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Non-enhancement of sodium cromoglycate intestinal absorption by quaternary ammonium ions. An effect of salt on ion-pair formation?

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Studies on the nature of rat small intestine perfusates indicate that this environment is thermodynamically unfavourable for the production of ion pairs between cromoglycate and alkylbenzyltrimethylammonium ions. This is suggested as being the reason why, unlike previously found for ocular absorption of cromoglycate, these quaternary ammonium ions do not alter cromoglycate intestinal absorption.

In their work on buccal absorption of sodium cromoglycate (SCG), Tomlinson & Davis (1976) found an approximately tenfold increase in the uptake of cromoglycate ion by the buccal mucosa in the presence of the quaternary ammonium salt dodecylbenzyltrimethylammonium chloride (C12BDAC) compared with uptake of the drug alone. Furthermore, Wilson et al (1981) found marked alterations in ocular penetration and disposition of SCG after instillation of a combination of SCG and C14BDAC compared with instillation of SCG or C14BDAC alone. Both phenomena can be explained by formation of ion pairs between SCG and ABDAC (Tomlinson & Davis 1980). In the light of these results, we have investigated whether ion-pair formation could also occur in the small intestine, and if so, whether the intestinal absorption of SCG could be enhanced in the presence of an ABDAC. Using a perfused small intestine of the rat as the model for intestinal absorption, we have developed a solution

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Table 1. Composition of a perfusion solution after one hour of perfusion.

Ion	Concentration (mmol litre ⁻¹)
HCO ₃	17.8 ± 1.8
Ca	1.50 ± 0.07
Mg	1.11 ± 0.01
Na	118.4 ± 2.17
K	5.19 ± 0.09
Cl	101.0 ± 2.65
H ₂ PO ₄	0.34 ± 0.02
SO ₄	2.0
Mannitol	71.1

Values for sulphate and mannitol are initial values, they were not measured after perfusion. Concentrations are given as mean ± s.e.m. with n = 9, except for bicarbonate, n = 3.

comparable to the composition of small intestinal fluid. The concentrations are given in Table 1 and are obtained after one hour perfusion of a 6–7 cm segment of jejunum of the rat. Mannitol (a non-absorbable polyalcohol) was used instead of glucose to obtain a minimal flux of water during perfusion.

With the obtained solution, the solubility of SCG was about 6.0×10^{-5} mol litre⁻¹ and of C12BDAC about 1.24×10^{-4} mol litre⁻¹ (25 °C). To examine for transfer of SCG in the presence of an ABDAC, a segment of jejunum was perfused with the above solution containing maximal amounts of SCG and C12BDAC before their coacervation, according to the method described by Ochsenfahrt & Winne (1969). However, no SCG could be detected in the blood using hplc with uv detection. To examine for ion-pair formation in-vitro, shake-flask experiments were carried out using aqueous phase-chloroform (mutually saturated) as the solvent pair. Phases were shaken for 2 h at 37 °C, and then separated. Both phases were then assayed for cromoglycate using uv light. With 0.9% NaCl in water as the aqueous phase, no cromoglycate could be found in the oil phase, indicating that ion-pair formation between cromoglycate and the quaternary ammonium ion had occurred; whereas using 5% mannitol solution as the aqueous phase, cromoglycate could be found in the chloroform phase, indicating that here ion-pair formation had occurred. With a perfusion of the small intestine of the rat with mannitol solution however, secretion of interstitial electrolytes into the perfusate was observed.

These results indicate that the intestinal environment does not favour ion-pair formation between SCG and C12BDAC, which may be explained by the influence of ionic strength of the test solution (0.13), which is comparable to the ionic strength of 0.9% NaCl (0.15).

REFERENCES

- Ochsenfahrt, H., Winne, D. (1969) *Naunyn-Schmiedeberg's Arch. Pharmacol.* 264: 55–75
Tomlinson, E., Davis, S. S. (1976) *J. Pharm. Pharmacol. Suppl.* 28: 75P
Tomlinson, E., Davis, S. S. (1980) *J. Colloid Interface Sci.* 4: 349–359
Wilson, C. G., Tomlinson, E., Davis, S. S., Olejnik, D. (1981) *J. Pharm. Pharmacol.* 31: 749–753