Effects of Secretin on Renal Hemodynamics and Excretion[1] (36362)

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Secretin is a gastrointestinal polypeptide hormone containing 27 amino acids in a single chain. It shares a sequence of 14 amino acids with glucagon, a hormone released from the pancreatic islet α cells. Workers investigating early secretin preparations noted that systemic administration induced a slight diuresis in dogs (1, 2). The onset of action was approximately 20 to 30 min after injection and was completely absent in pancreatectomized dogs. In 1957, Baron (3) suggested that the diuresis was an indirect consequence of the secretin-stimulated release of alkaline pancreatic juice into the duodenum where the rapid reabsorption of water and electrolytes presented the kidney with an "alkaline tide." Barbezat *et al.* (4) have reported that in dogs undergoing a saline diuresis, a significant increase in urinary volume (V), sodium excretion ($U_{Na}V$) and potassium excretion (U_KV) follows the systemic infusion of secretin or glucagon. In studies in which secretin was administered intravenously, systemic alterations such as changes in cardiac output, peripheral resistance, or secretory function of the pancreas, liver, or stomach could have influenced renal function. In order to determine if the effects of secretin could be due to a direct renal action and to minimize systemic effects, this agent was infused directly into a renal artery in dogs.

Methods. Mongrel dogs of either sex, weighing between 17 and 22 kg, were anesthetized with pentobarbital sodium (30 mg/kg, iv) and the trachea intubated. Mean arterial blood pressure (MAP) was monitored with a pressure transducer (Statham P23AA) via a carotid artery catheter. The femoral artery and vein were catheterized for the collection of blood and administration of solutions, respectively. An infusion of 0.4% inulin, 0.08% *p*-aminohippurate (PAH) in 0.9% NaCl, was administered at a rate of 0.25 ml/kg per min. A kidney was approached via a retroperitoneal flank incision and the ureter catheterized. If more than one renal artery was encountered, the contralateral kidney was used. A flow probe was placed around the renal artery and connected to a square wave electromagnetic flowmeter (Carolina Medical Electonics). This provided a direct measurement of total renal blood flow (RBF). MAP and RBF were recorded continuously on a Beckman Type R Dynograph. A 23 gauge scalp needle was passed retrograde into the renal artery for drug administration. A solution of NaCl (0.9%) was continuously infused at a rate of 1.0 ml/min.

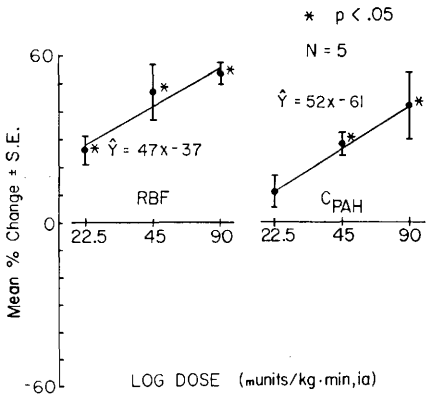

FIG. 1. Analysis of variance tests for linear regression and deviation from linearity.

When urinary volume had stabilized, three 10 min control urine samples were collected. Secretin was then infused, during the next three 10 min collection periods, directly into the renal artery. The secretin concentration

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TABLE I. Effects of Secretin on Renal Hemodynamics and Excretion (mean difference from control ± standard error).[a]

	(mU/kg • min, ia)		
	22.5	45	90
RBF (ml/min)	50 ± 5.4[b]	82 ± 7.8[b]	100 ± 9.5[b]
MAP (mm Hg)	−4.0 ± 2.0	−4.0 ± 5.2	2.0 ± 5.2
RVR (RU)	−.16 ± .05[b]	−.24 ± .08[b]	−.27 ± .06[b]
GFR (ml/min)	3.0 ± 1.8	4.6 ± 1.3[b]	6.0 ± 1.6[b]
C_{PAH} (ml/min)	9.0 ± 5.[illegible]	32 ± 4.5[b]	32 ± 5.5[b]
$U_{Na}V$ (μEq/min)	20 ±19	8.2 ± 9.5	44 ±17
U_KV (μEq/min)	3.0 ± 2.3	2.6 ± 3.6	5.0 ± 2.2
V (ml/min)	.2 ± .13	.1 ± .12	.3 ± .14
FF	−.01 ± .01	−.04 ± .01[b]	−.04 ± .01[b]

[a] $N = 5$.

[b] Significant difference from control ($p < .05$).

was varied to provide different doses at the same infusion rate. Five animals were studied at each dose. Blood was collected at the midpoint of each collection period. Significant differences from control was determined by a Student's t test (paired comparison) (5).

Renal vascular resistance (RVR) is expressed as resistance units (RU) and was calculated by dividing MAP (mm Hg) by RBF (ml/min). Filtration fraction (FF) was calculated by dividing GFR (ml/min) by C_{PAH} (ml/min). Glomerular filtration rate (GFR) was estimated from the clearance of inulin. Inulin was determined by the method of Schreiner (6) and PAH was determined by the method of Smith *et al.* (7). Sodium and potassium concentrations were determined with a Coleman flame photometer.

In five experiments, dogs were pretreated on the day before the experiment with deoxycorticosterone acetate[3] (DOCA) and vasopressin[4] in oil (10 mg and 5 units, im, respectively). On the day of the experiment an iv infusion containing 330 mU% of aqueous vasopressin and 10% mannitol was given. When V and RBF had stabilized, secretin was infused directly into a renal artery. Plasma and urine osmolalities were determined using a Fiske model G osmometer. Solute-free water reabsorption ($T^c_{H_2O}$) was determined by subtracting V from the calculated osmolal clearance.

[3] Percorten, CIBA.

[4] Pitressin, Parke-Davis.

Pure porcine (GIH) secretin[5] was used in all experiments. Dilutions were made from 75 unit ampules with 0.9% NaCl.

Results. The lowest dose (22.5 mU/kg • min, ia) produced a significant increase in RBF and a significant decrease in RVR (Table I). The middle dose (45 mU/kg·min, ia) produced a significant increase in RBF, GFR and C_{PAH}, while RVR and FF were significantly decreased. At the highest dose (90 mU/kg·min, ia) RBF, GFR and C_{PAH} were significantly increased. RVR and FF were significantly decreased. $U_{Na}V$, U_KV or V were not significantly altered at any dose, nor was MAP.

An analysis of variance tests for linear regression and deviation from linearity was performed for each parameter. The slope of the regression lines of RBF and C_{PAH} differed significantly from zero but there was no significant deviation from linearity (Fig. 1). Although GFR and RVR appeared to be changing in a dose related manner, the slopes of their regressions did not differ significantly from zero.

In Table II, the effect of secretin (45 mU/kg·min, ia) during the $T^c_{H_2O}$ experiments is shown. A Student's t test (grouped comparison) indicated no significant difference between control dogs and DOCA + vasopressin pretreated dogs for any parameter. $T^c_{H_2O}$ was not significantly different from control.

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TABLE II. The Effects of Secretin (45 mU/kg • min, ia) on Renal Hemodynamics and Excretion during $T^c_{H_2O}$ Experiments (mean difference from control ± standard error).[a]

RBF (ml/min)	130 ± 14[b]
MAP (mm Hg)	0.0 ± 0.0
RVR (RU)	−0.23 ± 0.05[b]
GFR (ml/min)	5.0 ± 1.8[b]
C_{PAH} (ml/min)	41 ± 6.6[b]
$U_{Na}V$ (μEq/min)	41 ± 36
U_KV (μEq/min)	−8.0 ± 4.8
V (ml/min)	0.7 ± 0.19[b]
FF	−0.04 ± 0.01[b]

[a] $N = 5$.

[b] Significant difference from control ($p < .05$).

Discussion. The absence of a significant increase in V and $U_{Na}V$ following intraarterial administration indicates that the diuresis and natriuresis observed following systemic administration (1, 2, 4) is related to other actions of secretin. Such an effect could be an indirect action such as the "alkaline tide" hypothesis postulated by Baron (3).

Although Ross (8) observed no effects after intraarterial injection on the renal vasculature of cats by either secretin or glucagon the dog would appear to respond differently. In a study in the dog, Stowe and Hook (9) reported that glucagon produced a significant increase in RBF, V and $U_{Na}V$ following intraarterial infusion. Although they did not rule out a direct tubular action for glucagon, they suggested that the increased $U_{Na}V$ was dependent upon the increase in RBF. Thus it appears that both hormones produce a marked renal vasodilatation in dogs following intraarterial infusion. They differ in that glucagon increases $U_{Na}V$ and V, whereas secretin does not. Agents previously reported to increase RBF while decreasing RVR also produce a concomitant increase in $U_{Na}V$ (10–12). Since the changes in renal hemodynamics produced by secretin correspond to the changes seen with other renal vasodilators, it is surprising that no increase in $U_{Na}V$ was observed. The reason for an absence of a natriuresis is not apparent at this time.

Summary. The infusion of secretin directly into a renal artery produced a dose related increase in RBF and C_{PAH} and reduction in RVR. V and $T^c_{H_2O}$ were unaffected and no increase in $U_{Na}V$ was observed. This is surprising because dilators of renal vasculature produce a natriuresis which correlates with the increase in RBF.

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