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On the permeability of the pancreatic duct membrane

At slow secretory rates, the HCO_3^- concentration of pancreatic juice falls, accompanied by a corresponding rise in the Cl^- concentration. The concentrations of the two major cations, Na^+ and K^+, however, remain constant at all secretory rates. Two hypotheses have been proposed to account for the changes in anion concentrations: an ad-mixture theory, which assumes that pancreatic juice comprises two or more components of different composition, and an exchange theory, which postulates a primary secretion of a HCO_3^--rich fluid whose composition is modified by the exchange of HCO_3^- for Cl^- across the duct membrane. By perfusing the main duct of the cat pancreas with artificial "pancreatic juice" at different flow rates, we have shown that exchange of ions across the duct membrane is certainly an important factor affecting the final composition of pancreatic juice[1]. This present communication has been motivated by the recent publication in this journal of a paper by WAY AND DIAMOND[2], in which the electrical potential difference between the main pancreatic duct and blood of anaesthetised cats was measured under three conditions: at rest, during secretion and during perfusion of the main duct with simple salt solutions. The observations described below, which arose out of our original investigation[1], suggest that the results obtained by WAY AND DIAMOND during duct perfusion should be treated with caution.

Fasted cats were anaesthetised with intravenous chloralose (37.5 mg/kg) and urethane (450 mg/kg). The splanchnic nerves were sectioned extraperitoneally and the pylorus occluded. To perfuse the main duct, it is necessary to cannulate it both at the point where it pierces the duodenal wall and at the tail of the gland. Cannulation at the tail end was achieved in an indirect manner, identical to that subsequently described by WAY AND DIAMOND, in which a length of fine polythene tubing was threaded along the duct from the duodenal end and withdrawn from the tail end, the final few millimeters remaining in the duct and being sutured in place. Conventional analytical techniques were used as previously described[1].

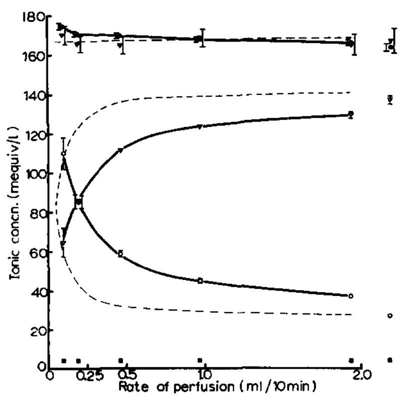
A fluid containing Na^+, K^+, Cl^- and HCO_3^-, at the concentrations found in pancreatic juice secreted at maximal rate, was perfused through the duct in a proximal-to-distal direction at five rates from a motor-driven syringe. During passage through the duct, the composition of this artificial "pancreatic juice" altered: the concentration of HCO_3^- fell, while that of Cl^- rose, and the sum of the two also tended to rise (Fig. 1). Such alterations occurred at all perfusion rates, but were especially noticeable at the slower rates. Na^+ and K^+ concentrations, which were constant at all perfusion rates, remained equal to their concentrations in the perfusate, and their sum was approximately equal to the sum of the two anions. In one experiment, in which pancreatic juice was first obtained from the pancreas by stimulating maximally with secretin and was then perfused through the main duct of the same animal, an identical picture was observed.

Since only a part of the main duct trunk was being perfused, these alterations seemed excessively large. Direct cannulation of the duct at the tail of the gland was therefore attempted so as to eliminate any possible damage to the duct epithelium resulting from the threading procedure. Observations from these experiments have already been published[1], but are represented in Fig. 1 for comparison. It is obvious that, although exchange of Cl^- for HCO_3^- still occurred, the magnitude of the exchange was considerably less than that in the first series of experiments described here.

The simplest explanation of these changes in anionic concentration is that HCO_3^- and Cl^- diffuse passively through the ductal epithelium down their respective concentration gradients. This can be tested by substituting the observations in an integrated form of the Fick equation described by DEFARES AND SNEDDON[3]:

$$\ln (u-a) = \ln (u_0-a) - (2\pi rlh)\cdot 1/V_0$$

where u_0 and u are respectively the ionic concentration of the fluid entering and leaving the duct, a is the ionic concentration in the extracellular fluid, r and l are the radius and length of the duct, h the permeability coefficient and V_0 the flow rate. In any one experiment, only u and V_0 are variable, and a graph of ln $(u—a)$ against $1/V_0$ will be linear if Fick's law is applicable. The data described here have been analysed in this way (Fig. 2). The points for Cl^- and HCO_3^- both fall on straight lines, but the gradients of the two lines are different. Again the data obtained from the experiments in which the duct was cannulated in a direct manner is shown for comparison, and it can be seen that in this case the lines are parallel. The slope of the lines is determined by the expression $(2\pi rlh)$; since πrl is constant in any one experiment, the difference in gradient for Cl^- and HCO_3^- must be due to a difference in permeability of the duct to the two ions.



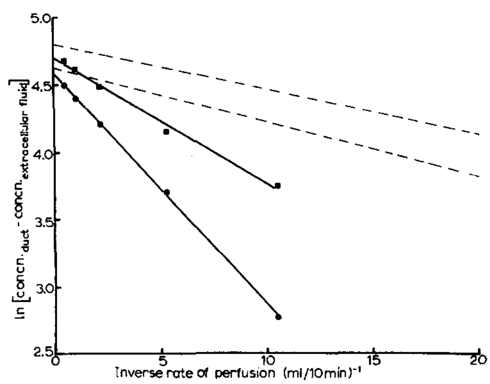


Fig. 1. The change in composition of artificial "pancreatic juice" (8 experiments) and secretin-stimulated juice (1 experiment) perfused at five rates through the main pancreatic duct, after cannulation had been achieved in an indirect way. The points represent the mean ± S.E. of the mean in all 9 experiments except at the slowest rate (4 experiments) for $[HCO_3^-]$ (▽—▽), $[Cl^-]$ (○—○), and $[HCO_3^- + Cl^-]$ (●—●), and 8 experiments (3 experiments at the slowest rate) for Na^+ (▼) and $[K^+]$ (■). The points at the right hand side of the figure represent the composition of the perfusion fluid. The interrupted lines, which illustrate the changes observed after cannulation had been achieved in a direct way[1], are included for comparison and represent, from the top downwards, $[HCO_3^- + Cl^-]$, $[HCO_3^-]$ and $[Cl^-]$.

Fig. 2. The diffusion of HCO_3^- and Cl^- across the pancreatic duct wall. Application of the equation of DEFARES AND SNEDDON[3] to data obtained in the series of duct perfusion experiments. The concentrations of HCO_3^- and Cl^- in extracellular fluid (22.1 and 126.0 mequiv/kg of plasma water, respectively) were taken from CASE *et al.*[1]. The regression lines were calculated using the mean values represented in Fig. 1; the upper one representing HCO_3^- behaviour and the lower one Cl^- behaviour. The result of analysing in the same way the data obtained after direct cannulation of the duct are illustrated by the interrupted lines, which again are taken from CASE *et al.*[1].

It seems therefore that the process of indirect cannulation of the tail of the pancreas, in which polythene tubing is threaded along the duct, causes extensive damage to the ductal epithelium, increasing the permeability of the duct and resulting in exaggerated exchange of HCO_3^- and Cl^-. Since this method of cannulation was employed by WAY AND DIAMOND in their perfusion experiments, it seems likely that their measurements of diffusion potentials across perfused ducts, and the relative permeability coefficients which they calculated from these measurements, will be inaccurate. These considerations do not affect their conclusions concerning the existence of a secretin-stimulated potential difference due to active HCO_3^- transport and concerning the identification of active and passive ion fluxes.

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1 R. M. CASE, A. A. HARPER AND T. SCRATCHERD, *J. Physiol.*, 201 (1969) 335.
2 L. W. WAY AND J. M. DIAMOND, *Biochim. Biophys. Acta*, 203 (1970) 298.
3 J. G. DEFARES AND I. N. SNEDDON, *An Introduction to the Mathematics of Medicine and Biology*, North Holland Publishing Co., Amsterdam, 1960, p. 342.

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