Evidence for an Hepatic Role in the Control of Sodium Excretion[1] (34487)

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The liver has been proposed by several workers to be a source of a natriuretic factor. Milies (1), in 1959, reported that a concentrate of hepatic perfusate had diuretic and natriuretic properties. The active component was purported to be a globulin, but no further work has followed this interesting initial report by this investigator. Haberich (2) has proposed that the liver contains osmoreceptors and therefore has a regulatory function in regard to salt and water balance. His experiments differ from those to be presented here in that he studied the effects of hypotonic loading conditions on diuresis. He suggested that the liver influences the kidney *via* vagal stimulation.

Daly *et al.* (3) have investigated selective saline loading in their experiments dealing with an hepatic influence on sodium excretion. Five per cent sodium chloride was infused into anesthetized dogs at the small rate of 0.075 ml/kg/min for 35 min through the liver *via* the portal vein or systemically *via* the femoral vein. The authors claimed to have found a statistically significantly greater natriuretic response when the portal route was compared to the femoral. However, comparisons were made by determining the total increase in sodium excretion from a preinfusion control level until the rate again returned to the control level. The end point of such responses varied depending on whether a baseline was reestablished above, below, or at the original excretion rate. Criteria for such decisions appeared to be variable, thus the determination of the end point was not clear. Since a variable end point might have resulted in the apparent difference found, we have reexamined the problem by comparing control rates of sodium excretion to those determined at the peak response period. Thus the same criteria were used for all animals.

Methods. Mongrel dogs weighing between 12 and 22 kg, were deprived of food 24 hr before the experiment. They were anesthetized intravenously with 30 mg/kg of sodium pentobarbital. The trachea was intubated for free passage of air and one carotid artery was cannulated to record blood pressure. A femoral artery was cannulated to obtain blood samples, and a femoral vein was cannulated to administer infusions. A midline incision was made, and both ureters were cannulated. The portal vein was cannulated *via* the splenic vein. The position of this cannula was verified at the end of the experiment. Two hours before the start of control collections an intramuscular injection of 10 mg of DOCA and 5 U of vasopressin tannate in oil was given.

A solution containing inulin and aqueous vasopressin in 2.5% mannitol was infused 30 min prior to and throughout the experiments at 0.1 ml/kg/min.

All urine collections were 20 min long, and a heparinized blood sample was withdrawn at the midpoint of each urine collection for analyses. Urine from two or three control periods was collected before an infusion of 5% sodium chloride was given. This solution was infused at the rates of 0.025, 0.05, 0.1, or 0.4 ml/kg/min for 30 min. The saline was given by both routes in each animal, but the order of administration was varied so that half the animals received the saline first *via* the portal and the other half first *via* the femoral vein.

The data from the last control period were compared with the second saline loading col-

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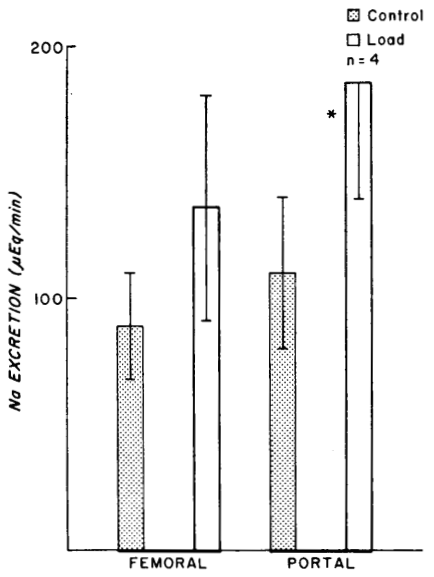

FIG. 1. Femoral *vs* portal saline loading with 5% NaCl at 0.05 ml/kg/min. (*) indicates change from control is significantly greater after portal infusion ($p < .05$).

lection period, determined to be the peak of the natriuretic response, for the two routes by means of an analysis of variance, randomized complete block design, and Duncan's new multiple-range test (4).

Inulin was determined by the method of Schreiner (5) and used to estimate the rate of glomerular filtration (GFR). Sodium concentration was determined with a Coleman flame photometer.

Results. When 5% sodium chloride was infused at a rate of 0.025 ml/kg/min *via* the portal or femoral routes, renal sodium excretion was not increased significantly, nor did GFR change from control levels.

A rate of 0.05 ml/kg/min increased sodium excretion significantly only by the portal route of administration. The increase in sodium excretion above control averaged 47 μeq/min after systemic loading and 74 μeq/min after portal loading (Fig. 1).

Excretion data obtained when a rate of 0.1 ml/kg/min was given are presented in Fig. 2. This rate of saline infusion resulted in an increased rate of sodium excretion in all test periods and in a natriuresis by both routes that was significantly different from control. While control levels of sodium excretion varied somewhat within and between experiments, the overall basal excretion rates were not different from each other. Femoral loading resulted in an increase in sodium excretion of 82 μeq/min, or 279% of control, while portal loading resulted in an increase in sodium excretion of 142 μeq/min or 375% of control. These results are significantly different from each other. No difference in GFR was observed between the routes.

Figure 3 shows the results of experiments on six dogs in which the rate of infusion of 5% saline was increased to 0.4 ml/kg/min. Again, control levels of sodium excretion were not different from each other. Saline loading by either route resulted in an increased natriuresis. However, the means of the natriuretic responses were not different from each other. No significant alterations in GFR occurred.

In another series of experiments, systemic loading was compared with posthepatic loading (into the right atrium) rather than through the liver. Figure 4 compares a rate of infusion (0.1 ml/kg/min) that produced a significantly greater natriuresis than systemic loading when infused into the hepatic circulation. Control excretion rates were not different from each other. Excretion rates at the

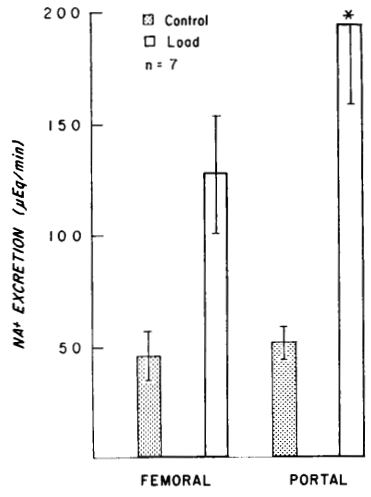

FIG. 2. Femoral *vs* portal saline loading with 5% NaCl at 0.1 ml/kg/min. (*) indicates change from control is significantly greater after portal infusion.

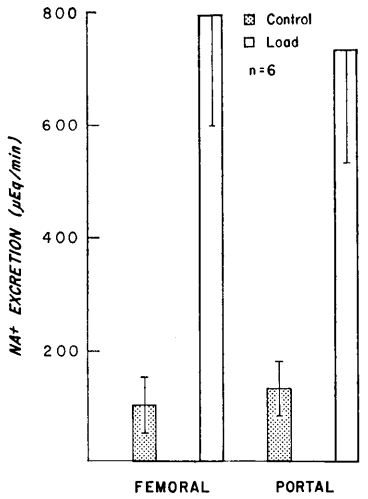

FIG. 3. Femoral *vs* portal saline loading with 5% NaCl at 0.4 ml/kg/min.

peak of the natriuretic responses were not significantly different from each other. Also, no difference between these two routes was detected at a lower infusion rate (0.025 ml/kg/min).

To determine whether an increase in osmolality or an increase in sodium concentration in the portal blood was the stimulus, 56% sucrose (isosmotic with 5% saline) was infused by the portal and femoral routes at 0.1 ml/kg/min for 30 min. In three experiments no difference between routes was found. The increase in sodium excretion after femoral loading averaged 36 μeq/min and after portal loading, 35 μeq/min.

Discussion and Conclusions. The increased natriuresis found after a small hypertonic sodium chloride load was infused into anesthetized dogs was found to be greater when the stimulus was administered directly into the hepatic circulation than when it was infused systemically *via* the femoral vein. In addition, the response appears to be dose-related within limits. At 0.05 ml/kg/min a significant natriuresis was obtained only after portal loading. At double this rate, significant increases in sodium excretion occurred with both routes of administration, but the increase after portal loading was more than 50% greater. At a higher rate of infusion (0.4 ml/kg/min) no difference was observed between routes. It would appear that the liver exerts a modest influence on sodium excretion and that the modest contribution of an hepatic component is obscured by other components of the natriuretic response to saline loading when the load of saline is increased.

Data obtained when 5% saline was infused distal to the hepatic circulation into the right atrium indicate no difference from systemic loading. Since an infusion rate was used (0.1 ml/kg/min) which resulted in a difference when infused *via* the portal vein, these experiments provide additional support for the involvement of the liver in the natriuretic response.

Substitution of a 56% sucrose solution, isosmotic with 5% sodium chloride, resulted in no difference between portal and femoral infusion when infused at 0.1 ml/kg/min for 30 min. Thus, the liver would appear to be responsive to an increase in sodium concentration rather than to an increase in osmolality in the portal blood.

Daly *et al.*, using similar stimulus parameters, reached similar conclusions by means of a different experimental design. Although our experiments were undertaken because of our reservations to their experimental design, we concur with their conclusion of an hepatic influence on sodium excretion based on our experiments. Additional experiments presented here, which indicate that a dose-related response occurs with increased portal levels of sodium, provide further evidence for the involvement of the liver in the control of sodium excretion.

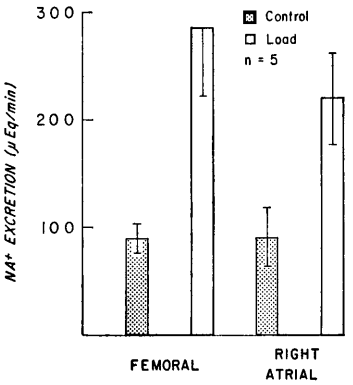

FIG. 4. Femoral *vs* right atrial saline loading with 5% NaCl at 0.1 ml/kg/min.

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1. Milies, E., Acta Physiol. Latinoamer. **10**, 178 (1959).

2. Haberich, F. J., Fed. Proc. **27**, 1137 (1968).

3. Daly, J. J., Roe, J. W., and Horrocks, P., Clin. Sci. **33**, 481 (1967).

4. Steel, R. G. D. and Torrie, J. H., "Principles and Procedures of Statistics", McGraw-Hill, New York (1960).

5. Schreiner, G. E., Proc. Soc. Exp. Biol. Med. **74**, 117 (1950).

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