The effect of ion-association on the transcorneal transport of drugs

S.S. DAVIS[1], E. TOMLINSON[2]
& C.G. WILSON[3]
(introduced by J. CROSSLAND)

[1]*Department of Pharmacy, University of Nottingham,* [2]*School of Pharmacy and Pharmacology, University of Bath and* [3]*Department of Physiology and Pharmacology, Medical School, Queen's Medical Centre, Nottingham*

Ionized species are not normally well transported across biological membranes and it has been suggested that organic ions might penetrate in the form of less polar complexes formed with some material normally present in the body. Others have proposed that the coulombic association that can occur between large organic ions of opposite charge could be exploited to provide an enhanced absorption of a poorly lipid soluble drug species.

We wish to report the probable involvement of a drug-surfactant assoication species (ion-pair) in the membrane uptake and penetration of a dianionic drug. We have studied the model system sodium cromoglycate (SCG) (dianion) and dodecylbenzyldimethyl-ammonium chloride (DBDAC) (a benzalkonium salt) (cation).

The formation of an ion-associated species in water was confirmed using a conductimetric titration method (Mukhayer, Tomlinson & Davis, 1975). The transport of such associated species from an aqueous to a lipid environment was studied using two *in vitro* methods; a partition system (water/chloroform) and a membrane diffusion model employing a polymeric film (nylon 6). In both methods we found that SCG and DBDAC were well transported when the two large ions were used together. In contrast neither of the large organic ions was transported when used without the other.

The *in vivo* transport of the ion-association species has been investigated using the corneal membrane. The two large ions, suitably radiolabelled, were instilled in the form of an aqueous solution into an eye of female white New Zealand rabbits. At various time intervals a small volume of the aqueous humour (50 µl) was removed by paracentesis under local anaesthesia (1% amethocaine) and the concentration of the large ion(s) determined using a double isotope counting technique. When one large ion was administered without the other no detectable amounts were found in the aqueous humour. However, when the SCG and DBDAC were administered together both species could be detected in the aqueous humour and the change in these levels with time, could be followed. The effect of two concentrations of the two species have also been measured.

We conclude that the transport of a large organic ion such as SCG through the cornea can be enhanced considerably by the formation of an association species with a large ion of opposite charge. An enhanced loss of SGC from the buccal cavity due to the presence of DBDAC has been reported elsewhere, Tomlinson & Davis (1976).

References

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Effect of adrenoceptor and ganglion blocking agents on the *in situ* uterus of the anaesthetised rat

L. MARY PICKFORD

Department of Physiology, University of Brisbane and Department of Physiology and Pharmacology, Medical School, Queen's Medical Centre, Clifton Boulevard, Nottingham NG7 2UH

Using the technique of Deis & Pickford (1964) for recording from the uterus *in situ* of the anaesthetised rat (pentobarbitone 30 mg/kg i.p.), some observations have been made on the effects of an alpha-adrenoceptor and a beta-adrenoceptor antagonist and ganglion blocking drugs. Each uterine-horn of the anaesthetised rat (body weights 175–200 g) was attached to an isometric transducer and spontaneous contractions and relaxations were recorded on a polygraph (Grass Instruments Ltd.). It was confirmed that in the dioestrus animal alpha-adrenoceptor blockade (phentolamine 50 µg i.v.) increased the size of spontaneous contractions (Deis & Pickford, 1964). Beta-adrenoceptor blockade (propranolol 100 µg i.v.) reduced the size

of spontaneous contractions. On the other hand beta-adrenoceptor blockade (propranolol), after alpha-adrenoceptor blockade (phentolamine) also reduced the size of contractions (5/5 rats). Phentolamine given after propranolol slightly increased contraction size but did not return it to normal (3/5 occasions).

In rats given progesterone (100 mg i.m.) 24 h before observation the responses to the antagonists were reversed, that is, phentolamine reduced the size of the contractions (8/9 rats). Propranolol given after phentolamine (8 observations) increased the amplitude of spontaneous contractions on one occasion; on 4/8 occasions there was only slight increase and in the other 3 rats no change or a further reduction in the size of the contractions. In rats pretreated with progesterone (100 mg i.m.) together with stilboestrol (5 mg i.m.) the results were similar to those obtained when progesterone alone was given.

Tetraethylammonium (2 mg) or hexamethonium (4 mg) given intravenously were previously reported, like alpha-adrenoceptor blockage, to increase the size of the contractions (Deis & Pickford, 1964). In the present series, (15 observations) combined alpha- and beta-adrenoceptor blockade generally decreased the size of contractions. When a ganglion blocking agent was given after phentolamine and propranolol, there was a tendency to an increase in the size of spontaneous contractions.

The effects of combined alpha- and beta-adrenoceptor blockade on the amplitude of spontaneous uterine contractions are not the same as those of ganglion blockade. The reason for the difference remains to be determined.

Reference

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Characterisation of acid secretory responses of the rat isolated gastric mucosa to electrical field stimulation

A.W. BAIRD & I.H.M. MAIN

Department of Pharmacology, The School of Pharmacy, 29/39 Brunswick Square, London WC1N 1AX

The rat isolated gastric mucosa (Main & Pearce, 1978a) has been used to study the effects of drugs on acid secretion in the absence of circulating hormones or extrinsic nerves. The present objective was to investigate the effect of electrical field stimulation on this preparation.

Paired mucosal preparations from rats weighing 80–100 g were mounted in organ baths containing buffered serosal solution (Main & Pearce, 1978a). Unbuffered solution superfused the mucosal surface at 0.5 ml/min then passed to a vessel in which it was titrated continuously to pH 7. Field stimulation was applied via platinum ring electrodes (ring diameter 7.5 mm) placed above and below the mucosa (diameter 11.2 mm). Voltage was monitored on an oscilloscope. In six experiments on unpaired preparations, stimulation at 2 V, 10 Hz, 1 ms for 10 min caused an increase in acid output of 0.94 ± 0.21 μmol (mean ± s.e. mean, results expressed as increase over extrapolated basal output). The second and third responses, obtained at 90 min intervals, were 1.03 ± 0.23 and 0.64 ± 0.18 μmol respectively. Subsequent stimuli gave progressively smaller responses. Secretion increased within 5 min and reached a peak at approximately 15 minutes. During prolonged periods of stimulation, responses were poorly maintained. Voltages greater than 5 V caused changes in acid output which were partly dependent on the polarity of the electrodes. Stimulus frequencies of between 1 and 10 Hz gave graded responses.

The secretory response to electrical stimulation was abolished by tetrodotoxin (10^{-6} M) which did not block histamine (5×10^{-5} M) and by atropine (3×10^{-6} M) which blocked methacholine (5×10^{-7} M) but not histamine. It was potentiated by eserine (3×10^{-5} M). The response was abolished by Ca^{2+}-free solutions and recovered on restoring Ca^{2+} to 0.9 or 3.6 mM, whereas the effects of pentagastrin and histamine are not inhibited by Ca^{2+}-free solutions (Main & Pearce, 1978b). In contrast to its inhibitory effect on the field-stimulated mouse isolated whole stomach (Angus & Black, 1978), hexamethonium (2.6×10^{-4} M) had no effect on the rat mucosa. When added to one mucosal preparation from each pair 60 min prior to the second period of stimulation, the second response expressed as a percentage of the first, was $52.7 \pm 10.1\%$ and $55.5 \pm 21.8\%$ ($n = 6$) for control and hexamethonium-treated groups respectively. Metiamide (10^{-5} M), which partly inhibits gastrin but not methacholine in this preparation (Main & Pearce, 1978c), had no significant effect on electrical stimulation (control $89.5 \pm 7.2\%$, metiamide $83.4 \pm 11.7\%$, $n = 6$).