AT_1-receptor antagonism reverses the blood pressure elevation associated with diet-induced obesity

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Boustany, Carine M, David R. Brown, David C. Randall, and Lisa A Cassis. AT_1-receptor antagonism reverses the blood pressure elevation associated with diet-induced obesity. Am J Physiol Regul Integr Comp Physiol 289: R181–R186, 2005. First published March 17, 2005; doi:10.1152/ajpregu.00507.2004.—Previous studies in our laboratory demonstrated that rats exhibiting obesity in response to a moderately high-fat (MHF) diet developed hypertension associated with activation of the local and systemic renin-angiotensin system. In this study, we examined the effect of the angiotensin type 1 (AT_1)-receptor antagonist, losartan, on blood pressure in obesity-prone (OP) and obesity-resistant (OR) rats fed a MHF diet. Using telemetry monitoring, we characterized the evolution of blood pressure elevations during the development of obesity. Male Sprague-Dawley rats were implanted with telemetry transducers for chronic monitoring of blood pressure, and baseline measurements were obtained. Rats were then switched to the MHF diet (32 kcal as fat) and were segregated into OP and OR groups at week 5. At week 9 on the MHF diet, OP rats exhibited significantly greater 24-h mean arterial blood pressure compared with OR rats (OP: 105 ± 4 mmHg; OR: 96 ± 2 mmHg; P < 0.05). Elevations in blood pressure in OP rats were manifest as an increase in systolic pressure. Administration of losartan to all rats at week 9 resulted in a reduction in blood pressure; however, losartan had the greatest effect in OP rats (percent decrease in mean arterial pressure by losartan: OP: 19 ± 4, OR: 10 ± 2%; P < 0.05). These results demonstrate that elevations in blood pressure occur subsequent to established obesity in rats fed a high-fat diet. Moreover, these results demonstrate the ability of losartan to reverse the blood pressure increase from diet-induced obesity, supporting a primary role for the renin-angiotensin system in obesity-associated hypertension.

METHODS

Animals and procedures. All procedures involving animals were approved by the Institutional Animal Care and Use Committee at the University of Kentucky. Fifteen male Sprague-Dawley rats (470 g, Charles River) were housed individually in an isolated room with a 12:12-h light-dark cycle and were provided a normal laboratory chow diet. All rats were anesthetized with pentobarbital sodium (50 mg/kg), and a blood pressure telemetry transducer was implanted to record abdominal aortic blood pressure. Briefly, a transmitter-catheter module (TA11PA-C40; Data Sciences International, St. Paul, MN) was inserted into the abdominal aorta below the origin of the renal arteries, pointing upstream against the blood flow. The transmitter was placed in the peritoneal cavity and sutured to the abdomen at the incision site. After surgery, animals were left to recover for 1 wk, during which they were fed normal laboratory chow diet. Baseline measurements of blood pressure and heart rate were performed for 1 wk, after which all rats were switched to the MHF diet (D12266B, 32 kcal as fat; Research Diets) for 10 wk, and measurements were continued until the end of the study. Food intake, water intake, and body weight were recorded weekly in all rats.

At week 5 in the study, rats were segregated based on their body weight gain frequency distribution as previously described (33).
Briefly, rats were ranked based on their body weight gain. This led to five rats in the OP group with the highest body weight gain, and five rats in the obesity-resistant (OR) group with the lowest body weight gain. The efficiency of weight gain was calculated by dividing total body weight gain (g) by total amount of energy consumed (MJ) during 10 wk on the MHF diet. The adiposity index was calculated from the sum of the individual fat pad weights: (epididymal fat, retroperitoneal fat)/(body wt − sum of fat pads) × 100. After 9 wk on the MHF diet, rats were treated with losartan (a gift from Merck) at a dose of 10 mg·kg⁻¹·day⁻¹ in the drinking water for 1 wk. After correction for water intake, the average daily dose of losartan was 11.8 ± 0.6 and 11.6 ± 0.6 mg/kg for OP and OR rats, respectively. In addition to rats in the chronic study, we included a group of male Sprague-Dawley rats (571 g; n = 7); these rats were fed normal rat chow and implanted with telemetry implants for blood pressure measurements. Blood pressure was recorded 24 h/day for 7 days, and then all rats were administered losartan (denoted by arrow) was administered during week 10 and did not influence body weight in either group. *Significantly different from OR group, P < 0.05.

**RESULTS**

Development of obesity in response to a MHF diet. Before the onset of the MHF diet, body weights did not differ significantly between OP and OR rats (OP: 478 ± 9 g, OR: 462 ± 11 g) (Fig. 1). By week 3 on the MHF diet, OP rats exhibited significantly greater body weights compared with OR rats. Administration of losartan did not influence body weight in either group. On the final day, body weights differed between OP and OR rats by ~100 g (OP: 734 ± 20 g, OR: 641 ± 21 g; P < 0.05). Overall, total body weight gain achieved by week 10 on the MHF diet was significantly greater in OP rats compared with OR rats (OP: 262 ± 11 g, OR: 181 ± 12 g; P < 0.05). Food intake of OP rats was increased compared with OR rats (Fig. 2). Daily food intake was modestly, but significantly, reduced in both groups administered losartan compared with their food intake during week 9 on the diet (percent decrease in daily food intake was 11 ± 4% for OP and 10 ± 2% for OR). Water intake did not differ significantly between groups and was not altered by losartan (data not shown). The efficiency of weight gain was significantly higher in OP rats (OP: 8.2 ± 0.1 g/MJ, OR: 6.6 ± 0.2 g/MJ; P < 0.05). The adiposity index was increased in OP rats compared with OR rats (OP: 7.1 ± 1.1%, OR: 4.5 ± 0.6%; P < 0.05).

![Graph showing body weight changes over weeks with losartan administration.](image1)

**Fig. 1.** Body weights of obesity-prone (OP) and obesity-resistant (OR) rats over 10 wk on the moderately high-fat (MHF) diet. At baseline (week 0), body weights did not differ between groups. By week 3 on the MHF diet, OP rats exhibited significantly greater body weights compared with OR rats. Data are means ± SE from n = 5 rats/group. Losartan (denoted by arrow) was administered during week 10 and did not influence body weight in either group. *Significantly different from OR group, P < 0.05.

![Graph showing food intake changes over weeks with losartan administration.](image2)

**Fig. 2.** Food intake of OP and OR rats during the 10 wk on the MHF diet. Food intake was significantly reduced in OR rats compared with OP rats throughout the study. Data are means ± SE from n = 5 rats/group. Losartan administration (week 10, denoted by arrow), significantly reduced food intake in both OP and OR groups, compared with week 9. *Significantly different from week 9 within a group, P < 0.05.
Development of hypertension in response to a MHF diet. Baseline MAP, SBP, and DBP were not different between groups (Fig. 3). Blood pressure was not significantly different between groups until week 9 on the MHF diet, when MAP and SBP were significantly elevated in OP rats compared with OR rats. DBP, although it tended to be higher in the OP group (P < 0.06) at week 9, was not significantly different between groups (Fig. 3). Moreover, SBP was significantly elevated in OP rats at week 9 compared with at baseline (week 0). DBP (bottom) did not vary significantly between groups. Losartan administration (week 10, denoted by arrows) resulted in a significant decrease in MAP, SBP, and DBP in both groups. *Significantly different from OR group, P < 0.05. #Significantly different from OP group at week 0.

FIG. 3. Mean arterial (MAP), systolic (SBP), and diastolic (DBP) blood pressure (average of 24-h recordings) of OP and OR rats over 10 wk on the MHF diet. Data are means ± SE from n = 5 rats/group. At week 9, MAP (top) and SBP (middle) were significantly increased in OP rats compared with OR rats. Moreover, SBP was significantly elevated in OP rats at week 9 compared with at baseline (week 0). DBP (bottom) did not vary significantly between groups. Losartan administration (week 10, denoted by arrows) resulted in a significant decrease in MAP, SBP, and DBP in both groups. *Significantly different from OR group, P < 0.05. #Significantly different from OP group at week 0.

DISCUSSION

We examined the evolution of blood pressure simultaneously with body weight in a rat model of diet-induced hypertension. At baseline, MAP, SBP, and DBP were not different between groups (Fig. 3). Blood pressure was not significantly different between groups until week 9 on the MHF diet, when MAP and SBP were significantly elevated in OP rats compared with OR rats. DBP, although it tended to be higher in the OP group (P = 0.06) at week 9, was not significantly different between groups (Fig. 3). Moreover, SBP was significantly elevated in OP rats at week 9 compared with baseline (week 0). Compared with previous measurements of plasma renin activity in low-fat-fed Sprague-Dawley rats (4.3 ± 0.8 ng/mL·h⁻¹; Ref. 2), administration of losartan led to a marked increase in plasma renin activity in OP and OR rats (OP: 45.5 ± 4.5 ng/mL·h⁻¹; OR: 52.3 ± 5.7 ng/mL·h⁻¹). Losartan administration significantly reduced MAP, SBP, and DBP in both groups (Fig. 3). Heart rate did not differ significantly between groups throughout the study, and losartan administration did not exert a significant effect on heart rate in any group (Fig. 4). MAP and heart rate did not differ significantly between day and night cycles within a group (data not shown). However, differences in MAP between OP and OR rats at week 9 were evident during the night cycle but not during the light cycle (nighttime MAP: 105.1 ± 4.3 mmHg for OP and 97.5 ± 2.2 mmHg for OR, P < 0.05; daytime MAP: 98.7 ± 3.4 mmHg for OP and 93.8 ± 0.9 mmHg for OR). The wavelet of arterial blood pressure was not different at baseline between groups but was significantly increased at week 9 in OP rats compared with OR rats (Fig. 5). The wavelet analysis of arterial blood pressure was not significantly altered by losartan treatment in either group (Fig. 5).

We calculated the percent decrease in blood pressure (MAP, SBP, and DBP) in OP and OR rats treated with losartan for 1 wk (Fig. 6). In addition, we determined the effect of losartan on these measures in age-matched Sprague-Dawley rats fed rat chow (572 ± 6 g body wt). Treatment with losartan for 1 wk resulted in similar MAP between OP and OR rats, giving rise to a greater percent decrease in OP rats (20%) compared with control groups (10% for OR and 5% for control; Fig. 6). In contrast, the percent decrease in the wavelet with losartan was not significantly different between OP and OR rats (percent decrease: 7 ± 1% for OP and 4 ± 3% for OR).
obesity. Our findings demonstrate an increase in blood pressure by week 9 in OP but not in OR rats, well after differences in body weight were significant in obese rats. Administration of an AT1-receptor antagonist eliminated differences in blood pressure between OP and OR rats, suggesting a mechanistic link between the RAS and obesity-induced hypertension. In addition, through examination of the wavelet of blood pressure around 0.4 Hz, our data suggest an elevation in sympathetic nerve activity in obese hypertensive rats. However, in contrast to the efficacy of losartan to eliminate blood pressure elevations in obese hypertensive rats, blockade of the RAS did not reduce the wavelet.

In accordance with previous reports, rats fed the MHF diet segregated into OP and OR, with considerable differences in their body weight and adiposity (2, 14, 29, 30, 33). Monitoring of food intake confirmed a condition of hyperphagia combined with an increased efficiency of weight gain in OP rats, as previously described (2, 14, 31). Interestingly, administration of the AT1-receptor antagonist losartan resulted in a modest, but significant, decline in food intake. This finding agrees with a previous report by Crandall et al. (10) and is suggested to result from ancillary properties of the drug. Importantly, the decline in food intake with losartan administration did not significantly alter body weight gain.

Previous studies in our laboratory (2) have demonstrated an increase in MAP and SBP in OP rats compared with OR rats when measured by tail artery catheter on week 11. Using telemetry recordings, we were able to detect significant differences in blood pressure between OP and OR rats as early as 9 wk from the onset of the diet. Previously, Dobrian et al. (14, 15) reported an elevation in SBP, measured by tail cuff, in OP rats compared with OR rats by week 8–10. Importantly, our findings demonstrate that the elevation in blood pressure (week 9) in OP rats occurred well after a significant increase in body weight was detected (week 3). Moreover, because OR rats consuming the high-fat diet did not exhibit an increase in blood pressure, these results demonstrate that hypertension develops in response to the obesity. Interestingly, the modest elevation in baseline blood pressure in OP rats, although not significant, supports a genetic predisposition of OP rats to develop hypertension with chronic obesity. Thus it would be interesting to examine the blood pressure status in rats selectively bred to become OP or OR (28).

In agreement with our previous findings in rats with diet-induced obesity, results from this study suggest that elevations in SBP rather than DBP mediate the increase in MAP. Elevated SBP is a common feature of hypertension in obese patients (11, 13). In parallel with the blood pressure increase, heart rate was modestly, but not significantly, higher in OP rats. This agrees with Dobrian et al. (15), in which a modest elevation in heart rate of OP rats was shown that reached significance by week 16 on the diet. A heightened heart rate has been described as a common characteristic of obese hypertensive subjects (12, 20, 35, 37). Together, these results highlight similarities in the hypertension from diet-induced obesity in rats to human obesity-related hypertension. In addition, previous studies have shown that diet-induced obese rats exhibit hyperinsulinemia and hypertriglyceridermia (14, 31), which are also characteristics of the metabolic syndrome.

Previously, our group (2) has shown that blood pressure power at 0.4 Hz increases in OP rats by week 11 on the high-fat diet. We now extend these findings using a wavelet tuned to 0.4 Hz, which detected a heightened concentration of power at this frequency consistent with an elevated sympathetic nerve activity (4). The region around this frequency is of particular interest because alterations in sympathetic nerve activity and arterial blood pressure are tightly coupled at 0.4 Hz (3). In clinical obesity-hypertension, elevations in systemic catecholamines and muscle sympathetic nerve activity have been previously demonstrated (9, 18, 22). Importantly, in this study, an increase in the wavelet was not present at the onset of obesity but coincided with a rise in blood pressure. Thus, in agreement with previous studies negating an effect of neonatal sympathectomy on the development of diet-induced obesity in Sprague-Dawley rats, our results do not support a role of the sympathetic nervous system in the development of obesity (32).

Previous work from our laboratory (2) revealed pronounced elevations in plasma ANG II concentrations in obese hypertensive rats, suggesting a role for ANG II in the blood pressure elevation with diet-induced obesity. To determine the role of the RAS in obesity-associated hypertension, we examined the effect of an AT1-receptor antagonist administered after the onset of hypertension. Our results demonstrate the efficacy of losartan to normalize the blood pressure of OP rats. These findings demonstrate that blockade of ANG II effects at the AT1 receptor eliminates obesity-induced elevations in blood pressure. Clinical trials have revealed a better efficacy for angiotensin-converting enzyme inhibitors to lower blood pressure in obese hypertensive humans compared with other antihypertensive drugs (12, 38). Our results support these findings and highlight the contribution of the RAS to the blood pressure increase in obesity-hypertension.

Interestingly, administration of losartan to OP rats did not significantly reduce the wavelet of arterial blood pressure. We suggest that these results dissociate, at least partially, the effects of ANG II from the sympathetic nervous system in mediating the hypertension with diet-induced obesity. Moreover, given that losartan administration was able to reverse the blood pressure increase without significantly altering the wavelet, these results thus suggest that sympathetic activation is not the primary mediator of the hypertension in rats with diet-
induced obesity. Future studies are warranted to investigate mechanisms whereby ANG II elevates blood pressure in obesity-hypertension.

In summary, results from this study demonstrate that elevations in SBP and MAP occur subsequent to significant increases in body weight from diet-induced obesity. Although these results support heightened sympathetic activity at the onset of hypertension in rats with diet-induced obesity, the efficacy of losartan to reduce blood pressure was independent of the wavelet of blood pressure at 0.4 Hz. Results from this study demonstrate that AT1-receptor antagonism with losartan reversed the blood pressure elevation with diet-induced obesity, supporting a primary role for the RAS in obesity-related hypertension.

GRANTS

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REFERENCES


