The Effect of Theophylline on Glucose and Fluid Transport across the Rat Jejunum

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The net absorption of fluid and electrolytes by the mammalian small intestine may be changed to a state of net secretion by the administration of agents that elevate the cyclic AMP content of the mucosal epithelium, e.g. cholera toxin, theophylline, dibutyryl cyclic AMP [for reviews see Banwell & Sherr (1973), Sladen (1973), Field (1974) and Kimberg (1974)]. In contrast with the wealth of data on the movements of electrolytes across the small intestine in the presence of these agents, there has been little work on the ways in which sugar and amino acid transport are affected by secretory stimuli. This is surprising in that the movements of non-electrolytes are thought to be tightly coupled to the movement of ions, in particular sodium. The present communication examines the effect of theophylline on glucose and fluid transport across an intact preparation of the rat jejunum in vitro.

Isolated segments of rat jejunum, 20–30 cm long, were perfused through the lumen in a gas-lift apparatus similar to that of Fisher & Parsons (1949). The loops were suspended in liquid paraffin, and transported fluid, exuded at the serosal surface of the gut, appeared as droplets of liquid, which sank beneath the liquid paraffin and could be collected for volume measurement and glucose analysis. The segments were incubated

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![Fig. 1. Appearance of fluid and glucose in serosal exudate](image)

Fluid appearance is shown in (a) and glucose appearance in (b). ●, Control; ○, theophylline (10 mM) added at 30 min as indicated by arrow. Values are means ± S.E.M. of at least seven determinations.
Fig. 2. Glucose concentrations in mucosal and serosal fluids
Control loops are shown in (a) and the effect of theophylline (10 mM) added at 30 min in (b). ■, Mucosal-fluid glucose concentration; □, serosal-fluid glucose concentration. Values are means ± S.E.M. of at least seven determinations.

at 37°C in Krebs/Ringer bicarbonate medium containing 11.1 mM-glucose, the glucose being added after a 10 min preincubation period. The total incubation time was 70 min, and 10 mM-theophylline was added to the luminal fluid of a number of incubations at 30 min. Serial samples of the mucosal medium, and the serosal exudate were taken for glucose measurement by the automated fluorimetric method of Leese & Bronk (1972). Glucose disappeared linearly from the mucosal fluid of control loops at a rate of 8.2 ± 0.9 μmol/h per cm (S.E.M., n = 9), and the rate of glucose uptake was unaltered by theophylline [7.7 ± 0.4 μmol/h per cm (n = 6)]. This finding agrees with those of others, who have shown from measurements of sugar fluxes or sodium fluxes dependent on glucose that cyclic AMP-mediated secretion does not affect the coupled influx of sodium and glucose at the brush border of the epithelial cells (Carpenter et al., 1968; Serebro et al., 1968; Grayer et al., 1970; Field, 1971; Field et al., 1972; Kinzie et al., 1973). A similar conclusion has also been inferred from clinical measurements of the disappearance of glucose and fluid from the lumen of patients with cholera, and from observations on the use of oral glucose/electrolyte solutions in the treatment of these patients (Hirschhorn et al., 1968; Pierce et al., 1968; Nalin et al., 1970; Schafer et al., 1971).

Fig. 1(a) shows that 10 mM-theophylline drastically decreases the serosal-fluid transfer of control loops of rat jejunum, in agreement with findings from other species and confirming that the rat small intestine can be used as a model in studies of this type (Strombeck, 1972). In parallel with this inhibition of water movement, theophylline also diminishes substantially the appearance of glucose in the serosal fluid (Fig. 1b). As far as we are aware, there is only one other report on the effects of theophylline on
serosal permeability to sugars (Holman & Naftalin, 1975). With a preparation of the mucosa of rabbit ileum and the sugar galactose, these authors were able to show that, although theophylline and dibutyryl cyclic AMP had no effect on the entry or exit permeabilities to galactose at the mucosal pole of the epithelium, both the serosal entry and the exit permeability were decreased to 30% of control values. When the present results are expressed in terms of sugar concentration rather than absolute amounts (Fig. 2), they show that the glucose concentration in the serosal exudate continues to rise throughout the incubation period in the presence of theophylline, whereas in control preparations it reaches a steady state. This is significant in that Holman & Naftalin (1975) similarly reported that theophylline increased the steady-state concentration of galactose in the tissue water of the rabbit mucosa.

We think the most likely explanation of our results is in terms of the intercellular spaces bordering the lateral and basal aspects of the epithelial cells. These spaces are usually distended when fluid is being absorbed by the epithelium, but under conditions of diminished salt absorption brought about by a rise in mucosal cyclic AMP concentration, the spaces are extremely small, and the membranes bordering them in tight apposition (Di Bona et al., 1974; Holman & Naftalin, 1975). Under these conditions there is likely to be less wash-out of the intercellular spaces, leading to the build-up of the high solute concentration reflected in the serosal exudate.


Glucose Accumulation by Rings of Small Intestine from Normal and Schistosome-Infected Mice

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Numerous studies have been carried out on schistosomiasis in man and experimental animals (e.g. Warren, 1973), but very little is known about the effects of the parasite Schistosoma mansoni on the structure and function of the host small intestine. Such information is likely to be important, since the parasite normally resides in the mesenteric blood vessels draining that part of the gut. The present studies were carried out with