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Influence of lipophilic counter ions on the transport of ionizable hydrophilic drugs

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Abstract—The influence of lipophilic counter ions on the transport of the hydrophilic drugs pholedrine and bretylium across artificial lipid membranes has been studied using a permeation model system. The transport of both drugs was markedly enhanced by hexylsalicylate and by salts of fatty acids with a maximum at decanoate. The transport of pholedrine was additionally increased by bile salts such as desoxycholate.

Ion-pair transport may be affected by a number of factors (Neubert 1989). Lee et al (1987) found that the transport of a series of drugs through a silicon rubber membrane was ion-pair size dependent. Neubert & Dittrich (1989) studied the influence of a series of counter-ions on the transport of ampicillin across dodecanol collodion membranes owing to steric effects, only dodecylsulphate significantly increased the transport rate of ampicillin.

In the present study, the influence of different lipophilic counter ions on the transport of the hydrophilic drugs bretylium and pholedrine has been examined. The study was focused on physiological counter-ions because the use of lipophilic counter-ions with physiological compatibility is desirable for the practical use of ion-pair transport (Neubert 1989). The permeation apparatus with dodecanol collodion membranes described previously served as the model system (Fürst et al 1980).

Materials and methods

Materials. Pholedrine sulphate was obtained from VEB Isis Chemie (Zwickau, Germany). Bretylium tosylate was a gift of VEB Arzneimitel-werk Dresden (Dresden, Germany). Dehydrocholate was supplied by VEB Berlin Chemie (Berlin, Germany). 1-Hydroxynaphthoate, 1-naphthylsulphonate, octanoate, decanoate, dodecanoate, hexadecanoate, collodion (4% w/w), and benzalkonium bromide were purchased from VEB Laborchemie (Apolda, Germany). Desoxycholate was obtained from SERVA (Heidelberg) and dodecanol from Merck (Darmstadt, Germany). Hexylsalicylate was synthesized as described previously (Neubert et al 1987). All other reagents were of analytical grade.

Model system. The influence of the counter ions on the transport of bretylium and pholedrine was studied in the permeation model system described by Fürst et al (1980). The donor and the acceptor compartments (each 20 mL in volume) were separated by a dodecanol collodion membrane. The effective permeation area was 15·8 cm^2. The phases were agitated with a vibrator (Thyr 2, VEB Labortechnik, Ilmenau, Germany). Four permeation cells were simultaneously used at 37°C. Usually, 1·0 mmol L^{-1} of the drug and the counter ion, respectively, were dissolved in Sörensen phosphate buffer pH 7·2. Twenty mL of this solution was placed in the donor compartment and 20 mL of the buffer was filled into the acceptor compartment. Samples (2·0 mL) were periodically removed from both cells over 3 h, and assayed for the drug content and for the counter ion content when the counter ion could be assayed.

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Calculation of the flux. For the evaluation of the experiments the flux from the donor compartment into the membrane (F_{DM}) and from the membrane into the acceptor compartment (F_{MA}) was calculated according to the following equations:

$$F_{MA} = \frac{C_{AC} V_{AC}}{At} \quad (1)$$

$$F_{DM} = \frac{(C_O - C_{DC})V_{DC}}{At} \quad (2)$$

Where:
C_{DC}, C_{AC} are the substance concentrations and V_{DC}, V_{AC} are the volumes of the compartments. C_o is the initial substance concentration, A is the membrane area, and t is the time.

Analytical assays. Pholedrine was determined by measuring the UV-absorption at 275 nm using a spectral-photometer VSU-2P (VEB Carl Zeiss, Jena, Germany). Bretylium was determined after ion pair extraction with picric acid in dichloromethane. After separation of the organic phase, picric acid was determined at 375 nm. The counter ions 1-hydroxynaphthoate, 1-naphthylsulphonate, and hexylsalicylate were assayed by measuring the UV-absorption at 334, 328 and 305 nm.

Results and discussion

The study was focused on the application of physiological counter-ions such as bile salts (desoxycholate and dehydrocholate) and salts of fatty acids (octanoate, decanoate, dodecanoate, and hexadecanoate). Further lipophilic counter ions were used such as naphthyl derivatives (1-hydroxynaphthoate and 1-naphthylsulphonate) and hexylsalicylate. All counter ions used are ionized in the buffer (pH = 7·2) used.

Influence of certain counter ions on the transport of pholedrine. As shown in Fig. 1 the transport of pholedrine across the dodecanol collodion membranes is significantly increased by all counter ions used in comparison with the transport of pholedrine sulphate. Both F_{DM} and F_{MA} of pholedrine were enhanced by the counter ions studied. However, a marked increase in the flux of pholedrine (F_{DM} as well as F_{MA}) was measured when desoxycholate, hexylsalicylate, and dodecanoate were used. When the influence of the salts of the fatty acids was examined a maximum permeation of pholedrine for dodecanoate was observed. 1-Hydroxynaphthoate could be only used as a suspension and, in this case, it was not possible to calculate F_{DM}. In contrast to desoxycholate, only a slight increase of the flux of pholedrine was observed when dehydrocholate was used. This seems to be caused by the ability of desoxycholate to form a hydrogen bond with the phenolic -OH of pholedrine additional to the ion pair interaction. Also, the naphthylderivatives and adamantoate significantly increased the transport rate of pholedrine. However, the increase caused by those ions was much lower than that caused by dodecanoate, desoxycholate, or hexylsalicylate; the lipophilicity of the former ions seems to be too low to achieve the same influence as the latter. As shown in Fig. 1 the flux of pholedrine was significantly decreased by benzalkonium bromide, which has the same charge as pholedrine. The result shows

that the increase of the flux observed is caused by the counter ions and not by the action of the surfactant on the structure of the membrane.

Further, it was observed that the transport of pholedrine from the donor compartment into the membrane (F_{DM}) was significantly higher than that from the membrane into acceptor compartment (F_{AC}) when desoxycholate, dehydrocholate and dodecanoate were used. Under those conditions some pholedrine remained in the membrane.

Gasco et al (1984) found that the transport of propranolol is increased by taurodeoxycholate, and Green & Hadgraft (1987) reported that oleate enhances the transport of β-blocking agents. The ability of physiological ions, such as bile salts, to increase the transport of pholedrine and of drugs with similar structure, by ion-pairing, appears to be important for their absorption. Despite their hydrophilicity these drugs are absorbed. For example, the absolute bioavailability of pholedrine (n-octanol–water partition coefficient,P, = 0·09, Neubert 1989) amounts to approximately 80% (Fürst et al 1990) and that of the β-blocking agent atenolol (P = 0·02) amounts to 60–80% (Hinderling et al 1984).

Taking the in-vitro results discussed in this paper into consideration the presence of salts of bile acids as physiological counter-ions seems to be responsible for the high bioavailability of these drugs.

Influence of certain counter ions on the transport of bretylium. As shown in Fig. 2 the flux of bretylium into the acceptor compartment was increased by the salts of the fatty acids, by hydroxynaphthoate, by naphthylsulphonate, by desoxycholate, and, as already described, by hexylsalicylate (Neubert et al 1987), compared with the flux of bretylium in the presence of tosylate. The salts of the fatty acids influenced the transport of bretylium in the same way as that of pholedrine with a maximum at dodecanoate. The transport of bretylium was not influenced by the salts of the bile acids. Only a slight increase of F_{MA} was observed when desoxycholate was used. In contrast to pholedrine, there is no possibility of forming hydrogen bonds between bretylium and desoxycholate.

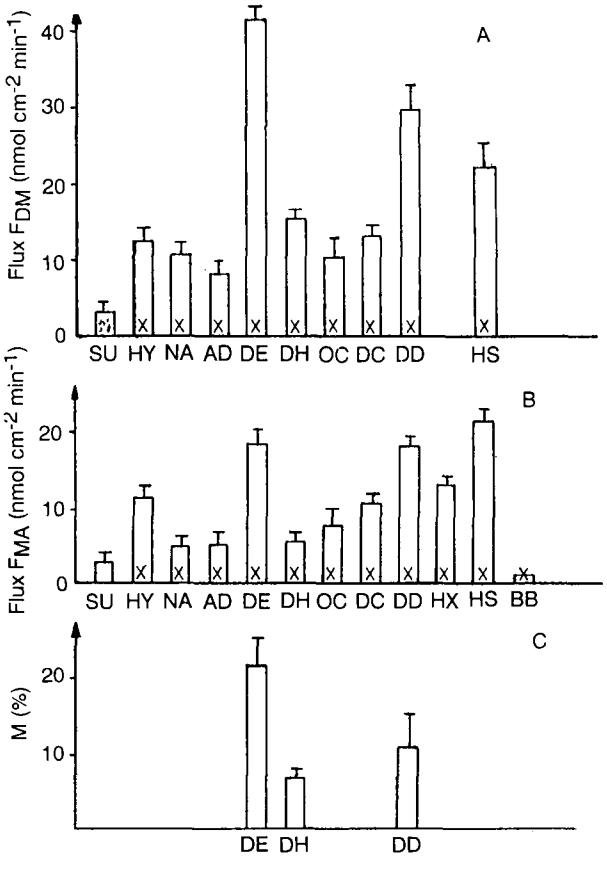

FIG. 1. Influence of counter ions on the transport of pholedrine. SU, sulphate; HY, hydroxynaphthoate; NA, naphthylsulphonate; AD, adamantoate; DE, desoxycholate; DH, dehydrocholate, OC, octanoate; DC, decanoate; DD, dodecanoate; HX, hexadecanoate; HS, hexylsalicylate; BB, benzalkonium bromide. x Significantly different from value for SU.

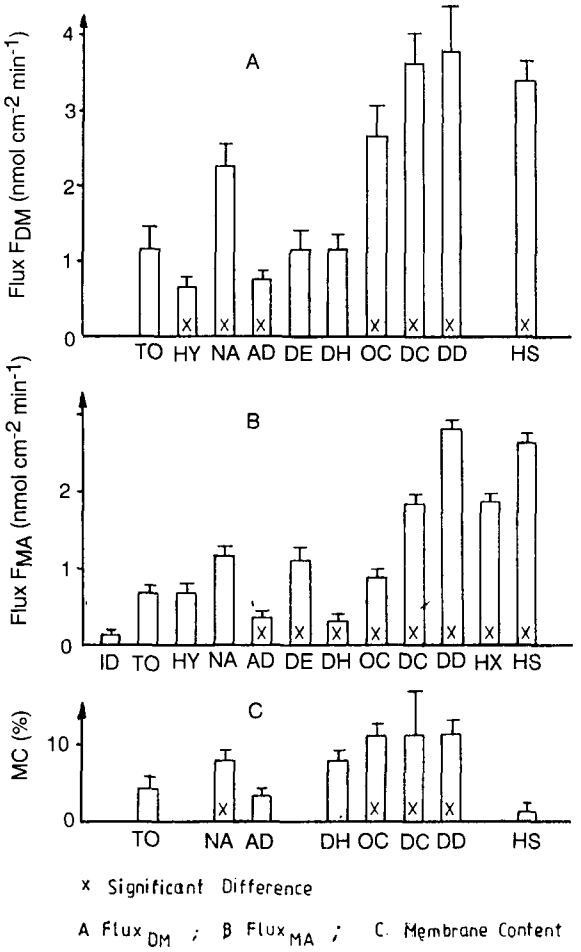

FIG. 2. Influence of counter ions on the transport of bretylium. IO, iodide; TO, tosylate; HY, hydroxynaphthoate; NA, naphthylsulphonate; AD, adamantoate; DE, desoxycholate; DH, dehydrocholate; OC, octanoate; DC, decanoate; DD, dodecanoate; HX, hexadecanoate; HS, hexylsalicylate. x Significantly different from value for TO.

On the other hand, using hydroxynaphthoate, adamantoate, or dehydrocholate the increase of the lipophilicity caused by ion pairing seems to be insufficient to influence the membrane transport of bretylium.

The influence of counter ions on the transport of bretylium is associated, except for hydroxynaphthoate and desoxycholate, with a significant membrane accumulation of bretylium. In contrast, pholedrine could be detected in the membrane only in the presence of desoxycholate, dehydrocholate and dodecanoate. However, the membrane content of both drugs did not exceed 20% so that the flux could still be used for evaluating transport (see also Neubert et al 1988).

The results show that ion-pair transport across lipid membranes depends not only on the lipophilicity of the ion-pair

formed but also, as shown, on additional interactions (e.g. H-bonds) and on the shape of the ion-pair, as indicated by the differences in membrane accumulation of both drugs studied.

One reason for the wide variation in bioavailability of bretylium (Garrett et al 1982) may be the ability of the salts of fatty acids to influence the membrane transport of bretylium markedly by ion-pair transport. The absorption of bretylium seems to be strongly dependent on the presence of these salts. Therefore, the addition of appropriate salts of fatty acids to dosage forms of bretylium may be useful for maintaining a constant absorption rate of bretylium as well as for increasing the bioavailability of these drugs.

Influence of pholedrine and bretylium on the accumulation of selected counter ions in the membrane. The influence of pholedrine and bretylium on the accumulation of hydroxynaphthoate, naphthylsulphonate, and hexylsalicylate in the membrane is shown in Fig. 3. It was found that only hexylsalicylate significantly accumulated in the membrane in the presence of both drugs. The mechanism of ion-pair transport proposed in the literature (Neubert et al 1984; Green & Hadgraft 1987; Neubert 1989) was supported by those results. According to this mechanism, lipophilic counter ions such as hexylsalicylate accumulate in the lipid membrane and facilitate the transport of hydrophilic drug molecules.

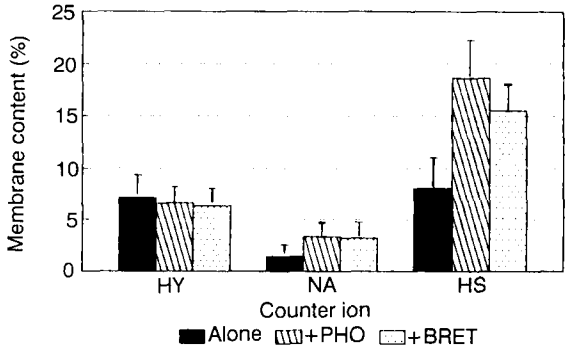

FIG. 3. Accumulation of the counter ions hydroxynaphthoate naphthylsulphonate and hexylsalicylate in the membrane. Solid columns, no drug. Hatched columns, with pholedrine. Dotted columns, with bretylium.

Only a slight, or zero, increase of the membrane content of hydroxynaphthoate or naphthylsulphonate was observed in the presence of the drugs, as their transport was minimally influenced by these ions. Unfortunately, analytical methods were not available to assess the membrane content of the bile salts and of the salts of the fatty acids.

References

Fürst, W., Neubert, R., Reppel, L. (1980) Arzneimittelpermeation. 10.Mitteilung: Einfluß der Diffusionsschichten. Pharmazie 35: 106–109

Fürst, W., Sziegoleit, R., Neubert, R. (1990) Pharmakokinetik des Pholedrins. Ibid. In press

Garrett, E. R., Green, J. R., Bialer, M. (1982) Bretylium pharmacokinetics and bioavailabilities in man with various doses and modes of administration. Biopharm. Drug Disp. 3: 129–164

Gasco, M. R., Trotta, M., Eandi, M. (1984) The influence of bile salts on the absorption in vitro and in vivo of propranolol. J. Pharm. Biomed. Anal. 2: 425–439

Green, P. G., Hadgraft, J. (1987) Facilitated transfer of cationic drugs across a lipoidal membrane by oleic acid and lauric acid. Int. J. Pharm. 37: 251–255

Hinderling, P., Schmidlin, O., Seydel, J.K. (1984) Quantitative relationships between structure and pharmacokinetics of beta-adrenoceptor blocking agents in man. J. Pharmacokin. Biopharm. 12: 263–287

Lee, S.J., Kurihara-Bergström, T., Kim, S.W. (1987) Ion paired drug diffusion through polymer membranes. Int. J. Pharm. 47: 59–73.

Neubert, R. (1989) Ion pair transport across membranes. Pharm. Res. 6: 743–747

Neubert, R., Dittrich, T. (1989) Ampicillin Ionenpaartransport im Vergleich mit dem Transport weiterer Penicilline. Pharmazie 44: 67–68

Neubert, R., Böhm, W., Dabow, S., Fürst, W. (1984) Arzneimittelpermeation, 17. Mitteilung: Zum Mechanismus der Ionenpaarpermeation. Ibid. 39: 401–403

Neubert, R., Fürst, W., Schleiermacher, H., Bergmann, P., Stolte, E. (1987) Arzneimittelpermeation. 21. Mitteilung: Ionenpaar-transport mit Alkylsalizylsäuren. Ibid. 42: 309–311.

Neubert, R., Förtsch, R., Beyrich, G., Leisner, R., Fürst, W., Botze, L. (1988) Auswertung von Daten der Arzneimittelpermeation mit dem Dreiphasenmodell. Acta Pharm. Helv. 63: 249–253