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Absorption and Excretion of Drugs. XL.[1] Enhancement of the Rectal Absorption of Pharmaceutical Amines with Lauryl Sulfate and Saccharinate Anions

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The absorption of ion pair complexes was studied in rats by means of *in situ* rectal perfusion technique. Two combinations, sodium lauryl sulfate-basic drugs and saccharin sodium-basic drugs were examined in detail. The disappearance from the perfusate of both components were determined in order to elucidate the mechanism of ion pair absorption.

Basic drugs except some quaternaries tested were absorbed much faster in the presence of lauryl sulfate and saccharinate anions but the converse could not be applied for the anionic components. Blood level analyses of basic drugs also demonstrated such absorption enhancement effect.

Enhancement of the absorption of cationic drugs could better be related to the binding behavior of those drugs to the rectal mucosal preparations than their apparent chloroform or benzene/water partition coefficients.

Extensive research on the mechanism of absorption of drugs has been carried out in the last two decades and the gastro-intestinal absorption of most drugs has been interpreted to proceed mainly by the passive transfer of unionized molecules. Recent studies in this laboratory[3,4] have shown that drug absorption from the rat rectum or the colon was more consistent with pH-partition hypothesis[5] than the absorption from the small intestine. According to this hypothesis, pharmaceutically important amines and quaternary ammonium compounds having pK_a of more than 8 would be expected not to be absorbed to a considerable extent since physiological pH in the alimentary tract seldom exceeds 8.0.

Certain ionized molecules associate with counter-ions in aqueous solution to form ion-pair complexes.[6,7] Consequently it appears of biopharmaceutical interest to investigate the possibility of enhancing the absorption of such poorly absorbable compounds by lipoid-soluble ion-pair complex formation.

Present paper describes the effect of lauryl sulfate and saccharinate anions on the rectal absorption of poorly absorbable basic drugs and discusses the mechanism of absorption of such ion-pair complexes.

Experimental

Materials——Sodium lauryl sulfate (SLS) was used after recrystallization from ethanol (mp 195°). Other reagents were of the analytical grade.

Apparent Partition Coefficients——Aqueous solutions containing basic drugs (0.2mM) were prepared with isotonic buffered solution of pH 7.4 or 5.0 (KH_2PO_4–Na_2HPO_4 system). Four ml portions of the

1) Part XXXIX: K. Kakemi, H. Sezaki, K. Okumura, and S. Ashida, *Chem. Pharm. Bull.* (Tokyo), **17**, 1332 (1969).
2) Location: *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto.*
3) K. Kamemi, T. Arita, and S. Muranishi, *Chem. Pharm. Bull.* (Tokyo), **13**, 861 (1965).
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5) L.S. Schanker, P.A. Shore, B.B. Brodie, and C.A. Hogben, *J. Pharmacol. Exptl. Therap.*, **120**, 538 (1957).
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aqueous solution were kept in a constant temperature water-bath at 37°. After equilibration, drug content in the aqueous phase was determined and the paparent partition coefficient was calculated. For the organic phase, 8 ml of chloroform or benzene was used.

Surface Tension——Surface tension was measured at 20° with a Du Nöuy interfacial tensiometer.

Absorption Experiment——Details of the experiment has been described previously.[8] After one hour perfusion, perfusate was collected in a volumetric flask by washing out with the same buffer solution, and drugs were determined. Heart blood was withdrawn for the determination of total ephedrine (free and norephedrine), quinine, and metoclopramide in plasma.

Measurement of % Binding of Various Drugs to the Rat Rectal Mucosal Preparation——Mucosal preparation was obtained by the modified method of Dickens and Weil-Malherbe.[9] Rat rectum, washed as in the absorption experiment, was isolated and both the mucosal and the serosal sides were rinsed well with saline. Cut open a length of approximately 5 cm, and spread on a glass plate with the mucous membrane facing upward. Carefully blot with filter paper to remove adhering moisture and solid matters, and scrape off the mucosa with the edge of microscope slide glass. Mucosal homogenate was prepared in a Potter-Elvehjem teflon homogenizer with the buffer solution used in the absorption experiment. Basic drugs were dissolved in the buffer solution to make a drug concentration of 0.2 mM. Ten ml of the drug solution was placed in a 50 ml conical flask containing 2 ml of the mucosal homogenate (corresponding to the rectal mucosa of one rat), and shaken for one hour at 37° in a constant temperature bath. After separation, the drug concentration in supernatant was determined. Percentage of binding was calculated from the difference of drug concentration in the presence and the absence of mucosa.

Analytical Methods——All spectrophotometric analyses were performed with a Shimadzu QV-50 spectrophotometer.

a) Homatropine, isopropamide, and propantheline were determined by a modification of the method of Biles.[10] Eight ml of sample was placed in a glass-stoppered test-tube, and 15 ml of 5 mM tropaeolin 00 dye solution and 15 ml of chloroform were added. After shaking vigorously for 25 minutes and centrifuging, the chloroform phase separated and measured at 425 mμ. Determination of these drugs in the presence of SLS was carried out after elimination of the latter with Amberlite CG-IR 45.

b) Metoclopramide was determined by the following method; 1 ml of sample was placed in a glass-stoppered test-tube, and 3 ml of 0.5 mM bromothymol blue dye solution and 6 ml of chloroform were added. After shaking vigorously for 15 minutes and centrifuging, the aqueous phase was removed by aspiration. Bromothymol blue in 1 ml of organic solvent was extracted into 5 ml of 0.1N sodium hydroxide, and the aqueous phase was measured at 620 mμ.

c) Saccharin was determined by an ultraviolet spectrophotometric procedure. Five ml of sample was placed in a glass-stoppered test-tube, and 6 ml of 0.5N hydrochloric acid and 5 ml of chloroform were added. After shaking vigorously for 15 minutes and centrifuging, the aqueous phase was removed by aspiration. Four ml of the organic phase was transferred to a glass-stoppered test-tube containing 5 ml of 10% Na_2CO_3. After shaking for 25 minutes and centrifuging, the aqueous phase was measured at 267 mμ.

d) Procaine was determined as follows; 5 ml of sample was placed in a glass-stoppered test-tube, and 0.5 ml of 1N sodium hydroxide and 20 ml of ethylene dichloride were added. After shaking for 40 minutes and centrifuging, the aqueous phase was removed. Four ml of the organic phase was transferred to a glass-stoppered test-tube containing 5 ml of 0.1N hydrochloric acid. After shaking for 20 minutes and centrifuging, the aqueous phase was separated and measured at 280 mμ.

e) Following compounds were analyzed by previously described methods: aminopyrine (Brodie),[11] ephedrine (Axelrod),[12] quinine (Josephson),[13] 2-allyloxy-4-chloro-N-(2-diethylaminoethyl)benzamide hydrochloride (A.C.D.B.) (Kakemi),[14] tetraethylammonium chloride (Michell),[15] and SLS (Allan Moore).[16]

f) Blood levels were analyzed by the following methods: Ephedrine was determined as total amines (free and norephedrine) by the method of Axelrod.[12] Quinine was determined by the method of Josephson.[13] Metoclopramide was determined as total amines; 5 ml of sample was placed in a glass-stoppered test-tube containing 1 ml of 1N sodium hydroxide. After shaking vigorously for 30 minutes, 20 ml of ethylene dichloride was added. After shaking for 20 minutes and centrifuging, 10 ml of organic phase was transferred to a glass-stoppered test-tube containing 2 ml of tropaeolin 00 solution and 15 ml of buffer solution of pH 6 (KH_2PO_4, NaOH).

8) K. Kakemi, T. Arita, and S. Muranishi, *Chem. Pharm. Bull.* (Tokyo), **13**, 861 (1965).
9) F. Dickens and H. Weil-Malherbe, *Biochem. J.*, **35**, 7 (1941).
10) J.A. Biles, F.M. Plakogiannis, B.J. Wong, and P.M. Biles, *J. Pharm. Sci.*, **55**, 909 (1966).
11) B.B. Brodie and J. Axelrod, *J. Pharmacol. Explt. Therap.*, **99**, 171 (1950).
12) J. Axelrod, *J. Pharmacol. Exptl. Therap.*, **99**, 171 (1950).
13) E.S. Josephson, *J. Biol. Chem.*, **168**, 341 (1947).
14) K. Kakemi, H. Sezaki, and S. Horiuchi, *Yakuzaigaku*, **27**, 229 (1967).
15) R. Michell and B.B. Clark, *Proc. Soc. Exptl. Biol. Med.*, **81**, 165 (1952).
16) W. Allan Moore and R.A. Kolberson, *Anal. Chem.*, **28**, 161 (1956).

The mixture was shaken for 20 minutes and centrifuged. After the separation of aqueous phase, tropaeolin 00 in organic phase was re-extracted into 5 ml of 1N hydrochloric acid, and the aqueous phase was measured at 530 mμ.

Results

Effect of SLS on the Partition Behavior of Ephedrine to Organic Solvent

Effect of SLS on the partition behavior of cationic drugs was first examined with ephedrine as a typical mono basic amine. Ephedrine, having pK_a value of 9.6, is almost completely ionized in the physiological pH range. As shown in Fig. 1, apparent chloroform/water partition coefficient of ephedrine is extremely small in a pH of below 6.0. This value, however, markedly increased by the addition of SLS, which indicates possible formation of lipoid-soluble ion pair complex between lauryl sulfate anion and ephedrine cation. Even at pH 7.4, the pH of the rectal secreting fluid, significant contribution of complex formation is observed. In Fig. 2, apparent partition coefficient is plotted as a function of SLS concentration at pH 7.4. Apparent partition coefficient of ephedrine increased with the increase of SLS concentration and reached a maximum value at a higher SLS concentration range. Under the condition studied, observed critical micelle concentration of SLS was 0.6 mM. This suggests, but does not prove, that the effect of micelle formation can be excluded below 0.6 mM.

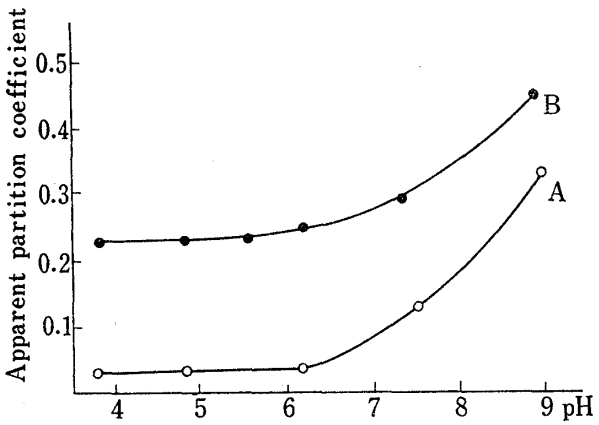

Fig. 1. pH Profile of the Apparent Chloroform/water Partition Coefficient of Ephedrine

key: A, 0.2 mM ephedrine; B, 0.2 mM ephedrine with 0.4 mM SLS

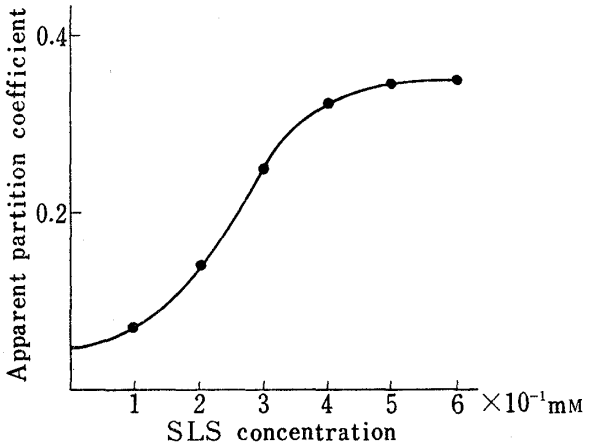

Fig. 2. Effect of SLS Concentration on the Apparent Chloroform/water Partition Coefficient of Ephedrine at pH 7.4

Concentration of ephedrine is 0.2 mM.

Effect of SLS on the Absorption of Ephedrine

Rectal absorption experiment was carried out at pH 7.4 using the same buffer solution with partition study. Fig. 3 shows the effect of SLS concentration on the one-hour-absorption of ephedrine.

At this pH, 2.9% of ephedrine was absorbed without SLS, whereas absorption increased by the addition of SLS. The maximum absorption of ephedrine was observed at the SLS concentration of 0.4 mM, twice the initial concentration of ephedrine.

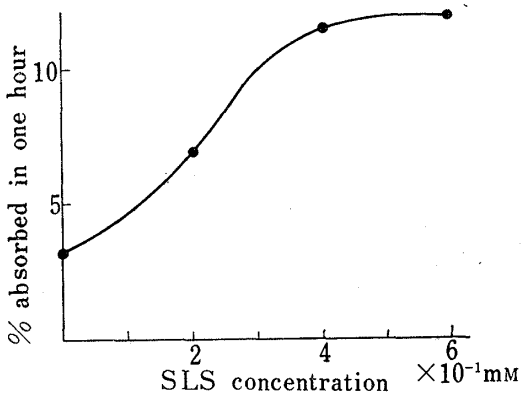

Fig. 3. Effect of SLS on the Rectal Absorption of Ephedrine

Concentration of ephedrine is 0.2 mM. Each point represents the mean of five experiments.

Effect of SLS on the Partition Behavior to Organic Solvent and Absorption of other Basic Drugs

With the above in mind, it became desirable to determine the effect of SLS on the absorption of other basic drugs. The particular systems used were chosen on the basis of their optimum pK_a and ready availability of the materials. Basic drugs having pK_a values of 5.0 or above were chosen and their partition behavior to chloroform or benzene/water was examined at pH 7.4. Table I gives these results. Increase in apparent partition coefficient was noted

Table I. Effect of SLS on the Apparent Partition Coefficient of Various Amines at pH 7.4

Amines (0.2 mM)	pK_a	Apparent partition coefficient			
		Chloroform		Benzene	
		Alone	With SLS (0.4 mM)	Alone	With SLS (0.4 mM)
Aminopyrine	5.0	—	—	6.77	7.00
A.C.D.B.[a]	7.9	∞	∞	37.10	102.18
Quinine	8.4	∞	∞	1.45	12.60
Procaine	9.0	11.17	44.64	—	—
Ephedrine	9.6	0.07	0.22	—	—
Fuchsin "Basic"	—	0.77	31.49	—	—
Homatropine	10.4	0.72	3.50	0.01	0.11

a) 2-Allyloxy-4-chloro-N-(2-diethylaminoethyl)benzamide hydrochloride

Apparent partition coefficient is given by the following equation.

$$\text{apparent partition coefficient} = \frac{\left(\begin{array}{c}\text{drug concentration in water phase}\\ \text{before the distribution is carried out}\end{array}\right) - \left(\begin{array}{c}\text{equilibrium concentration}\\ \text{in water phase}\end{array}\right)}{(\text{equilibrium concentration in water phase})}$$

in all the drugs examined except aminopyrine which is largely un-ionized at this pH. Absorption experiment on these ion pair complexes were carried out at pH 7.4 and the results are summarized in Table II.

Table II. Effect of SLS on the Rectal Absorption of Various Amines at pH 7.4

Drug	% absorbed in one hour	
	Alone	With SLS
Aminopyrine	21.2 (2)	26.5 (2)
A.C.D.B.	22.8 (2)	27.8 (2)
Quinine	14.9 (3)	30.7 (3)
Procaine	0.8 (3)	8.9 (3)
Ephedrine	2.9 (5)	7.1 (5)
Fuchsin "Basic"	7.0 (4)	13.4 (4)
Homatropine	7.2 (4)	24.5 (4)

Numbers in parentheses represent number of experiments.

Although the absorption enhancing effect of SLS on aminopyrine and 2-allyloxy-4-chloro-N-(2-diethylaminoethyl)benzamide (A.C.D.B.) is not remarkable because of the large contribution of their un-ionized molecular species, absorption of procaine, ephedrine, homatropine, and fuchsin "basic" was distinctly enhanced by the presence of SLS. It is interesting to note that despite the relatively high partition coefficient shown in Table III, no absorption of strong quaternary ammonium compounds could be detected.

Similar phenomena were observed by Wong and Biles[17] in their studies on the absorption of some quaternaries across the rat small intestine. Except 2-pyridine aldoxime methiodide

17) B.J. Wong and J.A. Biles, Abstracts of papers presented to the APhA Academy of Pharm. Sci., page 55 (1967).

Table III. Effect of SLS on the Apparent Partition Coefficient and the Rectal Absorption of Quaternary Ammonium Compounds at pH 7.4

Drug (0.2 mM)	pK_a	Apparent partition coefficient Chloroform Alone	Chloroform With SLS (0.4 mM)	Benzene Alone	Benzene With SLS (0.4 mM)	% absorbed in one hour Alone	% absorbed in one hour With SLS (0.4 mM)
Isopropamide	strong	0.20	∞	0 09	0.29	1.8 (3)	2.4 (3)
Propantheline	strong	—	—	0.23	4.73	0 (3)	1.0 (3)
T.E.A.C.[a]	strong	0.003	0.10	0	0	0 (3)	0 (3)

Numbers in parentheses represent number of experiments.
a) tetraethylammonium chloride

(2-PAM) iodide, addition of various alkyl sulfates did not enhance the absorption of quaternary ammonium ions. For the amine drugs of relatively low pK_a values, effect of pH on the ion pair formation was studied at pH 5.0. As shown in Table IV, fraction of complexed amine at pH 5.0 seems larger than at pH 7.4, which is reflected upon the partition behavior of these drugs with and without SLS. Difference is also noted in the rate of absorption at pH 5.0. In A.C.D.B., rate of absorption increased nearly twenty times and even aminopyrine absorption was enhanced at this pH. This absorption enhancing effect of SLS was also confirmed by the blood level analyses of the drugs.

Table IV. Effect of SLS on the Apparent Partition Coefficient and Absorption of Amines at pH 5.0

Drug (0.2 mM)	pK_a	Apparent partition coefficient Chloroform Alone	Chloroform With SLS (0.4 mM)	Benzene Alone	Benzene With SLS (0.4 mM)	% absorbed in one hour Alone	% absorbed in one hour With SLS (0.4 mM)
Aminopyrine	5.0	14.68	28.79	3.25	7.70	10.4 (5)	16.6 (5)
A.C.D.B.	7.9	14.60	269.6	0.78	20.63	1.0 (3)	19.5 (3)
Quinine	8.4	—	—	0.06	37.23	6.5 (3)	24.0 (3)

Numbers in parentheses represent number of experiments.

Table V shows the rat plasma levels of ephedrine and quinine determined in the absence and the presence of SLS in perfusate. Drug solutions were perfused for one hour and heart blood was taken after the end of the perfusion, and analyzed. Blood levels of drugs in relatively early stage of drug transfer was increased in the presence of SLS. This would be an absorptive phase for these drugs and complications like change of metabolic pattern or distribution by drug interaction and other factors would not be operating predominantly.

Table V. Effect of SLS on the Blood Levels of Amines

Drug (0.2 mM)	pH of perfusion fluid	Plasma levels (mM) Alone	Plasma levels (mM) With SLS (0.4 mM)
Ephedrine	7.4	5.6×10^{-2} (4)	13.2×10^{-2} (4)[a]
Quinine	5.0	2.5×10^{-3} (4)	3.3×10^{-3} (4)[a]

Numbers in parentheses represent number of experiments.
a) significant as compared to the control ($p<0.05$)
Blood sample (3 ml) was taken by cardiac puncture immediately after the end of one-hour perfusion of drug solutions.

Effect of Saccharin Sodium on the Rectal Absorption of Ephedrine

Since SLS may exert a direct action on the mucous membrane as a surface-active agent even below its critical micelle concentration, observed enhancement effect by SLS may complicate the interpretation of the mechanism of absorption. In view of these considerations, saccharin, having pK_a of 2.2 and not surface-active, was selected as a model anionic drug.

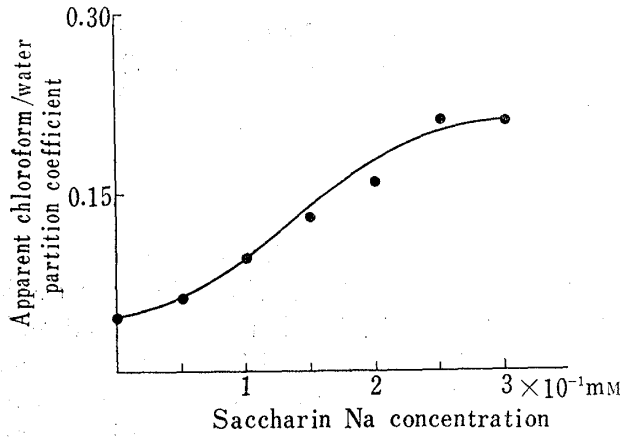

Fig. 4. Effect of Saccharin on the Apparent Partition Coefficient of Ephedrine at pH 7.4

Concentration of ephedrine is 0.2 mM.

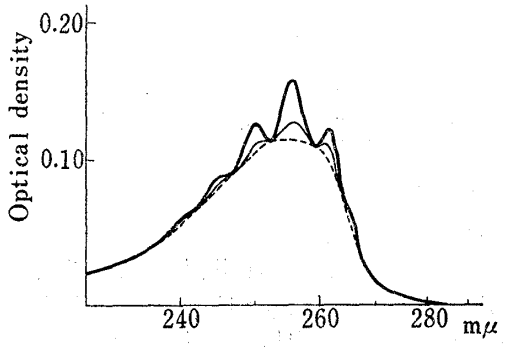

Fig. 5. Ultraviolet Absorption Spectra of Ephedrine in the Presence of Saccharin at pH 7.4

——: ephedrine 0.8 mM
——: ephedrine 0.8 mM, saccharin Na 0.2 mM
------: ephedrine 0.8 mM, saccharin Na 0.4 mM

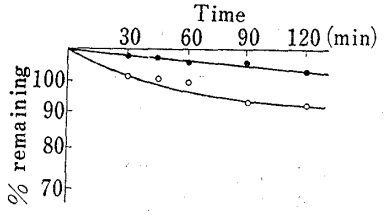

Fig. 6. Time Course of Absorption of Ephedrine

—●—: ephedrine HCl 2 mM
—○—: ephedrine HCl 2 mM, saccharin Na 2 mM

As shown in Fig. 4 and 5, interaction between the two drugs and the increase of apparent partition coefficient of ephedrine by saccharin are evident.

Results of the rat rectal absorption experiments at pH 7.4, shown in Fig. 6, indicate that in the absence of saccharin, ephedrine is poorly absorbed due to its ionization and the time course plot gives a good straight line on a semilogarithmic scale. In the presence of equimolar amount of saccharin, however, ephedrine is absorbed much faster but the time course plot does not fit to a straight line.

Effect of Saccharin on the Absorption of other Basic Drug

Effect of Saccharin on the absorption of various amines were determined and the results are summarized in Table VI.

Table VI. Effect of Saccharin on the Rectal Absorption of Various Amines at pH 7.4

Drug (0.2 mM)	pK_a	% absorbed in one hour		% absorbed of saccharin
		Alone	With saccharin (0.4 mM)	
Quinine	8.4	17.8 (3)	26.8 (3)	0 (3)
Metoclopramide (pH 5.0)	9.0	0.4 (4)	4.1 (4)	0.6 (4)
Ephedrine	9.6	2.9 (4)	8.8 (4)	0.5 (4)
Homatropine[a]	10.4	14.8 (4)	22.7 (5)	0 (5)
Propantheline[b]	strong	6.5 (3)	13.6 (3)	—

Numbers in parentheses represent number of experiments.
a) concentration of homatropine: 2.0 mM concentration of saccharin: 2.0 mM
b) three-hour perfusion

Absorption enhancing effect of saccharin is remarkable in quinine, metoclopramide, and homatropine. Propantheline, a quaternary ammonium compound, was absorbed at a slow but measurable rate during 3 hr. Although the absorption of the cationic drugs themselves was remarkably increased by the presence of saccharin, they did not exert any effect on saccharin absorption. Plasma levels were determined immediately after one hour perfusion of ephedrine or metoclopramide. As shown in Table VII, plasma levels of these drugs increased about 2.5 times in the presence of saccharin.

Table VII. Effect of Saccharin Sodium on the Blood Levels of Amines

Drug (10 mM)	pH of perfusion fluid	Blood Levels (mM) Alone	With saccharin (10 mM)
Ephedrine	7.4	1.0×10^{-1} (3)	2.5×10^{-1} (3)[a]
Metoclopramide	5.0	3.5×10^{-3} (5)	9.0×10^{-3} (3)[a]

Numbers in parentheses represent number of experiments.
a) significant as compared to the control ($p<0.05$)
Blood sample (3 ml) was taken by cardiac puncture immediately after the end of one-hour perfusion of drug solutions.

While the absorption enhancing effect of saccharin was observed, the possibility existed that the compound may exert direct action on the membrane. To investigate such possibility, change of absorption behavior of metoclopramide was measured after the pretreatment of rectal membrane by 0.4 mM of saccharin. Saccharin solution was perfused for 15 minutes and the drug was washed out with a sufficient amount of saline followed by the perfusion with the solution of the basic drug. No effect on metoclopramide absorption was observed indicating that the absorption enhancing effect of saccharin is not the direct action on the absorptive surface as was supposed in the case of SLS.

Effect of Amines on the Absorption of Saccharin; Mutual Effect

If an ion pair diffuses itself through the absorptive membrane, absorption of saccharin should be enhanced almost equal extent with ephedrine in molar basis. This mutual effect in absorption was studied in ephedrine-saccharin system. From the results shown in Fig. 7, it is evident that although the absorption of ephedrine is enhanced with the increase of saccharin concentration, rate of absorption of saccharin is negligible and is hardly affected at all by the addition of varying concentration of ephedrine.

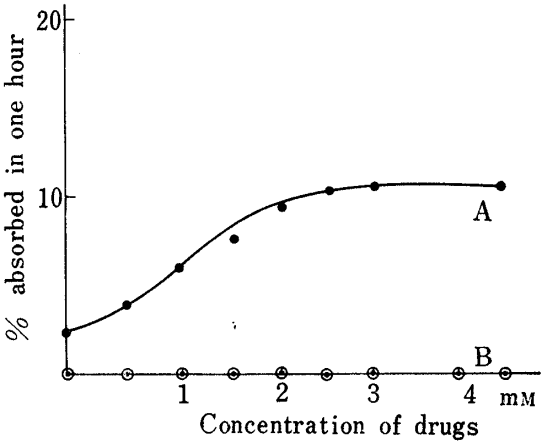

Fig. 7. Plots showing the Mutual Effect of Ephedrine and Saccharin on Their Absorption

Each point represents the mean of three or four experiments. Initial concentration of one of the components is kept constant at 2 mM while the concentration of the other component is varied up to 4.5 mM.
key: A, ephedrine (2 mM), B, saccharin (2 mM)

Effect of Other Anions on the Absorption of Ephedrine

Six anions of varying structure were chosen and their effect on the absorption of ephedrine and vice versa were investigated. Results are summarized in Table VIII.

Every anion except chloride seemed to form lipoid–soluble ion pair complex and it is clear from the Table VIII that although the absorption of ephedrine is enhanced by bromothymol blue and salicylate anions, the converse dose not apply for anions.

Table VIII. Mutual Effect of Ephedrine and Various Anionic Drugs on Their Rectal Absorption

Drugs (0.4 mM)	% absorbed of ephedrine (0.2 mM)	% absorbed of anionic drugs	% absorbed of anionic drugs in the absence of ephedrine
Control	2.9 (5)		
Cl^-	3.1 (3)		
Methyl Orange	2.8 (2)	—	—
Saccharin	8.8 (4)	0.5 (4)	0 (3)
SLS	7.1 (5)	21.4 a)(3)	21.1 a)(3)
Bromothymol blue (0.2 mM)	20.3 (3)	3.0 (4)	1.5 (2)
Salicylic acid	22.0 (4)	8.6 (4)	7.9 (3)

% Absorbed in one hour is expressed as the mean for the number of experiments given in parentheses.
a) values include adsorption to the membrane surface

Binding of Amines to the Rat Mucosal Preparations

From the foregoing observations, it is not likely that in the process of rectal absorption, an ion pair complex is transferred as such without dissociation. In our earlier communications it has been pointed out[18,19] that the intestinal absorption of barbituric acid derivatives as well as many other anionic and cationic drugs are related not to their lipoid/water partition coefficient but rather to the binding tendency to the intestinal mucosal preparations. This technique was used to study the binding behavior of the amines to the rectal mucosa to elucidate the mechanism of absorption of ion pair complexes. Tables IX and X show the result of the binding study. The binding to the mucosal preparations of amines tested in the experiment except isopropamide was enhanced by the presence of SLS or saccharin.

Table IX. Effect of SLS on the Binding of Amines to the Rectal Mucosal Preparations

Drug (0.2 mM)	pH	% bound Alone	% bound With SLS (0.4 mM)
Isopropamide	7.4	0 (3)	0 (3)
Ephedrine	7.4	13.2 (5)	17.9 (5)
Quinine	7.4	0.1 (3)	2.8 (3)

The percentage bound is expressed as the mean for the number of experiments given in parentheses.

Table X. Effect of Saccharin on the Binding of Amines to the Rectal Mucosal Preparations

Drug (0.2 mM)	pH	% bound Alone	% bound With saccharin (0.4 mM)
Metoclopramide	5.0	0 (2)	2.3 (2)
Ephedrine	7.4	0.3 (3)	4.3 (3)
Quinine	7.4	9.9 (3)	12.5 (3)

The percentage bound is expressed as the mean for the number of experiments given in parentheses.

18) K. Kakemi, T. Arita, R. Hori, and R. Konishi, *Chem. Pharm. Bull.* (Tokyo), **15**, 1883 (1967).
19) K. Kakemi, T. Arita, R. Hori, R. Konishi, K. Nishimura, H. Matsui, and T. Niishimura, *Chem. Pharm. Bull.* (Tekyo), **17**, 255 (1969).

Discussion

Present study shows that although relatively strong organic anions such as SLS and saccharin can enhance the rectal absorption of ionized pharmaceutical amines, absorption of the anions themselves are not always increased. Therefore it appears that the surface might have a dissociating effect on the complexes and such ion pair complexes dissociate on the surface of the absorptive membrane. In a study of the lipoid–soluble acidic dye complexes absorption from the rat small intestine, Levy and Matsuzawa[20] expressed the view that dye complexes were dissociated by interaction of either or both components with the outer protein layer, but did not mention about the increase of the absorption of cationic species investigated. Recently, in their study on the mechanism and kinetics of ion pair extraction, Higuchi and Michaelis[21] have shown that the extractive process of dextromethorphanium ion was rate–limited by the diffusional step. The idea is an attractive one and deserves consideration with respect to the mechanism of ion pair absorption.

In the case of the effect of SLS on the absorption of amines, there was a subject to concern, possible deterioration effect of SLS on the membrane. It is generally agreed that SLS, being an anionic surfcae active agent, has direct action on the membrane. To investigate such possibility, rectal mucosal surface of the rat was examined microscopically after one hour perfusion with 0.4 mM of SLS. Fig. 8 and 9 show optical microscopic pictures of the normal rat rectal mucosa and the mucosa obtained after the perfusion of SLS solution respectively.

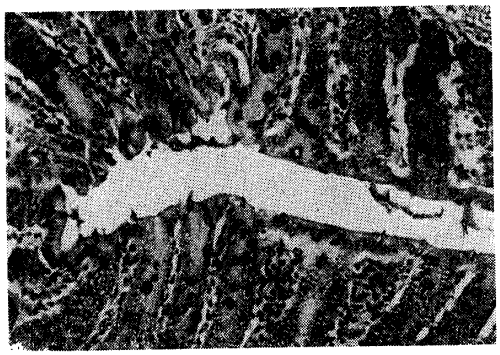

Fig. 8. Photomicrograph of a Representative Control Section of Normal Rectal Mucosa of Rat (×45)

Paraffin embedded specimens were stained with hematoxylin and eosin.

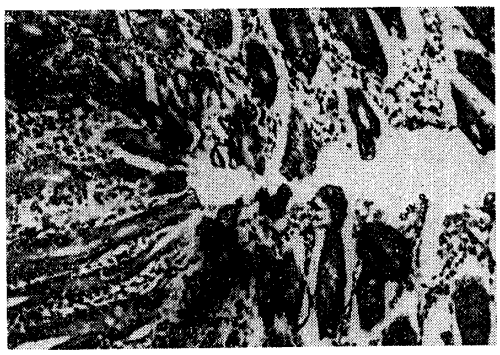

Fig. 9. Photomicrograph of a Section from the Rectal Mucosa of Rat after One Hour Perfusion of 0.4 mM Solution of SLS (×45)

The apertures between epithelium cells are opened with SLS suggesting the possibility of deterioration of the rectal mucosa. In spite of such damage, absorption of the strong bases were hardly detected whereas that of the weaker bases were markedly increased. Previous report from this laboratory[22] also indicated that the absorption of sulfisoxazole from the rat rectum was hardly affected by the presence of low concentration of SLS. Accordingly, possibility of the absorption enhancement due to the direct effect of SLS to mucosa can be ruled out under the present experimental conditions.

Considering the extraneous coats of the mucous membrane, it is conceivable that some ionized drug species may reach the absorptive rate–limiting barrier and bind to protein like substances on the surface. When a drug and its counter ion exist in the same medium, it

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frequently happens that the binding of the drug to protein increases.[23] Results shown in Tables IX and X support such a view.

The present experiment thus supports the view that increase in the lipoid–solubility or burying of charges by ion pair complex formation alone dose not explain the mechanism of absorption of such complexes and the binding behavior to mucosa seems to be a more predominant factor in the absorptive processes. Thus although the drug absorption from the rectum has been regarded as more consistent with pH partition hypotheses than the small intestine, mucosal binding again has been found to play an unique role for organic ion absorption from this part of the intestinal tract.

This aspect of drug absorption is now being studied and will be the subject of a futute communication from this laboratory.