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Transport of cycloserine across the mucosae of rat colon and the human mouth

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The permeability of the mucosa of the mammalian colon to several acidic and basic drugs was increased by the percentage of each compound present in the unionized form and was also proportional to the degree of lipid solubility (Schanker 1959). Similar considerations apply to the passage of a much wider range of compounds across the mucosa of the human buccal cavity (Beckett & Hossie 1971). Moreover, results of these buccal absorption studies have been used to predict the passage of drugs across other biomembranes, for example, the kidney tubule (Beckett & Triggs 1967) and the small intestine (Beckett & Pickup 1975). A parallelism has been indicated between the absorptive properties of the mouth and colon with reference to certain drugs and nutrients (Evered 1973).

D-Cycloserine, a 'broad spectrum' antibiotic, and its inactive L-isomer pass across the mucosa of mammalian small intestine (Wass & Evered 1971). Both isomers have low solubilities in lipid and are highly ionized at physiological pH values. D-Cycloserine has been shown to pass across the human buccal mucosa (Evered 1972). In the present study some of the transport characteristics of mucosa from both colon and the buccal cavity were compared with respect to D- and L-cycloserine.

Everted sacs of muscle-free colon from female Wistar albino rats were prepared and used in vitro by the method of Parsons & Paterson (1960) with modifications (Evered & Nunn 1968). After incubation 0·2 ml aliquots of serosal and mucosal fluids were deproteinized with 1·8 ml of 5% w/v aqueous trichloroacetic acid and centrifugation at 3000 *g* for 10 min. Since cycloserine is relatively unstable in acid solutions, assays were completed immediately after deproteinization (Wass & Evered 1971).

Absorption from the human mouth in vivo was by the method of Beckett & Triggs (1967) with modifications (Manning & Evered 1976) entailing the use of a buccal 'blank', a pre-incubation period and the use of a physiological buffer solution. Portions of the buccal washes, suitably diluted, were centrifuged at 3000 *g* for 10 min to sediment any debris before analysis. Most of the experiments on buccal absorption were carried out with a female Caucasian subject aged 25 years.

Both cycloserine isomers were assayed spectrophotometrically by the method of Jones (1956) using a Pye-Unicam SP1800 spectrophotometer.

The relationship between the rate of transport of D- and L-cycloserine against initial concentration for both the everted sacs of rat colon (Fig. 1) and the buccal mucosa (Fig. 2) indicated that the process involved was passive diffusion. These results correlated with those of a similar study using rat small intestine (Wass & Evered 1971). The curvilinear relationship shown by the buccal absorption of these compounds should not be taken to indicate carrier-mediated transport as the buccal absorption of a number of drugs has shown this response (Beckett & Hossie 1971). This effect is presumably due to limitations of blood flow or permeability barriers to polar molecules. There was no evidence of stereospecificity for the transport rates in both systems which again is compatible with passive diffusion.

Changes in the initial pH of the D-cycloserine solutions had little effect on its rate of transport in both systems (Table. 1) Assuming that only the unionized species of the molecule will readily cross biological membranes, this result was as expected. Calculations of the extent of ionization of each ionizable group over the pH range studied (Albert & Serjeant 1962) showed that the acidic hydroxy group was almost 100% ionized at pH 7·5 and the basic amino group was almost 100% ionized at pH 4·5. At pH 6·0 each group was approximately 97% ionized. Thus, over the pH range of the study at least one group is almost fully ionized and the molecule exists mainly as a zwitterion.

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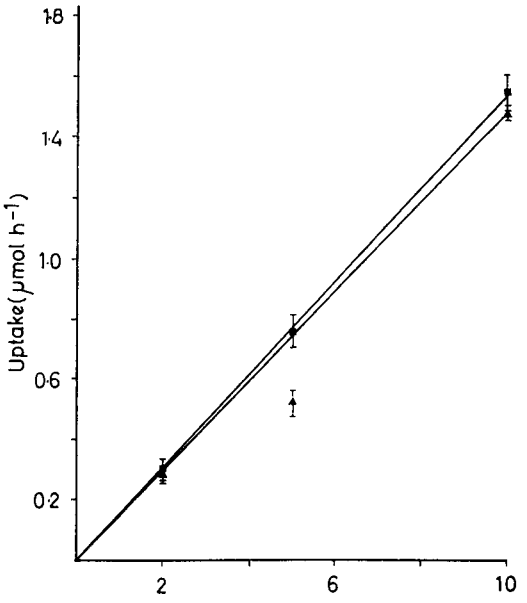

FIG. 1. Effect of initial concentration on the transfer of cycloserine isomers across rat colon in vitro at pH 7·4. ● D-Cycloserine. ▲ L-Cycloserine. Each point is the mean of 6 experiments ± s.e.m. Abscissa: initial concn (mM).

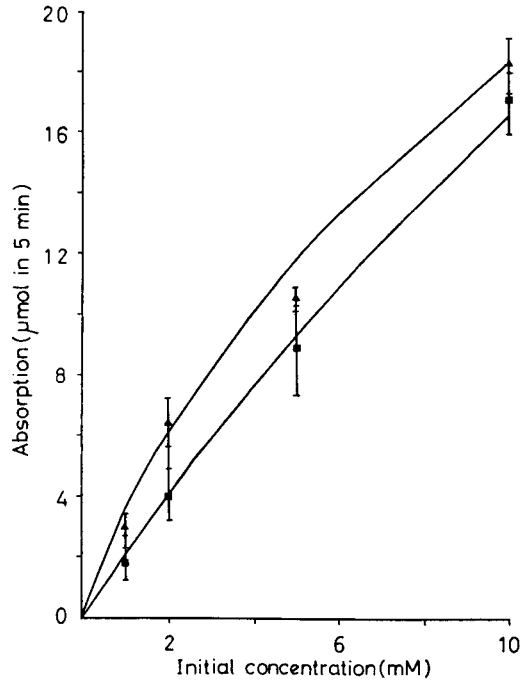

FIG. 2. Effect of initial concentration on the absorption of cycloserine isomers from the human buccal cavity at pH 6·0. ● D-Cycloserine. ▲ L-Cycloserine. Each point is the mean of 6 experiments ±s.e.m.

Overall the extent to which cycloserine was transported across these membranes was small. In the rat colon experiments the final serosal/mucosal concentration ratios were on average approximately 0·33 and in the buccal absorption experiments only about one-tenth of the cycloserine placed in the mouth was absorbed. This poor rate of absorption could probably be attributed to its extremely low solubility in lipid in addition to its high degree of ionization.

Table 1. Effect of pH on the transport of D-cycloserine across (a) rat colon and (b) human buccal mucosa.

Mucosal pH	(a) μmol/h from 5 mM soln	(b) μmol/5 min from 2 mM soln
4·5	0·78 ± 0·055*(5)**	5·4 ± 0·26*(6)**
5·5	0·72 ± 0·014 (4)	5·4 ± 0·27 (6)
6·5	0·71 ± 0·030 (6)	5·0 ± 0·59 (6)
7·5	0·68 ± 0·007 (4)	5·1 ± 0·45 (6)

* Mean ± s.e.m.
** (Number of experiments.)

In conclusion, the permeability of the buccal and colonic mucosa to D- and L-cycloserine has been shown to be qualitatively similar and passive transport was likely. A quantitative comparison cannot be drawn since one system was in vivo and the other in vitro.

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