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

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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

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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