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Review

Ion Pair Transport Across Membranes

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The present review discusses drugs and counter ions suitable for ion pair transport (IPT). Ion pairing is shown to effectively increase the lipophilicity and transport rate of polar drugs across lipid membranes. The proposed mechanisms of IPT are discussed in detail. A marked change in drug properties upon ion pair formation is necessary to improve the bioavailability of hydrophilic ionizable drugs.

KEY WORDS: ion pair transport (IPT); mechanism of IPT; hydrophilic drugs; counter ions; effects on pharmacokinetics.

INTRODUCTION

Early studies on ion pair transport (IPT) focused on ion pair absorption from the gastrointestinal tract. However, the movement of ionizable drugs across membranes can be facilitated by ion pair formation throughout the entire body. The IPT topic was reviewed by Lippold (1) and Jonkman and Hunt (2). The present Review covers the recent literature on IPT, with the focus on the following questions. First, which drugs and counter ions are suitable for IPT? Second, how does lipid partitioning affect the transport through artificial membranes? Third, can one affect the pharmacokinetics of suitable drugs by ion pair formation and attendant increased lipophilicity?

SUBSTANCE SUITABLE FOR IPT

Both drugs and counter ions undergoing IPT have to fulfill certain requirements. Jonkman and Hunt (2) reported that the transport of certain drugs was unaffected by IPT both *in vitro* and *in vivo*. However, the physicochemical basis of the failure of these drugs to undergo IPT remained unclear.

Plakogiannis *et al.* (3) found that decylsulfate does not affect the disappearance of highly lipophilic drugs from rat intestine. For similar reasons, IPT did not affect the transport of the lipophilic substances used by Jonkman (4). It therefore appears that ion pair formation affects partition and transport only of those drugs that are hydrophilic and ionized in the media where ion pairing is to take place. Table I shows physicochemical and pharmacokinetic properties of drugs that can be influenced by IPT. The physicochemical properties of these drugs are associated with a low absolute bioavailability, and except for bretylium, with a short elimination half-life *in vivo*.

Counter ions used in the past included alkylsulfates, trichloracetate, alkylcarboxylates, cholate, desoxycholate, taurocholate, and phosphocholate. The arguments against the *in vivo* application of these counter ions include the contention that these counter ions are too irritative at the required dosages (2). Therefore, counter ions with the following properties are needed: high lipophilicity, sufficient solubility, physiological compatibility, and metabolic stability. Alkylated salicylic acids (5–8) and alkonoic acids (9,10) are examples of counter ions with a better physiological compatibility. Similarly, 1-dodecylazacycloheptan-2-on (azone) was found to be an effective enhancer of the transport of salicylic acid through artificial lipid membranes (11).

ION PAIR TRANSPORT *IN VITRO*

The lipophilicity of hydrophilic ionized drugs can be increased by ion pair formation with lipophilic counter ions. For example, Lippold *et al.* (12,13) found that the partition coefficients of hydrophilic quarternary ammonium compounds can be increased by the lipophilic counter ions, *n*-alkylsulfates and *n*-alkylcarbonates. Neubert *et al.* showed that the partition coefficient of the hydrophilic drugs buformine (14), bretylium, and pholedrine (5) is markedly increased by lipophilic ions such as hexylsalicylate. Further, the lipophilicity of doxorubicin is enhanced by the counter ions dioctylsulfosuccinate and dodecylsulfonate in the pH range 1.1–7.0 (15) (see also Table II). Langguth and Mutschler (16) synthesized lipophilic ion pairs of tropsium chloride with *n*-alkylsulfates and *n*-sulfonates; while the lipophilicity of both series of ion pairs increased with the number of carbon atoms in the anion, the lipophilicity of the alkylsulfonate ions pairs were significantly higher than that of the alkylsulfonates.

Recent studies have focused on the kinetics of IPT, rather than the thermodynamics of ion pair formation. The two main experimental approaches include the influence of ion pair formation on the transport of hydrophilic drugs by suitable counter ions and the mechanism of IPT through artificial lipid membranes. Several *in vitro* membrane systems served as experimental model systems. Using the absorption

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Table I. Some Physicochemical and Pharmacokinetic Properties[a] of Drugs Suitable for Ion Pairing

Drug	pK_a Value	Partition Coefficient, *n*-Octanol/Water	$t_{1/2}$ (hr)	Absolute Bioavailability (%)
Bretylium bromide	—	<0.01	8.9	22–27
Buformine hydrochloride	13.2	0.055	2.0–2.5	40
Pholedrine sulfate	9.18	0.09	3.1	29
Ampicillin	2.65, -COOH 7.2, $-NH_2$	1.0		40
Timolol maleate	8.8	0.59	1.0[b]	30
Atenolol	9.55	0.02	3–4	40–50

[a] In humans.
[b] MRT.

simulator of Stricker (17), Lippold and Lettenbauer (12) found that the rate constants for the permeation across *n*-octanol membranes increase with increasing chain length of the counter ion up to a limiting value. Furthermore, Lippold and Schneider (13) ascertained that the rate constants of homologous benzilonium-*n*-alkylsulfonates can be increased by lipophilic counter ions. Dioctylsulfosuccinate, dodecylsulfate, and decanesulfonate were found to be capable of increasing the diffusion rate constants of doxorubicin using the absorption simulator of Stricker (17). The transfer rates of tropsium across everted intestine [everted sac technique (18)] and human abdominal skin, respectively, were enhanced by lipophilic counter ions such as *n*-alkylsulfonates and *n*-sulfates (16). However, the hydrophilic ion pairs (partition coefficient of *n*-octanol/water <1) did not permeate more readily through the skin or the gut wall, while maximum permeation of tropsium was observed in the range of medium chain length of the counter ions ($n = 7$, $n = 9$).

The transport of ionized hydrophilic drugs through lipid membranes can also be improved by IPT because of the increased lipophilicity (5,9,10,14,19,20; see Table II). On the other hand, in addition to the lipophilicity, further parameters are capable of influencing IPT. Lee *et al.* (21) found that permeation of a series of drugs through a silicon rubber membrane was ion pair size dependent. Further, Neubert and Dittrich studied the influence of a series of lipophilic counter ions on the transport of ampicillin across dodecanol collodion membranes (22). However, only dodecylsulfate significantly increased the ampicillin transport rate because of steric effects.

Languth and Mutschler (16) were able to enhance skin permeability of ionizable drugs by IPT. Further, Young *et al.* (23) found that *in vitro* percutaneous penetration of isopropramide through mouse skin was increased in the presence of sodium salicylate. Similarly, the studies by Hadgraft *et al.* (11,24,25) concerning the permeability of ionizable drugs through isopropyl myristate membranes were performed in order to influence skin permeability by IPT. Estimating the relation between the increase in lipophilicity and the transport rate, a linear relationship was found between the log of the *n*-octanol/buffer partition coefficients and the diffusion rate constants (15). Usually, the increase in lipophilicity caused by ion pairing was much higher than that in the transport rate (see Table II).

On the other hand Schurgers *et al.* found no enhancement of sodium cromoglycate intestinal absorption by quarternary ammonium ions (26), in contrast to previous results (27). The environment of rat small intestine seems to be unfavorable for the formation of ion pairs between cromoglycate and alkylbenzyldimethylammonium ions. Further, bile salts do not enhance the transport of phenothiazine cations across IPM membranes, probably because of the lipophilicity of the phenothiazines (28).

MECHANISM OF IPT

The transfer of hydrophilic ionizable drugs across lipid membranes can be facilitated in the presence of suitable counter ions. Carrier-facilitated mechanisms have been identified in biological membranes. Studies of the mechanism of IPT are important to obtain a better understanding of transport mechanisms of ionizable drugs across biological membranes and to utilize IPT systematically to improve the pharmacokinetics of these drugs. First, it was supposed that the ion pair permeates across lipid membranes at an equimolar ratio as shown in the upper part in Fig. 1 (1,2,10,21,29). However, there is evidence that in certain circumstances the mechanism of IPT is more complex. Based on studies of the influence of lipophilic counter ions on the transport of cationic drugs, it was found by Neubert *et al.* that the lipophilic counter ions accumulate in the lipid membrane (5,14). Therefore, more hydrophilic drug molecules than counter ions are transported into the receptor compartment. Excess drug molecules transported into the receptor compartment must be balanced by ions from the receptor compartment. When a pH gradient (pH of the donor phase > pH of the receptor phase) or a Na^+/Li^+ gradient is established, a countertransport of protons (30) and lithium ions (31) from the receptor into the donor compartment was observed. Consequently, lipophilic counter ions accumulated in the membrane facilitate the transport of the cationic drug molecules and cause the transport of protons and litium ions, respectively, in the opposite direction (Fig. 1, lower part). Additionally, the transport of the entire ion pair (Fig. 1, upper part) takes place. A countertransport of ions through artificial lipid membranes was also found using inorganic—substances and organic counterionic carrier molecules (32–34). The mechanism of IPT was proposed in Fig. 1 was confirmed by results

Table II. Influence of Lipophilic Counter Ions on the Lipid Partition and the Transport of Ionizable Drugs *in Vitro*

Drug	Counter Ion	Membrane	Factor of the Partition Coefficient	Increase in Transport Rate	Ref. No.
Tropsium hydrochloride	Heptyl-sulfates, *n*-sulfonates	Human skin, everted rat intestine	19 46	3–4	16
Metoprolol tartrate	Oleate	Membrane filter impregnated with isopropyl myristate	45	4[a]	10
Oxoprenolol hydrochloride	Oleate		38	4[a]	10
Propranolol hydrochloride	Oleate		30	2[a]	10
Propranolol hydrochloride	Taurodeoxycholate	Membrane filter impregnated with dodecanol	40	5–6	19
Timolol maleate			50	7	9
Doxorubicine	Dioctylsulfosuccinate	Membrane filter impregnated with dodecanol		11	15
	Dodecylsulfate			17	15
	Decanesulfonate			11	15
Salicylic acid	Azone	Membrane filter impregnated with isopropyl-myristate		1.7	11
	Ethomeen S 12			3	11
Ampicillin	Dodecylsulfate	Dodecanol collodium		15	22
Bretylium bromide	Hexylsalicylate		>100	7	5
Buformine hydrochloride	Hexylsalicylate		10	12	5
Pholedrine sulfate	Hexylsalicylate		>100	8.5	5
Quinine hydrochloride	Hexylsalicylate		2.5	2	5
Chloramphenicol succinate	*p*-Ethoxybenzyltri-phenylphosphonium	Polyethylene impregnated with 1-octanol		10	41

[a] Oil–water partition coefficients; all other experiments, 1-octanol/water or buffer partition coefficients.

obtained by Green and Hadgraft (10), who found that a pH gradient (pH of the donor phase > pH of the receptor phase) can serve as the driving force for the transport of the cationic drugs against their own concentration gradient when lipophilic counter ions are present in the membrane.

A similar mechanism of IPT for anionic drugs was proposed by Hadgraft *et al.* (11). Using the rotating diffusion cell of Albery *et al.* (35) and membrane filters impregnated with isopropyl myristate, azone and ethomeen S 12 were found to be capable of enhancing the transport of salicylate because of ion pair formation (11,24,25,36). The scheme of this facilitated transport mechanism is outlined in Fig. 2. When the lipophilic carrier is added to the membrane, a pH gradient (pH of the donor phase < pH of the receptor phase) has been reported to operate as the driving force and to cause a symport of salicylate anions and protons from the donor to the receptor compartment.

EFFECTS OF IPT ON PHARMACOKINETICS

The increased lipophilicity and *in vitro* transport rate of hydrophilic drugs because of ion pair formation could serve to improve the low bioavailability of these drugs. However, the use of IPT *in vivo* requires that sufficient counter ions must be available at the site where ion pairing is to take place, and information on the plasma levels of counter ions should be available to assess the potential of overall pharmacokinetic changes.

As indicated by an increase in the area under the curve (AUC), it was found that primarily the bioavailability of hy-

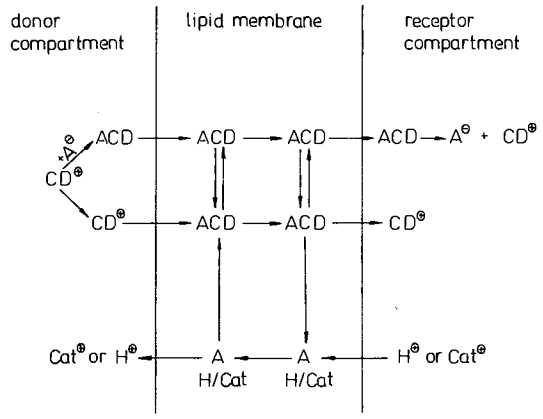

Fig. 1. Proposed facilitated transport scheme for cationic drugs when the lipophilic carrier is added to the donor compartment according to Neubert *et al.* (14). CD^+, cationic drug; A^-, anionic lipophilic carrier; Cat^+, cation from receptor compartment such as Li^+; H^+, proton.

drophilic drugs was increased by IPT following oral and rectal administration. Thus, the AUC of propranol was reported by Gasco *et al.* to be increased in the presence of taurodeoxycholate (19). Further, hexylsalicylate was found to be capable of enhancing the AUC of hydrophilic drugs such as pholedrine and bretylium after oral and rectal application, respectively (7,8). The AUC of ampicillin was found be increased in the presence of 3,7-di-t-butylnaphthalene-1,5-disulfonate (37) (for detailed information see Table II).

The increase in the bioavailability following oral and rectal administration shows that the absorption of hydrophilic drugs can be influenced mainly by IPT. However, results have been published indicating that the pharmacokinetics of hydrophilic drugs are influenced following i.v. and i.p. administration, respectively. It was found that 1-methyl-palmitate and hexylsalicylate are able to prolong the MRT of quinine after i.p. and i.v. application, respectively (6,38).

When the more lipophilic drug quinine was used, only the MRT, and not the AUC, was influenced by IPT after i.v. and i.p. application (6). The prolongation of MRT of quinine appears to be caused by an increase in the apparent distribution volume. These findings were confirmed by Shim, who reported that the apparent distribution volume of methylene blue in rats was increased in the presence of taurodeoxycholate (39).

Only a slight increase in the transport rate caused by IPT was observed when a drug such a quinine was used (see Table II). No influence of hexylsalicylate on the pharmacokinetics of quinine was therefore obtained after rectal administration (6).

In contrast, an increase in the AUC of bretylium was observed in the presence of hexylsalicylate after i.v. application (8). The results also indicate that the elimination can be influenced by IPT when a hydrophilic drug such as bretylium is used. Because bretylium is excreted primarily in the bile, the intestinal reabsorption of bretylium appears to be increased by IPT with hexylsalicylate. Recently, these results were confirmed. It was found that the biliary excretion of bretylium is markedly increased in the presence of hexylsalicylate (40). Further, following i.v. administration the plasma levels of bretylium were sufficiently high to affect the pharmacokinetics of the counter ion hexylsalicylate (8). Under these conditions hexylsalicylate is also undergoing enterohepatic circulation (40). The influence of ion pairing on enterohepatic circulation seems to be an interesting object for further studies. On the other hand, following i.v. application of the hydrophilic drug pholedrine (7), the high metabolization rate prevents the influence of IPT.

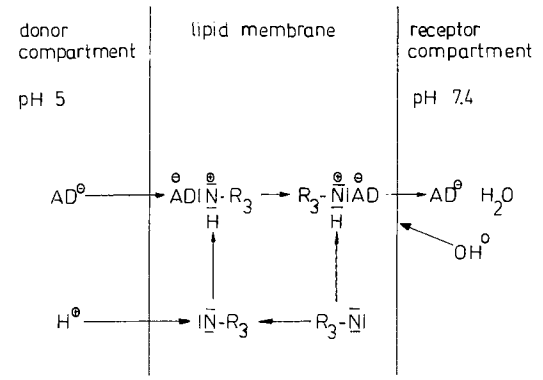

Fig. 2. Proposed facilitated transport scheme for anionic drugs when the carrier is used to the membrane according to Hadgraft *et al.* (28). AD^-, anionic drug; H^+, proton; $N\text{-}R_3$, tertiary amine as lipophilic carrier.

CONCLUSIONS

The ability of ion pair formation to influence the behavior of drugs depends strongly on the physicochemical properties of both the drugs and the counter ions. Improved lipophilicity and transport can be achieved only with hydrophilic ionizable drugs by ion pair formation with suitable lipophilic counter ions. The transport of ion pairs across lipid membranes (ion pair transport) appears to follow a specific transport mechanism, with the lipophilic counter ions acting as carriers for hydrophilic drug molecules. Hence, IPT can be considered as a facilitated transport, particularly when pH and alkali ion gradients are established.

Only a marked change in drug properties upon the ion pair formation measured can be expected to improve the bioavailability of hydrophilic ionizable drugs. Using suitable counter ions it seems to be possible to increase the bioavailability following oral and rectal administration, respectively, by a factor of approximately 2. This increase will be useful for drugs with an absolute bioavailability of 30–40%. In contrast, the concept of IPT was still not extensively used in the field of dermal and transdermal administration. However, the key for the further use of IPT will be the search for specific lipophilic counter ions with a convenient physiological compatibility.

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