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THE EFFECT OF SECRETIN ON ELECTRICAL POTENTIAL DIFFERENCES IN THE PANCREATIC DUCT

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SUMMARY

1. Electrical potential differences (PD's) have been measured between the major pancreatic duct and blood of anesthetized cats during free flow of pancreatic juice and during perfusion of the duct with simple salt solutions. The measured PD's were corrected for junction potentials.

2. During free flow the hormone secretin shifts the duct potential in the negative direction by 7 mV, approximately in phase with the secretin-stimulated juice flow.

3. During perfusion secretin shifts the duct PD in the negative direction by about 3 mV, independent of the composition of the perfusion solution used.

4. Relative ionic permeability coefficients for Na^+, K^+, Cl^-, and HCO_3^- in pancreatic duct have been calculated from diffusion potentials and are unaffected by secretin.

5. The ion fluxes stimulated by secretin are up the electrochemical gradient for HCO_3^-, down the gradient for Na^+, K^+, and Cl^-.

6. It is concluded that the effect of secretin on the pancreas is to stimulate active HCO_3^- secretion, as in the liver; and that the secretin-induced PD during free flow is due partly to a change in diffusion potential, partly to the direct effect of active ion transport.

INTRODUCTION

The pancreas secretes a HCO_3^--rich juice in response to the hormone secretin. Although knowledge of electrical potential differences (PD's) across pancreatic epithelia is essential to identifying the secretory mechanisms and determining whether a given ion is distributed passively or transported actively, few measurements of PD's have been reported for the pancreas[1,2]. Recent analysis of PD's in the duct system of the liver[3], which also responds to secretin by producing a HCO_3^--rich fluid, has shown that secretin affects the liver by stimulating active anion secretion.

Abbreviation: PD, electrical potential difference.

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The present study analyzes PD's measured in the main pancreatic duct of the anesthetized cat during free flow or during perfusion, and indicates that secretin also stimulates active anion secretion in the pancreas.

As background, the basic facts of pancreatic secretion may be briefly summarized. The blind proximal ends of the smallest pancreatic ducts join blind spaces that are called the acini, from which fluid passes *via* the intercalated ductules to the main duct, but direct approaches to localizing transport functions in the acini or ducts by micropuncture methods have just begun[1,4]. Regarding the composition of the final juice collected at the end of the main duct, its osmolarity is the same as that of plasma or of fluid perfused through the blood vessels[5,6]; $[Na^+]$ and $[K^+]$ in juice are constant at near-plasma levels, independent of the flow rate; $[HCO_3^-]$ and $[Cl^-]$ vary with rate in reciprocal fashion, such that $[HCO_3^-]$ asymptotically approaches a concentration several times that of plasma and $[Cl^-]$ approaches a concentration a fraction that of plasma with increasing flow rate; fluid secretion nearly ceases in the absence of secretin in the cat (though not in the rabbit); and the hormone pancreozymin controls the release of pancreatic digestive enzymes but has little effect on juice volume. Two hypotheses have been advanced to explain the variation in anion concentrations with flow rate: that a primary HCO_3^--rich fluid is secreted proximally and that HCO_3^- diffuses at a more distal site down its concentration gradient from juice to blood in exchange for Cl^-, the exchange being more complete at lower flow rates; or that two primary fluids, one Cl^--rich and the other HCO_3^--rich, are formed at separate sites at varying rates. Recent work[1,7] suggests that both these factors contribute.

METHODS

Surgical techniques

Mongrel cats weighing 1.8–4.8 kg were deprived of food but not of water for 18 h prior to an experiment and were anesthetized intraperitoneally with sodium pentobarbital. *Via* a midline upper abdominal incision the common bile duct was ligated, a short incision was made in the duodenal wall opposite the common entry point of the pancreatic and bile ducts, and a PE-60 polyethylene catheter was threaded several millimeters into the pancreatic duct. A suture placed in the wall of the duodenum and then tied around the intramural portion of the duct secured the catheter. A fine (PE-10) polyethylene catheter placed in one femoral vein was used as a conduit for administration of secretin and further anesthetic, while a larger (PE-260) catheter inserted into the opposite femoral vein and intermittently flushed with 154 mM NaCl to maintain patency served to accommodate one of the salt bridges for PD measurements.

Electrical measurements

PD's were measured with a Keithley 600A electrometer connected through calomel half-cells to finely-tapered polyethylene bridges containing 154 mM NaCl in 4 % agar. The fine end of one bridge was advanced into the pancreatic duct catheter to a position near the intrapancreatic end of the catheter, while the other bridge was passed into the iliac vein through the large catheter in the femoral vein. Pairs of bridges were selected that gave asymmetry potentials (the PD when both bridges

dipped into the same solution) of less than 0.5 mV. Asymmetry potentials were measured at 5-min intervals throughout an experiment, were always constant within at least 0.2 mV over this interval, and were subtracted from all experimental PD measurements. The cat was electrically shielded by a grounded cage of aluminum foil. All PD's are given as the potential of the duct lumen with respect to that of the bloodstream.

Perfusion techniques

The following procedure permitted measurement of PD's while the main pancreatic duct was being perfused with experimental solutions rather than during free flow of pancreatic juice. After the duodenal end of the pancreatic duct had been catheterized, a piece of fine (PE-10) polyethylene tubing was passed through the catheter down the length of the main duct, brought through the wall of the duct proximally so that a length of only a few millimeters remained within the duct lumen, and then sutured in place. Perfusion of a length of 10–12 cm of the main duct *via* this tubing was carried out in the proximal-to-distal direction (the direction for natural flow of pancreatic juice) under gravity at a flow rate of 0.33 ml/min, which is several times higher than the maximal rate of juice flow in response to secretin. Controls showed that PD's remained the same when the perfusion rate was increased to 2.4 ml/min, implying that over this range of high flow rates the changes in perfusate composition due to diffusional exchanges and to fluid entering from some small ducts were negligible during the brief transit time down the duct. The perfusion solutions used were preheated to 37° and had the composition: 154 mM NaCl; 154 mM $NaHCO_3$; 77 mM NaCl + 77 mM KCl; and 77 mM NaCl + 150 mM mannitol. The PD with 154 mM NaCl as the perfusate was measured before and after measuring the PD with each other solution.

Analytical methods

$[Na^+]$ and $[K^+]$ were determined by flame photometry, $[Cl^-]$ by electrometric titration on a Buchler chloridometer, and osmolalities by freezing-point depression on an Advanced Instrument osmometer. $[HCO_3^-]$ was measured by adding 0.2 ml of pancreatic juice to 1.0 ml of 0.1 M HCl, heating the mixture to boiling, cooling to room temperature, and backtitrating to pH 7.0 with 0.2 M NaOH using a Radiometer titrator and glass electrode. Protein concentration was determined by transmission at 280 mμ on the Beckman DB spectrophotometer by comparison with bovine serum albumin as a standard.

All errors are expressed as standard errors of the mean, with the number of determinations given in parentheses.

Junction potential corrections

The PD measured directly in these experiments consists of the sum of the PD across the pancreatic duct itself *plus* two liquid junction potentials, between one salt bridge and blood and between the other salt bridge and pancreatic juice (or perfusion fluid). Since the PD's across the duct are small (up to 8 mV) and comparable in size to the liquid junction potentials, careful correction for junction potentials is necessary. The common procedure of eliminating junction potentials by using saturated KCl bridges is unsatisfactory for accurate measurement of small PD's, because

the potentials of the resulting junctions are dependent upon the junctional profile and hence time-dependent, are several millivolts in value rather than zero, and are difficult to estimate theoretically. In the present study 154 mM NaCl bridges were chosen because the junctions between these bridges and the experimental solutions used are of either the so-called biionic or else the so-called dilution type and hence the junction potentials are constant with time, well-defined, and calculable from a modified Henderson formula:

$$E'' - E' = -\frac{RT}{F}\left[\frac{(U'' - V'') - (U' - V')}{(U'' + V'') - (U' + V')}\right] \log \frac{U'' + V''}{U' + V'} \qquad (1)$$

where superscripts '' and ' refer to the two solutions on opposite sides of the junction, E is the electrical potential, $U \equiv [Na^+]\gamma_{Na^+}u_{Na^+} + [K^+]\gamma_{K^+}u_{K^+}$, $V \equiv [Cl^-]\gamma_{Cl^-}u_{Cl^-} + [HCO_3^-]\gamma_{HCO_3^-}u_{HCO_3^-}$, u's are mobilities (*not* limiting mobilities at infinite dilution), γ's are activity coefficients, and the factor RT/F is 61.6 mV at 37°. Mobility ratios at 37° and at the ionic strength of the experimental solutions were taken from the tables of PARSONS[8], γ's at 37° from ROBINSON AND STOKES[9]. The calculated junction potentials are given in Table I, and all PD's reported in this paper have been corrected for these junction potentials. Detailed discussion of how to obtain time-independent junction potentials and how to determine their values will be found in a paper by BARRY AND DIAMOND[10].

TABLE I

JUNCTION POTENTIALS

The junction potentials are those obtained with 154 mM NaCl bridges at 37°. They were calculated from Eqn. 1 of the text. See Table II for the composition of cat serum, secretin-stimulated juice, and resting juice.

Solution	*Potential of solution with respect to 154 mM NaCl (mV)*
77 mM NaCl + 150 mM mannitol	−3.9
154 mM $NaHCO_3$	−7.9
77 mM NaCl + 77 mM KCl	−2.5
Cat serum	−3.2
Secretin-stimulated juice	−4.6
Resting juice	+0.5

RESULTS

Juice composition

Following a rapid intravenous injection of pure natural secretin (purchased from GIH Research Unit, Karolinska Institute, Stockholm, Sweden) a flow of pancreatic juice appeared within less than 1 min, remained maximal for about 15 min, and subsided within 30–40 min. Dose–response curves were determined for seven cats, by giving each cat six different doses of secretin (0.0625, 0.125, 0.25, 0.5, 1.0, and 2.0 units/kg), the order of administration corresponding to a Latin square design. Maximal flow rates (1.7 ± 0.1 ml (n = 17) in the first 15 min) were attained

at 0.5, 1.0, or 2.0 units/kg, while 0.0625 unit/kg yielded 0.7 ± 0.2 ml ($n = 4$) in the first 15 min. At the dose of 1.0 unit/kg selected for use in the subsequent electrical experiments, pancreatic juice pooled over the first 15 min had the composition given in Table II ('secretin-stimulated juice'). These figures are close to those obtained by CASE *et al.*[7] for anesthetized cats responding to maximal doses of secretin ($[Na^+] = 158$, $[K^+] = 3.8$, $[Cl^-] = 24$, $[HCO_3^-] = 142$ mM). $[Na^+]$ and $[K^+]$ were independent of dose or flow rate, while $[Cl^-]$ increased to 50 ± 4 mM ($n = 2$) and $[HCO_3^-]$ declined to 115 ± 4 mM ($n = 3$) in juice samples pooled over the first 15 min at a dose of 0.0625 unit/kg.

TABLE II

IONIC COMPOSITION OF CAT SERUM AND PANCREATIC JUICE

The table gives average values (in mM) ± S. E., with the number of determinations in parentheses. The values for $[Na^+]$, $[K^+]$, and $[Cl^-]$ in resting juice are assumed, not measured, values: $[Na^+]$ and $[K^+]$ were taken as equal to the values in secretin-stimulated juice, and $[Cl^-]$ was taken as $([Cl^-] + [HCO_3^-])$ in secretin-stimulated juice *minus* $[HCO_3^-]$ in resting juice, since the values of $[Na^+]$, $[K^+]$, and $([Cl^-] + [HCO_3^-])$ in pancreatic juice are independent of flow rate[7].

	$[Na^+]$	$[K^+]$	$[Cl^-]$	$[HCO_3^-]$
Serum	149 ± 1 (27)	3.6 ± 0.1 (27)	113 ± 3 (17)	24 ± 3 (7)
Secretin-stimulated juice	158 ± 2 (7)	3.3 ± 0.1 (7)	40 ± 3 (7)	137 ± 7 (7)
Resting juice	158	3.3	148	29 ± 3 (25)

Comparison with the ion concentrations determined for cat serum and also listed in Table II shows that secretin-stimulated juice has much higher $[HCO_3^-]$, much lower $[Cl^-]$, very slightly higher $[Na^+]$, and nearly the same $[K^+]$ as serum. The osmolalities of serum (304 ± 1 mosM ($n = 5$)) and of secretin-stimulated juice (302 ± 5 mosM ($n = 12$)) were the same. The protein concentration was 98 ± 3 mg/ml ($n = 8$) in serum, 6 ± 1 mg/ml ($n = 18$) in secretin-stimulated juice.

A few small samples (approx. 0.1 ml) of resting juice recovered from the cannula before secretin administration were found to have $[HCO_3^-]$ of 40 mM or less. In conscious cats with a chronic pancreatic fistula an average value of 29 ± 3 mM ($n = 25$) was obtained for $[HCO_3^-]$ in resting juice not stimulated by secretin (L. WAY, unpublished observation).

PD's during free flow

In the resting pancreas before injection of secretin or at 60–130 min after injection, nineteen measurements in ten cats yielded a PD of +2.0 ± 0.3 mV, *i.e.* duct lumen positive to the bloodstream. All values fell between −0.5 and +4.5 mV.

When 1.0 unit/kg of secretin was rapidly injected intravenously, the PD went more negative in the course of 1 min by about 7 mV and decayed again with approximately the same time-course as the stimulated flow of juice, *i.e.* in 30–40 min. By waiting 1 h between injections of secretin, it proved parctical to measure the secretin-stimulated PD up to 3 times in some cats. In fifteen determinations on nine cats this maximally negative value of the PD after secretin injection was −4.9 ± 0.2 mV, with a range of −3.5 to −7.3 mV.

It is worth restating explicitly that, of the 7-mV shift in PD caused by secretin,

only 1.8 mV is recorded directly (*i.e.* before correction for the junction potentials at the NaCl bridges). The larger part of the secretin-induced PD shift is obscured by a shift in the junction potential between juice and the NaCl bridge by 5.1 mV in the opposite direction, due to the change in juice composition produced by secretin. Thus, disregard of junction potentials could easily cause the shift in PD after secretin to be overlooked. As will be discussed (p. 306), an estimate of the secretin-induced PD can also be obtained under conditions involving no shift of junction potential and agrees well with the corrected value during free flow.

PD's during perfusion with 154 mM NaCl

The secretin-stimulated PD during free flow might represent in part a change in diffusion potential between duct and blood, since resting juice and secretin-stimulated juice differ in ionic composition. In order to eliminate a possible contribution from a change in ion concentration gradients, the effect of secretin was determined during rapid perfusion of the duct with 154 mM NaCl. Before injection of secretin twenty-nine determinations in seven cats yielded a PD of + 2.5 ± 0.2 mV. Upon injection of 1.0 unit/kg of secretin, the PD went more negative by about 3 mV within 1 min, remained at this level for about 10 min, and gradually decayed again over the course of 30 min. In five cats the average PD at the height of this negative-going phase was −0.2 ± 0.7 mV, *i.e.* an average change of −2.7 mV from the unstimulated condition.

Diffusion potentials in perfused ducts

In order to determine the relative permeabilities of the pancreatic duct to $[Na^-]$, $[K^+]$, $[Cl^-]$, and $[HCO_3^-]$ and to examine whether secretin altered these relative permeabilities, PD's were measured during perfusion of the duct with 77 mM NaCl + 150 mM mannitol (to create a blood-to-duct gradient of NaCl), with 154 mM $NaHCO_3$ (to create gradients of Cl^- and HCO_3^-), and with 77 mM KCl + 77 mM NaCl (to create gradients of K^- and Na^+). PD's were first determined with all three solutions in random order before injection of secretin, and then again at 2–5 min after injection of secretin, when the secretin-stimulated PD during free flow or during 154 mM NaCl perfusion was at its maximally negative value. Table III summarizes the results from seven cats. The signs of the PD's, or the shifts in PD's from the value observed during 154 mM NaCl perfusion, indicate that the duct is more permeable to Cl^- than to Na^-, more permeable to Cl^- than to HCO_3^-, and more permeable

TABLE III

DIFFUSION POTENTIALS ACROSS PERFUSED PANCREATIC DUCT WITH AND WITHOUT SECRETIN

The table gives average values ± S.E., with the number of determinations in parentheses.

Perfusion solution	*PD (mV)*	
	Secretin	*No secretin*
154 mM NaCl	−0.2 ± 0.7 (5)	+2.5 ± 0.2 (29)
77 mM NaCl + 150 mM mannitol	−3.8 ± 0.2 (4)	−1.0 ± 0.3 (6)
154 mM $NaHCO_3$	−8.0 ± 0.2 (6)	−5.0 ± 0.3 (6)
77 mM NaCl + 77 mM KCl	−2.4 (1)	−0.1 ± 0.4 (3)

to K^+ than to Na^+. Secretin shifts the PD by about the same amount (2.3–3.0 mV) in each of the four perfusion solutions, meaning that secretin causes no change in relative ionic permeabilities and that the secretin-stimulated PD simply adds to any diffusion potential resulting from ion concentration gradients.

DISCUSSION

Locus of the PD's

All PD's described here were measured in the main collecting duct of the pancreas. On anatomical grounds it seems likely, though unproved, that similar PD's exist in the distal parts of the intercalated ducts, since the resistance of the intervening solution is slight, but there would be no justification for assuming the PD's in the more proximal parts of the pancreas (*e.g.* the acini) to be the same. On operational grounds one can say that the measured PD's refer to at least part of the site of secretin-activated transport, wherever that may be located, since transport PD's activated by secretin were recorded (see p. 306 for discussion). In the rabbit pancreas, which unlike the cat pancreas produces juice at moderate rates even in the absence of secretin, SCHULZ *et al.*[1] showed by micropuncture techniques that the entire duct system participates in secretin-stimulated HCO_3^- transport and is electrically negative to blood by several millivolts, as in the secreting cat pancreas. REBER *et al.*[2] state in a preliminary report that secretin causes the PD recorded in the main duct of rabbit pancreas to go more negative by several millivolts, as in the cat.

Active and passive ion movements

From knowledge of the PD (−4.9 mV), serum composition ($[Na^+]$ = 149, $[K^+]$ = 3.6, $[HCO_3^-]$ = 24, $[Cl^-]$ = 113 mM), and juice composition ($[Na^+]$ = 158, $[K^+]$ = 3.3, $[HCO_3^-]$ = 137, $[Cl^-]$ = 40 mM) during maximal secretin stimulation, one may identify which ion fluxes are active distally by applying the Nernst equation. Substitution of the above-mentioned values yields the conclusion that the concentrations of Na^+, K^+, and Cl^- are below, HCO_3^- above, electrochemical equilibrium in pancreatic juice. Since secretin causes an increased output of all four ions, the hormone's effect must depend upon active HCO_3^- transport, and Na^+, K^+, and Cl^- could all diffuse into the juice passively down their electrochemical gradients (this does not preclude the possibility that the mechanism of HCO_3^- secretion actually depends upon H^+ or OH^- transport, or that other ions are subject to active transport proximally). A further conclusion concerns the experimental demonstration[7] of a process whose existence had frequently been postulated to explain the rate dependence of anion concentrations in juice, namely, the diffusion of HCO_3^- at low flow rates down its concentration gradient from juice to blood and of Cl^- down its concentration gradient from blood to juice. The Nernst calculation implies that these anion exchange fluxes are down electrochemical gradients and presumably passive.

Active Na^+ transport was proposed as a driving force for pancreatic secretion by ROTHMAN AND BROOKS[11] on the grounds that replacement of Na^+ by Li^+ inhibits secretion, and by RIDDERSTAP AND BONTING[12] on the grounds that pancreas possesses a (Na^+-K^+)-activated ouabain-inhibited ATPase and that juice secretion is inhibited by ouabain. Neither line of evidence seems compelling: almost all mammalian cells

possess an ouabain-inhibited, Li^+-rejecting, (Na^+–K^+) pump to regulate cell volume and intracellular ion concentrations, and disruption of this pump might well cause failure of other cell functions. The Nernst calculation provides no evidence for active Na^+ transport distally. A possible indication of active Na^+ transport is the observation[6] that isosmotic partial replacement of NaCl with sucrose in a vascular perfusate yields values of [Na^+] in juice double those in the perfusate, but the bearing of this finding on the question of active *versus* passive transport cannot be evaluated until PD's have been measured under the same conditions.

Passive permeability ratios

Relative ionic permeability ratios may be calculated from the diffusion potentials measured during perfusion of pancreatic duct with solutions of known composition. These permeability ratios will then be used in the remainder of this discussion to evaluate the origin of the secretin-induced PD.

The equation used is the so-called constant-field equation[13,14], which reads at 37°:

$$\Delta E = -61.6 \log \frac{c''_{Na^+}\gamma''_{Na^+}P_{Na^+} + c''_{K^+}\gamma''_{K^+}P_{K^+} + c'_{Cl^-}\gamma'_{Cl^-}P_{Cl^-} + c'_{HCO_3^-}\gamma'_{HCO_3^-}P_{HCO_3^-}}{c'_{Na^+}\gamma'_{Na^+}P_{Na^+} + c'_{K^+}\gamma'_{K^+}P_{K^+} + c''_{Cl^-}\gamma''_{Cl^-}P_{Cl^-} + c''_{HCO_3^-}\gamma''_{HCO_3^-}P_{HCO_3^-}} \quad (2)$$

where ΔE is the potential (in mV) of the juice with respect to blood, superscript '' refers to juice and ' to blood, c's are concentrations, γ's activity coefficients estimated from ROBINSON AND STOKES[9], and P's the relative permeability coefficients. Into this equation were inserted the PD's measured during perfusion in the absence of secretin and listed in Table III, *plus* the ion concentrations in cat serum and the perfusion solutions. The procedure was to assume values for P_{K^+}/P_{Cl^-} and $P_{HCO_3^-}/P_{Cl^-}$ in order to evaluate P_{Na^+}/P_{Cl^-} from the PD during perfusion with 77 mM NaCl + mannitol, then to calculate $P_{HCO_3^-}/P_{Cl^-}$ from the PD with 154 mM $NaHCO_3$ and P_{K^+}/P_{Cl^-} from the PD with 77 mM NaCl + 77 mM KCl, and finally to repeat the calculations using these first estimates of the ratios. The permeability ratios thus arrived at were:

$$P_{Cl^-} : P_{K^+} : P_{HCO_3^-} : P_{Na^+} = 1.00 : 0.90 : 0.59 : 0.52$$

These values are similar to the ratios of the free-solution mobilities in solutions of comparable ionic strength at the same temperature (1:00 : 0.95 : 0.58 : 0.63), implying that the main pancreatic duct discriminates only to a limited extent between passively permeating ions.

When the duct was perfused with isotonic NaCl in the absence of secretin, a PD of + 2.5 mV was recorded (Table III). Small concentration differences of Cl^- and HCO_3^- were present between duct and serum in this situation. When the permeability ratios calculated above and the ionic concentrations of serum and 154 mM NaCl are inserted into Eqn. 2, a PD of + 3.5 mV is predicted, close to the experimental value. Similarly, from the compositions of serum and resting juice a PD of + 3.0 mV is predicted for the resting duct during free flow, close to the experimental value of + 2.0 mV. Thus, in the absence of secretin the small PD's may be accounted for as diffusion potentials, and there is no need to postulate active transport processes.

The secretin-induced PD

The most unequivocal evidence for a PD arising directly from secretin-induced active transport of ions comes from the perfusion experiments. When the duct was perfused with solutions of constant ionic composition, at rates sufficiently high that there was no change in PD (hence in perfusate composition) with flow rate, secretin established a negative-going PD shift of 2.7 mV in phase with the secretin-induced juice production. This value is not subject to any uncertainty associated with junction potentials at the bridges, since there is no change in the junction potentials during perfusion with an unchanging solution. The magnitude of this PD was independent of the ionic composition of the perfusate; or, expressed alternatively, a given change in ionic composition caused the same change in PD before and after secretin. Since secretin causes no change in permeability and produces a PD in the absence of any change in ion concentration gradients, the secretin-induced PD during duct perfusion cannot represent a change in diffusion potential but must be due directly to active ion transport.

An alternative estimate of the secretin-induced PD comes from the free-flow experiments. In non-perfused ducts secretin shifted the PD in the negative direction by 7 mV, considerably larger than the value recorded during perfusion. However, resting juice and secretin-stimulated juice differ considerably in ionic composition, so that part of the PD change must represent a change in diffusion potential across the duct wall. If the ion concentrations of serum and secretin-stimulated juice *plus* the relative permeability ratios listed on p. 305 are inserted into Eqn. 2, a diffusion potential of −1.2 mV during free flow stimulated by secretin is predicted, *i.e.*, a shift of several mV from the value in the absence of secretin (p. 305). Since the measured PD, −4.9 mV, is considerably larger, the difference of −3.7 mV must be due directly to secretin-stimulated active ion transport. This calculated estimate of −3.7 mV is in reasonable agreement with the value of −2.7 mV obtained directly from perfusion experiments. Thus, the secretin-induced PD during free flow represents in part a change in diffusion potential due to the change in the HCO_3^- and Cl^- gradients, in part a direct manifestation of active ion transport.

The sign of the secretin-induced PD, duct-negative, implies that secretin causes the active secretion of anions rather than of cations. From the Nernst equation calculations, which showed that the ion influxes caused by secretin are against the electrochemical gradient for HCO_3^- but down the gradient for Cl^-, Na^+, and K^+, one can say more specifically that secretin causes active HCO_3^- transport.

In the liver as in the pancreas, secretin causes an outpouring of a HCO_3^--rich juice, and establishes a duct-negative PD which cannot be explained as a diffusion potential[3]. Thus, the mechanism of secretin action in the liver and in the pancreas is probably similar.

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