium-independent relaxation (Cameron & Cotter 1992), and increased (Taylor et al. 1994) or decreased (Hassan et al. 2011) contraction response to phenylephrine (PE). Moreover, human type 2 diabetes is associated with decreased basal and stimulated release of nitric oxide (NO) (Woodman et al. 2006). In addition, both human type 1 (Indran et al. 2004) and type 2 (Singhania et al. 2008) diabetes mellitus are associated with increased oxidative stress.

Experimental models of hypertension are associated with cardiovascular changes. They are associated with impaired endothelium-dependent relaxation (Wheal & Randall 2009), impaired (Ajay et al. 2007) or intact (Pacher et al. 2002) endothelium-independent relaxation, and enhanced contraction response to PE (Ajay et al. 2007). Also, the models are associated with increased oxidative stress (Bauersachs et al. 1998) and have been linked to both decreased (Schäfer et al. 2004) and increased (Chang et al. 2002) NO availability and release.

Despite a high rate of occurrence of both diabetes and hypertension in humans, the cardiovascular effects of the
simultaneous conditions have rarely been investigated. However, it has been shown that the coexistence of diabetes and hypertension results in enhanced sensitivity of mesenteric arteries to alpha-1 adrenoceptor stimulation (Hendriks et al. 1993), no change in endothelium-dependent and endothelium-independent (Beenen et al. 1996) relaxations, and increased markers of oxidative stress (Friedman et al. 2003).

The objective of this study was to examine the effects of simultaneous type 2 diabetes mellitus and renal hypertension on endothelial functions in rats. Type 2 diabetes mellitus was induced by intraperitoneal injections of nicotinamide (NA) and streptozotocin (STZ), and two-kidney, one-clip renal hypertension was induced by placement of solid Plexiglass clips on left renal arteries.

Methods and materials

Materials
Nicotinamide, PE, nitro-l-arginine methyl ester (l-NAME), acetylcholine (Ach) and sodium nitroprusside (SNP) were purchased from Sigma-Aldrich Chemical Co. (Steinheim, Germany), and STZ was obtained from Teva Parenteral Medicine Inc. (Irvine, CA, USA). Streptozotocin and NA were dissolved in 0.9% sodium chloride.

Animals and experimental design
Male Sprague-Dawley rats (n = 35), weighting 200–250 g, were obtained from Laboratory Animal Breeding Centre, Shiraz University of Medical Sciences, Shiraz, Iran, and kept under standard conditions (light/dark cycle; 12 h, humidity; 25–35%, and temperature; 22–28 °C) with standard diet and water ad libitum. All procedures were approved by the Institutional Committee for Care and Use of Animals.

Animals were allocated to five groups (n = 5–7 each), including a diabetic control group (DM2-C), a type 2 diabetic group (DM2), a renal hypertensive group (HTN), a sham-operated group as a control for the renal hypertensive group (DM2), and a group with simultaneous type 2 diabetes mellitus and renal hypertension (DM2 + HTN).

Experimental protocol
Induction of diabetes and hypertension. Type 2 diabetes was induced by injecting animals with single intraperitoneal administrations of NA (110 mg/kg) 15 min before single intraperitoneal administrations of STZ (60 mg/kg). Seven days later, animals’ blood glucose were determined using a Glucometer (Accu-check® active, Mannheim, Germany), and those with fasting blood glucose (FBG) levels higher than 126 mg/dl were taken as having type 2 diabetes (Shirwaikar et al. 2006). Six weeks after the injection of NA and STZ or normal saline, animals were subjected to the placement of solid Plexiglass clips on left renal arteries to induce two-kidney, one-clip renal hypertension or sham-operation. Two-kidney, one-clip renal hypertension was induced as described previously (Nekooeian & Mashhoodi 2007). Briefly, under Ketamine (60 mg/kg) and Xylazine (8 mg/kg) anaesthesia incisions were made in left flanks, and left renal arteries and veins were exposed. The arteries were gently dissected from the veins, and solid Plexiglass clips (internal diameter of 0.20–0.22 mm) were placed on left renal arteries. The abdominal wall and skin incisions were then sutured using absorbable (catgut-3/0) and non-absorbable (silk-3/0) suture materials respectively. Sham-operated animals were subjected to the same procedure, but no clip was placed on left renal arteries.

The animals were kept in single cages, and their systolic blood pressure (SBP) and heart rate (HR) were measured weekly using non-invasive tail-cuff (CHART 5.0 software, PowerLab 4/30; AD Instruments Inc., Sydney, Australia) method. Three consecutive measurements of blood pressure, which had a difference of <5 mmHg, were considered as valid. The mean of such three measurements were recorded as a valid value of blood pressure in every occasion.

Four weeks after the sham-operation or induction of renal hypertension, animals were anaesthetized with Ketamine (60 mg/kg) and Xylazine (8 mg/kg). Blood samples were obtained for the measurement of FBG, and serum levels of malondialdehyde (MDA) and insulin. Afterwards, glucose tolerance test (GTT) was performed by injecting glucose (0.5 g/kg) into the animals’ tail veins (Frangioudakis et al. 2008), and measuring blood glucose 5, 15, 30 and 60 min later using the Glucometer. Blood samples for the measurement of MDA, which has been used as a measure of oxidative stress, and insulin were allowed to clot for 30 min. They were then centrifuged at 1000 g for 20 min, and their serums separated and stored at −80 °C until analysis.

Isolated aortic ring studies
Animals were killed after the GTT test, and their thoracic aortas were isolated, cleaned of surrounding fat and connective tissues, cut into 3- to 4-mm rings, and used for concentration-response studies to PE, Ach and SNP. Concentration-responses to such chemicals have been used as a measure of endothelial/smooth muscle function. The comparison of PE concentration-response curves in the absence and presence of l-NAME is used as a criterion for the basal release of NO. Acetylcholine concentration-response curves show whether or not the stimulated release of NO is impaired, and those of SNP is an indication of vascular smooth muscle responsiveness to exogenous NO. Aortic rings were mounted on hooks connected to force transducers in isolated tissue organ baths (K30; Hugo Sachs Electronik, March, Germany) filled with 20 ml physiological solution containing the following composition (mmol/L): NaCl 118, KCl 4.7, KH2PO4 1.2, CaCl2 2.5, MgSO4 1.2, NaHCO3 25 and d-glucose 11.1. The solution was bubbled constantly with 95% O2 and 5% CO2 at a pH of 7.4 and a temperature of 37 °C. Tension was recorded by a four-channel polygraph (model 705/1, Hugo Sachs Electronik).

The tissues were allowed to stabilize for 60 min, during which they were washed every 20 min. Afterwards, a full
concentration-response to PE was performed. Then, the tissues were allowed to equilibrate for 30 min, during which they were washed twice (15 min apart). Each ring was again contracted with PE using the concentration that caused 50% of the maximal contraction. Concentration-response to Ach or SNP was performed at the plateau of contraction response to PE. For the examination of basal release of NO, full concentration-responses to PE were performed in the absence and presence of L-NAME (10⁻⁵ M) (Wong et al. 2006). Phenylephrine concentration-response curves were compared using EC₅₀ (concentration that caused 50% contraction) and maximal response (Eₘₐₓ). Acetylcholine or SNP concentration-response curves were compared using IC₅₀ (concentration that caused 50% relaxation) and Eₘₐₓ.

Biochemical measurements

Serum levels of insulin and MDA were determined using radioimmunoassay (DRG Instrument GmbH, Marburg, Germany) and Rat MDA ELISA (Cusabio Biotech LTD, Wuhan, China) kits respectively.

Statistical analysis

Data, presented as mean ± SEM, were analysed using one-way Analysis of Variance (ANOVA). Where a significant difference was obtained with one-way ANOVA, the source of the difference was located using Duncan’s multiple range test. Within group comparisons were made using paired t-test. The data were analysed using SIGMASTAT statistical software version 3.0 (San Jose, CA, USA). A P-value of ≤0.05 was considered statistically significant.

Results

Blood pressure and heart rate

The weekly SBP and HR of all groups are shown in Table 1. There was no significant difference in the SBP of DM2-C, DM2 and Sham groups at week 1, 2, 3 or 4 after sham-operation. The SBPs of the HTN group at such times were significantly higher than those of the relevant control groups as well as those of the DM2 group. Moreover, SBPs of the DM2 + HTN group at weeks 1 and 3 were significantly higher than those of the HTN group, whereas the differences at weeks 2 (P = 0.217) and 4 (P = 0.259) did not reach statistical significance. The HRs of the DM2 group at weeks 1, 2, 3 or 4 after sham-operation was significantly lower than those of the DM2-C group at identical times. There was no significant difference between HR of the Sham and HTN groups at week 1 after the placement of clips; however, HRs of the HTN group at weeks 2, 3 and 4 were significantly higher than that of the Sham group at such times. Moreover, HRs of the DM2 + HTN groups at 1, 2, 3 and 4th

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The values (mean ± SEM) of systolic blood pressure (SBP) and heart rate (HR) from the diabetic control (DM2-C), diabetic (DM2), sham-operated (Sham), renal hypertensive (HTN) and simultaneously diabetic and renal hypertensive (DM2 + HTN) groups (n = 7 each) at 1, 2, 3 and 4 weeks (W₁–W₄) after sham operation or placement of clips around left renal arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td><strong>HR (bpm)</strong></td>
</tr>
<tr>
<td>W₁</td>
<td>W₂</td>
</tr>
<tr>
<td>DM2-C</td>
<td>122.8 ± 1.37</td>
</tr>
<tr>
<td>DM2</td>
<td>126.4 ± 2.8</td>
</tr>
<tr>
<td>Sham</td>
<td>120.8 ± 1.7</td>
</tr>
<tr>
<td>HTN</td>
<td>142.1 ± 1.74*</td>
</tr>
<tr>
<td>DM2 + HTN</td>
<td>153.6 ± 4.4†</td>
</tr>
</tbody>
</table>

*Denotes significant (P < 0.05) difference from the respective control groups (DM2-C or Sham).
†Denotes significant (P < 0.05) difference from the DM2 group.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>The values (mean ± SEM) of blood levels of glucose (mg/dl) at fasting and during glucose tolerance test at 5, 15, 30 and 60 min after glucose injection (0.5 g/kg) in diabetic control (DM2-C), diabetic (DM2), sham-operated (Sham), renal hypertensive (HTN) and simultaneously diabetic and renal hypertensive (DM2 + HTN) groups (n = 7 each)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting</strong></td>
<td>5 min</td>
</tr>
<tr>
<td>DM2-C</td>
<td>112.2 ± 3.03</td>
</tr>
<tr>
<td>DM2</td>
<td>209.6 ± 9.15*</td>
</tr>
<tr>
<td>Sham</td>
<td>115.3 ± 2.54</td>
</tr>
<tr>
<td>HTN</td>
<td>122.6 ± 3.52</td>
</tr>
<tr>
<td>DM2 + HTN</td>
<td>190.85 ± 10.3†</td>
</tr>
</tbody>
</table>

*Denotes significant (P < 0.05) difference from the respective control groups (DM2-C or Sham).
†Denotes significant (P < 0.05) difference from the DM2 group.

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postclipping weeks were significantly higher than those of
the control, Sham and DM2 groups at such times.

**Blood glucose**

Baseline FBG and blood glucose levels during GTT are
shown in Table 2. There was no significant difference among
blood glucose levels of Sham, DM2-C and HTN groups at fasting
or during GTT at 5, 15, 30 or 60 min after glucose injec-
tion. However, blood glucose levels in the DM2 and DM2 +
HTN groups at fasting or at 5, 15, 30 or 60 min after glu-
cose injection were significantly higher than those of the
DM2-C, Sham and HTN groups (Table 2). Moreover, there
was no significant difference between FBG of DM2 and
HTN + DM2 groups, whereas blood glucose levels of
HTN + DM2 at 5, 15, 30 and 60 min after glucose injection
were significantly lower than those of the DM2 group at
identical times. Serum insulin levels of the DM2 and DM2 +
HTN groups were significantly lower than those of the
DM2-C, Sham and HTN groups (Figure 1). Moreover, serum
levels of MDA in the DM2, HTN and DM2 + HTN
groups were significantly higher than those of the DM2-C
and Sham groups (Figure 2).

**Isolated aortic ring studies**

The $E_{\text{max}}$s of PE in the absence of l-NAME in the DM2,
HTN and DM2 + HTN groups were significantly higher
than those of the Sham and DM2-C groups (Figure 3).
However, there was no significant difference among the
$E_{\text{max}}$s of PE in the DM2, HTN and DM2 + HTN
groups (Figure 3). The $EC_{50}$s of PE in the absence of l-NAME in
the DM2 and HTN groups were significantly lower than
those of the relevant control groups (Table 3). Also, $EC_{50}$s
of PE in the HTN and DM2 + HTN groups were signifi-
cantly lower than that of the DM2 group.

The PE concentration-response curves for each group in
the presence and absence of l-NAME are shown in Figure 4.
The $E_{\text{max}}$s of contraction responses to PE in the presence of
l-NAME in the DM2-C and Sham groups were significantly
higher than the respective $E_{\text{max}}$s in the absence of l-NAME.
However, the $E_{\text{max}}$s of contraction responses to PE in the
presence of l-NAME in the DM2, HTN and HTN + DM2
group were significantly lower than the respective $E_{\text{max}}$s in

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**Figure 1** The concentrations (mean ± SEM, $n = 7$ each) of fasting serum insulin in diabetic control (DM2-C), type 2 diabetic (DM2), sham-operated (Sham), renal hypertensive (HTN) and simultaneously type 2 diabetic and renal hypertensive (DM2 + HTN) groups. *Denotes significant ($P < 0.05$) difference from the DM2-C or Sham group. †Indicates significant ($P < 0.05$) difference from the HTN group.

**Figure 2** The concentrations (mean ± SEM, $n = 7$ each) of serum malondialdehyde (MDA) in diabetic control (DM2-C), type 2 diabetic (DM2), sham-operated (Sham), renal hypertensive (HTN) and simultaneously type 2 diabetic and renal hypertensive (DM2 + HTN) groups. *Denotes significant ($P < 0.05$) difference from the DM2-C or Sham group.

**Figure 3** Phenylephrine (PE) concentration-response curves ($n = 6$ each) in the absence of nitro-l-arginine methyl ester (l-NAME) in aortic rings from diabetic control (DM2-C), diabetic (DM2), sham-operated (Sham), renal hypertensive (HTN) and simultaneously diabetic and renal hypertensive (DM2 + HTN) groups. The response (contraction %) was calculated as the percentage of PE maximal response in the control groups.

International Journal of Experimental Pathology
Table 3: The values (mean ± SD) of effective concentration 50 (EC$_{50}$) of phenylephrine (PE) in the absence and presence of nitro-l-arginine methyl ester (l-NAME), and the inhibitory concentration 50 (IC$_{50}$) of acetylcholine (Ach) and sodium nitroprusside (SNP) from the diabetic control (DM2-C), diabetic (DM2), sham-operated (Sham), renal hypertensive (HTN) and simultaneously diabetic and renal hypertensive (DM2 + HTN) groups ($n = 5$–7 each)

<table>
<thead>
<tr>
<th></th>
<th>EC$_{50}$ (–Log M)</th>
<th>IC$_{50}$ (–Log M)</th>
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<tbody>
<tr>
<td></td>
<td>PE (–LNAME)</td>
<td>PE (+LNAME)</td>
</tr>
<tr>
<td>DM-C</td>
<td>–6.70 ± 0.10</td>
<td>–6.67 ± 0.12</td>
</tr>
<tr>
<td>DM2</td>
<td>–7.05 ± 0.10*</td>
<td>–6.75 ± 0.07*</td>
</tr>
<tr>
<td>Sham</td>
<td>–6.77 ± 0.10</td>
<td>–6.65 ± 0.10</td>
</tr>
<tr>
<td>HTN</td>
<td>–7.33 ± 0.09*</td>
<td>–6.47 ± 0.32*</td>
</tr>
<tr>
<td>DM2 + HTN</td>
<td>–7.31 ± 0.07*§</td>
<td>–6.48 ± 0.37*§</td>
</tr>
</tbody>
</table>

*Denotes significant ($P < 0.05$) difference from respective control groups (DM2-C or Sham).

†Denotes significant ($P < 0.05$) difference from in the absence of l-NAME.

§Denotes significant ($P < 0.05$) difference from the DM2 group.

Figure 4: Phenylephrine (PE) concentration-response curves ($n = 5$ each) in the absence (–) and presence (+) of nitro-l-arginine methyl ester (l-NAME) in aortic rings from (a) diabetic control (DM2-C), (b) diabetic (DM2), (c) sham-operated (Sham), (d) renal hypertensive (HTN) and (e) simultaneously diabetic and renal hypertensive (DM2 + HTN) groups. The response (contraction %) was calculated as the percentage of PE maximal response in the absence of l-NAME.

the absence of l-NAME (Figure 4a–e and Table 3). There was no significant difference between the EC$_{50}$s of PE in the DM-C or Sham groups in the absence and presence of l-NAME. However, the EC$_{50}$s of PE in the presence of l-NAME in the DM2, HTN and HTN + DM2 groups were significantly higher than the respective EC$_{50}$s in the absence of l-NAME (Table 3).

Concentration-response curves to Ach and SNP and their IC$_{50}$s are shown in Figure 5a,b, and Table 3 respectively. Compared with those of the Sham and DM2-C groups, the
maxs of relaxation responses to Ach were significantly lower in the DM2, HTN and HTN + DM2 groups (Figure 5a). Moreover, the $E_{\text{max}}$ of Ach response in the HTN + DM2 group was significantly lower than that of the HTN or DM2 group. There was no significant difference between the IC$_{50}$s of Ach responses in the DM2 or HTN group and their respective controls (Sham or DM2-C). However, the IC$_{50}$ of the Ach response in the HTN + DM2 group was significantly higher than those in the Sham, DM2-C, DM2 and HTN groups (Table 3). There was no significant difference in $E_{\text{max}}$ or IC$_{50}$s of SNP relaxation responses in the Sham, DM2-C, DM2, HTN and DM2 + HTN groups (Figure 5b and Table 3).

Discussion

The main objective of the present study was to examine the effects of simultaneous renal hypertension and type 2 diabetes on glucose tolerance as well as endothelial-dependent and independent relaxations in rat aortic rings. The main finding of the study was that simultaneous renal hypertension and type 2 diabetes improved glucose tolerance and exacerbated endothelial dysfunction.

To the best of our knowledge, the present report represents the first study of an experimental model of simultaneous type 2 diabetes and renal hypertension. Previous studies on simultaneous models of hypertension and diabetes focused mainly on simultaneous type 1 diabetes and hypertension in spontaneously hypertensive rats (Hendriks et al. 1993; Beenen et al. 1996; Muharis et al. 2010) and rats with renal hypertension (Mall et al. 1987; Fischer et al. 1992), and type 2 diabetes in spontaneously hypertensive rats (Sato et al. 1995; Ohtomo et al. 2008) and rats with deoxycorticosterone acetate (DOCA)-salt-induced hypertension (Jadhav & Upasani 2011).

The present study showed that hypertension, type 2 diabetes and simultaneous hypertension and diabetes were associated with enhanced contraction responses to PE in the absence of l-NAME. Such a finding is in agreement with earlier reports (Hendriks et al. 1993; Matsumoto et al. 2004; Ajay et al. 2007) and might be due to the up-regulation of alpha-1 adrenergic receptors on vascular smooth muscle (Hendriks et al. 1993; Matsumoto et al. 2004).

The present study showed that hypertension, diabetes, and simultaneous hypertension and diabetes were associated with the impairment of endothelium-dependent relaxation to Ach. Such a finding is in agreement with previous reports (Ajay et al. 2007; Matsumoto et al. 2004). The relaxation response to Ach has been used as a measure of endothelial function, namely the release of stimulated NO. Therefore, our finding suggests that the three models were associated with reduced endothelial function. Such an endothelial dysfunction has been attributed to increased measures of oxidative stress such as serum levels of MDA (Higashi et al. 2002), which was increased in the three models in the present study. The model of simultaneous hypertension and type 2 diabetes was associated with a greater impairment of endothelium-dependent relaxation than that of hypertension or diabetes alone as indicated by lower $E_{\text{max}}$ and higher IC$_{50}$ of Ach. The greater impairment of endothelium-dependent relaxation in the face of similar levels of serum MDA suggests that mechanisms other than increased oxidative stress might be involved.

The three models examined were associated with impaired contraction response to PE in the presence of l-NAME. The comparison of contraction responses to PE in the presence and absence of l-NAME has been used as a measure of basal release of NO (Wong et al. 2006). Accordingly, blunted contraction response to PE in the presence of l-NAME in this study indicates that these models are associated with reduced basal release of NO. This finding is similar to those of earlier reports (Gouvea et al. 2004; Crabos et al. 1997; Schafer et al. 2004) and might be due to increased oxidative stress (Higashi et al. 2002).

The study showed that models of diabetes and hypertension were associated with reduced and increased HR

![Figure 5 Acetylcholine (a) and sodium nitroprusside (SNP) (b) concentration-response curves in aortic rings from the diabetic control (DM2-C), diabetic (DM2), sham-operated (Sham), renal hypertensive (HTN) and simultaneously diabetic and renal hypertensive (DM2 + HTN) groups (n = 5–7 each). The response (relaxation %) was calculated as the percentage of maximal responses to acetylcholine or SNP in the control groups.](image-url)
respectively. The diabetes-induced decrease in HR is in agreement with earlier reports (Howarth et al. 2007, 2009) and has been attributed to chronic hyperglycaemia, which could affect the expression of some specific genes that encode potassium channel proteins, or to the direct effect of STZ on the heart (Howarth et al. 2009). The hypertension-induced increase in HR is in agreement with an earlier report (Souza et al. 2008), and may be attributed to increased sympathetic activity (Souza et al. 2008). The study showed that in rats with simultaneous hypertension and diabetes, hypertension prevented the diabetes-induced decrease in HR. This finding is similar to that of a previous report on simultaneous DOCA-salt-induced hypertension and type 1 diabetes (Jadhav & Upasani 2011) and might be due to sympathetic hyperactivity (Souza et al. 2008).

The present study showed that rats with hypertension alone or simultaneous hypertension and type 2 diabetes showed higher SBP than that of the control or diabetic rats. It also showed that although significant at some weeks (weeks 1 and 3) and not significant on other weeks (weeks 2 and 4), the SBP of rats with simultaneous renal hypertension and diabetes was higher than that of rats with hypertension alone. This might be due to the greater impairment of endothelial function as evidenced by greater impairment of endothelium-dependent relaxation.

The study showed that rats with diabetes alone, or simultaneous renal hypertension and type 2 diabetes demonstrated impaired glucose tolerance compared with control rats. It also showed that the presence of hypertension with diabetes improved glucose tolerance in rats with simultaneous hypertension and diabetes. The impairment of glucose tolerance in diabetes is not unexpected and is in agreement with earlier reports (Masiello et al. 1998). The improvement of glucose tolerance by hypertension in rats with simultaneous diabetes and hypertension is a new finding and suggests that hypertension, at least in early stages, might have improved responses of islets of Langerhans to increased blood glucose during GTT. The mechanism of this effect is not clear; however, it would be interesting to examine this finding using models with a longer duration of renal hypertension.

Hypertension or diabetes alone as well as simultaneous hypertension and diabetes was associated with increased serum levels of MDA. This finding is similar to earlier reports showing that oxidative stress increased in diabetic (Friedman et al. 2003), hypertensive (Friedman et al. 2003) and simultaneously hypertensive and diabetic animals (Friedman et al. 2003; Ohtomo et al. 2008). The serum levels of MDA were not significantly different among the three models examined in the present study. Such a finding is not in agreement with a previous report that Cohen Rosenthal diabetic hypertensive rats exhibited higher oxidative stress than that of rats with either hypertension or diabetes alone (Friedman et al. 2003).

In conclusion, the findings of the present study suggest that the model of simultaneous type 2 diabetes and renal hypertension was associated with a greater impairment of endothelial function than that of either hypertension or diabetes alone. Such a greater impairment might account for the higher blood pressure in that model. They also show that simultaneous type 2 diabetes and renal hypertension was associated with improved glucose tolerance. Moreover, they show that hypertension has reversed the attenuating effects of diabetes on the HR.

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International Journal of Experimental Pathology


