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Effects of Dietary Linoleic Acid on Blood Pressure and Renal Function in Subtotally Nephrectomized Rats (42404)

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Abstract. The effect of a high linoleic acid diet on blood pressure, renal function, and urinary prostaglandin excretion was studied in rats with decreased renal mass. Subtotally nephrectomized (5/6 nephrectomy) male rats received either a 15% linoleic acid (high linoleic acid, HLA) diet containing 20% safflower oil or a 0.28% linoleic acid (low linoleic acid, LLA) diet containing 20% coconut oil. Sham-operated rats were also placed on either HLA or LLA diet. The subtotal nephrectomized rats developed similar degrees of hypertension during the first 3 weeks after subtotal nephrectomy. However, 4 weeks after subtotal nephrectomy, the rats on HLA diet had significantly lower blood pressure than the rats on LLA diet [HLA 152 ± 3 (mean ± SE) mm Hg versus LLA 171 ± 3 mm Hg]. This difference persisted until termination of the experiment at 7 weeks after subtotal nephrectomy (HLA 159 ± 7 mm Hg versus LLA 192 ± 6 mm Hg). The GFR measured 7 weeks after subtotal nephrectomy was significantly lower in both of the subtotally nephrectomized groups. However, the HLA subtotal nephrectomized rats had significantly higher GFR than the LLA-treated rats (HLA 0.23 ± 0.05 ml/min100 g versus LLA 0.12 ± 0.02 ml/min/100 g, $P < 0.05$). There was no difference in the GFR or blood pressure in the sham-operated rats treated with HLA or LLA diet. PGE_2 excretion was lower in the two groups of subnephrectomized rats, but, there was no difference between the HLA and LLA treated rats. Urinary 6-keto$PGF_1\alpha$ was not decreased by subtotal nephrectomy and there was no difference between the dietary groups. However, TXB_2 excretion was higher in the groups with subtotal nephrectomy, but there was no difference between the two dietary groups. In conclusion, the HLA diet attenuates the rise in blood pressure after subtotal nephrectomy in the rat and preserves renal function. There was no difference in urinary excretion of PGE_2, 6-keto-$PFG_1\alpha$, or thromboxane B_2 between the two dietary groups.

Prostaglandins have been implicated in the pathogenesis of hypertension. Hypertensive patients have been shown to have low urinary PGE_2 by Tan *et al.* (1). Others have reported increased TXB_2 excretion in patients with essential hypertension (2, 3). Diets deficient in prostaglandin precursors cause significant hypertension in the rat and impair the capacity of the kidney to excrete a water or sodium load (4). Linoleic acid is converted to arachidonic acid which in turn is the major precursor of prostaglandins (5). Studies using diets high in linoleic acid have been shown to prevent the development of hypertension in human subjects (6, 7) and in salt-loaded rats (8, 9). Tobian *et al.* (10) reported a delayed increase in blood pressure in Dahl salt-sensitive rats receiving a high linoleic acid diet and high salt intake.

On the other hand, Codde *et al.* (11) found no difference in blood pressure in rats with the one kidney, one clip model of hypertension, fed either cod liver oil/linseed oil or sunflower oil. This was in spite of a significant decrease of tissue prostaglandin biosynthesis and urinary excretion of prostaglandins in the cod liver oil/linseed oil-treated rats. These results suggest that prostaglandins do not play a significant role in this model of hypertension (11). Moreover, Mogenson *et al.* (12) showed that diets high in linoleic acid increased blood pressure in spontaneously hypertensive rats. Rats in which 70–80% of the renal mass is removed develop volume-dependent hypertension (13). The present study was performed to examine the effect of high dietary linoleic acid (HLA) on blood pressure and renal function in rats with volume-dependent hypertension due to reduced renal mass.

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Materials and Methods. Sprague–Dawley male rats (215–240 g) were fed a normal diet (Wayne, Chicago, Ill.) The animals were randomly divided into two groups. One group was given a subtotal nephrectomy and the other was sham operated as control. Subtotal nephrectomy was carried out according to the method of Pamnani *et al.* (14). Under sodium pentobarbital anesthesia, the two poles of the left kidney were cut following tight stricture with silk sutures. Next, the right kidney was removed. Approximately 80% of the renal mass was removed in this manner. After the subtotal nephrectomy and sham operations, one group of subtotal nephrectomized rats and sham-operated rats were given a 15% linoleic acid diet as powdered Purina chow containing 20% safflower oil for 7 weeks. The other groups of subtotal nephrectomized rats and sham-operated rats were given a 0.28% linoleic acid diet as powdered Purina chow containing 20% coconut oil for the same number of weeks. The sodium content of this diet was 1%. Blood pressure (tail plethysmography) and body weight were monitored weekly for 7 weeks. Seven weeks after the operations, all rats were killed by decapitation and blood samples were collected from the neck vessels in tubes containing 2 mg disodium EDTA for measurement of active renin and creatinine. Twenty-four-hour urine samples were collected 7 weeks after the operations for measurement of prostaglandin E_2 (PGE_2), 6-keto-$PGF_1\alpha$, thromboxane B_2 (TXB_2), creatinine, and sodium. Plasma active renin was measured by radioimmunoassay (RIA) of generated angiotensin I using a New England Nuclear Corporation (Billerica, Mass.) kit. Plasma (50 μl) was incubated with rat renin substrate (100 μl) in the presence of the angiotensinase and converting enzyme inhibitors 8-hydroxyquinoline, dimercaprol, and EDTA. After 1 hr incubation at 37°C (pH 7.4), the generated angiotensin I was assayed by RIA. GFR was measured by the endogenous creatinine clearance. Plasma and urinary creatinine was determined by a standard colorimetric assay using a kit from Sigma (St. Louis, Mo.). Extraction of urinary TXB_2 was carried out using a column of octadecylsilyl silica (Sep-Pak, Water Associates, Milford, Mass.) following the method of Powell (15). The Sep-Pak was pretreated with ethanol (5 ml) followed by water (5 ml). One milliliter of urine containing [^{3}H]TXB_2 (1200 cpm) to estimate recovery was acidified to pH 3.0 with 1 *N* HCl and applied to the Sep-Pak. The Sep-Pak was treated with 5 ml of ethanol/water (15/85), 5 ml of petroleum ether, and TXB_2 was eluted with 10 ml of methyl formate. The methyl formate fraction was collected and evaporated under air. The extraction residue was reconstituted in buffer for assay of TXB_2 using a ^{3}H–RIA kit from New England Nuclear. Urinary PGE_2 and 6-keto-$PGF_1\alpha$ were isolated by high-performance liquid chromatography (HPLC; Varian Model 5020). One milliliter of urine containing [^{3}H]PGE_2 and [^{3}H]6-keto-$PGF_1\alpha$ (1200 cpm each) for recovery was acidified to pH 3.0 with 1 *N* HCl and passed through a Sep-Pak for the initial extraction (as for the TXB_2 extraction). The extract was reconstituted with HPLC solvent (800 μl acetonitrile/17 m*M* of phosphoric acid, 34/66 by vol) and filtered by using microfilters (Millipore Corp., Bedford, Mass.). The total volume of sample passed through the filter was injected onto the HPLC column (Altex, Ultrasphere-ODS; 25 cm × 4.6 mm i.d.). The retention times of 6-keto-$PGF_1\alpha$ and PGE_2 standards were 6 and 14 min, respectively, at a flow rate of 1.4 ml/min. Fractions corresponding to these retention times were collected after sample injection and the acetonitrile in the column effluent was evaporated. The phosphoric acid remaining was removed with a Sep-Pak and the eluted prostaglandins were reconstituted in buffer for assay of PGE_2 and 6-keto-$PGF_1\alpha$ using a ^{125}I–RIA kit and a ^{3}H–RIA kit, respectively (New England Nuclear). Recoveries of PGE_2, 6-keto-$PGF_1\alpha$, and TXB2 were 64, 55, and 71%, respectively. Urinary sodium was measured by flame photometry (Instrumentation Laboratory Inc.).

Results are presented as means ± SE. Statistical analysis was performed by the Student *t* test for unpaired variables; *P* values of less than 0.05 were considered statistically significant.

Results. Figure 1 shows the time course of changes in systolic blood pressure. The blood pressure began to rise 1 week after the operations but during the first 3 weeks after nephrectomy there was no significant difference between the two dietary groups. However, the blood pressure of the subtotal nephrectomized

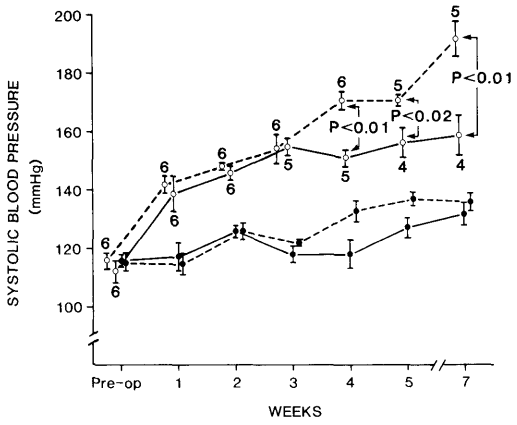

FIG. 1. Time course of changes in systolic blood pressure in the rats with subtotal nephrectomy fed HLA diet (SN + HLA, ---○) or LLA diet (SN + LLA, — ○) and with sham-operated rats fed HLA diet (SO + HLA, ---●, n = 6) or LLA diet (SO + LLA, — ●, n = 6). All values are means ± SE. The numerals beside each bar express the number of rats in the subtotally nephrectomized rats.

rats on HLA diet was significantly lower at 4, 5, and 7 weeks after the operation compared to those on LLA diet (4 weeks: 152 ± 2 mm Hg vs 171 ± 3 mm Hg; 5 weeks: 156 ± 6 vs 173 ± 2; 7 weeks: 158 ± 7 vs 192 ± 6). Sham-operated rats fed the LLA and HLA diets developed moderate increases in blood pressure during the experiment, but there was no significant difference between the two dietary groups.

As shown in Fig. 2, subtotal nephrectomy markedly decreased urinary PGE_2 in both dietary groups (from 24.8 ± 3.6 to 2.9 ± 0.6 ng/day with the HLA diet and from 24.5 ± 5.0 to 2.7 ± 0.4 ng/day with the LLA diet). However, there was no significant difference in urinary PGE_2 between the two dietary groups in either the sham-operated or subtotal nephrectomized rats. Urinary 6-keto-$PGF_1\alpha$ was not changed by subtotal nephrectomy and there was no difference between the two dietary groups. Urinary TXB_2 was increased by subtotal nephrectomy from 39.3 ± 2.6 to 62.5 ± 3.7 ng/day in the rats fed the HLA diet and from 24.9 ± 1.4 to 54.8 ± 11.7 in the rats fed the LLA diet. TXB_2 was significantly higher in sham-operated rats fed the HLA diet than those fed the LLA diet. Plasma active renin was suppressed by subtotal nephrectomy, from 20.8 ± 2.1 to 2.4 ± 0.1 ng AI/ml/hr in the rats fed the HLA diet and from 12.7 ± 3.8 to 2.5 ± 0.2 in the rats fed the LLA diet (Fig. 3). Active renin in the sham-operated rats fed the HLA diet was significantly higher than in those fed the LLA diet. Active renin was not significantly different in the subtotal nephrectomized rats on either diet.

Figure 4 shows that subtotal nephrectomy lowered GFR from 0.43 ± 0.04 to 0.23 ± 0.05 ml/min/100 g in the rats fed the HLA diet, and from 0.33 ± 0.06 to 0.12 ± 0.02 ml/min/100 g in the rats fed the LLA diet. GFR in subtotal nephrectomized rats fed HLA diet was significantly higher than in rats fed the LLA diet.

As shown in Fig. 5, there were no significant differences in urinary sodium. Subtotal nephrectomy increased urine volume from 10.9 ± 0.6 to 21.3 ± 4.9 ml/day in the HLA diet

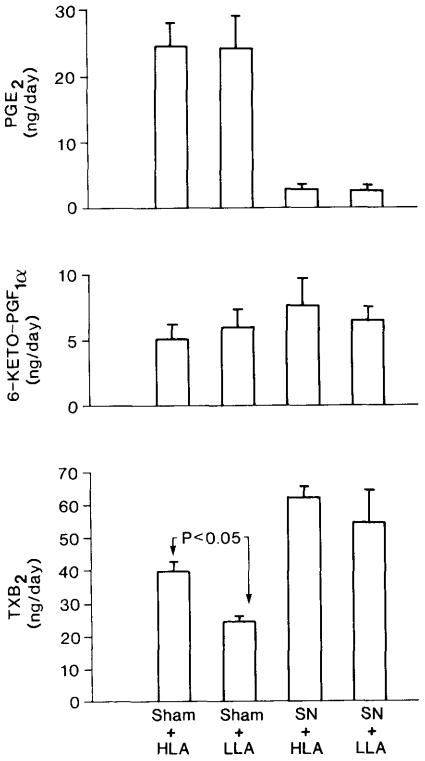

FIG. 2. Urinary PGE_2, 6-keto-$PGF_1\alpha$, and TXB_2 in rats with subtotal nephrectomy fed HLA diet (SN + HLA, n = 4) or LLA diet (SN + LLA, n = 5) and with sham-operated rats fed HLA diet (SO + HLA, n = 6) or LLA diet (SO + LLA, n = 6) 7 weeks after the operations. All values are means ± SE.

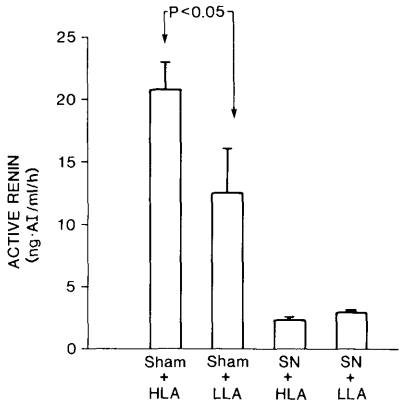

FIG. 3. Plasma active renin in rats with subtotal nephrectomy fed HLA diet (SN + HLA, $n = 4$) or LLA diet (SN + LLA, $n = 5$) and with sham-operated rats fed HLA diet (SO + HLA, $n = 6$) or LLA diet (SO + LLA, $n = 6$) 7 weeks after the operations. All values are means ± SE.

group, and from 10.1 ± 0.5 to 23.6 ± 3.7 in the LLA diet group. No difference in urine volume was observed between the two dietary groups in either subtotal nephrectomized or sham-operated rats.

Body weight was significantly lower in the subtotal nephrectomized rat than in the sham-operated rats [SN + HLA: 334 ± 11.7 g vs SHAM + HLA, 384 ± 6.9 g ($P < 0.02$); SN + LLA, 312 ± 14.5 vs SHAM + LLA, 376 ± 13.4 g ($P < 0.02$)], but there was no significant difference between the two dietary groups.

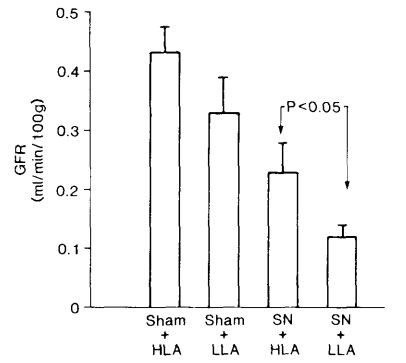

FIG. 4. GFR in rats with subtotal nephrectomy fed HLA diet (SN + HLA, $n = 4$) or LLA diet (SN + LLA, $n = 5$) and with sham-operated rats fed HLA diet (SO + HLA, $n = 6$) or LLA diet (SO + LLA, $n = 6$) 7 weeks after the operations. All values are means ± SE.

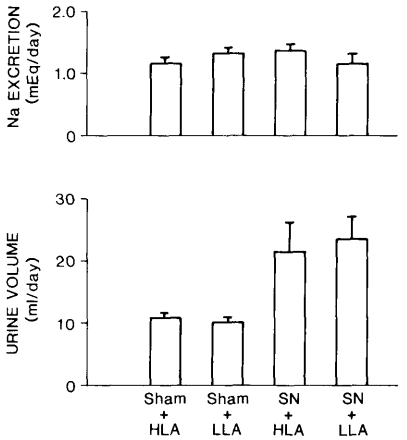

FIG. 5. Urine volume and Na excretion in rats with subtotal nephrectomy fed HLA diet (SN + HLA, $n = 4$) or LLA diet (SN + LLA, $n = 5$) and with sham-operated rats fed HLA diet (SO + HLA, $n = 6$) or LLA diet (SO + LLA, $n = 6$) 7 weeks after the operations. All values are means ± SE.

Discussion. Diets enriched with linoleic acid have been shown to retard the development of hypertension (6, 8, 9). High linoleic acid diet lowered blood pressure in experimental animals with salt-loading hypertension, and Goldblatt hypertension (6, 8, 10, 16). There is controversy regarding the role of prostaglandins in spontaneously hypertensive rats. While some investigators have shown that essential fatty acid deficient diets exacerbated hypertension in spontaneously hypertensive rats (SHR) (18), others reported that a high linoleic acid diet increased the blood pressure in this model of hypertension (12). Codde *et al.* (15) showed higher urinary PGE_2 and 6-keto-$PGF_1\alpha$ in rats receiving a linoleic acid-rich diet. Contrary to their results, our study showed no differences in PGE_2 and 6-keto$PGF_1\alpha$ excretion between our two dietary groups. However, in the present study, the HLA diet significantly blunted the rise in blood pressure following reduction of renal mass. Since dietary linoleic acid serves as a precursor for arachidonic acid, the beneficial effects could occur through increased prostaglandin synthesis. Further support for this concept is the fact that indomethacin prevents the blood pressure-lowering effect of a high linoleic acid diet (9).

Urinary PGE_2 is believed to derive from renal production. The origin of urinary 6-keto-

$PGF_1\alpha$ and TXB_2 is less clear. Unchanged urinary PGE_2 and 6-keto-$PGF_1\alpha$ after 4 weeks of a linoleic acid-enriched diet has been reported in male Sprague–Dawley rats (20). On the other hand, several investigators have shown changes in tissue levels of prostaglandins after linoleic acid-rich diets (8, 10, 17, 19). Dissociation between urinary PGE_2 and medullary PGE_2 synthesis has also been reported (21).

In our experiments, subtotal nephrectomy markedly suppressed urinary PGE_2, but 6-keto-$PGF_1\alpha$ excretion was not changed. This result supports the theory that urinary PGE_2 originates from renal tissue, while the absence of change in urinary 6-keto-$PGF_1\alpha$ with reduced renal mass suggests that urinary 6-keto-$PGF_1\alpha$ is mainly produced extrarenally. A similar phenomenon was reported by Baer *et al.* (22) who showed that uninephrectomy did not cause a reduction of urinary 6-keto-PGF_1 while PGE_2 was significantly reduced.

Another interesting finding is the increase in urinary TXB_2 after subtotal nephrectomy. Synthesis of PGI_2 and TXA_2 occurs in the kidney (23, 24) and vascular wall (25, 26). Therefore, urinary TXB_2 and 6-keto-$PGF_1\alpha$ may reflect renal and systemic production of TXA_2 and PGI_2, respectively. It is possible that the elevation of urinary TXB_2 may be due to increased systemic TXA_2 production in the rats with reduced renal mass hypertension.

Another possibility is that the increased thromboxane productions resulted from renal injury due to subtotal nephrectomy. Increased thromboxane excretion has been reported in other conditions associated with renal damage, including humans and rats with lupus nephritis and during episodes of rejection in patients with kidney transplants (26, 28). Moreover Purkerson *et al.* recently reported that rats with reduced renal mass have increased excretions of thromboxane B_2 and that treatment of these rats with the thromboxane inhibitor OKY 1581 ameliorated the progression of renal disease and lowered the blood pressure (30).

Increase in urinary TXB_2 in patients with hypertension has been reported (2, 3), but no direct relationship between high blood pressure and urinary TXB_2 has been shown. One possibility is that the rise in blood pressure increases TXA_2 production. On the other hand, it is conceivable that this potent vasoconstrictor may have a role in the pathogenesis of hypertension, as it is suggested by the findings of Purkerson *et al.* (30).

The significantly higher GFR in subtotal nephrectomized rats fed the HLA diet suggests a beneficial effect of linoleic acid on renal function. A decreased renal flow rate has been reported in isolated perfused kidneys of rats fed a linoleic acid-deficient diet (9). Furthermore, it has been shown that subtotally nephrectomized rats fed a linoleic acid supplement diet had lower serum creatinine than rats receiving a normal diet (31).

The linoleic acid-rich diet increased renin release in sham-operated rats, but did not influence renin release in subtotal nephrectomized animals. It may be possible that the reduced renal mass might have led to too small of a response to linoleic acid for measurable differences in renin release.

Our experiments show that a high linoleic acid diet has therapeutic effects through changes in blood pressure and GFR. A rational explanation for the changes in these parameters seems to be dependent on an increase in arachidonic acid and consequently, higher production of prostaglandins. However, changes in PGE_2, 6-keto-$PGF_1\alpha$, and TXB_2 excretion to support the above theory did not occur in the present experiments. Whether the HLA diet leads to the formation of other metabolites of arachidonic acid besides PGE_2, PGI_2, and TXA_2 is not known. Recently Ferreri *et al.* (32) described a cytochrome P-450 pathway that leads to the formation of some arachidonic acid metabolites with vasodilatory and natriuretic properties. Alternatively, it may be that the beneficial effect of HLA diet may be due to increased tissue prostaglandin synthesis that is not detected in the urine.

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