Inhibition of glucose absorption by prostaglandins E_1, E_2 and $F_2\alpha$

Some drugs inhibit glucose absorption from the small intestine, for example the non-anthraquinone laxatives oxyphenisatin, bisacodyl and phenolphthalein inhibit glucose absorption in the small intestine of the rat (Hart & McColl, 1967). The prostaglandins have a wide spectrum of pharmacological activity but little is known of their action on the epithelial cells of the small intestine. We have measured the effects of intraluminal prostaglandins (PG) E_1 E_2 and $F_2\alpha$ on glucose absorption in the rat *in vivo*.

Male albino Wistar rats, 250 g, were anaesthetized with 30 mg of pentobarbitone sodium subcutaneously and the lumen of 50 cm of proximal small intestine was gently washed through with warm saline. In control experiments the loops were perfused with 20 ml of normal saline (0·9%) containing D(+)-glucose (10mM) for 20 min. Test perfusions were identical but also included the test drug in the saline-glucose solution. The solution was initially pH 5·6 and was maintained at 37° while being continuously recirculated through the lumen by gas lift using 5% carbon dioxide in oxygen as described by Nissim (1965). At the end of the experiments the rats were killed by bleeding, and the perfusion fluid volume was measured and its glucose concentration estimated by a glucose oxidase-peroxidase method (Boehringer Corporation Ltd.) on an Auto Analyser. The loops were weighed and results are expressed as the amount of glucose absorbed per unit weight of wet tissue during the 20 min perfusion (mg/g in 20 min). In further experiments, the same preparation of 2 rats was perfused with glucose-free saline containing phloridzin (2×10^{-4}M) and in 3 other rats with glucose-free saline containing PGE_1 ($1{\cdot}4 \times 10^{-4}$M).

In the glucose-saline experiment, phloridzin caused statistically significant dose-related inhibition of glucose absorption. PGE_1 at a concentration of $1{\cdot}4 \times 10^{-5}$M did not affect absorption but $1{\cdot}4 \times 10^{-4}$M did cause a significant decrease. PGE_2 and $PGF_2\alpha$ $1{\cdot}4 \times 10^{-4}$M, also reduced absorption to similar values (residual prostaglandins were not measured). Dibutyryl cyclic 3′,5′-adenosine monophosphate (dibutyryl 3′,5′-c AMP) caused a small enhancement of absorption significant at $P = 0{\cdot}05$. The results are summarized in Table 1.

The glycoside phloridzin is a potent inhibitor of glucose uptake from the small intestine and acts by inhibiting the initial binding of glucose to its carrier on the epithelial cell microvilli (Stirling & Kinter, 1966). The results in Table 1 show that relatively high concentrations of the prostaglandins also cause inhibition of glucose absorption.

The experiments using glucose-free saline show that in at least one respect the

Table 1. *Glucose absorption from the lumen of the rat jejunum* in vivo.

Drug (concn (M)		No. of animals	Glucose mg/g lumen in 20 min	*P*
Controls	—	12	9·09 ± 0·29	—
Phloridzin	5×10^{-5}	4	5·27 ± 0·27	0·0005
Phloridzin	10^{-5}	4	6·96 ± 0·15	0·0025
PGE_1	$1{\cdot}4 \times 10^{-5}$	4	9·13 ± 0·63	n.s.
PGE_1	$1{\cdot}4 \times 10^{-4}$	4	6·85 ± 0·13	0·0005
PGE_2	$1{\cdot}4 \times 10^{-4}$	4	6·81 ± 0·76	0·0025
$PGF_2\alpha$	$1{\cdot}4 \times 10^{-4}$	3	6·73 ± 0·50	0·0025
Dibutyryl 3′,5′-c AMP	2×10^{-4}	4	10·26 ± 0·57	0·05

The mean glucose absorption is expressed as the number of mg of glucose lost from the jejunum per unit wet weight in the 20 min perfusion (mg/g in 20 min) together with the standard error of the mean.

effects of phloridzin and PGE_1 differ from those of oxyphenisatin. After perfusing with glucose-free saline in the presence of phloridzin (2×10^{-4}M) and PGE_1 ($1{\cdot}4 \times 10^{-4}$M) for 1 h, no glucose appeared in the luminal fluid. Hart & McColl (1967) showed that oxyphenisatin, under the same conditions, caused leakage of glucose back into the lumen while phloridzin did not. It was suggested that oxyphenisatin, unlike phloridzin, blocked some active transport stage rather than mere entry of glucose into the epithelial cells. PGE_1 may block the entry of glucose but more evidence is required—such as its potency on the serosal side of the epithelial cells where the Na^+ pump is said to be located (Stein, 1967).

In many instances the prostaglandins act by influencing adenyl cyclase and so cause a change in the amount of intracellular 3′5′-cyclic adenosine monophosphate (3′5′,-c AMP), (Horton, 1969). It is known that PGE_1 and PGE_2 stimulate the epithelial cells of the small intestine to secrete fluid and electrolytes into the lumen (Pierce, Carpenter & others, 1971). Cholera enterotoxin is also a potent stimulant of intestinal fluid secretion. Its action, like that of the prostaglandins, is mediated by increasing intracellular concentrations of 3′5′-cAMP (Sharp & Hynie, 1971; Kimberg, Field & others, 1971) but it does not prevent glucose absorption (Iber, McGonagle & others, 1969). Our results indicate that the prostaglandins are inhibitors of glucose absorption in the small intestine of the rat. If this effect is also mediated in the same way as fluid secretion (by stimulation of adenylcyclase) then it would be expected that the soluble derivative dibutyryl 3′5′-cAMP would inhibit absorption. However, it produced a small, but significant, enhancement indicating that the prostaglandin-induced fluid secretion and the inhibition of glucose absorption probably involve two distinct mechanisms. It is possible that the relatively high concentrations of prostaglandins may have reduced glucose absorption indirectly by affecting intestinal motility, mucosal blood flow or systemic blood pressure. The effects of PGE_1, A_1 and $F_2\alpha$ in producing fluid secretion in the dog jejunum are greater on the serosal than mucosal side of the epithelial cells (Pierce & others, 1971). Whether low concentrations of prostaglandins modify glucose absorption in the rat when infused into the mesenteric artery is now under examination.

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