Pathogenesis of Weight-Related Changes in Blood Pressure in Dogs

Albert P. Rocchini, Catherine P. Moorehead, Susan DeRemer, and Diane Bondie

We have previously shown that weight gain in the dog results in an increase in blood pressure. To study the pathogenesis of the rise in blood pressure associated with weight gain, we compared the serial changes in blood pressure, body weight, sodium balance, plasma volume, and three hormones known to affect sodium balance (norepinephrine, insulin, and aldosterone) in seven dogs fed a high fat diet for 6 weeks and seven dogs fed a control diet. The sodium content of both diets was equal. During a 2-week control period, no differences were noted between the two groups. Weight gain was associated with a progressive increase in blood pressure (mean pressure increased by 18.5±2.1 mm Hg in the high fat group) and plasma volume (plasma volume increased from 1,426±202 to 2,053±250 ml in the high fat group). Sodium retention occurred after 1 week of the high fat diet and persisted. Over the 6-week period, the dogs on the high fat diet increased their cumulative sodium balance by 2,024±462 meq versus an increase of only 289±97 meq for the dogs on the control diet. In the high fat diet group of dogs, there was a significant relation between change in cumulative sodium balance and the change in blood pressure and plasma volume. After 1 week of the high fat diet, norepinephrine was the only hormone that significantly increased from baseline. Over the next 5 weeks norepinephrine increased no further, whereas fasting insulin and aldosterone progressively increased. Over the entire study period, fasting insulin was the hormone that best correlated with the change in blood pressure observed in the high fat diet dogs. Thus, the change in blood pressure associated with weight gain in the dog is directly related to sodium retention. The observed change in sodium balance also appears to relate initially to a change in plasma norepinephrine concentration and later to a change in fasting insulin and aldosterone concentrations. (Hypertension 1989;13:922–928)

Although it is well accepted that body weight and arterial pressure are related, the mechanism of this association is poorly understood. One of the physiological changes that may contribute to obesity hypertension is sodium retention with a concomitant increase in blood volume and cardiac output. Although an increased cardiac output and blood volume have been previously reported in obese individuals, the differences between lean and fat individuals disappear when they are indexed for either surface area or weight.1–4 Normalization for size, however, may not be appropriate in the obese subject. Lesser and Deutsch5 and Messerli and coworkers2 have suggested that the increment in adipose tissue blood flow and volume is disproportionately small for the amount of adipose tissue mass. Therefore, blood flow and blood volume in nonadipose tissue may be increased in the obese individual. To date, there have been no detailed studies of fluid and electrolyte balance during weight gain. We recently reported the development of a dog model of weight gain-induced hypertension.6 In our preliminary studies we demonstrated that weight gain in the dog model was associated with an increase in blood pressure, cardiac output, and plasma volume. However, in that study we did not serially follow the changes in cardiac output and plasma volume that occurred with weight gain, and we did not do detailed measurements of fluid and electrolyte balance. The purpose of the present report is therefore to evaluate the serial changes in the following variables: fluid and electrolyte balance, blood pressure, cardiac output, plasma volume, and three hormones known to affect sodium balance (norepinephrine, aldosterone, and insulin) that are associated with weight gain in the dog.

Materials and Methods

Fourteen adult mongrel dogs (six male and eight female) were trained to lie quietly on a padded...
table. All dogs were then surgically instrumented with an ascending aortic catheter and right and left atrial catheters. After surgery, the dogs were allowed to recover for 3 weeks before baseline measurements were made. All dogs were then fed a control diet of one can of dog food (Ken-L-Ration) and an additional 45 meq of sodium chloride per day for 8 weeks. The high fat diet group (n=7) received the control diet for 2 weeks followed by 6 weeks of a high fat diet consisting of 2 pounds of cooked beef fat or lard in addition to their regular diet of one can of dog food. All dogs were housed in metabolic cages during the entire study and were fed between the hours of 1:00 PM and 3:00 PM each day. Blood pressure, heart rate, body weight, and fluid and electrolyte balance were measured daily. Cardiac output, plasma volume, serum electrolyte, glucose, insulin, aldosterone, and norepinephrine were measured twice a week during the entire study. All measurements were made between 8:00 AM and 11:00 AM before the daily feeding (the dogs had not been fed since 5:00 PM the previous day). Fecal electrolyte excretion was measured on six of the dogs (three dogs on the control diet and three dogs on the high fat diet). Since the fecal excretion of sodium and potassium were found to be similar in the two groups of dogs and insignificant when compared with the urinary excretion of these electrolytes, fecal electrolyte excretion was not used in the calculation of sodium or potassium balance. Sodium values for the high fat diet group were 1.06±0.37 meq K/wk during the control period and 1.95±0.81 meq K/wk during the 6 weeks of the high fat diet. Sodium values for the control group were 1.09±0.43 meq Na/wk during the control period and 1.16±0.28 meq Na/wk during the remaining 6 weeks, and potassium values were 1.13±0.35 meq K/wk during the control period and 1.88±0.59 meq K/wk during the remaining 6 weeks. All the procedures in this study were in accordance with the University of Michigan guidelines on animal experimentation.

**Laboratory Measurements**

Arterial pressure was measured with P23Db Statham pressure transducers (Statham, Oxnard, California) and recorded on an AR6 optical recorder (PPG Biomedical Systems, Hershey, Pennsylvania). Cardiac output was measured with cadiogreen dye and a green-dye cardiac-output computer (Waters Instruments, Rochester, Minnesota). Plasma volume was measured with Evans blue dye,7 plasma glucose was measured by the glucose oxidase method, plasma insulin and aldosterone were measured by radioimmunoassay,8 plasma and urinary electrolytes were measured by flame photometry, and plasma norepinephrine was measured by high-pressure liquid chromatography with electrochemical detection.9

**Statistical Analysis**

All values are mean±SEM. Weekly blood pressure, heart rate, body weight, and fluid and electrolyte balance were determined by averaging the daily values for each week. Weekly cardiac output, plasma volume, insulin, aldosterone, and norepinephrine were determined by averaging the two values obtained each week. The change in cumulative sodium balance was determined by the following: \( \Sigma(\text{dietary sodium intake for week}_i\text{− urinary sodium excretion for week}_i)\) where \( \text{dietary sodium intake for control week} \)−\( \text{urinary sodium excretion for the control week} \) where \( i \) ranges from 1 to 8 for the 8 weeks of the study. Within each group, a repeated-measures analysis of variance was performed for each variable to determine whether a significant change in the variable occurred as a result of the diet the dog received. A two-factor analysis of variance for repeated measures was then performed for each variable to assess differences between the dogs fed the high fat diet and dogs fed the control diet. The interrelations among variables were assessed with product-moment correlations, partial correlations, and regression methods.

**Results**

During the 2-week control period, no significant differences were noted between the two groups for any of the measured variables. The seven dogs on the high fat diet significantly increased their body weight from 20.9±1.9 to 23.4±1.6 kg (\( p<0.001 \)) over the 6-week period of the high fat diet. Whereas, the seven dogs who were fed the control diet for 6 weeks experienced no change in body weight (19.3±1.4 to 19.5±1.1 kg) (Figure 1). In the high fat diet group, the gain in weight was associated with a significant increase in arterial pressure (\( p<0.001 \)). Systolic, diastolic, and mean arterial pressure increased by 21±2, 15±3, and 18.5±2.1 mm Hg, respectively, in the high fat group, as compared with a small decrease in arterial pressure of \(-11.3±3,\) \(-8±3,\) and \(-10.2±2.2\) mm Hg, respectively, in the control group.

A stepwise multiple regression model (with an \( \alpha \)-to-enter of 0.150 and \( \alpha \)-to-remove of 0.150) was used to select the only variable that predicted the change in mean arterial pressure that occurred in the group of dogs fed the high fat diet for 6 weeks. This variable was the change in cumulative sodium balance (Table 1). As is also depicted in Figure 1, the high fat diet group of dogs retained significantly more sodium than the control group (the 6-week cumulative change in sodium balance for the high fat group was 2,024±462 meq vs. an increase of only 289±97 meq in the control group, \( p<0.001 \)). We also observed a significant increase in potassium balance in the seven dogs that received the high fat diet (the 6-week cumulative increase in potassium balance was 498±205 meq, \( p<0.01 \)).
Serum sodium and potassium were not significantly altered in either group of dogs.

The dogs in the high fat diet group also experienced a progressive increase in plasma volume and cardiac output \((p<0.001, \text{ Figure 2})\) and a decrease in systemic vascular resistance \((p<0.01)\). Specifically, cardiac output increased by \(2.9\pm0.22 \text{ l/min}\) during the control period to \(4.2\pm0.1 \text{ l/min}\) after 6 weeks of the high fat diet; plasma volume increased from \(1,426\pm202 \text{ ml}\) during the control period to \(2,053\pm250 \text{ ml}\) after 6 weeks of the high fat diet; and systemic vascular resistance decreased from \(34.8\pm2.4 \text{ mm Hg/l/min}\) during the control period to \(28.1\pm1.8 \text{ mm Hg/l/min}\) after 6 weeks of the high fat diet. When compared with the dogs fed the control diet for 6 weeks, the dogs fed the high fat diet experienced a significant increase in plasma volume \((p<0.01)\) and cardiac output \((p<0.01)\) and a significant decrease in systemic vascular resistance \((p<0.02)\). We also observed that there was a significant correlation between the change in both cardiac output \((r=0.43, p<0.05)\) and plasma volume \((r=0.64, p<0.01)\) and the change in cumulative sodium balance. The high fat diet group of dogs also developed a significant increase in heart rate during the 6-week diet \((104\pm3 \text{ beats/min control period and } 126\pm2 \text{ beats/min after 6 weeks of the high fat diet})\), whereas a small decrease in heart rate was observed in the control group of dogs \((106\pm6 \text{ beats/min control period and } 99\pm6 \text{ beats/min after 6 weeks of the control diet})\).

In an attempt to determine the cause of the sodium retention associated with weight gain, three hormones known to affect sodium balance (insulin, aldosterone, and norepinephrine) were serially followed in the two groups of dogs. No significant changes in plasma insulin, aldosterone, or norepinephrine were observed in the seven dogs that received the control diet for 6 weeks. In contrast, 6 weeks of the high fat diet resulted in a significant increase in plasma insulin \((p<0.001)\), norepinephrine \((p<0.05)\), and aldosterone \((p<0.03)\) (Figure 3).

As is illustrated in Figure 3, plasma norepinephrine increased rapidly during the first week of the high fat diet, and both plasma insulin and aldosterone progressively increased over the entire 6 weeks of the high fat diet. A stepwise multiple regression model (with an \(a\)-to-enter of 0.150 and \(a\)-to-remove of 0.150) was used to determine the variables that best predicted the change in cumulative sodium balance that occurred during the 6 weeks of the high fat diet. During the first week of the high fat diet, the change in plasma norepinephrine was the only variable selected; for weeks 3–4, the change in insulin was the only variable selected, and for weeks 5–6, both the changes in insulin and aldosterone were selected (Table 2). Plasma renin activity did not change in either group during the entire study (for the high fat diet group, \(0.99\pm0.18 \text{ ng/ml/hr during the control period and } 0.81\pm0.1 \text{ ng/ml/hr after 6 weeks of the high fat diet})\); for the control group, \(0.89\pm0.17 \text{ ng/ml/hr during the control period and } 0.7\pm0.07 \text{ ng/ml/hr after 6 weeks of the control diet})\).

**Discussion**

Since the original report by Dahl and coworkers\(^1\) in 1958, controversy has existed as to the importance of sodium in the pathogenesis of obesity hypertension.\(^1\)-\(^4\) In 1987, we reported, the development of a dog model of weight gain–induced hypertension.\(^6\) In that preliminary report, we documented that weight gain induced by feeding dogs a high fat diet was associated with an increase in blood pressure, cardiac output, and plasma volume. In the present study, we confirmed and expanded our original observations; we documented that weight gain–induced hypertension in the dog was associated not only with chronic sodium retention but also that the sodium retention was directly correlated with the associated change in mean arterial pressure. It is, however, important to note that
although we demonstrated an association between sodium retention and weight gain–induced hypertension, we have not yet proven that the sodium retention was the sole cause of the hypertension. Further studies are planned to directly evaluate the importance of sodium in the pathogenesis of weight gain–induced hypertension.

In addition to showing that weight gain is associated with sodium retention, we also demonstrated that the change in cumulative sodium balance directly correlated with the increase in cardiac output and plasma volume that also occurred (Figure 2). Our results are consistent with the reports of Reisin and coworkers, Andersson and coworkers, and Raison and coworkers. These reports have shown that weight reduction in obese hypertensive human subjects is associated with a reduction in blood pressure, heart rate, and cardiac output. Our observation of an increased plasma volume with weight gain in the dog is in conflict with the findings of Andersson et al. These investigators reported that blood volume was unchanged or even increased during weight loss in obese hypertensive men. We believe that the discrepancy between our study and the study of Andersson et al may be due to the fact that their obese human subjects had both long-standing obesity and hypertension and were in a catabolic rather than anabolic state. Since Ulrych has demonstrated that plasma volume in adults with chronic essential hypertension is negatively correlated with mean arterial pressure, it is possible that if we studied our dogs over a longer period of time, we might have seen plasma volume return to control values.

In an attempt to determine the cause of the sodium retention associated with weight gain, three hormones known to affect sodium balance (insulin, aldosterone, and norepinephrine) were serially followed during the development of weight gain. We observed that weight gain induced by a high fat diet was associated with a rapid and sustained increase in plasma norepinephrine concentration and a more gradual but progressive increase in plasma insulin and aldosterone. By using a stepwise linear regression model, we determined that the changes in each of these hormones were important for prediction of the resultant change in sodium balance. During the first week of the high fat diet, the change in sodium balance appeared to best relate to the change in plasma norepinephrine; whereas, during the latter weeks of the high fat diet, the change in plasma insulin and aldosterone appeared to better predict the observed changes in sodium balance. Our finding that weight gain in the dog was associated with an increase in plasma insulin, norepinephrine, and aldosterone is consistent with other reports in human obesity.

Hyperinsulinemia, insulin resistance, and even glucose intolerance are frequently observed in human obesity. Numerous studies, including those presented in this report, suggest that a strong relation exists between hyperinsulinemia, sodium retention, and hypertension. There are at least three potential mechanisms whereby hyperinsulinemia could result in chronic sodium retention. First, it has been known for many years that insulin can directly enhance sodium reabsorption in the proximal or distal tubules of the kidney. In addition, we have recently demonstrated that in obese adoles-

### Table 1. Multiple Regression Analysis of the Change in Blood Pressure Associated With Weight Gain in Dog

<table>
<thead>
<tr>
<th>Week</th>
<th>Coefficient</th>
<th>p value</th>
<th>r value</th>
<th>p value</th>
<th>SEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cum Na</td>
<td>0.02</td>
<td>0.028</td>
<td>0.808</td>
<td>&lt;0.028</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>4.28</td>
<td>0.027</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Cum Na</td>
<td>0.016</td>
<td>0.048</td>
<td>0.665</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>5.28</td>
<td>0.045</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Cum Na</td>
<td>0.008</td>
<td>0.033</td>
<td>0.926</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>5.28</td>
<td>0.035</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Cum Na</td>
<td>0.007</td>
<td>0.032</td>
<td>0.864</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>8.75</td>
<td>0.046</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Cum Na</td>
<td>0.004</td>
<td>0.025</td>
<td>0.684</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>9.43</td>
<td>0.045</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Cum Na</td>
<td>0.001</td>
<td>0.002</td>
<td>0.893</td>
<td>&lt;0.007</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>8.13</td>
<td>0.042</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SEE, standard error of the estimate; Cum Na, cumulative sodium balance.
FIGURE 2. Plots of changes from control week values in cumulative sodium balance (ΔNaB), plasma volume, and cardiac output that were experienced by dogs that received either 6 weeks of high fat diet or 6 weeks of control diet. Only dogs on high fat diet experienced significant increase in plasma volume (p<0.01) and cardiac output (p<0.001).

FIGURE 3. Plots of changes from control week values in fasting plasma insulin (ΔINS), aldosterone (ΔALDO), and norepinephrine (ΔNOREPI) that occurred in dogs that received either 6 weeks of high fat diet or 6 weeks of control diet. Only dogs on high fat diet experienced significant increase in insulin (p<0.001), aldosterone (p<0.03), and norepinephrine p<0.05).

Schwartz et al29 have demonstrated in the rat that fat, in the form of lard, added to the normal rat chow diet increases sympathetic nervous system activity. Although the mechanism whereby a high fat diet results in stimulation of sympathetic nervous system activity is not well understood, Schwartz and coworkers29 have speculated that it may be mediated by hyperinsulinemia or by an increase in cholecystokinin.

Tuck and coworkers12 have demonstrated that with weight loss both plasma renin activity and plasma aldosterone concentration decrease. Scavo et al30,31 reported that although obese adults have normal plasma renin activity, they have an increased plasma aldosterone concentration and an increased aldosterone secretion rate. In obese adolescents32 and now in the dog, we also have demonstrated that, despite the presence of a normal plasma renin activity, plasma aldosterone is increased in overweight subjects. Since we observed that weight gain in the dog was associated with an elevation in heart rate and plasma norepinephrine are also consistent with this conclusion. In addition,
aldosterone despite no change in either plasma renin activity or plasma potassium concentration, we speculate that adrenal sensitivity to angiotensin II may be increased by weight gain. Although we do not know the cellular basis for the possible increased adrenal sensitivity to angiotensin II associated with weight gain, there are data based on the work of Vierhapper and coworkers that suggest that hyperinsulinemia may, in part, mediate this phenomenon.

In summary, we demonstrated that weight gain induced by feeding dogs a high fat diet results in hypertension that correlates with increased sodium retention and a concomitant increase in cardiac output and plasma volume. In addition, we have demonstrated that the sodium retention may be due to the combined effects of hyperinsulinemia, hyperaldosteronism, and increased sympathetic nervous system activity. More work, however, is necessary to explain the potential interrelations between these three hormones and the sodium retention associated with weight gain.

References

TABLE 2. Multiple Regression Analysis of Change in Cumulative Sodium Balance Associated With Weight Gain in Dog

<table>
<thead>
<tr>
<th>Week</th>
<th>Coefficient</th>
<th>p value</th>
<th>r value</th>
<th>p value</th>
<th>SEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Norepinephrine</td>
<td>1.707</td>
<td>0.012</td>
<td>0.864</td>
<td>&lt;0.012</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>-12.2</td>
<td>0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>Norepinephrine</td>
<td>1.752</td>
<td>0.042</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
<td>114.3</td>
<td>0.031</td>
<td>0.782</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>679</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>Insulin</td>
<td>267.0</td>
<td>0.028</td>
<td>0.797</td>
<td>&lt;0.008</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>114.1</td>
<td>0.097</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>Insulin</td>
<td>121.7</td>
<td>0.04</td>
<td>0.702</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>94.7</td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 5</td>
<td>Insulin</td>
<td>152.9</td>
<td>0.01</td>
<td>0.776</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td></td>
<td>Aldosterone</td>
<td>9.42</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>-432</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 6</td>
<td>Insulin</td>
<td>142.1</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aldosterone</td>
<td>11.2</td>
<td>0.105</td>
<td>0.964</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>-703</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values indicate variables that best predicted the change in cumulative sodium balance that occurred during 6 weeks of high fat diet. SEE, standard error of the estimate; Insulin, fasting insulin; Aldosterone, plasma aldosterone concentration.

KEY WORDS: sodium loading • insulin • norepinephrine • aldosterone
Pathogenesis of weight-related changes in blood pressure in dogs.
A P Rocchini, C P Moorehead, S DeRemer and D Bondie

Hypertension. 1989;13:922-928
doi: 10.1161/01.HYP.13.6.922

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/13/6_Pt_2/922