Influence of Antidiuretic Hormone on Peritoneal Membrane Area and Permeability

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ABSTRACT The present study was carried out to determine if antidiuretic hormone (ADH) altered the solute handling characteristics of the peritoneal membrane. Lightly anesthetized dogs primed with urea-^{14}C (60 mol wt) and inulin (5200 mol wt) were volume expanded with hypotonic saline solution to suppress endogenous ADH as assessed by urine/plasma osmolality. With ADH suppressed, two to three control peritoneal dialysis exchanges were carried out. A constant infusion of ADH in a physiologic dose of 150 mU/hr in saline was begun and the urine/plasma osmolality followed until it was significantly greater than one. Two to three experimental dialysis exchanges were then carried out. Dialysance across the peritoneal membrane was calculated for inulin (D_I) and urea (D_U). In 16 such studies D_U fell in all but three (the mean value for the fall was 2.8 $\pm$2.6 ml/min; $P < 0.001$). D_I varied randomly and showed no significant change. In all 16 studies D_I/D_U rose ($D_I/D_U = 0.054 \pm 0.054$; $P < 0.005$). Seven dogs were studied with an identical protocol but saline was infused without ADH. D_U and the dialysance ratio varied randomly. D_U fell in one and did not change or rose in four and D_I/D_U rose in two and fell in three. The data are interpreted to show a fall in area but an increase in mean pore radius of the "peritoneal membrane" in response to physiologic amounts of intravenous ADH. The fall in area is consistent with a decreasing splanchnic blood flow.

INTRODUCTION

The permeability characteristics of a variety of biologic and synthetic membranes have been worked out using comparative transmembrane diffusion rates of solutes of differing sizes. Description of these permeability characteristics using the concept of water-filled pores through which the solute diffuses has proven to be useful even when histologic study fails to identify these discrete anatomic pores. In the following discussion such classical pore theory will be used recognizing that electron microscopic studies (1) provide only suggestive evidence for such pores in the membranes considered.

Previous studies (2, 3) in patients with chronic renal failure undergoing peritoneal dialysis have demonstrated wide variations with time in peritoneal membrane permeability. Permeability was assessed by alterations in the dialysance ratio of uncharged solutes of widely discrepant molecular size. Variations in vasopressin blood level has been suggested as a possible mechanism for these changes. The present experiments were undertaken to determine what role ADH [1] played in these alterations. Peritoneal dialysance was determined for urea and inulin from blood to dialysis fluid across the peritoneal membrane. Dialysance (milliliter per minute) is a first-order rate constant for solute movement from blood into the peritoneal space modified to express the number of milliliters of whole blood (urea) or plasma (inulin) cleared of solute per minute. Dialysance is a function of both membrane area and permeability. An index of membrane permeability is obtained by comparing the dialysances in ratio fashion, as membrane area for solute transfer of the two solutes is identical and cancels out of the ratio. Although dialysance of an individual solute is a function of both membrane area and permeability, it is apparent that dialysance of urea, a small, uncharged solute with a comparatively high diffusivity in water, will reflect alterations in membrane area for diffusion more closely than dialysance of the large inulin molecule. Alterations in inulin dialysance, on the other hand, will more closely reflect changes in the mean pore radius.

Received for publication 17 March 1971 and in revised form 26 May 1971.

[1] *Abbreviations used in this paper:* ADH, antidiuretic hormone; D_I, inulin dialysance; D_u, urea dialysance; GFR, glomerular filtration rate.

METHODS

Following an overnight fast, healthy mongrel dogs weighing 16–29 kg were anesthetized with a dose of thiopental not exceeding 20 mg/kg and maintained with a slow drip infusion of a 2.5% solution. An endotracheal tube was inserted and connected to a Harvard respirator.[2] Bladder urine was collected in females with a No. 16 Foley catheter (Pharmaseal Laboratories, Glendale, Calif.) and in males with a No. 14 plastic feeding tube placed transurethrally. Air washout with 50 cc was utilized to assure complete bladder emptying. A polyethylene catheter was introduced into the femoral artery and threaded into the aorta to monitor arterial blood pressure and provide a route for obtaining arterial blood samples. With the animal supine, a small incision was made over the linea alba below the falciform ligament and carried down into the peritoneal cavity. 500 ml of lactated Ringer's solution at 37°C containing 1000 units of heparin was introduced into the peritoneal cavity by gravity. Lactated Ringer's solution was chosen to eliminate the osmotic gradient developed across the peritoneal membrane by commercially available 1.5% glucose-containing solutions. A flexible silicone rubber peritoneal dialysis catheter was then introduced into the peritoneal cavity with the tip of the catheter in the rostral aspect of the left peritoneal gutter. The opening was closed around the catheter with a purse-string suture to make a watertight closure.

Endogenous ADH release was suppressed with 0.45% saline infused at a rate of 25 ml/min until a steady-state urine flow rate exceeded 10 ml/min (range 10–23 ml/min) and the ratio of urine to plasma osmolality dropped well below one. A hypotonic saline load of 50–100 ml/kg was usually required depending on the state of hydration of the animal. Once a steady-state diuresis was established, the infusion rate was kept constant until ADH was administered and then the infusion slowed to just match urine losses.

Priming doses of inulin (100 mg/kg) and urea-^{14}C[3] were given. The latter was calculated to give a plasma concentration of 2000–3000 counts per ml at 100% efficiency assuming a 60% volume of distribution within the animal. A sustaining infusion of the solutes was started immediately thereafter. The first exchange was left in the peritoneal cavity for 50 min to allow equilibration of the priming and sustaining dosages and then discarded. Thereafter dialysis exchanges were carried out using gravity for filling and drainage with the following pattern: inflow time approximately 2.0 min; combined inflow and dwell time precisely controlled to 35.0 min; drainage time of 15.0 min. The exact total exchange time was 50 min. Light manual pressure over the abdomen was often required for complete drainage. At the midpoint of each exchange mean systemic blood pressure was measured with an aneroid manometer and 12 ml of blood was removed and placed in a heparinized tube for analysis.

For protocol I following several control periods of endogenous ADH suppression as judged by stable urine flow rates and a urine to plasma osmolality ratio of less than 0.80 (Table III), an infusion was started of 0.9% saline (1 ml/min) to deliver either 150 mU/hr or 300 mU/hr of vasopressin.[4] Three or four more exchanges were completed after starting the vasopressin infusion. 14 dogs received the 150 mU/hr infusion and 2 dogs the 300 mU/hr infusion. For protocol II seven dogs were infused with 0.9% saline without added vasopressin to serve as time controls. Urine was collected every 25 min once steady-state diuresis had been established and assayed for inulin and osmolality.

The alkali stable fraction of inulin was measured in the plasma, dialysate, and urine utilizing the method of Walser, Davidson, and Orloff (4). This method was selected because it measures a comparatively larger and more homogeneous molecular weight fraction of polymers within the total inulin population. Osmolalities of urine, plasma, and dialysate were measured on either a Fiske Model G or Osmette osmometer.[5] To solubilize plasma proteins, we added equal volumes of plasma and dialysate to a fivefold greater volume of Soluene[6] and incubated for 3–4 hr at 37°C. Either 0.2 ml sample and 1.0 ml Soluene, or 0.4 ml sample and 2.0 ml Soluene, were added to 20 ml of Bray's solution and sample vials counted in a model 3320 Packard Tri-Carb Liquid Scintillation Spectrometer.[6] A standard quench curve for urea-^{14}C was derived and counts per minute were converted to disintegrations per minute for all samples.

Calculation of data. Dialysance for inulin mol wt 5200, and urea-^{14}C mol wt 60 were calculated for each exchange period according to a formula previously described (2).

$$D = \frac{\ln\left(S_D/S_B \times \frac{V_B + V_D}{V_B}\right)}{t} \cdot \frac{V_D \times V_B}{V_D + V_B}$$

where

D = dialysance in ml/min
S_D = concentration in dialysate
S_B = concentration in blood
V_B = volume of distribution within the body of urea (60% of body weight in kilograms) or inulin (20%)
V_D = volume of dialysate returned at the close of an exchange
t = time in minutes from initiation of inflow until the completion of drainage

Since the blood samples were taken at the midpoint of each exchange, the direct dialysate and plasma concentration could be utilized to compute the S_D/S_B ratio. The volume of dialysate chosen for infusion was 0.5 liters. This held the S_D/S_B ratio low enough so that variations in V_B of up to 2–3 liters did not significantly influence the final dialysance value (2). Experiments were excluded in which suppression of endogenous ADH during the control exchanges was not achieved as judged by changes in the urine to plasma osmolality ratio. Dogs were excluded in which drainage was mechanically unsatisfactory or in which leakage occurred around the catheter. Several dogs exhibited high permeability to urea with S_D/S_B of 0.8 or greater. These dogs were excluded as the near equilibrium of blood and dialysis fluid for one of the solutes renders the calculation of the dialysance ratio inaccurate. The volume of dialysate drained varied by ±15% from that infused. Actual volumes of dialysate drainage were used in the calculation rather than the 0.5 liter that was infused. The usual pattern was for the drainage to slightly exceed the dialysate infused. The first period during vasopressin infusion was not used since maximal ADH effect as judged by urine

[2] Harvard Apparatus Co., Inc., Millis, Mass.

[3] Urea-^{14}C was obtained from New England Nuclear Corp., Boston, Mass.

[4] Aqueous Pitressin 20 pressor U/cc; Parke, Davis & Company, Detroit, Mich.

[5] Fiske Associates, Uxbridge, Mass.

[6] Packard Instrument Co., Inc., Downers Grove, Ill.

TABLE I

Protocol I Results—Dialysance of Inulin and Urea with ADH Given

Dog	Inulin dialysance			Urea dialysance			Dialysance ratio		
	Control	Experiment	Delta	Control	Experiment	Delta	Control	Experiment	Delta
		ml/min			*ml/min*				
3	1.43	1.93	0.50	9.9	13.8	3.9	0.144	0.144	0
4	1.25	1.26	0.01	11.0	9.0	−2.0	0.116	0.139	0.023
5	1.56	2.03	0.47	9.3	9.5	0.2	0.172	0.221	0.049
7	4.30	3.60	−0.70	16.6	12.1	−4.5	0.270	0.295	0.025
8	2.82	3.05	0.23	16.7	13.7	−3.0	0.163	0.226	0.063
9	3.89	3.07	−0.82	19.1	11.7	−7.4	0.208	0.263	0.054
12	1.71	3.70	1.99	11.6	9.6	−2.0	0.149	0.385	0.236
13	1.54	2.19	0.65	17.2	14.3	−2.9	0.093	0.149	0.056
14*	1.40	1.37	−0.03	11.5	8.7	−2.8	0.124	0.156	0.032
15	1.73	2.99	1.26	16.3	16.4	0.1	0.174	0.184	0.010
23	4.10	3.70	−0.40	11.5	9.6	−1.9	0.350	0.390	0.040
24	4.09	4.13	0.04	18.6	16.1	−2.5	0.221	0.254	0.033
25	0.86	0.69	−0.17	13.3	9.2	−4.1	0.065	0.073	0.008
26	1.38	1.26	−0.12	11.7	7.9	−3.8	0.118	0.161	0.043
27*	2.05	2.69	0.64	15.7	10.8	−4.9	0.131	0.255	0.124
28	2.97	3.17	0.20	20.8	14.2	−6.6	0.140	0.216	0.076
Mean	2.32	2.55	0.23	14.4	11.7	−2.8	0.164	0.219	0.054
SEM	1.15	1.01	0.68	3.5	2.7	2.6	0.070	0.083	0.054

* Dogs given 300 rather than 150 mU/hr of ADH.

osmolality was not reached during this exchange. Renal clearance of inulin and osmolar clearance were calculated using conventional techniques (5). Dialysance for inulin (D_I), urea (D_U), and the dialysate ratio ($D_R = D_I/D_U$) were calculated for each exchange. Mean values and their standard deviations for dialysance and dialysance ratio were calculated and the control and experimental exchanges compared. The difference of the means was assessed using the method for nonindependent samples described by Croxton (6).

RESULTS

Of 28 animals studied, three were discarded because of urea equilibration ratios that were unacceptably high. Two others were discarded for technical reasons (poor drainage, peritoneal bleeding). Of the remaining 23 animals, 16 were studied using protocol I and 7 using protocol II. Table I gives individual dialysance figures for inulin and urea as well as their dialysance ratios for

TABLE II

Protocol II Results—Dialysance of Inulin and Urea with No ADH Given

Dog	Inulin dialysance			Urea dialysance			Dialysance ratio		
	Control	Experiment	Delta	Control	Experiment	Delta	Control	Experiment	Delta
		ml/min			*ml/min*				
10	2.82	1.89	−0.93	14.8	9.5	−5.3	0.191	0.199	0.008
11	2.93	4.16	1.23	20.9	20.2	−0.7	0.142	0.243	0.101
17	3.12	2.27	−0.85	12.2	18.5	6.3	0.256	0.123	−0.133
16	2.18	2.84	0.66	25.7	27.7	2.0	0.090	0.080	−0.010
18	1.05	0.92	−0.13	16.6	16.1	−0.5	0.063	0.057	−0.006
20	6.66	4.60	−2.06	15.0	11.7	−3.3	0.443	0.393	−0.050
21	7.83	9.24	1.41	16.2	15.2	−1.0	0.482	0.602	0.120
Mean	3.80	3.70	−0.10	17.3	17.0	−0.4	0.238	0.242	0.004
SEM	2.29	2.55	1.19	4.2	5.6	3.5	0.154	0.181	0.077

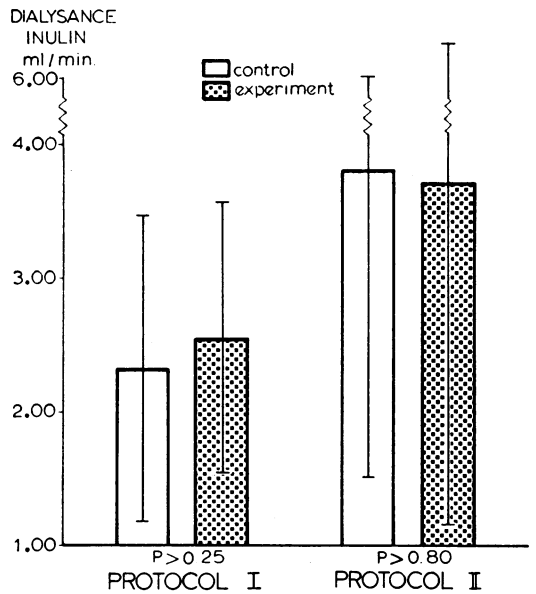

FIGURE 1 Dialysance of inulin compared for control and experimental observations in protocol I (ADH given) and protocol II (no ADH). One standard deviation about the mean is shown. *P* values for the significance of the difference of the mean is given along the abscissa.

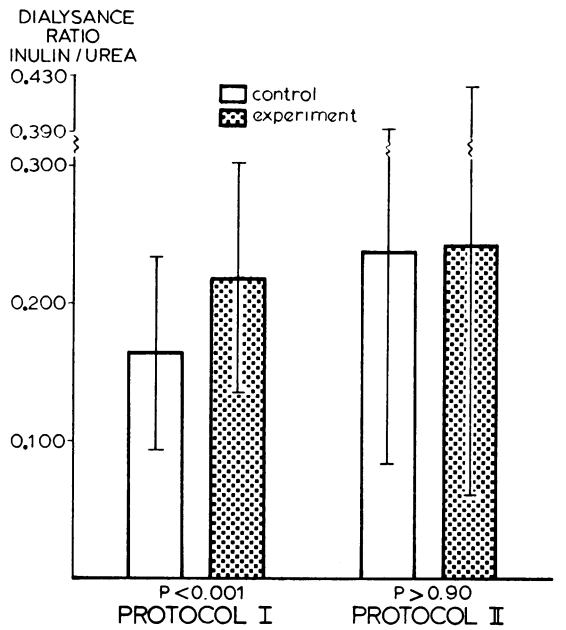

FIGURE 3 Ratio of inulin to urea dialysance compared for control and experimental observations in protocol I and II. One standard deviation about the mean is shown. *P* values for the significance of the difference of the means is given along the abscissa.

all studies in protocol I. The change in dialysance for inulin, urea, and their ratio from control (ADH suppression) to experimental (ADH infused) periods is given as well. Table II provides comparable data for protocol II. Fig. 1 is a bar graph plot of mean inulin dialysance. For protocol I, inulin dialysance in the control period was 2.32 ±1.15 ml/min and after ADH infusion 2.55 ±1.01 ml/min. The difference (0.23 ±0.68 ml/min) is not statistically different when the means are compared. Fig. 2 is a plot of mean urea dialysance. Protocol I studies show a significant fall (14.4 ±3.5 to 11.7 ±2.7 ml/min; $P < 0.001$). The change from control value for

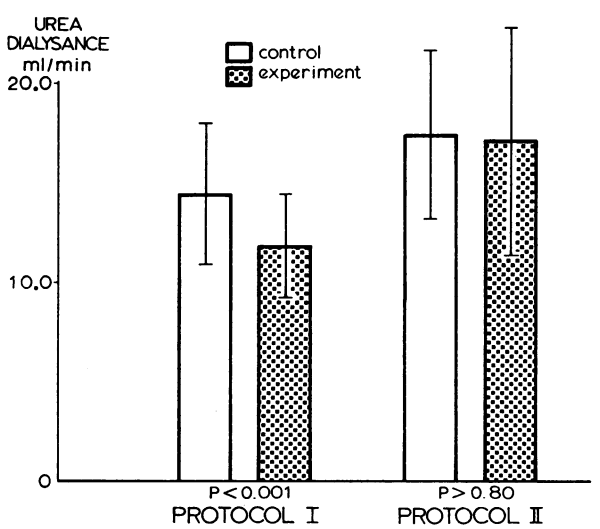

FIGURE 2 Dialysance of urea compared for control and experimental observations in protocol I and II. One standard deviation about the mean is shown. *P* values for the significance of the difference of the means is given along the abscissa.

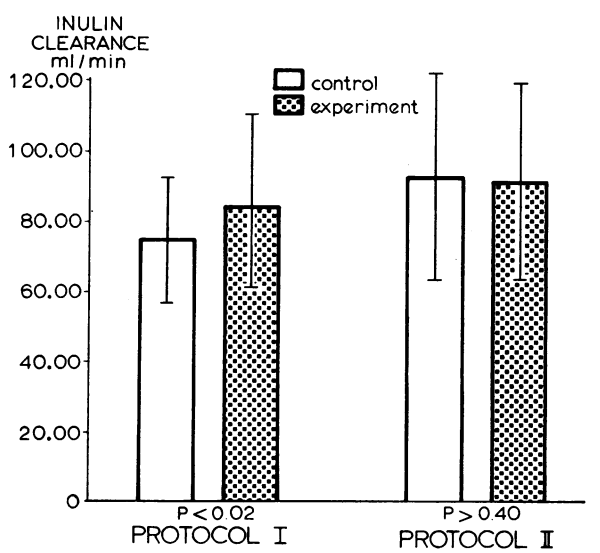

FIGURE 4 Renal clearance of inulin compared for control and experimental observations in protocol I (ADH given) and II (no ADH).

TABLE III

Renal Clearances of Inulin and Urine to Plasma Osmolality Ratios

Dog	U/P osmolality			C_{Inulin}		
	Control	Experiment	Delta	Control	Experiment	Delta
					ml/min	
			Protocol I			
1	0.841	1.830	0.989	51.3	60.4	9.10
2	0.428	1.650	1.222	105.0	120.0	15.00
3	0.314	1.310	0.996	83.2	76.6	−6.60
4	0.409	1.280	0.871	61.0	91.8	30.80
5	0.190	0.618	0.428	52.7	63.4	10.70
7	0.473	1.100	0.627	63.2	69.1	5.90
8	0.789	1.210	0.421	73.0	73.0	0
9	0.491	1.677	1.186	104.6	138.3	33.70
12	0.570	1.200	0.630	85.7	135.0	47.50
13	0.712	1.560	0.848	93.3	104.4	11.10
14*	0.510	1.100	0.590	78.6	81.2	2.60
15	0.573	3.120	2.547	97.3	108.9	11.60
23	0.682	0.864	0.182	77.3	65.9	−11.40
24	0.373	1.173	0.800	51.3	52.6	1.30
25	0.432	1.250	0.818	82.0	82.0	0
26	0.677	1.591	0.941	43.0	41.2	−1.80
27*	0.287	0.689	0.402	74.6	80.2	5.60
28	0.318	1.170	0.852	68.5	69.3	0.70
Mean	0.503	1.354	0.852	74.8	84.1	9.21
SEM	0.176	0.533	0.492	18.1	26.6	14.40
			Protocol II			
10	0.909	0.936	0.027	143.0	143.0	0.00
11	0.438	0.488	0.050	126.3	117.3	−9.00
16	0.528	0.678	0.150	88.5	88.6	0.10
17	0.454	0.602	0.148	83.0	79.4	−4.60
18	0.508	0.538	0.030	79.1	83.9	4.80
20	0.579	0.593	0.014	78.7	75.7	−3.00
21	0.558	0.503	−0.055	50.6	51.7	1.10
Mean	0.567	0.619	0.052	92.7	91.4	−1.51
SEM	0.148	0.144	0.063	29.1	27.7	4.13

* Dogs given 300 rather than 150 mU/hr of ADH

individual studies showed a fall in all but three studies. Fig. 3 is a plot of the mean dialysance ratio. The mean control ratio was 0.164 ±0.070 and the experimental ratio was 0.219 ±0.084. The increase is significant ($P < 0.001$).

By contrast, the protocol II group (Table II) which was handled identically except that ADH was withheld, showed random variation in inulin and urea dialysances as well as their ratios. Bar graph plots of the mean values are presented in Figs. 1–3 for comparison with protocol I. Four of the seven studies showed a negative dialysance ratio.

Table III shows urine to plasma osmolality ratios for studies using both protocols I and II. The renal inulin clearance is given as well. The mean change in the urine to plasma osmolality ratio for protocol I and II animals was 0.852 ±0.492 and 0.052 ±0.063, respectively. Of interest is the renal inulin clearance in the protocol I dogs which increased significantly (9.21 ±14.4 ml/min; $P < 0.02$) whereas the protocol II dogs showed an insignificant decrease (−1.5 ±4.1 ml/min; $P > 0.4$). Fig. 4 shows the changes in renal inulin clearance in bar graph fashion.

DISCUSSION

Data from the present experiments show a rising dialysance ratio for protocol I studies in all but 2 of the

16 instances in which ADH was given. The mean value for the increase over control values for the ADH-treated dogs (0.054) is highly significant ($P < 0.001$). This is interpreted as an increase in membrane permeability. Of interest is the significant fall in urea dialysance that occurred in all but three of the ADH-treated dogs. The mean fall in urea dialysance is interpreted as a decrease in the total membrane area available for diffusion. The mean inulin dialysance for the protocol I studies rose, but not significantly. Individual inulin dialysance rose or fell depending on whether the predominant change was membrane area decrease or permeability increase.

A decrease in peritoneal membrane area could well be the result of a decrease in splanchnic blood flow (7, 8). Hare, Valtin, and Gosselin (9) using the technique of peritoneal dialysis studied the movement across peritoneum of potassium and iodide in response to ADH addition to the dialysis fluid (20–115 U/liter) and found a fall in dialysance and a change in membrane permeability. They ascribe the fall in dialysance to decrease in splanchnic blood flow but because of the experimental design were unable to identify whether membrane permeability increased or decreased. It is of interest that in the present experiment ADH in physiologic quantities delivered intravenously also results in a shunting of blood away from the splanchnic circuit.

There are two mechanisms by which a fall in splanchnic blood flow could result in a rising dialysance ratio. First, the decrease in blood flow could limit solute delivery to the peritoneal membrane and result in a falling urea dialysance because the concentration of urea nitrogen in the capillary blood would be lower than the measured blood urea nitrogen used in the dialysance calculation. Experimental evidence against this mechanism is present in protocol I where studies 5 and 15 show an increase in urea dialysance with the increase in dialysance ratio, and the observation in this and previous studies that low peripheral venous blood urea nitrogen does not result in a low urea dialysance. Second, the loss of a low permeability portion of the membrane due to redistribution of blood flow could result in a rising dialysance ratio. The protocol I studies cited above again point away from this explanation as does the rising inulin dialysances in 10 of the protocol I studies. What seems most likely is that the peritoneal membrane is homogeneous with regard to permeability and that solute delivery to the membrane is not flow limited but rather that the increased dialysance ratio is the result of ADH acting on some component of the membrane to increase permeability. In support of this concept is the known action of ADH on the permeability of other biological membranes.

Dogs in which no ADH was given were studied as time controls in order to rule out the influence of repeated infusion of isotonic solutions into the peritoneum as etiologic in the increasing dialysance ratio and the decreasing urea dialysance. Four of these seven were the only animals in which the dialysance ratio fell. In two of these animals the urea dialysance rose. ADH administration then seems to be the etiologic agent in the observed changes in dialysance.

Indirect evidence from previous work (3) indicates that the "peritoneal membrane" involved in the solute transport discussed above is a composite of capillary endothelium, basement membrane, epithelium, and the peritoneal mesothelium. The work of Berndt and Gosselin (10) with rabbit mesentery has shown that this membrane reacts to pharmacologic agents in a way that is very similar to the intact capillary. Study of the passage of electron microscopic tracers across the mesothelium point up that some of its characteristics are similar to vascular endothelium (11). The work of Shear, Harvey, and Barry (12) is of interest in that an in vitro preparation of rabbit omentum exposed to a pharmacologic dose (33 mμ/ml in the bathing medium) of ADH showed an increase in permeability for sodium over the ADH-free state. Demonstration of a permeability change as measured by altered sodium-22 flux across the two layered mesothelium can be viewed as evidence for the ADH-sensitive structure being peritoneal (mesothelial) membrane and not capillary endothelium basement membrane or epithelium. The high dose required to demonstrate this effect and the low level of response (1.2 times control values), however, calls the biologic significance of this effect into question.

Nagel and Kuschinsky (13) studying dog mesentery in an in vitro setting have concluded that this membrane does not sterically hinder the passage of molecules as large as dextran at mol wt 500,000. Two lines of evidence resulted in this conclusion; first, the failure to demonstrate water flow across the membrane in response to an osmotic gradient established by dextran, and second, the similarity of the mesentery's permeability coefficient for dextran and dextran's diffusivity in water. This work points strongly to the capillary endothelium as the discriminating structure for mass transfer across the peritoneal membrane. In addition, it raises the interesting possibility that capillaries throughout the body will respond to ADH. The term capillary is used here for simplicity, recognizing that there are differences in permeability characteristics between the arteriolar and venular ends and that area of the more permeable venular as compared with the arteriolar capillary differs depending on the location within the body (14).

Additional work by Shear, Castellot, Shinaberger, Poole, and Barry (15) performed on anesthetized dogs showed an increase in fluid reabsorption from the peritoneal space in response to a pharmacologic (2 U) dose

of ADH placed on the peritoneal space but not when ADH was delivered in either physiologic (50 mU/kg per hr) or pharmacologic (1.7 U/hr) quantities intravenously. No index of endogenous vasopressin levels is available in this study. In view of no efforts to suppress ADH, it seems likely that the barbiturate anesthesia used resulted in high endogenous levels of hormone. Adding ADH to the peritoneum might not then result in further change. The observation that intraperitoneal ADH increased the rate of absorption of water from the peritoneum is at variance with the previously cited study by Hare et al. (9) in which reduction in membrane area appeared to be the predominant effect. The reason for this difference is unexplained, but might reflect the fact that bulk water flow is directly proportional to the fourth power of the pore radius while solute transport by diffusion is proportional only to its square.

Increase in glomerular filtration rate in response to ADH cannot be interpreted closely in the present study. The ready permeability of the glomerular basement membrane to ultrafiltered inulin (sieving coefficient = 1) prevents identification of increased glomerular membrane permeability as the reason for the higher clearance. In addition, no index of the area of filtering membrane or transmembrane hydrostatic driving force is available in the present study. The increase in GFR then could be the result of increased renal blood flow, increased glomerular permeability, increased glomerular basement membrane area, and/or an increase in hydrostatic driving force (adjustment of afferent/efferent resistances). An increase in glomerular basement membrane permeability analogous to that shown for the peritoneal membrane remains an attractive speculation. It is of interest that while ADH is not recognized to increase GFR in mammals that this effect has been identified in representatives of two other major phyletic groups of vertebrates, namely teleosts and lungfish (16, 17).

ACKNOWLEDGMENTS

We are pleased to acknowledge the technical assistance of Mr. Christopher Gent in the performance of the studies as well as Phyllis Ibach and Donna Gratch for the chemistry determinations.

This work was supported in part by U. S. Public Health Service Grant 00340, U. S. Public Health Service Grant 5TO1 AM 05634, Clinical Research Center Grant 5MO1 RR-40, and the John and Mary R. Markle Foundation.

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