Effect of Changes in Salt Intake on Arterial Pressure and Renal Function in Partially Nephrectomized Dogs

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Bilateral nephrectomy or severe damage to both kidneys is often, but not always, followed by hypertension. Orbison and associates showed that increased salt intake enhances the hypertensive effect of total nephrectomy in the dog, and Koletsky showed the same enhancing effect in partially nephrectomized rats. A markedly excessive dietary intake of salt will produce hypertension even in the normal rat and chicken. These results, as well as correlations between salt intake and hypertension in man, suggest that salt can play a significant role in hypertension and that hypertension brought about by damage to the kidneys may be associated with decreased ability of the kidneys to remove salt.

In the present paper it will be shown that salt intake is a critical factor in the development of hypertension following subtotal nephrectomy in dogs. The results provide a background for further investigation of mechanisms linking salt metabolism with renoprival hypertension.

Methods

Thirteen medium sized, female, mongrel dogs were chosen for this study. The trigone of the bladder was exteriorized in each animal; this made it possible to collect urine samples directly from the ureters. The dogs survived this procedure well and were in good condition five to six months later when the experiments were terminated.

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Each animal was then trained to lie on the table unrestrained while measurements were made by direct femoral artery puncture. As each dog became accustomed to the procedure, the recorded pressures became consistent and were considered to be good indications of normal arterial pressure.

The mean arterial pressure was recorded in each dog approximately three times each week during the 100-day period of study.

Eleven dogs were subtotal nephrectomized. The left renal artery was clamped, and approximately 20% of the kidney removed from each pole. The renal artery clamp was removed, and large bleeders were cauterized. Approximately three weeks after the partial left nephrectomy, the entire right kidney was removed through an incision in the flank. Two normal dogs served as controls.

The right kidney and that part of the left kidney removed during the first nephrectomy were examined histologically. The remnant of left kidney was removed from the partially nephrectomized dogs at the termination of the experiment and was also examined histologically to estimate the amount of scar tissue where the renal poles had been removed.

The following determinations were made each time the arterial pressure was measured, approximately three times each week: body weight, rate of urine formation, sodium concentration in urine and plasma, clearance of endogenous creatinine, and blood urea nitrogen (B.U.N.). Sodium concentrations were estimated by flame photometry and expressed as mEq per liter of plasma; no corrections were made for variations in plasma water. PAH clearance was measured twice in each animal before it was sacrificed in order to determine the minimum blood flow through the remaining renal tissue.

Two of the partially nephrectomized dogs drank tap water, and two drank 0.9% sodium chloride solution throughout the study. Seven drank tap water for two weeks, 0.9% saline for two weeks, tap water again for two weeks, and finally saline again for an additional two weeks. The two control animals drank 0.9% saline for the entire study.
**Results**

**Effect of Salt Loading on Mean Arterial Pressure in Partially Nephrectomized Dogs**

Alternation of High and Low Salt Intake.

Figure 1 represents average results from seven dogs which began drinking 0.9% NaCl in place of water three weeks after the second operation. These animals had had approximately 70% of their renal tissue removed.

Control mean arterial pressure for each dog was calculated as the mean of all pressures measured during 86 days before the dog was placed on 0.9% saline. The average control pressure for all seven dogs was 116 mm Hg. Immediately after each nephrectomy the pressure usually increased a few millimeters of mercury as can be seen in figure 1, and it always became less stable. After isotonic saline was substituted for tap water, the mean arterial pressure increased 30% to 40% within 48 to 72 hours; this elevated pressure was maintained until the dogs were allowed to drink tap water again two weeks later. The average mean arterial pressure for the entire two-week period was 152 mm Hg, or 31% above the control level.

When the dogs were given tap water, arterial pressure decreased in every instance to control levels and remained there until the dogs were required to drink 0.9% saline again on the 86th day of the study. On the 86th day, 24 hours after replacing the tap water with saline, the arterial pressures had again increased 30%; two weeks later, just prior to terminating the experiment, the pressure was 48% above the control level. Average mean arterial pressure during the period was 158 mm Hg.

Table 1 gives the results of several different renal function studies performed during the course of these seven experiments. For purposes of comparison, the results are tabulated for four different stages as indicated below the table. Figure 2 illustrates typical renal function studies in a single dog during the 100-day period of the study. The results in this figure are representative of those for the other six animals.

Table 1 shows that the G.F.R. was reduced from an average initial value of 50 ml/min to 17 ml/min as a result of the nephrectomies, and figure 2 shows the typical time course of this change. After the final nephrectomy, the G.F.R. was reduced to 34% of its control value. A significant increase in G.F.R. occurred when 0.9% NaCl was substituted for tap water (Stage 4). There was an even greater transient increase in G.F.R. immediately after each of the dogs began drinking the 0.9% saline, as shown in figure 2. This transient effect was also seen in the control animals.

Table 1 and figure 2 also show that B.U.N. was more than doubled after the nephrectomies. It is interesting that the elevated B.U.N. was reduced almost to normal when the dogs were required to drink isotonic saline.

The plasma sodium concentration decreased from a mean of 147 ± 2.0 mM per liter before the nephrectomies (Stage 1 of the table) to 136 ± 1.5 mM per liter after the nephrectomies (Stage 3). When the dogs were required to drink 0.9% saline, the plasma sodium concentrations increased from a mean of 136 mM per liter in Stage 3 to 142 mM per liter in Stage 4. Even though the plasma sodium changes were small percentagewise, they were obviously present, without exception, in each
Renal Function

<table>
<thead>
<tr>
<th>Stage</th>
<th>Glomerular filtration rate (ml/min)</th>
<th>Blood urea nitrogen (mg/100 ml)</th>
<th>Urine flow (ml/min)</th>
<th>Plasma sodium (mM/liter)</th>
<th>Urine sodium (mM/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(11) 49.7 ± 5.5</td>
<td>(11) 18.7 ± 1.3</td>
<td>(10) 0.37 ± 0.02</td>
<td>(13) 147 ± 2.0</td>
<td>(11) 91 ± 9.5</td>
</tr>
<tr>
<td>2</td>
<td>(10) 51.9 ± 3.2</td>
<td>(10) 18.3 ± 1.1</td>
<td>(10) 0.28 ± 0.01</td>
<td>(10) 138 ± 3.6</td>
<td>(8) 80 ± 7.9</td>
</tr>
<tr>
<td>3a</td>
<td>(27) 17.1 ± 1.1</td>
<td>(10) 58.1 ± 2.1</td>
<td>(26) 136 ± 1.1</td>
<td>(34) 142 ± 1.3</td>
<td>(28) 69 ± 7.7</td>
</tr>
<tr>
<td>3b</td>
<td>(91) 22.8 ± 1.4</td>
<td>(30) 27.0 ± 1.0</td>
<td>(36) 27.0 ± 1.0</td>
<td>(34) 233 ± 8.0</td>
<td>(34) 233 ± 8.0</td>
</tr>
</tbody>
</table>

Mean values are shown ± the standard error of the means.

Numbers in parentheses indicate the number of observations.

*All values for stage 4 differed significantly from those of stage 3 with P values less than 0.001.

The decrease in plasma sodium after the nephrectomies was associated with a slight rise in mean arterial pressure, averaging 6 mm Hg, while the increase in the partially nephrectomized dogs drinking 0.9% saline was associated with a rise in mean arterial pressure to hypertensive levels.

Table 1 also shows that the urine sodium concentration decreased after the nephrectomies; at the same time, urine volume increased, and plasma sodium decreased. When partially nephrectomized dogs were required to drink 0.9% saline, the concentration of urine sodium increased greatly.

PAH clearances were measured in the partially nephrectomized dogs whose arterial pressures had been elevated by increased salt intake, and these were compared with the clearance of a dog with body kidneys normal and intact but drinking salt solution. Assuming the extraction ratio of PAH to be 0.6 and to have remained constant through the different stages of the experiments, the partially nephrectomized, hypertensive dogs had an average renal blood flow of 3.7 ± 0.2 ml/min per g, compared with 3.9 ml/min per g in the normotensive dog. In addition, the mean renal blood flow in the two partially nephrectomized dogs that were allowed to drink tap water during the entire study and, therefore, did not become hypertensive was 3.7 ml/min per g, which was the same as that in the hypertensive animals. These studies indicate that the kidney remnants in the hypertensive dogs received as adequate a blood supply per unit weight as the kidneys in the normotensive dogs.

The body weights of the partially nephrectomized dogs decreased slightly when they were required to drink isotonie saline as shown in figure 2; this was associated with an obvious decrease in food intake. In only one dog was there any indication of renal pathology at the beginning of the experiment. This dog was found to have chronic pyelonephritis that had resulted in dense scarring and hyalinization which involved a considerable amount of renal tissue. The results obtained from this dog differed from those of the other salt-loaded partially nephrectomized dogs in that the average increase of mean arterial pressure was 12% higher. The left kidney remnants were normal in all cases except in the animal which had chronic pyelonephritis.

Effect When Partially Nephrectomized Dogs Were Given Only Saline to Drink for 48 Days. The dashed curves in figure 3 show
SALT LOADING IN PARTIALLY NEPHRECTOMIZED DOGS

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FIGURE 2

Effect of salt loading on renal function and body weight in a representative partially nephrectomized animal.

Results from two partially nephrectomized dogs (second operation on the 49th day) that drank 0.9% saline beginning 12 days after the second nephrectomy and continuing for 48 days. The mean pressures during the 48-day period of high salt intake were 153 and 144 mm Hg respectively, averaging 38% above the control values. The increased pressure levels were maintained as long as the dogs were exposed to the high salt intake. One of these two dogs drank the salt solution without hesitation, while the other drank very little until the 10th day at which time he increased his intake considerably. This difference was reflected in the pressure responses, the pressure increasing significantly in 24 hours in the first dog while failing to show a substantial increase until the 10th day in the other. The kidney remnants from these two dogs were histologically normal.

CONTROL STUDIES

Effect of Partial Nephrectomy on Mean Arterial Pressure. Two dogs were partially nephrectomized but were allowed to drink tap water throughout the study. The results are shown by the solid lines in figure 3. The partial left nephrectomies were performed on the 40th day, and the right nephrectomies were done on the 58th day of the study. The arterial pressures became quite variable, ranging from 9% to 117% of the

control, suggesting a slight loss in stability of the arterial pressure control system. The means of all pressures measured after the nephrectomies were 9% above the control. This slight rise in pressure contrasts with the large rise in pressure caused by salt loading as discussed above.

Effect of Salt Loading on Mean Arterial Pressure; Both Kidneys Intact. The solid curve in figure 4 represents results obtained from a dog with normal kidneys. After the control pressure was established (21 days), the animal was given isotonic saline to drink for 79 days. At no time did this dog's pressure exceed 110% of its control value. Urine sodium concentration increased to 486 mM per liter as compared to a mean of 333 mM per liter in partially nephrectomized, hypertensive dogs under the same conditions. The increase in urine flow was only half as great as the increase in partially nephrectomized dogs.

A second dog chosen for control studies developed hypertension two weeks after exposure to the saline regimen (fig. 4). This animal died on the 65th day; autopsy revealed severe chronic pyelonephritis affecting large areas of both kidneys. The glomerular filtrati-
FIGURE 4

Effect of high salt intake on mean arterial pressure in dogs with both kidneys intact. Solid curve represents dog with normal kidneys. Dashed curve represents dog with severe chronic pyelonephritis.

tion rate in this animal before the salt regimen averaged 31.1 ml/min which was 38% less than the average control filtration rate for the other dogs of this study. It appears from this fortuitous study of salt loading in an intact dog with pyelonephritis that increased salt intake of the magnitude used in this study will cause hypertension equally well whether renal function is reduced by pyelonephritis or by surgery.

Discussion

These experiments have shown that dogs with about 70% of their renal tissue removed develop hypertension within a few days when their intake of sodium chloride is increased sufficiently. The hypertension disappears when the increased intake of salt is stopped. None of the hypertensive animals developed renal lesions even after they had been kept in a hypertensive state for more than 40 days. Histological study of the two ends of the kidney remnants in the hypertensive dogs showed that scar tissue did not invade the normal renal tissue by more than a millimeter or so, making it doubtful that a significant portion of the renal tissue had become ischemic as a result of the operative procedure. PAH clearances showed that the minimum renal blood flow per unit mass of renal tissue was at least as great in the hypertensive animals as in normals. For these reasons, we feel that the hypertension was not caused by renal secretion of a hypertensive agent in response to ischemia. Yet, the experiments do not completely rule out such a possibility, for the effect of a hypertensive agent could have remained masked until the animals were salt loaded. Likewise, the experiments do not eliminate the possibility that partial nephrectomy decreased the secretion of an antihypertensive agent, the effect of which might also have remained masked until the animals were salt loaded.

The plasma sodium increased significantly in the partially nephrectomized dogs when they were required to drink 0.9% saline. In contrast to these findings, other investigators have failed to show a change in plasma sodium when hypertension was caused in rats by the salt loading technique. The reason for these conflicting results is unknown.

Even though the plasma sodium concentration rose during salt loading of the partially nephrectomized dogs, it still did not rise to the preoperative control levels, as shown in table 1; yet, the arterial pressures rose 30% to 40% above the control values. Also, the 11 mM per liter fall in plasma sodium after partial nephrectomy was not accompanied by a decrease in arterial pressure but instead by a slightly increased pressure, as shown in figure 1. Thus, in both of these instances, there was no directional correlation between plasma sodium concentration and arterial pressure, indicating that increased plasma sodium concentration per se might not have been the cause of the hypertension in these experiments. Therefore, future studies should at least consider other possible causative factors such as changes in fluid volumes or changes in hormonal factors that might accompany salt loading.

Summary

Approximately 70% of the total renal tissue was removed in 11 dogs. Control values were then established for mean arterial pressure, urine and plasma sodium concentrations, blood urea nitrogen, glomerular filtration rate, total body weight, and rate of urine formation for these dogs and for two dogs whose kidneys were left intact. Two of the partially

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nephrectomized dogs were allowed to drink water for the duration of the study while the other animals were required to drink 0.9% sodium chloride solution for various periods of time. The increased salt intake resulted in a 30% to 40% increase in arterial pressure within 48 to 72 hours; plasma sodium concentration increased concomitantly with the development of hypertension. The elevated pressure could be reduced to normal levels within 24 hours by simply allowing the dogs to drink tap water again. Similar results were obtained in a single dog in which renal function had fortuitous been reduced by chronic pyelonephritis.

Acknowledgment

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References

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