Hypertension and Insulin Resistance Are Not Directly Related in Obese Dogs

Albert P. Rocchini, John Q. Yang, Amy Gokee

Abstract—In dogs fed a high-fat diet, we determined whether there was a direct relation between obesity-induced insulin resistance and obesity-induced hypertension. Thirty-six adult mongrel dogs were chronically instrumented and assigned to receive either a high-fat diet alone (n = 7) or a high-fat diet combined with a low-sodium diet plus furosemide (n = 6), prazosin plus atenolol (n = 7), clonidine (n = 10), or aspirin (n = 6). Blood pressure, heart rate, and body weight were measured daily. Insulin resistance was assessed with a single-dose euglycemic hyperinsulinemic clamp (2 mU · kg⁻¹ · min⁻¹) before and after 1, 3, and 6 weeks of the high-fat diet. The low-salt diet plus furosemide, prazosin plus atenolol, and clonidine treatments prevented the hypertension associated with feeding the dogs a high-fat diet. Only clonidine treatment totally prevented the development of insulin resistance, and high-dose aspirin, known to prevent insulin resistance by inhibition of the activity of IκB kinase-β, decreased the degree of insulin resistance by almost 70%. However, aspirin had no effect on the development of hypertension. We conclude that obesity-induced hypertension and obesity-induced insulin resistance are not directly related. In addition, there is a suggestion that insulin resistance in this experimental model is mediated through the central and or peripheral α₁-adrenoceptors, whereas hypertension is mediated through the α₁- and or β-adrenoceptors. (Hypertension. 2004;43:1011-1016.)

Key Words: hypertension ■ obesity ■ insulin resistance ■ sympathetic nervous system

The association of hypertension and obesity is well recognized; however, the mechanism involved in the pathogenesis of the increased blood pressure in obesity is not completely understood. Studies in our laboratory¹–⁴ and those performed by others⁵ have suggested a link between hyperinsulinemia, increased sympathetic nervous system activity, and obesity-related hypertension. Insulin resistance, ie, resistance to insulin’s ability to stimulate glucose uptake, has been speculated to be the common metabolic abnormality shared by these 3 conditions. This hypothesis is supported by numerous reports that document a relation between insulin resistance and hypertension.⁶,⁷ There are, however, a number of experimental observations that suggest that the relation between insulin resistance and obesity-induced hypertension is not so straightforward.⁸,⁹

We believe than an alternative hypothesis to explain the pathogenesis of obesity hypertension is that chronic central nervous system–induced sympathetic activation links insulin resistance and hypertension. Increased stimulation of the sympathetic nervous system occurs in obese individuals.¹⁰ Hall et al¹¹ have performed preliminary studies suggesting that 7 days of combined α- and β-adrenergic blockade reduced arterial pressure to a much greater extent in obese than normal dogs. The sympathetic nervous system function is strongly influenced by dietary intake. Fasting or caloric deprivation reduces whereas overfeeding stimulates sympathetic activity.¹² The effect of overfeeding is not due to caloric content but rather to the carbohydrate and fat content, because these 2 nutrients stimulate the sympathetic nervous system, even when total caloric is not increased.¹³ In addition, leptin, a hormone that is secreted from adipocytes in response to dietary intake, is also known to activate the sympathetic nervous system.¹⁴

The short-term administration of catecholamines is known to decrease insulin action. Diebert and DeFronzo¹⁵ demonstrated that epinephrine, acting primarily through a β-adrenergic receptor, markedly impaired both peripheral and hepatic resistance to the action of insulin. Jamerson et al¹⁶ demonstrated that a reflex increase in sympathetic tone in normotensive individuals can lead to acute insulin resistance in the forearm. These investigators speculated that reflex activation of the sympathetic nervous system caused a decrease in forearm glucose uptake that was mediated through a reduction in blood flow to the forearm. Central activation of imidazoline receptors by moxonidine can prevent both the hypertension and insulin resistance associated with a high-fructose diet in rats¹⁷ and the insulin resistance in obese, spontaneously hypertensive rats.¹⁸ Finally, we¹ have demonstrated that clonidine prevents the hypertension and insulin resistance associated with feeding dogs a high-fat diet. Thus, although it appears that activation of the central sympathetic nervous system is linked to obesity hypertension and insulin resistance, we do not know whether insulin resistance and hypertension are directly or indirectly related to each other. The current study was conducted to determine whether a direct relation exists between obesity-induced insulin resistance and obesity-induced hypertension.
Thirty-six adult mongrel dogs (20 males and 16 females) were trained to stand quietly in a padded sling. Results from 7 of the dogs were previously reported. All dogs were then surgically instrumented with an ascending aortic catheter and 2 right atrial catheters. Surgical instrumentation of the animals was performed under sodium methohexital induction (12 mg/kg) and isoflurane (0.5 to 1.5%) anesthesia. After surgery, the dogs were allowed to recover for 3 weeks before baseline measurements were made. Dogs were then assigned to 1 of the following 5 groups:

1. A high-fat diet, control group (n=7) that received the control diet, a regular diet of 1 can of dog food (Ken-L-Ration), for 2 weeks followed by 6 weeks of a high-fat diet consisting of ~0.8 kg of cooked beef fat in addition to their regular diet.

2. A high-fat, low-sodium, and furosemide group (low-salt group, n=6) that received ~20 mg/dl sodium and 10 mg/d furosemide, initiated 2 weeks before starting the high-fat diet and continued along with the fat diet for 6 weeks. This group was chosen to determine whether prevention of the hypertension by fluid restriction would also resolve the development of insulin resistance.

3. A high-fat, prazosin, and atenolol group (α+β-blockade group, n=7) that received 5 mg·kg⁻¹·d⁻¹ prazosin and 25 mg/d atenolol, initiated 2 weeks before starting the high-fat diet and continued along with the fat diet for an additional 6 weeks. This group was chosen to determine the role that peripheral α₁- and β-adrenergoreceptors play in the development of insulin resistance and hypertension associated with feeding dogs a high-fat diet. Adequate α₁-adrenergoreceptor blockade was defined as the failure of an intravenous dose of phenylephrine (that before blockade had increased arterial pressure by 10 mm Hg) to change arterial pressure. Adequate β-blockade was defined as the failure of a dose of isoprotenerol (that before β-blockade had increased heart rate by 20%) to increase heart rate.

4. A high-fat diet, clonidine group (clonidine group, n=10) that received 0.3 mg clonidine PO BID, initiated 2 weeks before starting the high-fat diet and continued along with the fat diet for an additional 6 weeks. This group was chosen to determine the role of the central α₂-adrenergoreceptors in the pathogenesis of insulin resistance and hypertension associated with feeding dogs a high-fat diet. The results from 7 of these dogs have previously been reported. No significant differences were noted for any of the measured variables between the 7 previously reported animals and the 3 new animals (weight: 22.4±0.8 kg before the fat diet and 26.9±1 kg after 6 weeks of the fat diet for 7 previously reported clonidine dogs vs 21.6±1 kg before the fat diet and 26.5±1 kg after 6 weeks of the fat diet for the 3 new clonidine-treated dogs; mean arterial pressure: 91±2 mm Hg before the fat diet and 90±2 mm Hg after 6 weeks of the fat diet for 7 previously reported dogs vs 89±3 mm Hg before the fat diet and 90±3 mm Hg after 6 weeks of the fat diet for the 3 new dogs; and insulin mediated glucose uptake: 73±6 μmol·kg⁻¹·min⁻¹ before the fat and 74±4 μmol·kg⁻¹·min⁻¹ after 6 weeks of the fat diet for 7 previously reported dogs vs 76±9 μmol·kg⁻¹·min⁻¹ before the fat diet and 75±12 μmol·kg⁻¹·min⁻¹ after 6 weeks of the fat diet for the 3 new dogs).

5. A high-fat, aspirin group (As group, n=6) that received 100 mg·kg⁻¹·d⁻¹ of enteric-coated aspirin, initiated 2 weeks before starting the high-fat diet and continued along with the fat diet for an additional 6 weeks. Kim et al. have recently demonstrated that high-dose salicylate can prevent fat-induced insulin resistance by inhibiting the activity of IκB kinases-β (IKKs-β). Therefore, we used this group to determine whether prevention of insulin resistance would also prevent the hypertension associated with high-fat feeding in dogs. The dose of aspirin used in the current study would be equivalent to a human dose of 6 to 10 g/d. This is a very high dose of aspirin, and we do not advocate its long-term use in humans in view of aspirin’s potential for long-term toxicity at this high dose.

In addition, all dogs received vitamin supplements (VAL syrup, Ft Dodge Laboratories) and antibiotics throughout the entire study. The dogs were housed in air-conditioned cages and were fed between 1 PM and 3 PM each day. Blood pressure, heart rate, and body weight were measured daily. Plasma glucose and insulin were measured twice a week during the entire study. All measurements were made between 8 AM and 11 AM before the daily feeding (the dogs not having been fed since 5 PM the previous day). All of the procedures in this study were in accordance with the University of Michigan guidelines on animal experimentation.

**Methods**

Arterial pressure was measured with a pressure transducer mounted at the level of the heart. Blood pressure signals were recorded, and the analog signals were sent to a computer to be analyzed. The computer calculated the average systolic, diastolic, and mean blood pressures and heart rate (during a 15- to 30-minute period). Insulin resistance was assessed with a single insulin dose (2 mU·kg⁻¹·min⁻¹) euglycemic hyperinsulinemic clamp. The euglycemic hyperinsulinemic clamp was performed in all dogs before starting the pharmacological intervention; after 2 weeks on the intervention but before starting the high-fat diet; and at 1, 3, and 6 weeks of the high-fat diet.

**Analytic Methods**

Blood for serum glucose determination was drawn, placed in untreated polyethylene tubes, and centrifuged in an Eppendorf microcentrifuge (Brinkman Instruments). The glucose concentration of the supernatant was then measured in duplicate by the glucose oxidase method in a glucose analyzer (model A23, Yellow Springs Instruments). Serum insulin was measured by double-antibody radioimmunoassay (ICN Biomedicals, Inc). Plasma electrolytes were measured by flame photometry.

**Statistical Analysis**

All values are mean±SE. Weekly blood pressures, heart rates, and body weights were determined by averaging the daily values for each week. Plasma glucose and insulin were determined by averaging the 2 values that were obtained each week. Because we had previously demonstrated in dogs fed a high-fat diet that hepatic glucose output was completely suppressed at an insulin infusion rate of >1 mU·kg⁻¹·min⁻¹, the amount of glucose required to maintain euglycemia during the last 30 minutes of each insulin infusion was used as our index of whole-body glucose uptake.

Within each group, a repeated-measures ANOVA was performed for each variable to determine whether a significant change in the variable occurred over time. A 2-factor ANOVA for repeated measures was then performed for each variable to assess differences among the 5 groups of dogs. Because of the multiple comparisons made in this study, P<0.01 was considered significant.

**Results**

**Hemodynamic, Hormonal, and Metabolic Data**

The hemodynamic, hormonal, and metabolic data for all 5 groups of dogs are summarized in the Table. During the regular diet and 2 weeks of the regular diet plus pharmacological treatment, no significant differences were noted among the 5 groups for any of the measured variables. There was a trend in the low-salt group for a slight increase in fasting insulin (P=0.10) and in the α+β-blockade group for a slight decrease in heart rate (P=0.09). During the 6 weeks of the high-fat diet, all groups increased their body weight to a similar degree.

Weight gain was not associated with any significant increase in blood pressure in the clonidine, low-salt, or α+β-blockade groups (Figure 1). The control and As groups experienced a significant increase in blood pressure associated with weight gain (14±4 mm Hg for controls and 15±4 mm Hg for the As
group; \( P<0.001 \). Weight gain resulted in a significant increase in heart rate in the control, low-salt, and As groups, whereas no change in heart rate was observed in the clonidine or the \( \alpha+\beta \)-blockade group.

Plasma glucose did not significantly change in any of the groups with feeding of the high-fat diet. We observed a significant increase in fasting insulin in the control, low-salt, \( \alpha+\beta \)-blockade, and As groups. However, in the As group, the increase in fasting insulin was significantly less than that in the control group (\( \Delta \)fasting insulin, 35±10 pmol/L for the As group vs 122±15 pmol/L for controls; \( P=0.09 \)). Only the clonidine-treated group did not experience any significant change in fasting insulin associated with weight gain. Weight gain was not associated with any significant changes in serum sodium or potassium in any of the groups.

### Euglycemic Hyperinsulinemic Clamp Data

During the euglycemic hyperinsulinemic clamp studies, the steady-state blood glucose concentration in all dogs averaged \( \approx 5.2 \) mmol/L and did not differ from the fasting concentration. The coefficient of variation of glucose level at insulin plateau was \( <5\% \).

To characterize the ability of the 5 groups to alter the insulin-mediated glucose uptake relation that occurs in dogs fed a high-fat

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Group (n=7; M/F=4/3)</th>
<th>Low-Salt+furosemide Group (n=6; M/F=3/3)</th>
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<td>Sodium, mmol</td>
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<td>Potassium, mmol/L</td>
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<th>Clonidine Group (n=10; M/F=5/5)</th>
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<td>( \alpha+\beta )-Blockade</td>
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<tr>
<td>Potassium, mmol/L</td>
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</table>

We have previously reported data from 7 of the clonidine-treated dogs\(^3\).

BP indicates mean blood pressure; HR, heart rate.

\(^*P<0.001\), control period vs 6 weeks of a high-fat diet.

\(†P<0.001\), treatment group vs control group.
diet, we used a single-dose euglycemic hyperinsulinemic clamp to measure insulin-mediated glucose uptake before and after 1, 3, and 6 weeks of the high-fat diet (Figure 2). As shown in Figure 2, feeding the dogs a high-fat diet was associated with the development of a reduction in insulin-mediated glucose uptake in all groups except the clonidine-treated groups. However, compared with the control group, the As group experienced a significantly lesser reduction in insulin-mediated glucose uptake after 6 weeks of the high-fat diet (33±5 μmol·kg⁻¹·min⁻¹ for controls vs 60±7 μmol·kg⁻¹·min⁻¹ for the As group; P<0.001). Compared with the clonidine-treated group, the As group experienced a significantly greater reduction in insulin-mediated glucose uptake after 6 weeks of the high-fat diet (73±5 μmol·kg⁻¹·min⁻¹ for the clonidine group vs 60±7 μmol·kg⁻¹·min⁻¹ for the As group; P<0.01).

**Figure 1.** Plot of the weekly values for mean arterial pressure in 7 dogs receiving a high-fat diet alone (control group), 6 dogs receiving a high-fat diet plus a low-sodium diet and furosemide (low-Na group), 7 dogs receiving a high-fat diet plus prazosin and atenolol (α+β-blockade group), 10 dogs receiving a high-fat diet plus clonidine (clonidine group), and 6 dogs receiving a high-fat diet plus aspirin (aspirin group). The control and aspirin groups significantly increased their mean arterial pressure during the 6-week high-fat diet (P<0.001). The high-fat diet did not significantly change mean arterial pressure in the salt, α+β-blockade, or clonidine groups.

Compared with the control group, both the low-salt and the α+β-blockade groups developed a similar degree of reduction in insulin-mediated glucose uptake (33±5 μmol·kg⁻¹·min⁻¹ for controls vs 27±6 μmol·kg⁻¹·min⁻¹ for the low-salt and 33±4 μmol·kg⁻¹·min⁻¹ for the α+β-blockade groups).

In all groups of dogs before starting the high-fat diet, the euglycemic hyperinsulinemic clamp resulted in a decrease in arterial pressure (−6±2 mm Hg for controls, −7±2 mm Hg for the low-salt group, −7±2 mm Hg for the α+β-blockade group, −6±2 mm Hg for the clonidine group, and −6±2 mm Hg for the As group). However, after 6 weeks of the high-fat diet, euglycemic hyperinsulinemia resulted in a decrease in arterial pressure in only the clonidine-treated dogs (−5±2 mm Hg in the clonidine group vs 0 mm Hg for controls, the low-salt group, the α+β-blockade group, and the As group; P<0.05).

**Discussion**

The goal of this study was to evaluate the relation between obesity-induced hypertension and obesity-induced insulin resistance. We had previously reported that the central-acting α₂-adrenergic agonist clonidine was able to prevent both the hypertension and insulin resistance associated with feeding dogs a high-fat diet. To determine whether inhibition of the sympathetic nervous system, not just prevention of hypertension, was responsible for the prevention of insulin resistance observed with clonidine treatment, we evaluated the effect of a low-sodium diet plus furosemide on the development of both obesity-induced hypertension and insulin resistance. We have demonstrated that a low-sodium diet plus furosemide prevented the hypertension associated with feeding dogs a high-fat diet; however, it did not prevent the development of insulin resistance. In fact, there was a trend toward increasing insulin resistance in these animals. These results are consistent with the observation of Kassab et al. Those investigators demonstrated that bilateral renal denervation prevented the hypertension and sodium retention associated with obesity in the dog. They concluded that the renal sympathetic nerves play an important role in mediating the sodium retention and hypertension associated with obesity. Kassab et al also found that renal denervation did not prevent the insulin resistance associated with feeding dogs a high-fat diet. Similar to our observation, Feldman and Schmidt and others have demonstrated that severe dietary sodium restriction can increase the resistance to the systemic effects of insulin. One possible explanation for why clonidine prevented both the hypertension and insulin resistance associated with high-fat feeding and a low-sodium diet plus furosemide did not is that although the sodium restriction prevented the fluid retention associated with the high-fat diet, it did not prevent activation of the sympathetic nervous system. As shown by our data, the low-sodium diet plus furosemide–treated animals still experienced significant tachycardia. This increase in heart rate is an indirect indication of sympathetic activation. Thus, based on the results of the low-salt group combined with that of the clonidine group, it is possible that activation of the sympathetic nervous system might be important in the pathogenesis of insulin resistance associated with feeding dogs a high-fat diet.

In an attempt to determine which portion of the sympathetic nervous system might be responsible for the insulin...
resistance and hypertension observe when feeding dogs a high-fat diet, we next studied the effect of combined peripheral α₁- and β-adrenergic blockade. We observed that peripheral α₁- and β-blockade with prazosin and atenolol, respectively, prevented the hypertension and tachycardia associated with feeding the dogs a high-fat diet. These results are consistent with those of a preliminary study reported by Hall et al in dogs, a study by Woford et al in humans, and a study by Antic et al in rabbits. Thus, our data as well as those of others would suggest that activation of the sympathetic nervous system is important in the pathogenesis of obesity hypertension. Because combined peripheral α₁- and β-blockade peripherally inhibit sympathetic outflow, one would have expected that this treatment combination should have affected insulin resistance, similar to the effect observed in the clonidine group. However, unlike clonidine, peripheral α₁- and β-blockade did not prevent the insulin resistance associated with obesity. The main mechanism that explains clonidine’s antihypertensive effect is a reduction in central sympathetic outflow, an effect mediated by activation of central α₁-adrenoceptors, thus reducing peripheral resistance by decreasing efferent sympathetic neuronal firing and also by reducing the release of norepinephrine from vascular neuroeffector junctions. In addition, it has recently been shown that a portion of the antihypertensive actions of clonidine are mediated through direct activation of endothelial α₁-adrenoceptors that are coupled to the L-arginine pathway, resulting in endothelial vasorelaxation mediated by nitric oxide release. Therefore, a possible explanation for the different results observed with clonidine versus peripheral α₁- and β-blockade could be that insulin resistance in this experimental model is mediated through the central and/or peripheral α₁-adrenoceptor receptors, whereas hypertension is mediated through the α₁- and/or β-adrenoceptor receptors.

There are a number of reports documenting altered α₁-adrenoceptor function in obesity. Pelat et al demonstrated that 9 weeks of feeding dogs a high-fat diet resulted in impaired presynaptic and/or central α₁-adrenoceptor function. Coatmellec-Taglioni et al demonstrated that hypertension in cafeteria-fed rats is associated with an alteration in renal α₁-adrenoceptor subtypes. Lembo et al demonstrated that insulin selectively enhances α₂-adrenergic endothelial vasorelaxation by potentiating endothelial nitric oxide production through a G protein-coupled process. This vasorelaxant mechanism of insulin is altered in both spontaneously hypertensive rats and obese dogs and humans. Similarly, in the current study, we observed that before starting the high-fat diet, all 5 groups of dogs experienced a decrease in blood pressure with the euglycemic hyperinsulinemic clamp. However, after 6 weeks of the high-fat diet, only the clonidine group still had a decrease in blood pressure during the euglycemic hyperinsulinemic clamp. Some investigators have suggested that the reduced rate of insulin-mediated glucose uptake that occurs in non–insulin-dependent diabetes mellitus, obesity, and hypertension might be due to impairment in the action of insulin to increase skeletal muscle blood flow. However, this mechanism is unlikely, because a large reduction in skeletal muscle blood flow does not impair glucose disposal or induce fasting hyperinsulinemia. Therefore, obesity-associated insulin resistance most likely involves a change in insulin signaling in peripheral tissues. Recent observations have described a possible linkage between heterotrimeric G proteins and insulin signaling. Targeted elimination of the Goi in fat, skeletal muscle, and liver in transgenic mice leads to insulin resistance. Tao et al have recently demonstrated that activation of Goi can suppress both the expression and activity of protein-tyrosine phosphatase-1B in insulin-sensitive tissues. A second way that α₁-receptors could participate in the development of insulin resistance is through alterations in plasma free fatty acid levels. Clonidine is known to suppress free fatty acid levels. This effect is mediated through activation of the α₁-adrenergic receptors. Griffin et al speculated that fatty acids cause insulin resistance through inhibition of pyruvate dehydrogenase and phosphofructokinase activity. Alternatively, Griffin et al demonstrated that increased plasma fatty acid levels result in insulin resistance through activation of protein kinases-θ that lead to serine phosphorylation of insulin receptor substrate-1 (IRS-1). Itani et al and Kim et al have suggested that the phosphorylation of IRS-1 is possibly mediated through activation of the serine kinase IKK-β. Therefore, it is possible that clonidine treatment could improve insulin resistance in fat-fed dogs by decreasing free fatty acid levels and thus, inhibiting IKK-β activity.

Finally, we attempted to determine whether prevention of insulin resistance with high-dose aspirin therapy would also prevent the hypertension associated with feeding dogs a high-fat diet. Kim et al have suggested that aspirin inhibits IKK-β activity and thereby prevents the high-fat diet–induced activation of a serine/threonine kinase cascade leading to decreases in tryosine phosphorylation of IRS-1 and IRS-1–associated phosphatidylinositol-3-phosphate kinase activity. We demonstrated that high-dose aspirin resulted in an almost 70% reduction in the degree of insulin resistance, yet it had no effect on the magnitude of the hypertensive or tachycardic response to feeding dogs a high-fat diet. Even though aspirin therapy significantly improved insulin sensitivity, it did not totally prevent the development of some insulin resistance; therefore, it is possible that had we totally prevented the development of insulin resistance, we might have also prevented the hypertension. However, if insulin resistance was responsible for the development of hypertension associated with high-fat feeding in dogs, we would have expected that a nearly 70% reduction in the degree of insulin resistance should have resulted in some amelioration in the degree of hypertension. Such was not the case. Aspirin-treated dogs increased their arterial pressure by 4 mm Hg versus an increase of 14 mm Hg for the control dogs. Therefore, we believe that the results from this experimental group suggest that insulin resistance does not directly cause hypertension.

**Perspectives**

The current study has demonstrated that obesity-induced insulin resistance and obesity-induced hypertension are not directly
related. In addition, the results suggest that activation of the sympathetic nervous systems is important in the pathogenesis of obesity hypertension, whereas insulin resistance associated with obesity might in part be mediated by alterations in the central and or peripheral $\alpha_2$-adrenergic receptors. Further studies will be necessary to clarify the cellular mechanism by which alterations in $\alpha_2$-adrenergic receptors might result in the development of insulin resistance. Finally, the development of new $\alpha_2$-adrenergic agonists and new inhibitors of IKK-β might be important novel therapeutic agents to treat the insulin resistance associated with obesity.

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References

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