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Effect of Anionic and Nonionic Contrast Media on Renal Extraction of Para-Aminohippurate in the Dog[1] (40075)

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In a previous study of the renal vascular effect of meglumine diatrizoate (1), we noted that when this substance was given into the renal artery of the dog a reversible depression in the renal extraction of para-aminohippurate (E_{PAH}) occurred. Neither isosmotic (0.9%) nor equiosmolar (4.5%) NaCl altered E_{PAH} whereas both meglumine diatrizoate and 4.5% NaCl caused a reversible decrease in renal vascular resistance. The depressive effect of meglumine diatrizoate on E_{PAH} was attributed to an effect of the organic iodinated molecule on cellular transport of PAH rather than to its osmotic properties.

The meglumine diatrizoate was given as Renografin-76 (E. R. Squibb and Sons, Princeton, NJ) which is 66% meglumine diatrizoate and 10% sodium diatrizoate. Ziegler and colleagues (2) reported that isosmotic replacement of serosal sodium chloride with sodium diatrizoate depressed short-circuit current and net isotopic sodium flux in the isolated toad urinary bladder. Although basal short-circuit current was depressed, the vasopressin-stimulated increment in short-circuit current was not affected. Separate experiments with hyperosmolar solutions (786 mOsm) demonstrated equivalent suppression of short-circuit current by sodium diatrizoate and by other solutions made hyperosmolar with glucose or sodium methylsulfate, implying a general or nonspecific effect of hyperosmolarity.

Thus, the diatrizoate ion appears to depress both sodium transport and PAH transport. This suggests that PAH transport and sodium transport might be linked in some fashion. Low concentrations of sodium in the external bathing medium have been shown to depress the uptake of PAH by rabbit kidney slices (3) and depress net PAH transport from bath to lumen in isolated perfused snake renal tubules (4).

Diatrizoate is an anionic single tri-iodinated ring compound. Metrizamide is a recently developed water-soluble nonionic single tri-iodinated ring compound (5). Ziegler and Olsen (6) recently reported that metrizamide did not depress basal short-circuit current in the isolated toad urinary bladder. These observations were interpreted to mean that anions (e.g. diatrizoate) may regulate sodium transport, possibly by regulating escape of transported sodium from the basolateral side of the epithelial cells.

The objective of these studies was to assess the effect of metrizamide on PAH transport in the intact dog kidney.

Materials and methods. All studies were performed on female mongrel dogs 15–25 kg in weight, fed a standard kennel ration. On the day prior to study all dogs were deprived of food but water was permitted ad libitum. On the day of the study the animal was anesthetized with intravenous sodium pentobarbitol 30 mg/kg and supplemental doses were added throughout the experiment to maintain anesthesia. The animal was intubated with an endotracheal tube and mechanically ventilated to maintain arterial pH between 7.35 and 7.45. Catheters were inserted into a femoral artery, the inferior vena cava via a femoral vein, and jugular vein to permit blood sampling, pressure measurement, and infusion of fluids. A retention catheter was placed in the urinary bladder. The left kidney was exposed via a subcostal incision and the renal artery dissected free, taking care to leave the renal nerves intact. An external electromagnetic flow probe was placed on the left renal artery and led to an electromagnetic flow meter (Carolina). This system was calibrated *in vivo* at the end of each experiment. A catheter was placed in the left renal vein via the left ovarian vein. A 25-

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gauge curved needle attached to polyethylene tubing and connected to a Harvard infusion pump was placed in the left renal artery against the direction of flow. At the conclusion of surgery a priming dose of PAH was given followed by a constant infusion of PAH in 0.9% NaCl at 1.0 ml/min to maintain a plasma concentration of 0.02 mg/ml. Following surgery a minimum of 60 min was allowed for equilibration and stabilization of solutions before beginning the experiment.

The Control Period (C) consisted of 20 min during which duplicate simultaneous samples of femoral arterial and left renal venous blood were obtained while 0.9% NaCl was being infused into the left renal artery at 3.82 ml/min. Then the left renal arterial infusion was changed to an experimental test infusion (Table I) at the same rate and following 15 min equilibration, the Experimental Period (E) was begun with sampling as noted above. Then the left renal arterial infusion was changed back to 0.9% NaCl at the same rate and following 15 min equilibration, the Recovery Period (R) was begun with sampling as noted above.

Mean arterial pressure (MAP) was measured with a pressure transducer and recorded with the electromagnetic flow meter output as renal blood flow (RBF) on a direct writing recorder (Beckman Dynograph). Renal vascular resistance (RVR) was calculated as MAP/RBF in mmHg/ ml/min. Plasma samples were analyzed for PAH by the method of Smith *et al.* (7). E_{PAH} was calculated as A_{PAH}-RV_{PAH}/A_{PAH} where A_{PAH} and RV_{PAH} are the arterial and renal venous plasma concentrations of PAH, respectively.

The data in the text, tables and figures are expressed as the mean ± SE. The Student's *t* test was used for statistical analysis of paired data within each group (8).

Results. The results are illustrated in Figs. 1–4. Mean arterial pressure was not affected by left renal arterial experimental test infusion. Figure 1 shows that, in contrast to isosmotic saline, hyperosmotic solutions, either saline or diatrizoate salts, produce a reversible renal vasodilatation (all $P < 0.01$). Control RVR was between 0.703 and 0.782 mmHg/ml/min for the four groups. Figure 2 shows that both hyperosmotic diatrizoate salts produced a reversible decrease in E_{PAH} (both $P < 0.01$) whereas neither isosmotic nor hyperosmotic NaCl affected E_{PAH}. Control E_{PAH} was between 0.713 and 0.795 for the four groups.

Figure 3 shows that isosmotic solutions of either NaCl, anionic (Hypaque) or nonionic

TABLE I. EXPERIMENTAL TEST INFUSIONS.

Solution	N[a]	Iodine, mg/ml[b]	Osmolality, mOsm/kg H_2O[c]
Renografin 76 66% meglumine diatrizoate 10% sodium diatrizoate	7	370	1500
Hypaque 60 60% meglumine diatrizoate	6	282	1350
Hypaque 13.4 13.4% meglumine diatrizoate	6	63	294
Metrizamide 34.8 34.8% metrizamide	6	168	297
4.5% NaCl	8	0	1500
0.9% NaCl	7	0	300

[a] Number of animals studied.
[b] Manufacturer's data.
[c] Measured by freezing-point depression.

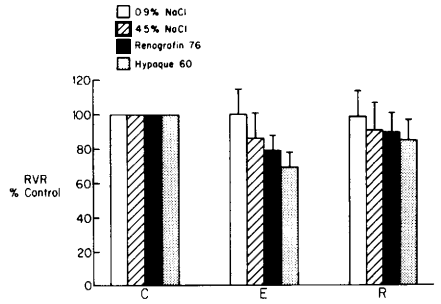

FIG. 1. Effect on renovascular resistance (RVR) of renal arterial infusion of hyperosmotic solutions. C = control period, E = experimental period, R = recovery period.

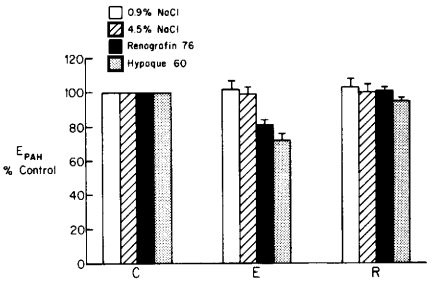

FIG. 2. Effect on renal extraction of para-aminohippurate (E_{PAH}) of renal arterial infusion of hyperosmotic solutions.

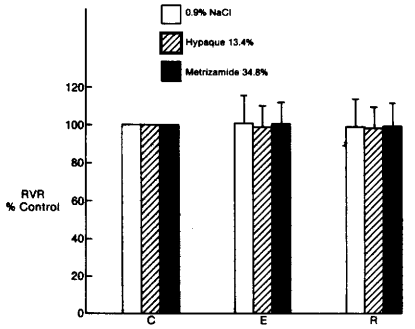

FIG. 3. Effect on RVR of renal arterial infusion of isosmotic solutions.

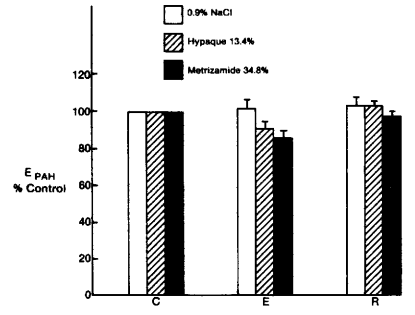

FIG. 4. Effect on E_{PAH} of renal arterial infusion of isosmotic solutions.

(Metrizamide) contrast media did not affect RVR. Control RVR was between 0.703 and 0.787 mmHg/ml/min for the three groups. Figure 4 shows that both isosmotic contrast media produced a reversible decrease in E_{PAH} (both $P < 0.05$). Control E_{PAH} was between 0.751 and 0.795 for the three groups.

Discussion. These studies demonstrate that hyperosmotic solutions infused into the renal artery produce renal vasodilation but that the depressive effect of iodinated contrast media on E_{PAH} is not related to their osmotic properties.

Since the circulating levels of PAH were about 2 mg%, the possibility that the depression of E_{PAH} was due to exceeding the maximal tubular capacity for PAH transport may be excluded. The possibility that the contrast medium competed with PAH for tubular transport and thus decreased E_{PAH} is unlikely since its excretion is almost totally by glomerular filtration (9). In our previous studies (1) Renografin did not alter intrarenal distribution of blood flow as measured with radioactive microspheres; therefore, it seems unlikely that the fall in E_{PAH} reflects a shift in renal blood flow from cortex to medulla. Since the contrast media significantly depressed E_{PAH} whether it was hyperosmotic or isosmotic and equiosmolar NaCl did not, it is clear that the effect is not due to the hyperosmotic nature of the contrast media. In accord with the studies of Danford *et al.* (10) it appears that the effect is mediated by the organic iodinated portion of the molecule.

Of interest is the fact that metrizamide depresses E_{PAH} but does not depress basal short-circuit current in the isolated toad urinary bladder. Thus, both the anionic (diatrizoate) and non-ionic (metrizamide) contrast media decrease E_{PAH} by a mechanism that is unrelated to their osmotic properties and probably dependent on the organic iodinated portion of the molecule. However, only the anionic form (diatrizoate) lowers basal short-circuit current in the isolated toad urinary bladder. These observations are in support of Ziegler and Olsen's view (6) that anions (e.g. diatrizoate) may regulate sodium transport but do not indicate that there is a dependent link between sodium transport and PAH transport.

Summary. Nonionic and anionic contrast media, isosmotic or hyperosmotic, decrease E_{PAH} while equiosmolar NaCl does not; this effect is mediated by the organic iodinated portion of the molecule.

1. Norby, L. H., and DiBona, G. F., J. Pharmacol. Exp. Ther. **193,** 932 (1975).
2. Ziegler, T. W., Ludens, J. H., Fanestil, D. D., and Talner, L. B., Kidney Int. **7,** 68 (1975).
3. Gerencser, G. A., Park, Y. S., and Hong, S. K., Proc. Soc. Exp. Biol. Med. **144,** 440 (1973).
4. Dantzler, W. H., and Bentley, S. K., Amer. J. Physiol. **230,** 256 (1976).
5. Holtermann, H., Acta Radiol. Suppl. **335,** 1 (1973).
6. Ziegler, T. W., and Olsen, L. S., Proc. Amer. Soc. Neph. **6,** 118 (1976).
7. Smith, H. W., Finklestein, N., Alaminosa, L., Crawford, B., and Graber, M., J. Clin. Invest. **24,** 388 (1945).
8. Hunstberger, D. V. and Leaverton, P. E., "Statistical Inference in the Biomedical Sciences", p. 254. Allyn and Bacon, Boston (1970).
9. Woodruff, M. W. and Malvin, R. L., J. Urol. **84,** 677 (1960).
10. Danford, R. O., Talner, L. B., and Davidson, A., Invest. Radiol. **4,** 301 (1969).

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