EFFECT OF TAURINE ON THE GASTRIC ABSORPTION OF DRUGS: COMPARATIVE STUDIES WITH SODIUM LAURYL SULFATE

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In order to clarify the mechanism of taurine-induced enhancement of drug absorption, some comparison was made between the actions of taurine and sodium lauryl sulfate (SLS), an anionic surfactant, by using the loop of rat stomach *in situ*.

SLS enhanced the gastric absorption of aspirin and salicylamide, and the SLS-induced enhancement seems to be Na^+ -dependent. SLS failed to enhance the absorption of both drugs when NaCl was completely replaced by mannitol or in the presence of ouabain even in the NaCl medium. In addition, even at the lower concentration of 0.05 mM, SLS enhanced the absorption of the two drugs, the extent of which is nearly corresponding to those of taurine. The actions of SLS and taurine on drug absorption are considered to have some similar points. The mechanism of the action was discussed in relation to the cyclic AMP system.

Keywords—sodium lauryl sulfate; taurine; gastric absorption; aspirin; salicylamide; Na^+ -dependency; ouabain; imidazole; dibutyryl cyclic AMP; cyclic AMP system

Our previous reports^{1,2)} have shown that some amino acid-like compounds, taurine, homotaurine, and glycine, enhanced the rate of absorption of some drugs (e.g. aspirin, salicylamide, and so on), not only from the small intestine but also from the stomach. The action of taurine was pointed out to be site-specific and substrate-specific, and to be greatly influenced by ionic components of the luminal solution employed. However, the mechanism by which taurine increases the drug absorption remains unresolved.

In this paper, sodium lauryl sulfate (SLS), an anionic surfactant, was introduced in order to have a further insight into the action of taurine. SLS is well known to interact with biological membranes and thereby to alter permeability characteristics.³⁻⁶⁾ We are reporting some interesting findings we have made by comparing the action of SLS on drug absorption with that of taurine in rat stomach.

MATERIALS AND METHODS

Materials—All the reagents, except aspirin

(Maruishi Pharmaceutical Co., Japan) and dibutyryl cyclic AMP (Db-cAMP, Yamasa Shoyu Co., Japan), used in this experiment were of the reagent grade from Nakarai Chemical Co., Japan.

Preparation of Drug Solutions—The components of luminal solutions, pH 1.1, employed were as follows: 0.1 M NaCl–0.1 N HCl, or 0.2 M mannitol–0.1 N HCl. The concentrations of drugs were 1 mM, unless otherwise indicated.

Procedure of Absorption Experiments—Wistar strain male rats, fasted overnight, weighing 160–200 g were employed and gastric absorption was examined by the method of *in situ* loop (volume, 4 ml) as described previously.¹⁾ The amount of drug absorbed in one hour was calculated by the difference of the amount of drug in the initial and final mucosal solutions.

Analytical Methods—Aspirin, salicylamide, and salicylic acid were all extracted with chloroform and determined spectrophotometrically.¹⁾ Sulfanilic acid was diazotized, coupled with 2-diethylaminoethyl-1-naphthylamine and the colored material was extracted with isoamyl-

alcohol and determined spectrophotometrically as described previously.¹⁾

RESULTS AND DISCUSSION

Table I summarizes the effect of SLS or taurine on the gastric absorption of aspirin, salicylamide, and sulfanilic acid both in the NaCl and mannitol media. SLS significantly enhanced aspirin absorption in the NaCl medium, but not in the mannitol medium. This finding suggests that the effect of SLS seems to be Na⁺-dependent, which is obviously consistent with that of taurine.²⁾ Our electrophysiological investigation showed that SLS at the concentration of 2 mM markedly changed the electrical parameters of the gastric mucosa and its direct action on the gastric mucosa was suggested.⁷⁾ However, the Na⁺-dependency observed would negate the possible contribution of the solubilization of the mucosal components to SLS-induced increase of aspirin absorption, since SLS was shown to have a solubilizing activity even in the mannitol medium, as de-

scribed later. Fig. 1 shows the effect of SLS on aspirin absorption as a function of SLS concentration, ranging from 0.05 mM to 20 mM. Aspirin absorption was markedly enhanced even at the lower concentration of 0.05 mM, the extent of which is reached nearly to the same degree as that of taurine and, thereafter, remained at fairly constant level up to 20 mM. The enhancement effect was invariably fixed even after simultaneous administration with taurine and no additional effect was observed.

On the other hand, SLS exerted a concentration-dependent biphasic action on the salicylamide absorption, that is to say an enhancement of transport at lower concentration of 0.05 mM, but a decrease at higher concentration of 20 mM (Table I). The reduction of transport is thought to be attributed to the micellar interaction. Parallel studies were thus performed to determine the extent of micelle-drug species in drug solutions by using Micropartition System (MPS-1, Amicon). Aspirin and salicylamide were found to interact

TABLE I. *Effect of Sodium Lauryl Sulfate (SLS) on Drug Absorption from Rat Stomach*

Drug ^{a)}	Adjuvant	% absorbed in 1 h	
		NaCl medium ^{b)}	Mannitol medium ^{c)}
Aspirin	None	34.3±0.9 (5)	35.4±0.2 (3)
	SLS (20) ^{d)}	38.6±0.9 (8)**	31.5±1.5 (4)
	Taurine (1)	41.4±1.7 (4)***	31.3±1.9 (4)
Salicylamide	None	41.8±1.5 (4)	42.5±1.8 (3)
	SLS (0.05)	54.1±1.1 (3)***	42.1±1.3 (5)
	SLS (1)	43.3±0.9 (6)	—
	SLS (20)	28.7±2.5 (4)***	33.2±2.1 (3)***
	Taurine (1)	47.2±1.3 (4)*	50.2±1.1 (4)*
Sulfanilic acid	None	1.4±0.1 (4)	0.3±0.0 (3)
	SLS (20)	8.3±0.9 (3)***	10.1±2.2 (3)***
	Taurine (1)	1.4±0.1 (4)	—

a) Drug concentrations: aspirin and salicylamide, 1 mM; sulfanilic acid, 0.5 mM.

b) 0.1 M NaCl–0.1 N HCl, pH 1.1.

c) 0.2 M mannitol–0.1 N HCl, pH 1.1.

d) Concentration of adjuvants in mM.

Results are expressed as the mean ± SEM followed by the number of experiments in parentheses.

****p* < 0.001; ***p* < 0.01; **p* < 0.05, compared with each control.

with SLS micelles (20 mM) up to 29.6 % and 27.0 %, respectively, while at lower SLS concentration (0.05 mM), they were thoroughly ignored. Aspirin absorption increased by SLS, however, remained at a constant level irrespective of the occurrence of micellar interaction. This matter is one of the currently pending questions. Table I also shows that the enhancement of salicylamide absorption at lower SLS concentration was completely cancelled out by removal of Na^+ from the luminal solution as in the case of aspirin, whereas the action of taurine was fairly maintained. This discrepancy suggests that the different mechanism of action of taurine toward aspirin and salicylamide absorption would exist. Moreover, the absorption of sulfanilic acid, a poorly absorbable drug, was remarkably increased by SLS regardless of the ionic composition of the luminal solution, while hardly affected by taurine. Accordingly, it is suggested that ability of SLS to solubilize membrane components and to increase the permeability would be irrelevant to the medium composition.

Although Na^+ -dependency has been frequently recognized in carrier-mediated transport processes, it is noteworthy that such a phenomenon

FIG. 1. Comparison of SLS- and Taurine-induced Enhancement of Aspirin Absorption as a Function of SLS Concentration in NaCl Medium

Key: ○, with SLS; ●, with both SLS and 1 mM taurine. Results are expressed as the mean $\pm$ SEM.

occurs even in materials transferred by passive diffusion. The resultant data prompted us to further examine the effect of ouabain, well known as an inhibitor of $(\text{Na}^+, \text{K}^+)\text{-ATPase}$. Table II indicates that ouabain completely abolished the absorption enhancement caused by SLS, as expected. Our previous report²⁾ has provided, likewise, that taurine-induced enhancement of aspirin absorption had been completely eliminated following the addition of ouabain to the NaCl medium. The cardiac glycoside has, however, been known to be rarely transported across the gastric mucosa because of its polarity, in common with the negligible transfer of taurine (unpublished data). Therefore, all these observations led us to suppose that ouabain acts on a certain surface of the gastric mucosal membrane associated with the site of action of taurine or SLS, not on the basolateral membranes, although there are some problems in view of the discriminated effect of taurine on salicylamide absorption. Besides, similar phenomena have been shown in the literature which reported SLS (17 mM)-induced increase in the absorption of phenolsulfonphthalein and pralidoxime from rat jejunum.⁸⁾

Briseid *et al.*⁸⁾ have found that SLS in concentrations above the critical micelle concentration caused graded increases in the absorption of phenolsulfonphthalein and pralidoxime from the rat jejunal loops. The increased absorption was potentiated by theophylline or Db-cAMP and reduced by ouabain or imidazole.⁹⁾ The determination of cyclic AMP (cAMP) levels in the intestinal mucosa both in the presence and in the absence of SLS further supported that the effect of SLS on the absorption would be, at least in part, ascribed to an increased level of cAMP.¹⁰⁾ Remembering this, the addition of Db-cAMP was examined in order to evaluate the relationship between taurine-induced enhancement effect and cAMP system. As shown in Table III, the increased absorption of aspirin and salicylamide, which were previously observed in the presence of taurine, appeared again by the addition of Db-cAMP, the extent of which was approximately corresponding to those of

taurine.¹⁾ In contrast, Db-cAMP showed no effect on salicylic acid absorption. This coincides exactly with the substrate-specific action of taurine. The action of taurine is thus supposed to be partly

TABLE II. *Effect of Ouabain on SLS-induced Enhancement of Gastric Absorption of Aspirin or Salicylamide from NaCl Medium*

Adjuvants	% absorbed in 1 h	
	Aspirin	Salicylamide
None	34.3±0.9 (5)	41.8±1.5 (4)
SLS	38.6±0.9 (8)	54.1±1.1 (3)
Ouabain	32.0±1.3 (3)	43.8±1.1 (4)
SLS + ouabain	34.2±0.6 (8)	37.7±0.9 (3)

Medium: 0.1 M NaCl- 0.1 N HCl, pH 1.1. Concentrations: aspirin and salicylamide, 1 mM; SLS, 20 mM for aspirin, 0.05 mM for salicylamide; ouabain, 1.5 mM. Results are expressed as the mean ± SEM followed by the number of experiments in parentheses. *** $p < 0.001$; ** $p < 0.01$.

TABLE III. *Effect of Dibutyrylcyclic AMP (Db-cAMP) on Drug Absorption from Rat Stomach*

Drug	% absorbed in 1 h	
	Control	With Db-cAMP
Aspirin	34.3±0.9 (5)	40.8±0.7 (4)***
Salicylamide	41.8±1.5 (4)	49.6±1.3 (4)**
Salicylic acid	55.7±1.5 (4)	57.2±1.6 (4)

Medium: 0.1 M NaCl- 0.1 N HCl, pH 1.1. Concentrations: drugs, 1 mM; Db-cAMP, 2.5 mM. Results are expressed as the mean ± SEM followed by the number of experiments in parentheses. *** $p < 0.001$, ** $p < 0.01$, compared with each control.

TABLE IV. *Effect of Imidazole on Gastric Absorption of Aspirin or Salicylamide in the Presence of SLS or Taurine*

Drug	Adjuvant	% absorbed in 1 h	
		Without imidazole	With imidazole
Aspirin	None	34.3±0.9 (5)	29.6±1.3 (4)
	SLS	38.6±0.9 (8)**	29.5±0.3 (4)
	Taurine	41.4±1.7 (4)***	40.2±0.7 (4)***
Salicylamide	None	41.8±1.5 (4)	44.1±1.2 (3)
	SLS	54.1±1.1 (3)***	35.7±0.3 (4)**
	Taurine	47.2±1.3 (4)*	51.1±0.2 (4)**

Medium: 0.1 M NaCl- 0.1 N HCl, pH 1.1. Concentrations: drugs, 1 mM; SLS, 20 mM for aspirin, 0.05 mM for salicylamide; imidazole, 25 mM. Results are expressed as the mean ± SEM followed by the number of experiments in parentheses. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, compared with the values in the absence of adjuvants.

related to cAMP system. In addition, the reduced absorption caused by ouabain is considered to be due to the inhibition of adenylyl cyclase present in cell membranes. This inhibitory action has been demonstrated in rat epididymal adipose tissue.¹¹⁾ Moreover, significance of Na⁺ for the enhancement effect is speculated to contribute to the regulation of affinity between taurine or SLS and adenylyl cyclase.

In order to further elucidate the relationship, imidazole, an activator of phosphodiesterase, was applied. It is noticeable from Table IV that SLS failed to enhance aspirin or salicylamide absorption in the presence of imidazole, whereas the actions of taurine persisted in. We cannot explain in full, at present, the reason why taurine keeps tenaciously its action even in the presence of its putative inhibitor. Moreover, no appreciable data could be obtained in respect to the effect of theophylline, an inhibitor of phosphodiesterase, or isoproterenol, an activator of adenylyl cyclase, on aspirin absorption (data not shown). Nakamura *et al.*¹²⁾ investigated, however, the effect of methylxanthines on the absorption of poorly absorbable dyes, phenol red and bromphenol blue, from the rat small intestine, and reported that the transfer of both dyes was significantly increased by the pretreatment or the presence of methylxanthines, but not by *i.v.* administration. They ascribed the enhanced absorption of hydrophilic dyes to the change in the permeability characteristics of the intestinal mucosa. These conflicting data are presumed to be due to the different organ and the different pH used in our experiment. Their experiments were carried out at pH 6.5, but ours at pH 1.1, where theophylline is believed to pass slowly across the cell membranes because of its low lipophilicity, thereby lowering its cellular effective concentrations necessary for the action.

Recently, Batzri and Dyer reported the cAMP-mediated aminopyrine uptake by gastric mucosal cells in guinea-pig, concerned with gastric acid secretion.¹³⁾ The relationship between cAMP and gastric acid secretion has been extensively studied.¹⁴⁻¹⁷⁾ Thus, we preliminarily examined

the effect of histamine or SCN⁻ on taurine-induced enhancement of aspirin absorption to clarify a possible relation to taurine to the acid secretion, but no plausible link was established (data not shown).

The results may be summarized as follows: the effect of SLS on drug absorption was investigated in rat stomach in comparison with that of taurine. They have some similar points, especially on aspirin absorption and thus it is suggested that cAMP system may, at least in part, contribute to the action of taurine.

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