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The Effects of Enprostil and RS-86505-007 on In-vitro Intestinal Permeability of Rabbit and Monkey

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Abstract—Enprostil is a prostaglandin E_2 analogue characterized as a racemic mixture of four stereoisomers. Enprostil and a single isomer, RS-86505-007, were evaluated for their effects on the permeability of actively and passively transported compounds in segments of small intestine from rabbits and monkeys. Consistent with human in-vivo studies, which have demonstrated decreases in absorption of D-xylose, both compounds inhibited D-glucose transport. The passively transported compounds mannitol and progesterone were also less permeable in this model in the presence of enprostil or RS-86505-007. In contrast to the concentration-dependent inhibition displayed by ouabain, RS-86505-007 had no effect on purifed Na^+K^+-ATPase. It is suggested that an effect of a general nature, possibly an increase in the barrier properties at the intestinal surface, may explain the transport inhibition. Of two other enprostil isomers, RS-86812-007 inhibited D-glucose transport in rabbit small intestine, while RS-86505-008 had no effect. The prostaglandin E_1 analogue misoprostol was ineffective in monkey and poorly effective in rabbit. This suggests that the inhibition of D-glucose transport by enprostil and its active stereoisomers is mediated through some structurally specific receptor interaction.

Prostaglandins are potent endogenous substances that may exert a wide range of effects in the gastrointestinal tract. Of the naturally occurring prostaglandins, the E, F, and I types in particular have been found in the gastric and intestinal mucosa and secretions, influencing a number of gastrointestinal functions (Miller 1983). Enprostil (Fig. 1) is a synthetic prostaglandin E_2 analogue currently under investigation for the treatment of gastric and duodenal ulcers. When administered orally in humans, the drug has been shown to decrease the absorption of D-xylose, as well as suppress post-meal serum levels of D-glucose and total triglycerides. The maximum plasma concentration (C_{max}) and area under the curve (AUC) of glucose are reduced by 8% and 44%, respectively, while the same parameters are reduced by 27% and 25% for xylose. Post meal serum total triglycerides are suppressed by 34% and 90% from their control C_{max} and AUC values (Schwartz et al 1987, 1988; Schwartz & Saito 1987).

However, it is difficult from in-vivo experiments to isolate direct effects on the intestinal tissue from possible prostaglandin-induced changes in gastrointestinal transit (Miller 1983). Hence, it has not been possible to elucidate the individual mechanism(s) responsible for the observed decreases in carbohydrate and lipid absorption. Therefore, an in-vitro system using excised tissue sections from both rabbit and monkey (Grass & Sweetana 1988) was used to investigate the effects of enprostil and its stereoisomers on the intestinal permeability of both actively and passively transported molecules.

Materials and Methods

Male albino New Zealand rabbits (Elkhorn), 2·5–3·5 kg were deprived of food overnight, and killed the next morning by rapid injection of sodium pentobarbitone (100 mg kg^{-1}) through a marginal ear vein. Following a midline incision, 40 cm of small intestine, extending from the apex of the proximal duodenum, was removed and placed in ice-cold oxygenated Krebs Ringer bicarbonate buffer (pH 7·4). Jejunal segments from cynomolgus monkeys of either sex were obtained from control animals (Department of Pathology, Syntex Research) killed by injection of sodium pentobarbitone and exsanguinated before surgery. The jejunum was removed within 10 min of death, and immediately submerged in ice-cold buffer. Tissue from both species was used within 20 min of death.

Single jejunal segments (either rabbit or monkey) were cut, beginning 12 cm from the duodenal end. Peyer's patches could be easily identified visually and sections containing them were not used in these studies. The individual segments were opened along the mesenteric border and the serosal muscle layers stripped off.

In-vitro experiments

Tissues were mounted in previously described diffusion cells (Grass & Sweetana 1988) (Precision Instrument Design, Los Altos, CA) preheated to 37°C. The cells were placed in an aluminium block heater which was maintained at 37°C throughout the studies. The reservoirs were filled with warmed oxygenated Krebs Ringer bicarbonate buffer which was circulated by gas lift (O_2/CO2 95 : 5), controlled by valves (Precision Instrument Design). The exposed surface area of the tissue section was 2·06 cm^2 and the volume of each half cell was 7·0 mL.

Samples of the mucosal bathing solution were taken immediately before its addition to the diffusion cells, and from the reservoir at the conclusion of the experiment. Serosal samples (1·0 mL) were taken at indicated times with replacement of the sampled volume by blank (compound-free) buffer. Samples were placed in scintillation vials, scintillation cocktail (Aquasol, New England Nuclear) was added, and examined using a scintillation spectrophoto-

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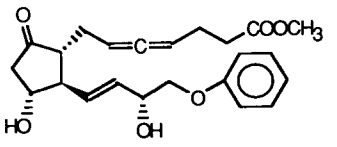
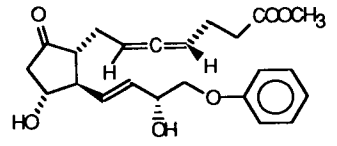
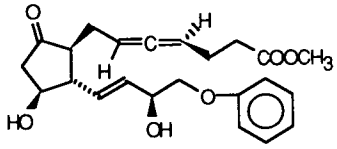


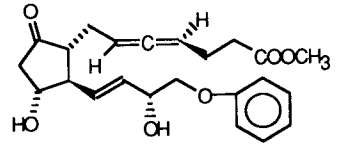
ENPROSTIL



RS-86505-007



RS-86505-008



RS-86812-007

FIG. 1. The chemical structures of enprostil and three of its stereoisomers.
RS 64167-004 9β-hydroxy enprostil acid
(±)-7-[(1*R**, 2*R**, 3*R**, 5*S**)-3,5-dehydroxy-2[(E)-(3*R**)-3-hydroxy-4-phenoxy-1-butenyl] cyclopentyl]Y.
where Y = -4,5-heptadienoic acid
RS-64719-006 9β-hydroxytetranoic acid
where Y = propanoic acid
RS-86505-007 (natural *R*-isomer)
Methyl (X)-3-hydroxy-4-phenoxy-1-butenyl]-5-oxocyclopentyl]-4,5-heptadienoate
where X = (4,5,6*R*)-7-[(1*R*,2*R*,3*R*)-3-hydroxy-2[(E)-(3*R*)-
RS-86812-007 (natural *S* isomer)
where X = (4,5,6*S*)-7[(1*R*,2*R*,3*R*)-3-hydroxy-2[(E)-(3*R*)-
RS-86505-008 (unnatural *S* isomer)
where X = (4,5,6*S*)-7[(1*S*,2*S*,3*S*)-3-hydroxy-2[(E)-(3*S*)-
RS-86812-008 (unnatural *R* isomer)
where X = (4,5,6*R*)-7[1*S*,2*S*,3*S*)-3-hydroxy-2[(E) (3*S*)-.

meter (Beckman LS 8100, Beckman Inst.) with an external standardization method. Owing to previously described limitations on tissue viability and active transport processes (Grass & Sweetana 1988), all experiments lasted for 2 h. In experiments designed to examine active transport, inhibitors were added to either the mucosal or serosal solutions as indicated in Tables 1–8. After each experiment the acrylic cells were sonicated in cleaning solution (Count-off, New England Nuclear) and thoroughly rinsed with distilled water.

In-vitro determination of effects on Na^+-ATPase

The activity of Na^+K^+-ATPase from dog kidney was assayed in 0·5 mL buffer, containing 125 m units mL^{-1} of enzyme, 3 mM Na_2ATP, 50 mM tris-HCl (pH 7·4), 100 mM NaCl, 20 mM KCl, and 5 mM $MgCl_2$. RS-86505-007 or ouabain were each added as aqueous solutions in the concentrations indicated in Fig. 2, and the enzyme-drug solution allowed to incubate for 10 min on a 37°C shaker bath before addition of the Na_2ATP. A mixture of 0·2 mL of 60% perchloric acid and 0·8 mL of 4·5% ammonium molybdate was added after 10 min to stop the reaction, and the mixture was then extracted with 3 mL of n-butyl acetate by mixing for 20 s. After centrifugation, 2 mL of the organic layer was removed for absorbance measurement at 320 nm (Yoda & Hokin 1970). All concentrations of test compounds and vehicle controls were run in triplicate. Percent inhibition values were calculated using vehicle (water) control values.

Preparation of solutions

Radiolabelled D-glucose, mannitol, and progesterone were purified by vacuum distillation immediately before use. Enprostil, RS-86505-007, RS-86505-008, and RS-86812-007 were obtained from the Institute of Organic Chemistry, Syntex Research; their structures are given in Fig. 1. Misoprostol was obtained as a gift from Searle Pharmaceuticals. Purified dog kidney ATPase was Grade IV: Ouabain sensitive (Sigma). All other chemicals were either reagent or analytical grade and were used as received.

Compound solutions were prepared by addition of tracer amounts of radiolabelled compound to oxygenated (O_2/CO_2 95:5) Krebs Ringer bicarbonate buffer (pH 7·4) which was prepared daily. Phlorizin and prostaglandin solutions were sonicated for 2 min to speed dissolution. To help maintain tissue viability, D-glucose (40 mM) was added to the serosal medium. Mannitol (40 mM) was added to the mucosal solution to provide an equivalent osmotic load between mucosal and serosal solutions, since even small amounts of glucose on the mucosal side markedly stimulate sodium and water absorption to the serosal side. For experiments in which transport of D-glucose was measured, 30 mM mannitol and 10 mM D-glucose were placed on the mucosal side. Ouabain was added to the serosal solution in selected experiments. All other drugs were administered mucosally unless otherwise indicated (Tables 1–8).

Statistical evaluations

For glucose transport studies, pair-wise comparisons of treatments against a control of pooled data from all glucose studies were conducted. Statistical significance was determined by ANOVA using Fisher's Least Significant Difference with treatment groups as indicated by the Tables. For mannitol or progesterone studies, analysis was also by ANOVA.

Results

Control values for the intestinal permeability of D-glucose, mannitol, and progesterone were determined in rabbits (Tables 1–4, 7). Known inhibitors of active transport (phlorizin and ouabain) decreased glucose permeability (Table 1). Consistent with previously published results (Schwartz et al 1987, 1988), enprostil and RS-86505-007 inhibited glucose transport over a range of 25 nM to 125 μM (Tables 2, 3), but no concentration response was observed. The minimum effective concentration for RS-86505-007

Table 1. In-vitro permeability of D-glucose in rabbit jejunum with co-administered inhibitors.

Inhibitor and concentration	Measured permeability $\times 10^{-6}$ (cm s^{-1}) mean (±s.e.m.)	n[a]	% Inhibition
Control (glucose)	10·17 (0·75)	42/9	—
Phlorizon (1 mM)	5·32 (0·43)	10/3	48[b]
Ouabain (0·2 mM)	7·50 (0·52)	15/5	26[b]
Misoprostol (2·5 μM)	7·69 (0·63)	11/3	24[c]

[a] Number of experiments/numbers of animals.
Treatment vs control, [b] $P<0·05$, [c] $P<0·1$.

Table 2. In-vitro permeability of D-glucose in rabbit jejunum with co-administered enprostil.

Enprostil (μM)	Measured permeability $\times 10^{-6}$ (cm s^{-1}) mean (±s.e.m.)	n[a]	% Inhibition
0 (control)	10·17 (0·75)	42/9	—
0·025	4·66 (0·51)	11/3	54[b]
0·25	6·76 (0·55)	17/5	34[b]
2·5	5·84 (0·26)	14/4	43[b]
12·5	5·97 (0·59)	9/3	41[b]

[a] Number of experiments/number of animals.
Treatment vs control, [b] $P<0·05$.

Table 3. In-vitro permeability of D-glucose in rabbit jejunum with co-administered RS-86505-007.

RS-86505-007 (M)	Measured permeability $\times 10^{-6}$ (cm s^{-1}) mean (±s.e.m.)	n[a]	% Inhibition
0 (control)	10·17 (0·75)	42/9	—
$2·5\times10^{-16}$	8·48 (0·94)	11/3	17[d]
$2·5\times10^{-14}$	9·47 (0·96)	10/3	7[d]
$2·5\times10^{-12}$	8·39 (1·04)	12/3	18[d]
$2·5\times10^{-10}$	6·36 (1·06)	9/3	38[b]
$2·5\times10^{-8}$	3·91 (0·34)	10/3	62[b]
$2·5\times10^{-7}$	6·51 (0·68)	13/4	36[b]
$2·5\times10^{-6}$	5·94 (0·50)	20/6	42[b]
$1·25\times10^{-4}$	4·92 (0·48)	13/4	52[b]

[a] Number of experiments/number of animals.
Treatment vs control, [b] $P<0·05$.
[d] Not significantly different from control, $P<0·1$.

Table 4. In-vitro permeability of D-glucose in rabbit jejunum serosal vs mucosal prostaglandin administration (prostaglandin concentration = 2·5 μM).

Prostaglandin	Location	Measured permeability $\times 10^{-6}$ (cm s^{-1}) mean (±s.e.m.)	n[a]	% Inhibition
Control	—	10·17 (0·75)	42/9	—
Enprostil	mucosal	5·84 (0·26)	14/4	43[b]
Enprostil	serosal	5·51 (0·46)	19/5	46[b]
RS-86505-007	mucosal	5·94 (0·50)	20/6	42[b]
RS-86505-007	serosal	3·90 (0·55)	10/3	62[b]

[a] Number of experiments/number of animals.
Treatment vs control, [b] $P<0·05$.
Difference between enprostil mucosal/serosal not significant at $P<0·1$.
Difference was significant for RS-86505-007, $P<0·05$.

Table 5. In-vitro permeability of D-glucose in monkey jejunum with co-administered test inhibitors.

Inhibitor and concentration	Measured permeability $\times 10^{-6}$ (cm s^{-1}) mean (±s.e.m.)	n[a]	% Inhibition
Control	12·17 (1·28)	19/5	—
Ouabain (200 μM)	4·48 (0·54)	17/5	60[b]
Phlorizin (2·5 μM)	1·92 (0·23)	14/4	84[b]
Misoprostol (2·5 μM)	9·78 (1·81)	16/4	20[d]

[a] Number of experiments/number of animals.
Treatment vs control, [b] $P<0·05$.
[d] Not significantly different from control, $P<0·1$.

Table 6. In-vitro permeability of D-glucose in monkey jejunum with enprostil and RS-86505-007.

Prostaglandin and concentration	Measured permeability $\times 10^{-6}$ (cm s^{-1}) mean (±s.e.m.)	n[a]	% Inhibition
Control	12·17 (1·28)	19/5	—
Enprostil (12·5 μM)	3·61 (0·45)	15/5	70[b]
Enprostil (2·5 μM)	5·67 (1·25)	17/5	53[b]
RS-86505-007 (1·0 μM)	4·35 (0·72)	15/5	64[b]

[a] Number of experiments/number of animals.
Treatment vs control, [b] $P<0·05$.

Table 7. In-vitro permeabilities of passively transported compounds in rabbit jejunum with coadministered prostaglandins.

Substrate and prostaglandin	Measured permeability $\times 10^{-6}$ (cm s^{-1}) mean (±s.e.m.)	n[a]	% Inhibition
Mannitol (0·2 μM)	3·38 (0·22)	16/4	—
Mannitol + enprostil (2·5 μM)	2·24 (0·27)	16/4	34[b]
Mannitol + RS-86505-007 (2·5 μM)	2·45 (0·17)	12/3	28[b]
Progesterone (7·6 nM)	1·36 (0·18)	22/4	—
Progesterone + RS-86505-007 (2·5 μM)	0·65 (0·10)	12/3	52[b]

[a] Number of experiments/numbers of animals.
Treatment vs control, [b] $P<0·05$.

appears to be between $2·5\times10^{-10}$ M and $2·5\times10^{-12}$ M. Monkey experiments (Tables 5, 6) suggest a similar effect. D-Glucose permeability was also inhibited when the prostaglandin analogues were placed in the serosal solution (Table 4). Misoprostol did not significantly inhibit D-glucose transport in monkey, but tended to do so in rabbit ($P<0·1$) (Tables 1, 5).

The effects of enprostil and RS-86505-007 on the passively transported compounds mannitol and progesterone were investigated in rabbit jejunum; the measured permeabilities of both were decreased (Table 7).

The single isomers RS-86505-007, RS-86505-008, and RS-86812-007 were examined for their relative effects on D-glucose transport at an inhibitor concentration of 2·5 μM (Table 8). Both 007 isomers produced a decrease in the permeability of D-glucose. RS-86505-008 was ineffective at the concentrations examined in these studies.

Table 8. In-vitro permeability of D-glucose in rabbit jejunum with co-administered isomers.

Isomer and concentration	Measured permeability $\times 10^{-6}$ (cm s^{-1} mean (±s.e.m.)	n[a]	% Inhibition
Control	10·17 (0·75)	42/9	—
Enprostil (2·5 μM)	5·84 (0·26)	14/4	43[b]
RS-86505-007 (2·5 μM)	5·94 (0·50)	20/6	42[b]
RS-86505-008 (2·5 μM)	11·98 (0·50)	11/3	−18[d]
RS-86812-007 (2·5 μM)	7·25 (0·68)	12/3	29[b]

[a] Number of experiments/number of animals.
Treatment vs control, [b] $P<0·05$.
[d] Not significantly different from control, $P<0·1$.
Effects of RS-86505-007 and RS-86812-007 were not significantly different, $P<0·1$.

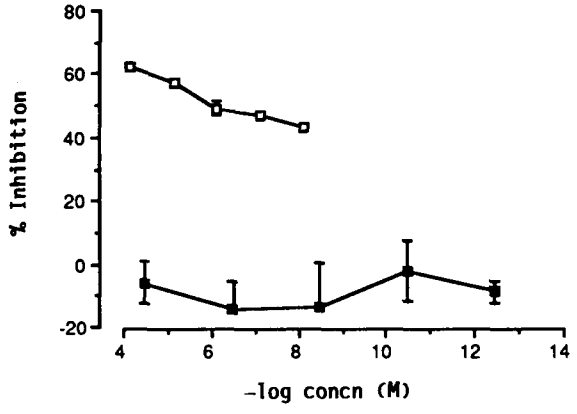


FIG. 2 Percent inhibition of Na-ATPase versus log concentration: results from an in-vitro assay. Error bars represent standard error of the mean for three experiments.

RS-86505-007 present over a wide concentration range ($2·5 \times 10^{-5}$ to $2·5 \times 10^{-12}$ M), had no effect on Na^+, K^+, ATPase, in-vitro (Fig. 2). However, a dose-response curve was obtained for ouabain, a known inhibitor.

Discussion

Both enprostil and RS-86505-007 have been shown to inhibit the in-vitro permeability of D-glucose in rabbit and monkey jejunum. This correlates well with the in-vivo human data previously obtained with enprostil (Schwartz et al 1987 1988; Schwartz & Saito 1987), as well as the results of Coupar & McColl (1972) who demonstrated inhibition of glucose absorption by prostaglandin E_1, E_2, and $F_{2\alpha}$ in in-vivo rat studies. Additionally, the results indicate that the effects demonstrated are not specific to a single species, and that this in-vitro method can mimic the in-vivo situation. These in-vitro studies suggest that the decreases in D-xylose absorption and post-meal D-glucose and triglyceride levels, demonstrated in-vivo, are at least in part due to a direct effect on the tissue. This experimental design, however, does not eliminate the potential contribution of altered gastrointestinal motility on decreased absorption (Miller 1983). Factors which may increase elimination of these nutrients from serum are also not addressed by this model.

Two additional stereoisomers of enprostil, RS-86505-008 and RS-86812-007 were examined for their inhibitory effects on glucose transport. Although RS-86812-007 was effective, RS-86505-008 was not. Misoprostol, a prostaglandin E_1 analogue, was evaluated for its effects on in-vitro transport of glucose, and tended to show some effect in rabbit but was ineffective in monkey at the concentrations examined. Misoprostol has been previously shown to be ineffective in lowering postprandial glucose levels in-vivo (Ebert et al 1987). These results suggest that the effects produced are strongly dependent on the stereochemistry of the agent and are indicative of the existence of a receptor interaction. For the individual isomers and misoprostol, only single concentrations were examined, and relative potencies were not determined for their activity.

Inhibition of glucose transport was also observed when potential inhibitors were present only on the serosal side of the tissue, suggesting that either the receptor is present on both sides of the tissue, or that the prostaglandin E_2 analogues are able to penetrate the tissue to the receptor location. The tissue permeability of these analogues was not examined.

Active absorption of sodium, water, and glucose by the intestinal mucosa is believed to be driven by the Na^+K^+ ATPase pump and its functional significance has been illustrated by specific inhibition with ouabain (Schultz & Zalusky 1964; Charney & Donowitz 1978). It was anticipated that this would be a logical site of action for the inhibitory effects of these prostaglandin analogues, since both PGE_1 and PGE_2 have been found to inhibit gastric Na^+K^+ATPase activity in humans (Mozsik et al 1974; Sharon et al 1984), and PGA_2 exhibits inhibitory effects on rat intestinal mucosa (Matsukawa et al 1981). To determine the activity of RS-86505-007 on D-glucose absorption via this mechanism, the in-vitro effects on enzyme activity were studied. They demonstrate that, at the concentrations examined, RS-86505-007 does not inhibit Na^+K^+ATPase activity. It should be noted that these enzyme studies do not eliminate the possibility of a requirement for some conformational environment which relies on direct interaction with cellular membrane components. The intact cellular systems could not be duplicated in these in-vitro experiments.

The decreased intestinal permeabilities of passively transported species further support the hypothesis of a site of action other than the Na^+K^+ATPase enzyme system. Both mannitol and progesterone transport were decreased in the presence of enprostil or RS-86505-007. This suggests an effect of a more general nature, possibly at the tissue surface. Because passively transported compounds are also effected, the underlying mechanism may be a general increase in the barrier properties of some part of the intestinal surface. Since a relatively hydrophobic molecule, i.e. progesterone, appeared to be inhibited to a greater extent than a hydrophilic compound, i.e. mannitol, this barrier behaves in a manner similar to an increased aqueous diffusion layer. The results determined with these passively transported substances correlated well with the work of Bjarnason et al (1986) who found significantly decreased absorption of EDTA in humans following administration of prostaglandin E_2.

It has been previously shown that the unstirred water layer associated with the intestinal surface can greatly influence

the movement of various compounds, including that of actively transported substrates such as glucose (Thomson & Weinstein 1979), and considerable attention has been given to the interactions of these substrates and the magnitude of this mucus barrier (Smithson et al 1981). It has been suggested that there are two components to the mucus content of the gastrointestinal tract: an adherent layer which forms a thin but continuous covering to the mucosal surface, and soluble mucus found in the lumenal juice (Thomson & Weinstein 1979). It is believed that the adherent mucus or barrier mucus rather than the soluble mucus would be most important physiologically in inhibition of transport of various compounds.

In general, prostaglandins of the E series type increase mucus secretion in animals (Bolton et al 1978; Bickel & Kauffman 1981) and man (Fung et al 1974; Domschke et al 1978; Johansson & Kolberg 1979; Wilson et al 1984). In rats, orally administered enprostil has been shown to increase the adherent mucus layer intragastrically. The oral route of administration resulted in a significantly greater increase in mucus stimulation than subcutaneous, suggesting a local or topical action on mucus secreting cells (Waterbury et al 1986). The increased aqueous barrier suggested in these experiments with actively and passively transported substances could be a result of the increased mucus production stimulated by these prostaglandin analogues.

In conclusion, enprostil and its stereoisomers, RS-86505-007 and RS-86812-007 decrease the in-vitro intestinal permeabilities of D-glucose, mannitol, and progesterone. The results of these studies are consistent with clinical studies demonstrating decreased absorption of glucose, xylose, and triglycerides due to enprostil. These effects appear to be mediated through a receptor interaction which increases the general barrier properties of the tissue, with this additional barrier appearing aqueous in nature. The source of this increased aqueous barrier may be attributable to the ability of prostaglandin E_2 analogues to increase surface mucus.

Acknowledgements

The authors wish to acknowledge the helpful discussions and suggestions provided by Dr Kenneth Schwartz.

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