Abnormal Pressure Natriuresis in the Dog Model of Obesity-Induced Hypertension

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Abstract Obesity is considered to be a major factor in the pathogenesis of hypertension in industrialized countries. Recent studies have suggested that the kidneys may play an important role in the development of obesity-induced hypertension. The purpose of this study was to determine whether obesity-induced hypertension is associated with abnormalities in the pressure-natriuresis relation. Renal function studies were performed in anesthetized control dogs (body weight, 20.2±0.8 kg) and obese dogs (body weight, 26.4±0.7 kg) that were maintained on a high-fat diet for 5 to 6 weeks. Mean arterial pressure averaged 122±5 mm Hg in the control group (n=6) and 148±7 mm Hg in the obese group (n=8). The effects of renal perfusion pressure on renal hemodynamics as well as sodium and water excretions were examined at five levels of renal perfusion pressure ranging from 75 to 165 mm Hg. Pressure-natriuretic and diuretic responses were reduced in the obese dogs by 40% to 50%. The renal blood flow and glomerular filtration rate autoregulatory responses and fractional lithium excretion responses to changes in renal perfusion pressure were similar in the control and obese dog groups. Associated with the attenuated natriuretic response to renal perfusion pressure in the obese dogs were significant elevations in plasma renin activity (4.3±1.6 versus 1.6±0.5 ng angiotensin I/mL per hour), plasma aldosterone concentration (34.4±6.4 versus 15.3±3.2 ng/dL), and plasma insulin concentration (30.5±6.8 versus 20.9±2.9 IU/mL). The results of this study establish that obesity-induced hypertension in the dog is associated with a shift in the pressure-natriuresis relation. The underlying mechanism responsible for the abnormal pressure-natriuresis relation in this model of obesity may be due to activation of various sodium-retaining systems such as the renin-angiotensin-aldosterone system. (Hypertension. 1994;23[suppl 1]:I-8-I-11.)

Key Words • sodium • renal circulation • body weight • blood pressure

Epidemiologic studies suggest that obesity is a major factor in hypertension in industrialized countries. Since the early 1920s, it has been known that body weight and blood pressure are closely related. Despite a strong association between body weight and high blood pressure, the etiologic basis of obesity-induced hypertension is unclear. The lack of knowledge about the pathogenesis of obesity-induced hypertension is in part due to the fact that very few animal models have been developed for its study. In 1987, Rocchini and colleagues characterized a dog model of obesity-induced hypertension that consisted of adding 2 pounds of cooked beef fat to the dogs' normal diet for 5 weeks, which resulted in significant weight gain. These researchers also demonstrated that this weight gain was associated with an increase in mean arterial pressure, heart rate, plasma volume, and cardiac output — features common to humans with obesity-induced hypertension.5,4 Although the mechanism for this increase in blood pressure after 5 weeks of a high-fat diet in the dog has not yet been fully elucidated, one common feature in most forms of hypertension is an abnormality in the relation between arterial pressure and sodium excretion.5,7 Normally, an increase in arterial pressure would elevate sodium excretion, a phenomenon usually referred to as pressure natriuresis.8 However, in hypertension, sodium excretion is normal despite elevated arterial pressure. This blunted effect of pressure on sodium excretion in hypertension is thought to be due to some underlying sodium-retaining abnormality.5,7 Although recently published and preliminary studies have supported a role for sodium retention in the development of obesity-induced hypertension in the dog,9,11 it is not known whether the pressure-natriuresis relation is altered in obesity-induced hypertension. Therefore, the purpose of this study was to determine whether the pressure-natriuresis relation is altered in the dog model of obesity-induced hypertension.

Methods All experiments were performed in accordance with rules and regulations of the USDA guidelines and with the approval of the Institutional Animal Care and Use Committee. A total of 14 weight-matched dogs were used for this experiment. The dogs were split into two groups: the control group (control dogs, n=6) and the experimental group (obese dogs, n=8), which was fed a high-fat diet. The dogs in the obese group were fed approximately 1.5 cans of Kennel Ration dog food plus 1.5 pounds of cooked beef fat per day for 5 to 6 weeks. The control dogs were fed only 1.5 cans of Kennel Ration canned dog food per day for the same 5- to 6-week period.

On the day of the experiment, dogs were anesthetized with sodium pentobarbital and prepared for hemodynamic and renal function measurements. Dogs were implanted with an aortic catheter above the renal artery for blood sampling and measurement of systemic arterial pressure and below the renal artery for measurement of renal perfusion pressure (RPP). A silicone elastomer occluder was placed around the aorta above both renal arteries and connected to a syringe pump. The
occluder along with an electronic servocontrol unit was used to control RPP precisely. An electromagnetic flow probe was placed around the left renal artery for continuous measurements of renal blood flow (RBF). The ureter was cannulated for the collection of urine. Glomerular filtration rate (GFR) was determined by the clearance of \(^{123}\)I]iothalamate. For estimation of proximal tubule handling of sodium, fractional excretion of lithium was also measured.

To increase the number of data points within the range of renal autoregulation, we performed bilateral carotid occlusions to increase systemic arterial pressure in the control and obese dogs. RPP was reduced in decrements of 15 to 20 mm Hg. Renal clearances (15 to 20 minutes) and hemodynamic data were obtained 15 to 20 minutes after the reduction in RPP. GFR, RBF, and excretion rates of sodium, water, and lithium were measured at each level of RPP. Blood samples for the measurement of plasma renin activity and plasma concentrations of aldosterone and insulin were obtained at the beginning of each experiment after bilateral carotid occlusion. Plasma renin activity and plasma aldosterone and insulin concentrations were measured by radioimmunoassay. Kidney weight was measured in each dog, and no significant difference was found between the two groups of animals.

Data are expressed as mean±SEM. Significance of differences in measured values in different groups of animals were evaluated using an unpaired \(t\) test. Linear-regression analysis was performed by the least-squares method, and between-group differences in the slopes of the relations were determined using an unpaired \(t\) test. A probability level <.05 was considered statistically significant.

**Results**

Fig 1 illustrates body weights and mean arterial pressures in anesthetized control and obese dogs. Body weight was 35% higher in the obese group (control dogs, 20.2±0.8 kg; obese dogs, 26.7±0.7 kg after a high-fat diet for 5 to 6 weeks). Associated with the increase in body weight, the obese dogs had a significantly higher mean arterial pressure (obese dogs, 148±7 mm Hg; control dogs, 122±5 mm Hg). These differences in arterial pressure between the two groups are consistent with what we have found in conscious, chronically instrumented dogs.

Fig 2 illustrates significant differences in the pressure-natriuresis and -diuresis curves between the control and obese dogs. At an RPP of 75 mm Hg, sodium excretion and urine flow rate were similar between the two groups. However, at higher levels of RPP, the obese dogs excreted significantly less sodium and water. Linear-regression analysis of the data indicated that the slope of the pressure-natriuresis relation was 40% to 50% lower in the obese dogs (0.23±0.04 versus 0.36±0.05, \(P<.05\)).

There were no significant differences in RBF or GFR between the two groups under basal conditions. GFR averaged 33±4 mL/min in control dogs and 26±3 mL/min in obese dogs under basal conditions. RBF measured 230±15 mL/min in control dogs and 199±17 mL/min in obese dogs. Fig 3 illustrates that the blunted pressure-natriuretic response to higher levels of RPP in the obese dogs does not appear to be due to differences in GFR and RBF responses to RPP. GFR and RBF were all well autoregulated between pressures of 80 to 145 and 160 mm Hg in both dog groups.

Fractional excretion of lithium was used to estimate proximal tubule sodium reabsorption in this study (Fig 4). Fractional excretion of lithium tended to be lower at low levels of RPP, but it was not statistically significant. At RPP values between 80 and 150 mm Hg, at which we saw the largest differences in the sodium excretory response to RPP, the fractional excretion of lithium responses were similar between the groups. This finding suggests that the difference in the sodium excretory response to RPP in the obese dogs is most likely due to abnormalities in renal handling of sodium beyond the proximal tubule.

To obtain a better understanding of possible mechanisms responsible for the blunted pressure natriuresis in
in the obese dogs, we measured plasma renin activity, plasma aldosterone concentration, and plasma insulin concentration in the two dog groups. Both plasma renin activity and plasma aldosterone concentration were significantly higher in the obese dogs. Plasma renin activity averaged 1.6±0.5 ng angiotensin I/mL per hour in control dogs and 4.3±1.6 ng angiotensin I/mL per hour in obese dogs. Plasma aldosterone concentration averaged 15.3±3.2 ng/dL in control dogs and 34.4±6.4 ng/dL in obese dogs. Plasma insulin concentration was also significantly higher in the obese dogs, averaging 30.5±6.8 IU/mL, which was 50% higher than in control dogs (20.9±2.9 IU/mL).

Discussion

In the present study, dogs maintained on a high-fat diet for 5 to 6 weeks weighed significantly more than dogs maintained on a normal dog chow diet. Body weight in the obese group was 35% higher than in the control group. Associated with this increase in body weight were significantly higher arterial pressures in the obese group. This significant association between body weight and arterial pressure in dogs is consistent with previous data reported by Rocchi et al.3

Although the exact mechanism responsible for the increase in blood pressure after 5 to 6 weeks of a high-fat diet in dogs has not been fully elucidated, recent studies suggest that obesity-induced hypertension may be related to abnormal renal handling of sodium. Several studies have indicated that the development of obesity-induced hypertension in the dog is associated with significant sodium retention and increases in plasma volume.6,9,10 We have also recently reported that the obese hypertensive dog excretes significantly less sodium and water than normotensive control dogs in response to an acute saline load.11 Furthermore, research indicates that obese hypertensive patients exhibit abnormal renal sodium handling.12 Thus, it appears that the regulatory mechanisms responsible for control of sodium excretion and extracellular fluid volume may be altered in obesity-associated hypertension.

Most forms of hypertension are associated with an abnormality in the relation between RPP and sodium excretion.5,7 A shift to the right in the pressure-natriuresis relation indicates an underlying abnormality in renal excretory function.5,7 Although recent studies support a role for altered sodium handling in the development of obesity-induced hypertension, it is not known whether the pressure-natriuresis relation is altered in obese dogs.7,9,10,13 The present study reports for the first time that both the pressure-natriuretic and -diuretic response is shifted in obese dogs. Our findings provide further experimental evidence that obesity-induced hypertension is associated with a reduction in renal excretory function. This abnormality may be an important mechanism involved in the pathogenesis of obesity-associated hypertension.

The shift in the pressure-natriuresis relation in the obese dogs may at least in part be due to slight differences in GFR and RBF in the obese and control dogs. Although basal levels of RBF and GFR were slightly lower in our obese dogs, there was no statistical difference between the anesthetized control and obese dogs. GFR and RBF were all well autoregulated between RPP values of 80 and 150 mm Hg in both the control and obese dogs. These findings indicate that the differences in the sodium excretory response to RPP are most likely caused by abnormalities in renal tubular reabsorption of sodium in the obese dogs. The finding that fractional excretion of lithium was similar between the two dog groups suggests that the abnormality may be beyond the proximal tubule.

Our finding that plasma renin activity is 170% higher in the obese dogs than in the control dogs suggests that the renin-angiotensin system may in part be responsible for the abnormal sodium handling in obesity. Enhanced activity of the renin-angiotensin system has also been reported in obese hypertensive patients. Elevated plasma levels of angiotensin II could mediate the blunted pressure-natriuresis relation in obese dogs. Consistent with this suggestion are studies indicating that angiotensin II causes a rightward shift in pressure
natriuresis, whereas converting enzyme inhibitors or angiotensin II receptor antagonists enhance pressure natriuresis. Further studies with converting enzyme inhibitors, angiotensin II receptor antagonists, or both will have to be performed to determine the quantitative importance of the renin-angiotensin system in altering the pressure-natriuresis curve in obese dogs.

In addition to angiotensin II, other sodium-retaining factors could also play a role in causing the blunted pressure-natriuretic response in obese hypertensive dogs, including aldosterone, insulin, and the renal sympathetic nervous system. Aldosterone has been shown to be elevated in obese hypertensive dogs and obese humans. Elevated levels of insulin previously have been suggested to play a role in the pathogenesis of obesity-related hypertension; however, chronic hyperinsulinemia fails to chronically alter pressure natriuresis. Finally, obesity or weight gain has been reported to be associated with enhanced activity of the sympathetic nervous system in humans and in the dog model of obesity-induced hypertension. Elevated levels of insulin previously have been suggested to play a role in the pathogenesis of obesity-related hypertension; however, chronic hyperinsulinemia fails to chronically alter pressure natriuresis. Finally, obesity or weight gain has been reported to be associated with enhanced activity of the sympathetic nervous system in humans and in the dog model of obesity-induced hypertension. Maintenance of enhanced renal sympathetic nervous activity could result in blunted pressure natriuresis in obese dogs. Thus, various sodium-retaining factors, such as aldosterone, insulin, and the renal sympathetic nervous system, could also play a role in causing the attenuated pressure-natriuretic response in the obese, hypertensive dog. Further experiments will be required to determine the quantitative importance of each of these systems in mediating the abnormal renal sodium handling in obesity.

In summary, feeding dogs a high-fat diet for 5 to 6 weeks results in significant weight gain and high blood pressure. The findings of this study indicate that obese, hypertensive dogs excrete significantly less sodium and water than normotensive control dogs in response to changes in RPP. This shift in the pressure-natriuresis relation may play an important role in the pathogenesis of obesity-induced hypertension.

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