Studies of the Effects of Essential Fatty Acid Deficiency in the Rat

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SUMMARY. We report a model of prostaglandin depletion induced in rats by fasting for 11 days, followed by institution of an essential fatty acid-deficient diet. Urinary prostaglandin E, 2 weeks after this diet had been implemented, was 22 ± 2 ng/24 hours compared to 113 ± 8.5 ng/24 hours in controls (P < 0.01). There was no difference in 24-hour urine volume or solute excretion in controls and essential fatty acid-deficient rats. Five hours after administration of NaCl, 10 mM/kg, essential fatty acid-deficient diet rats excreted 1.85 ± 0.78 ml urine compared to 6.2 ± 1.5 ml in control (P < 0.01) with Na⁺ excretion 447 ± 273 μEq in essential fatty acid-deficient rats vs 1483 ± 366 μEq in control (P < 0.01). Intravenous isotonic NaCl, 1.5% body weight, resulted in increased urine flow rate in control rats from 8.3 ± 2 μl/min to 28.7 ± 8.8 μl/min, with sodium excretion increasing from 0.19 ± 0.2 to 3.3 ± 0.9 μEq/min. In the essential fatty acid-deficient diet animals, there was no significant change in flow rate, 6.07 ± 2.43 to 9.85 ± 4.29 μl/min, or sodium excretion, 0.09 ± 0.03 to 0.40 ± 0.24 μEq/min, after saline infusion. There was no difference in the glomerular filtration rate or plasma aldosterone in the two groups after the salt load. When given a water load, 3 ml/100 g body weight, essential fatty acid-deficient diet rats excreted 2.5 ± 0.7 ml in 5 hours compared to 6.3 ± 1.4 ml in controls (P < 0.01). The defect in water excretion was not due to increased sensitivity to antidiuretic hormone, since similar sensitivity to this hormone was demonstrated in the essential fatty acid-deficient diet and control rats during a water diuresis. When isotonic saline was substituted for drinking water, there was an increase in systolic blood pressure in essential fatty acid-deficient diet rats from 124 ± 2 to 142 ± 3 mm Hg over 9 days (P < 0.01) compared to 122 ± 2 mm Hg after saline drinking in controls. The administration of linoleic acid for 4 days increased urinary prostaglandin E excretion to 114 ± 15 ng/24 hours from 23 ± 4 (P < 0.01), and the alterations in the ability to excrete a sodium and water load were reversed. In essential fatty acid-deficient diet animals made hypertensive by 9 days of saline drinking, the institution of linoleic acid to the diet normalized the blood pressure despite the continued administration of saline. These studies demonstrate that essential fatty acid-deficient diet animals develop salt-sensitive hypertension with a combined defect in both sodium and water excretion which is reversed following correction of the essential fatty acid deficiency. (Circ Res 51: 694–702, 1982)

RENAL prostaglandin synthesis has been postulated to have important effects on sodium and water excretion. This is supported by evidence that a natriuresis occurs with intrarenal infusions of either prostaglandin E₁, E₂, A₁ (Herzog, 1967; Johnston, 1967; Gross, 1973), or the essential fatty acid precursor of prostaglandin synthesis, arachidonic acid (Weber, 1975). In addition, it has been demonstrated that salt retention occurs in rats treated with nonsteroidal anti-inflammatory drugs (Feldman, 1978; Kadokawa, 1979) and occasionally occurs in patients treated with prostaglandin inhibitors (Lee, 1976). These observations, coupled with the fact that prostaglandins are synthesized in collecting ducts (Janszen, 1971) and medullary interstitial cells (Muirhead, 1973; Lee, 1978) makes a direct effect of prostaglandins on the fine control of sodium transport in the distal segment of the nephron an attractive hypothesis.

In addition to an effect on sodium absorption, Grantham and Orloff (1968) demonstrated that PGE₁ inhibits the response of the isolated collecting duct to vasopressin which could influence water excretion by the nephron. Efforts to determine the role of endogenous prostaglandin synthesis on salt and water metabolism has depended upon the use of agents that inhibit their synthesis by cyclooxygenase, e.g., indomethacin and salicylates (Ferreira, 1971), or antagonize their peripheral action, e.g., phosphorylated polymers of phloretin (Eakins, 1971). These inhibitors have been found to have no hydroosmotic effects themselves (Parisii, 1972; Wong, 1972; Albert, 1974) but to enhance the effect of vasopressin in most (Flores, 1972; Ozer, 1972; Parisii, 1972; Albert, 1974) but not all (Wong, 1972) in vitro studies. However, the possibility exists that these inhibitors may act to enhance the hydroosmotic effect of the collecting duct to vasopressin independent of prostaglandin inhibition. They could enhance the hydroosmotic effect of cyclic AMP (Albert, 1974) without invoking the prostaglandin system. In addition, in studies of water movement in the toad bladder, the action of cyclooxygenase inhibitors in the presence of endogenous prostaglandins suggests that at least some of their effect on water movement may be due to properties...
other than inhibition of prostaglandin synthesis (Albert, 1974).

Prostaglandin synthesis has been thought to play a role in control of blood pressure. An interrelationship of renin secretion and prostaglandin synthesis in several clinical and experimental circumstances makes an aberration in this control system a possible mechanism for development of hypertension (Rumpf, 1975). Worsening of hypertension and renal function is occasionally induced by administration of agents that inhibit the prostaglandin system in patients with renal disease (Walshe, 1979). However, most studies on the effect of prostaglandin synthesis inhibitors on blood pressure in humans have demonstrated little change.

In experimental animals, the action of prostaglandin inhibitors has been hampered by effects that result in severe toxicity, including bloody diarrhea, anorexia, and occasionally death (Wilhelmi, 1974). Depletion of the fatty acid precursor of prostaglandin synthesis, arachidonic acid, can be induced by the use of an essential fatty acid-deficient diet (EFAD), but these diets must be instituted when rats are weaned and be maintained for approximately 7 weeks before prostaglandin deficiency can be demonstrated (Van Dorp, 1971). The use of these diets in weanling rats also causes growth retardation which may alter the animals response and lead to difficulties in interpretation.

We report in this paper a method of developing essential fatty acid deficiency in mature rats utilizing an 11-day fast followed by institution of an essential fatty acid-deficient diet. Urinary prostaglandin E excretion falls significantly in these animals and changes in renal function and blood pressure control are found which can be reversed by repletion of essential fatty acids to the diet.

Methods

Sprague-Dawley rats weighing approximately 300 g were fasted for 7 days but were allowed free access to water. During the fasting period, mortality rate was approximately 20%. After the 7-day fast, the animals received 10% dextrose instead of drinking water for 4 more days. The average weight loss over the 11-day period was 120 g. At the completion of the fast and dextrose, the rats were placed on an essential fatty acid-deficient diet (Teklad Laboratories, diet #79132). After 2 weeks on this diet, the animals had regained their prefasting weight and were maintained for approximately 7 weeks before prostaglandin deficiency can be demonstrated (Van Dorp, 1971). The use of these diets in weanling rats also causes growth retardation which may alter the animals response and lead to difficulties in interpretation.

We report in this paper a method of developing essential fatty acid deficiency in mature rats utilizing an 11-day fast followed by institution of an essential fatty acid-deficient diet. Urinary prostaglandin E excretion falls significantly in these animals and changes in renal function and blood pressure control are found which can be reversed by repletion of essential fatty acids to the diet.

Hemodynamic Studies

Six control and six deficient rats were used to examine hemodynamic parameters in C and EFAD. Rats were anesthetized with sodium pentobarbital, 50 mg/kg, and catheterization of the left carotid and left femoral arteries was performed for measurement of arterial pressure and blood withdrawal, respectively. Radioactive microspheres (S3 Corp., 15 μm), were injected into the left ventricle followed by timed collections of blood from the femoral artery for measurement of cardiac output, renal and uterine blood flow. Cardiac output and organ blood flow were determined by a modified indicator dilution technique. The following calculations were used:

Cardiac output (ml/min)

\[ \frac{CPM \text{ injected}}{ \text{Total CPM in withdrawn blood} } \times \text{Blood withdrawal rate (ml/min)} \]

Renal blood flow (ml/min)

\[ \frac{CPM \text{ injected}}{ \text{Total CPM in kidney} } \times \text{Blood withdrawal rate (ml/min)} \]

Glomerular filtration rate (GFR) was measured by iothalamate clearance and renal plasma flow was calculated by the following equation:

\[ \text{Renal plasma flow} = \left( 1 - HCT \right) \text{(RBF)} \]

where HCT is the arterial hematocrit and RBF is renal blood flow.

Sodium Excretion Studies

In order to study the effect of prostaglandin depletion on the capacity to excrete a sodium chloride load, six control and six prostaglandin-depleted rats (PDR) were studied after intragastric and intravenous administration of sodium chloride. They were first given 0.3 M sodium chloride, 10 mmol/kg, by gastric tube and placed in metabolic cages for measurement of urinary volume and sodium and potassium excretion over the next 5 hours. Urine volume was collected by spontaneous voiding and suprapubic compression at the end of the 5-hour period. The animals then were placed in individual metabolic cages and allowed free access to food and water for 2 days of stabilization. On the 3rd day, the animals were studied for their response to an intravenous 0.9% saline load. Anesthesia was induced with sodium pentobarbital, 50 mg/kg, followed by a jugular vein catheterization. The animals received 0.6 ml of 5% dextrose in water as an intravenous infusion through the jugular vein catheter for 1 hour. Then a 0.9% saline solution was substituted for the 5% dextrose in water and was infused at 1.5% body weight over the next hour. This was followed by measurement of urine volume collected by bladder catheterization, sodium and potassium excretion, and determination of glomerular filtration rate by iothalamate.

Water Excretion Studies

To study the ability of prostaglandin-deficient rats to excrete a water load, six control and six deficient animals were given 3 ml water/100 g body weight by gavage with urine collected in individual metabolic cages for 5 hours after the gavage. The animals were returned to their individual metabolic cages and allowed free access to food and water for 2 days. To determine whether the defect in water excretion observed in the prostaglandin deficient animals
was due to increased sensitivity to antidiuretic hormone, ADH sensitivity was examined in these animals after an oral water load. Unanesthetized rats were given 10 ml of water by gavage, followed by 5 ml every 15 minutes until urine osmolality was less than 100 mOsm/kg H2O. This required approximately 130 minutes and the total administration of approximately 40 ml/animal. When urine osmolality was constant for three collection periods, 200 µU of aqueous pitressin (Parke-Davis) were given intravenously into the tail vein. Urines were collected by spontaneous voiding and suprapubic compression.

Studies of Potassium Excretion

The ability to excrete potassium was determined by administration of potassium chloride, 5 mEq/kg, in a 0.3 M solution given intraperitoneally after the ligation of the urethra to six control and six EFAD animals. Two hours after the administration of the potassium chloride, bladder urine was measured and blood was drawn by aortic puncture for serum potassium and plasma aldosterone.

Studies of Blood Pressure Control

Isotonic saline was given to six EFAD and six control animals as a substitute for drinking water. There was no demonstrable difference in the amount of saline ingested by the two groups. Systolic blood pressure was then measured daily by tail cuff plethysmography.

Repletion Studies

Linoleic acid (0.5 g) was given by gastric gavage daily to depleted animals for 4-6 days, followed by collection of a 24-hour urine for urinary PGE2. After urinary PGE2 had returned to control values, the above experiments were repeated.

Measurement of plasma aldosterone and urinary PGE2 were by immunoassay utilizing methods previously described (Galvez, 1977). Sodium and potassium were measured by flame photometry. All values are represented as the mean ± se. Statistical analysis of the results were carried out by Student’s t-test (Snedecor, 1967).

Results

Table 1 demonstrates the degree of prostaglandin deficiency in the animals fed the diet deficient in essential fatty acids compared to control animals. (These analyses were kindly performed by Dr. F. Holman at the Hormel Institute, Austin, MN.) In serum, liver, and kidney tissue, the percent of phospholipid that was arachidonic acid was markedly decreased in the deficient animals as compared to control animals, demonstrating a depletion in the precursor of prostaglandin synthesis, arachidonic acid. The degree of arachidonate depletion is similar to that reported in weanling rats maintained on a similar diet for 7 weeks. An analysis of the serum from the depleted animals demonstrated no difference in hematocrit, serum calcium, magnesium, total protein, alkaline phosphatase, total bilirubin, uric acid, SGOT, or serum electrolytes compared to controls. In addition, measurement of urinary prostaglandin E excretion, shown in Figure 1, demonstrates a decrease from 113 ± 8.5 ng/24 hours in control rats to 22 ± 2 ng/24 hours in rats on the deficient diet (P < 0.001).

Repletion Studies

In response to an intraperitoneal sodium chloride load, shown in Figure 2, urine volume excreted in the 5 hour period was significantly less at 1.85 ± 0.3 ml in the deficient animals compared to 6.42 ± 0.8 ml in the control animals. Sodium excretion was significantly less in the deficient animals averaging 447 ± 96 µEq/5 hours compared to 1484 ± 129 µEq/5 hours in the control animals (P < 0.01). The effect of intravenous sodium chloride loading is shown in Figure 3. There was no significant difference in glomerular filtration rate, urine volume, or solute excretion in the two groups of animals.

Sodium Excretion Studies

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| Table 1 Percent Phospholipid That Exists as Arachidonate (20: 4ω6) |
|-----------------|-----------------|---------------|
| Control         | Deficient       | P value       |
| Serum           | 17.8 ± 0.9%     | 9.15 ± 1.0%   | 0.001         |
| Liver           | 17.8 ± 0.9%     | 9.37 ± 1.2%   | 0.001         |
| Kidney          | 24.6 ± 0.5%     | 17.3 ± 1.0%   | 0.001         |

Figure 1. Urinary prostaglandin E excretion in control (C) and deficient (D) animals expressed in ng/24 hours.
**TABLE 2**

<table>
<thead>
<tr>
<th>BP (mm Hg)</th>
<th>CO (ml/min)</th>
<th>RBF (ml/min)</th>
<th>GFR (ml/min)</th>
<th>Filtration fraction</th>
<th>Kidney wts.</th>
</tr>
</thead>
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<tr>
<td>135</td>
<td>95</td>
<td>20.6</td>
<td>2.30</td>
<td>0.19</td>
<td>2.35</td>
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<tr>
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<td>0.09</td>
<td>2.34</td>
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<tr>
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<td>2.30</td>
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<tr>
<td>135</td>
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<td>12.6</td>
<td>2.42</td>
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</tr>
<tr>
<td>125</td>
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<td>17.4</td>
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<td>135.83 ± 6.11</td>
<td>102.9 ± 5.22</td>
<td>16.63 ± 0.94</td>
<td>2.07 ± 0.25</td>
<td>0.19 ± 0.01</td>
<td>2.55 ± 0.11</td>
</tr>
</tbody>
</table>

Prostaglandin-deficient rats

<table>
<thead>
<tr>
<th>BP (mm Hg)</th>
<th>CO (ml/min)</th>
<th>RBF (ml/min)</th>
<th>GFR (ml/min)</th>
<th>Filtration fraction</th>
<th>Kidney wts.</th>
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<tr>
<td>125</td>
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<tr>
<td>145</td>
<td>134.0</td>
<td>21.5</td>
<td>1.61</td>
<td>0.14</td>
<td>2.55</td>
</tr>
<tr>
<td>120</td>
<td>90.3</td>
<td>15.4</td>
<td>1.47</td>
<td>0.17</td>
<td>1.97</td>
</tr>
<tr>
<td>130</td>
<td>105.1</td>
<td>18.69</td>
<td>1.47</td>
<td>0.15</td>
<td>2.48</td>
</tr>
<tr>
<td>130</td>
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<td>20.1</td>
<td>2.01</td>
<td>0.18</td>
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</tr>
<tr>
<td>130</td>
<td>158.9</td>
<td>22.5</td>
<td>1.87</td>
<td>0.20</td>
<td>2.53</td>
</tr>
<tr>
<td>130.00 ± 3.41</td>
<td>118.80 ± 9.96</td>
<td>19.86 ± 1.03</td>
<td>1.68 ± 0.09</td>
<td>0.16 ± 0.008</td>
<td>2.47 ± 0.12</td>
</tr>
</tbody>
</table>

NS

**Water Excretion Studies**

There was a significant difference in urine volume after the water load in the two groups of rats, as shown in Figure 4. EFAD rats excreted only 2.5 ± 0.77 ml/5 hours or 28%, compared to 6.3 ± 1.4 ml/5 hours or 70% in controls. Although the EFAD rats were able to dilute the urine to below 100 mOsm/kg H₂O in the four periods prior to administration of ADH, urine osmolality was significantly higher than in control animals (Fig. 5). There was, however, no significant difference in the response to exogenous vasopressin in the EFAD animals compared to controls.

**Potassium Excretion Studies**

As shown in Figure 6, there was no significant difference in serum potassium between control or deficient animals after the potassium load. Two-hour urine volume in the deficient rats was 1.9 ± 0.1 ml, significantly less than the controls, 3.3 ± 0.2 ml. Potassium excretion in the deficient animals (470 ± 40 μEq) was significantly less than controls (656 ± 50 μEq) but urinary potassium concentration was higher.
FIGURE 4. Urine volume excreted 5 hours after a water load of 3 ml water per 100 g body weight, p.o., in control (C) and deficient (D) animals.

245 ± 20 mEq/liter, than in controls, 197 ± 7 mEq/liter (P < 0.05). In response to the potassium load, both sodium concentration, 21 ± 5 mEq/liter, and excretion, 30 ± 10 μEq/2 hours, was significantly less in the deficient animals than in controls, 84 ± 10 mEq/liter and 287 ± 44 μEq/2 hours, respectively (P < 0.01). There was no difference in plasma aldosterone following the potassium load (Fig. 7). Therefore, the defect in potassium excretion was independent of aldosterone secretion. Since urine volume and sodium excretion were significantly less following the K+ load in the EFAD rats, the defect may be caused by decreased flow to the distal and collecting tubule.

Studies of Blood Pressure Control

Figure 8 demonstrates a significant increase in systolic blood pressure in the deficient rats, 122 ± 138 ± mm Hg (P < 0.01), by the third day of the high salt diet, which persisted through the 9 days of the study. In contrast, there was no change in blood pressure in control rats, 117 ± 2.8 to 119 ± 2.3 mm Hg (NS).

Repletion Studies

Linoleic acid, 0.5 g daily, was given by gastric lavage to depleted animals. Urinary PGE returned to control values within 3–4 days after linoleic acid, and the alterations in the ability to excrete a sodium and water load were reversed in these animals (Fig. 9). In eight rats made hypertensive by 9 days of saline drinking, linoleic acid added to the diet normalized the blood pressure despite the continued administration of saline.

The Effect of Fasting without Essential Fatty Acid Depletion

Urinary PGE excretion before the fast was 76.3 ± 4 ng/24 hours and 74.5 ± 6 ng/24 hours, 2 weeks after institution of the synthetic diet supplemented with essential fatty acids. The animals before the fast weighed 279 g and at the initiation of the study, 308 g. Before fasting, in response to the sodium load, the
animals excreted 4.6 ml of urine, which represented 55.3 ± 2.1% of the administered load in 5 hours; after the fast, the response was similar—urine volume 6.3 ± 0.4 ml with an excretion of 57 ± 2.5%. Before the fast, the animals excreted 7.8 ± 0.6 ml of the water load in 5 hours, which represented 93 ± 7% of the administered water load; after the fast, 8.4 ± 0.5 ml with a fractional excretion of 90.8 ± 5.1% (NS). When saline was substituted for drinking water for 10 days, no change in systolic blood pressure occurred in animals before or after the fast; 125 ± 1.6 vs. 124 ± 1.66 mm Hg. Thus, neither the fast nor the synthetic diet caused the changes noted in the EFAD animals.

Discussion

In spite of intensive investigation over the past several years, the role of renal prostaglandin synthesis in the regulation of sodium and water excretion remains uncertain. Although both PGE₂ and PGI₂ are synthesized in the kidney and are natriuretic, their vasodilatory effects make interpretation of their natriuretic properties difficult. However, the possibility that prostaglandins may alter renal sodium excretion by a direct tubular action, separate from their vascular effect, has been suggested from two sources of evidence. First, PGE₂ has been shown to stimulate sodium transport in the toad bladder, an organ that bears many similarities to the mammalian collecting tubule (Lipson, 1971). Second, studies using either prostaglandin inhibitors (Herbaczynska-Cedro, 1974) (Susac, 1975) or direct infusion of prostaglandins into the renal circulation (Herzog, 1967) (Johnston, 1967) (Gross, 1973) have shown discrepancies between the changes occurring in renal hemodynamics and renal excretion of sodium, suggesting that these agents have a direct tubular action.

In contrast to the studies in the toad bladder, where prostaglandins appeared to stimulate sodium transport, Stokes and Kokko (1977) have reported that PGE₂ inhibited net sodium transport in the isolated cortical and medullary collecting tubules of rabbits, whereas Fine and Trizna (1977) were unable to demonstrate an inhibitory or stimulatory action of PGE₂ on sodium transport in isolated perfused tubular segments.

Results obtained in experiments with intact animals in which cyclooxygenase inhibitors were used to probe the function of the prostaglandin system in sodium excretion have also been conflicting. Acute administration of aspirin or indomethacin to anesthe-
tized or conscious rats and dogs have been reported to increase (Gill, 1975), decrease (Susic, 1975), or have no effect upon sodium excretion. Similarly, reports on the effect prostaglandins have on sodium reabsorption in the human kidney are equally conflicting. One group demonstrated no net sodium retention after 4 days of administration of indomethacin (Mountokalakis, 1978), whereas others have demonstrated that indomethacin reduced renal sodium excretion both in normal patients and in patients with underlying renal disease (Donker, 1976; Heyman, 1976; Kimberly, 1977). The diversity of the findings in the studies utilizing prostaglandin inhibitors may be the result of the diverse effects of cyclooxygenase inhibitors (Flower, 1974). Thus, indomethacin is not only a cyclooxygenase, but also a phosphodiesterase inhibitor. In addition, these drugs could be exerting effects on renal function and sodium and water metabolism independent of prostaglandin inhibition.

The model of prostaglandin deficiency we describe avoids these potential problems and demonstrates, both in conscious and anesthetized animals, that prostaglandin-depleted animals have a defect in excracting a sodium load, compared to controls, that cannot be attributed to change in glomerular filtration rate or renal blood flow. In addition, the development of hypertension with chronic high salt intake makes these rats similar to the Dahl strain of rats that become hypertensive with a high salt intake. Similarly, in Dahl sensitive animals there is reduced ability to excrete sodium and Tobian et al. (1980) have found that the sensitive strain has reduced renal papillary plasma flow and decreased papillary concentration of PGE2. Since urinary PGE2 excretion is felt to reflect prostaglandin production by the kidney (Frolich, 1975) papillary concentration of PGE2 in the EFAD rat probably was reduced. Also, papillary plasma flow may be reduced in these EFAD rats even though total renal blood flow was not different from that of control animals. Prostaglandin-inhibiting drugs reduce inner cortical blood flow in the dog (Kirschchenbaum, 1971), and we have reported that EFAD rats have reduced papillary blood flow (Ganguli, 1982). Since medullary nephrons contribute significantly to the final urinary sodium concentration (Lameire, 1977), a reduction in medullary PGE2 synthesis may reduce papillary plasma flow and increase sodium reabsorption in deep cortical nephrons.

In addition to the effect renal prostaglandins may have on sodium excretion, they may also exert a role on water excretion. It has been demonstrated that prostaglandins of the E series are antagonists of the hydroosmotic effect of antidiuretic hormone (ADH) under in vitro conditions in both the toad bladder (Herbacynska-Cedra, 1974) and the isolated rabbit (Anderson, 1975). ADH is felt to exert its biological effect by activation of the adenyl cyclase system, and prostaglandins may act as modulators of the hormone-adenyl cyclase reaction. Since PGE1, particularly in higher concentrations, can increase cyclic AMP accumulation and enhance water permeability in ADH-sensitive membranes, a unifying concept regarding the role of prostaglandins in altering water permeability has not clearly emerged. To complicate matters further, indomethacin, the cyclooxygenase inhibitor most frequently used to probe the involvement of the prostaglandin system on the hydroosmotic effect of vasopressin, has been shown to decrease total renal blood flow as well as fractional flow to the deep cortex (Kirschchenbaum, 1971). These changes may increase medullary tonicity and account for an effect on water excretion independent of vasopressin. In support of this concept was a study by Ganguli et al. (1977) in which they were not able to demonstrate any change in total renal blood flow or in papillary blood flow after indomethacin but did note an increase in papillary sodium concentration. Furthermore, Stoff et al. (1981) have demonstrated that inhibition of prostaglandin synthesis by indomethacin slows a water diuresis in both unanesthetized Sprague-Dawley rats and in Brattleboro rats with hereditary diabetes insipidus. In both of these studies, treatment with indomethacin and meclofenamate increased the osmolality of the renal papilla by raising sodium and urea content, and also increased the osmolality of the urine. These studies suggest that endogenous prostaglandins may influence water excretion by a mechanism independent of the presence of antidiuretic hormone.

In the EFAD rats, there was a defect in water excretion, but deficient animals were capable of diluting their urine to less than 100 mOsm/kg/H2O and had a normal response to the administration of antidiuretic hormone. The delay in attaining maximal urinary dilution and decreased ability to maximally dilute the urine may be caused by an initial hypertonic medullary interstitium. It is possible that the defect in both sodium and water excretion is due to increased medullary tonicity. Since water reabsorption from the descending limb of the loop of Henle is dependent upon medullary tonicity, the amount of filtrate presented to the ascending limb, particularly in juxtamedullary nephrons, might be decreased by medullary hypertonicity, which could result in a defect in excretion of both sodium and water. Alternatively, increased sodium chloride reabsorption may occur in the thick medullary ascending limb in prostaglandin-depleted animals which would be consistent with the findings of Stokes and Kokko in isolated perfused rabbit collecting tubules (Stokes, 1977).

If medullary hypertonicity is present in EFAD rats, sustained administration of a water or sodium load may ultimately normalize medullary tonicity. Although balance studies were not carried out in the animals drinking saline, any defect in sodium excretion would have been transient and, ultimately, sodium balance would be attained. How such a delay in sodium excretion could be the proximate cause of the hypertension is unknown. One could speculate, however, that an increase in blood pressure must occur to maintain sodium balance or correct the alteration in medullary tonicity.
The effect of prostaglandin synthesis in blood pressure control remains unclear. Ten Hoor et al. (1978) have demonstrated that rats fed a diet rich in linoleic acid (56% linoleic acid) had a 10–15% lower blood pressure than rats fed a control diet (2% linoleic acid) in response to drinking 1.5% NaCl. Also, Tobian et al. (1980) recently fed Dahl sensitive rats diets rich in linoleic acid with 4% NaCl and found the rats had a marked delay in the onset of hypertension, and the level of blood pressure attained was less than a comparably treated sensitive group of rats not receiving the additional linoleic acid. In our study, the deficient animals became significantly hypertensive in response to saline drinking compared to control animals, and when linoleic acid was added to their diet blood pressure fell significantly. The similarities between the Sprague-Dawley animals made prostaglandin deficiency by restriction of essential fatty acids and the Dahl sensitive hypertensive animals is interesting and may lead to further understanding of salt-sensitive hypertension. Administration of cyclooxygenase inhibitors can suppress renin release to a variety of stimuli (Data, 1978) but our essential fatty acid-depleted animals had plasma renin concentration that was not different from control animals.

In summary, we have presented a model of prostaglandin deficiency induced without the use of pharmacological agents. Although there may be unknown effects of essential fatty acid deficiency independent of prostaglandin depletion, the changes in sodium and water excretion and the development of hypertension during a high sodium intake make the model interesting and worthy of further study. Since the animals are vigorous and gain weight similar to controls, the model is particularly well suited for chronic studies of prostaglandin depletion.

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