Effects of Secretin and Glucagon on Intestinal Transport of Ions and Water in the Rat[1] (36208)

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Some nonbeta cell tumors of the pancreas secrete an unidentified substance that inhibits gastric acid secretion and causes diarrhea. Because secretin and glucagon are natural hormones that inhibit gastric acid secretion (1, 2), their effects on salt and water transport by the small intestine should be examined. Secretin does not alter movement of salt and water in the small intestine of the rat (3) or dog (4) in doses that cause maximal pancreatic secretion. At high doses of 6 units/kg in the rat, water absorption is diminished (5), but the influence of very high doses has not been determined. In Thiry–Vella loops in the unanesthetized dog, high doses of glucagon cause secretion of salt and water in the jejunum and reduce absorption in the ileum (6). This study examines the effect of high doses of secretin and glucagon on the net movement of electrolytes and water in the jejunum and ileum of the anesthetized rat.

Methods. Mature rats were fasted overnight and anesthetized with pentobarbital. A tracheostomy tube was inserted; and a femoral vein was cannulated. Segments of proximal jejunum and distal ileum about 25 cm long were cannulated at each end, washed with 20 ml of perfusion fluid that contained no labeled polyethylene glycol (PEG), and flushed with air. Segments were then washed again with 17.0 ml of perfusion fluid that contained labeled PEG (PEG 1,2-^{14}C glycol; New England Nuclear) and flushed into reservoir beakers with 6% CO_2–94% O_2. Exactly 7.0 ml of fluid were removed from each reservoir for analysis (initial sample). Segments were perfused by recirculating fluid at 2.5 ml/min from the reservoirs with a peristaltic pump. After 30 min, fluid in each circuit was drained into a reservoir and an aliquot was taken for analysis (final sample).

After the first perfusion period (control period), segments were again washed and perfused as described. Just before the start of the second 30 min perfusion period (treatment period), a 1 ml solution of secretin, glucagon, or saline, was injected through the femoral vein cannula. Secretin doses were: Boots 100 U/kg ($n = 2$), GIH 100 U/kg ($n = 2$), GIH 200 U/kg ($n = 2$). Glucagon (Lilly) doses were: 4 μg/kg ($n = 2$), 32 μg/kg ($n = 2$), 256 μg/kg ($n = 2$). Because responses of secretin and glucagon were unrelated to dose or manufacturer, data within each drug study were combined to calculate mean and variance.

Perfusion fluid composition was (mM): Na, 147; K, 4.5; Cl, 124.5; HCO_3, 25; PO_4, 2; mannitol, 25. The solution was gassed with 6% CO_2–94% O_2 and was isotonic with extracellular fluid (305 mOsm/kg). Sodium and potassium concentrations were measured with a flame photometer; chloride concentrations were determined amperometrically; bicarbonate was calculated from measurements of pH and pCO_2 with the Henderson-Hesselbach equation, using a $pK' = 6.1$; radioactivity of PEG 1,2-^{14}C glycol (cpm/ml) was determined with a Beckman scintillation counter.

The net fluxes were calculated with the following equations:

$$\text{net ion flux} = V_i(\text{ion}_f \frac{\text{PEG}_i}{\text{PEG}_f} - \text{ion}_i)$$

$$\text{net water flux} = V_i\,(\frac{\text{PEG}_i}{\text{PEG}_f} - 1),$$

V_i is the initial perfusion fluid volume. Ion_i and Ion_f are the initial and final ionic concentrations; PEG_i and PEG_f are the initial and final counts (cpm/ml). The sign indicates

[1] Supported in part by U.S. Public Health Service Grants AM 09022 and AM 5390 from the National Institute of Arthritis and Metabolic Disease.

TABLE I. Net Movement (mean ± SD) of Ions and Water in Jejunum.

	Treatment	Control[a]	Treatment[a]	Difference	Significant difference
Na^+	Saline	−109 ± 33	− 89 ± 44	+20	[b]
	Secretin	−124 ± 17	− 56 ± 38	+68	[c]
	Glucagon	− 79 ± 59	−125 ± 38	−46	[b]
K^+	Saline	+ 0.06 ± 2.18	+ 1.07 ± 1.83	+ 1.01	
	Secretin	− 0.42 ± 1.12	+ 0.40 ± 4.78	+ 0.82	
	Glucagon	+ 0.70 ± 2.06	+ 0.10 ± 2.76	− 0.60	
Cl^-	Saline	+ 23.0 ± 45.3	+ 25.8 ± 38.1	+ 2.8	
	Secretin	+ 5.8 ± 23.1	+ 52.1 ± 54.6	+46.3	
	Glucagon	+ 37.0 ± 41.2	+ 11.0 ± 28.8	−26.0	—[c]
HCO_3^-	Saline	−117 ± 29	−104 ± 24	+13	
	Secretin	−117 ± 15	− 90 ± 29	+27	
	Glucagon	−121 ± 22	−129 ± 26	− 8	—[c]
H_2O	Saline	− 0.70 ± 0.29	− 0.50 ± 0.30	+ 0.20	
	Secretin	− 0.82 ± 0.25	− 0.39 ± 0.28	+ 0.43	
	Glucagon	− 0.52 ± 0.38	− 0.66 ± 0.21	− 0.14	

[a] Units of electrolyte transport (μmoles × 30 min^{-1} × g of wet wt of $segment^{-1}$); units of water transport (ml × 30 min^{-1} × g of wet wt of $segment^{-1}$). Signs indicate movement into (+) or out of (—) the lumen.

[b] Differs from saline ($p < .05$).

[c] Glucagon and secretin differ ($p < .05$).

net flux into (+) and out of (—) the luminal fluid.

Net fluxes were analyzed statistically with an analysis of variance; significance of difference among means was calculated using Tukey's tables [cited in (7)].

Results. To determine the effects of the hormones on jejunal transport, differences in net movement between control and treatment periods were compared (Table I). Secretin reduced and glucagon enhanced sodium absorption, when compared with saline. Chloride secretion rose with secretin and fell with glucagon; bicarbonate absorption rose with glucagon and fell with secretin. The changes in anion movement caused by the hormones differed from each other but not from those obtained with saline.

In the ileum glucagon augmented and secretin reduced the absorption of chloride and water (Table II). The mean changes induced by the hormones differed from each other but not from those obtained with saline. Sodium behaved similarly to chloride but the variability of the response was greater.

Discussion. The high doses of secretin used in this study and others (5) reduced the absorption and enhanced the secretion of electrolytes and water. Secretin probably does not normally regulate intestinal electrolyte transport, however, because lower doses, which cause maximal pancreatic secretion, have no such effect (3, 4). In high concentrations of 30 units/liter, secretin (Vitrum) also reduces sodium, chloride, and water absorption in the distal third of the hamster small intestine *in vitro* (8).

In contrast to our findings in rats, glucagon enhanced secretion of sodium, chloride, and water, in Thiry–Vella loops of canine jejunum; in ileal loops, glucagon reduced absorption of sodium, chloride, and water and augmented bicarbonate secretion (6). Species differences and the use of anesthesia in our studies may account for the opposite response in dog and rat. Such differences emphasize that glucagon must be tested in man to determine if it could cause the diarrhea that accompanies some

TABLE II. Net Movement (mean ± SD) of Ions and Water in Ileum.

	Treatment	Control[a]	Treatment[a]	Difference	Significant difference
Na^+	Saline	− 56 ± 65	− 54 ± 91	+ 2	
	Secretin	−115 ± 39	− 66 ± 28	+49	
	Glucagon	− 88 ± 29	−124 ± 30	−36	
K^+	Saline	+ 1.96 ± 1.78	+ 2.70 ± 2.60	+ 0.74	
	Secretin	+ 0.33 ± 0.78	+ 2.03 ± 1.18	+ 1.70	
	Glucagon	+ 0.05 ± 0.51	− 0.24 ± 0.48	− 0.19	
Cl^-	Saline	−114 ± 43	−112 ± 64	+ 2	
	Secretin	−147 ± 37	−110 ± 29	+37	
	Glucagon	−116 ± 29	−160 ± 41	−44	—[b]
HCO^-_3	Saline	+ 32.5 ± 22.8	+ 39.3 ± 30.2	+ 6.8	
	Secretin	+ 27.4 ± 7.5	+ 39.9 ± 29.9	+12.5	
	Glucagon	+ 15.4 ± 12.2	+ 22.3 ± 18.5	+ 6.9	
H_2O	Saline	− 0.46 ± 0.22	− 0.40 ± 0.62	+ 0.06	
	Secretin	− 0.77 ± 0.30	− 0.47 ± 0.35	+ 0.30	
	Glucagon	− 0.46 ± 0.26	− 0.87 ± 0.21	− 0.41	—[b]

[a] Units of electrolyte transport (μmoles × 30 min^{-1} × g of wet wt of $segment^{-1}$); units of water transport (ml × 30 min^{-1} × g of wet wt of $segment^{-1}$). Signs indicate movement into (+) or out of (—) the lumen.

[b] Glucagon and secretin differ ($p < .05$).

nonbeta cell tumors of the pancreas.

Although glucagon and secretin usually cause similar secretory and motor responses, glucagon inhibits and secretin stimulates pancreatic secretion (9). In this study, the hormones have also been shown to have opposite effects on net electrolyte and water movement in the small intestine of the anesthetized rat.

Summary. Secretin reduced and glucagon enhanced absorption of ions and water from the small intestine of the rat, when administered intravenously in high doses.

The author thanks Mrs. Mary Denton for her skilled technical assistance.

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Received Sept. 1, 1971. P.S.E.B.M., 1972, Vol. 139.