Bile Salt-Induced Permeability Changes in the Isolated Rat Intestine[1] (34360)

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(Introduced by N. Back)

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Physiologic concentrations of conjugated bile salts can markedly alter the permeability of various biologic membranes (1–5). Studies utilizing the everted rat small intestine show that sodium taurodeoxycholate increases the permeability of this membrane to salicylate (1) and various other drugs (unpublished observations). Bile salt-induced changes in the permeability of the isolated rat intestine are accompanied by pronounced irreversible changes in the gross histology of the tissue. While conjugated bile salts are highly damaging to intestinal tissue *in vitro* they are apparently innocuous *in vivo*.

Bile is a solution of mixed micelles containing bile salts, cholesterol, and lecithin (6). In the intestine, the mixed micelle may also contain appreciable amounts of monoglycerides and fatty acids, particularly during digestion (6). The interaction between bile salts and other constituents of bile and of the digestive tract may play a role in reducing the toxicity of these salts *in vivo*. To explore this possibility, the effects of lecithin and fat digestion products on the permeability of the everted rat intestine in the presence of sodium taurodeoxycholate (STDC) were examined.

Materials and Methods. Everted jejunal intestinal segments (7), from male Sprague-Dawley rats (200–225 g), were incubated at 37° in Krebs phosphate buffer (pH 6.0) containing 10 m*M* STDC[3] alone or in the presence of various concentrations of egg lecithin[4] or oleic acid[5] and glyceryl monooleate.[6] The segments contained 2 ml of buffer solution on the serosal side. After incubation, they were rinsed and placed in a solution of 2.0 mg/ml of sodium salicylate in Krebs phosphate buffer (pH 6.0). Two ml of buffer served as serosal solution. Mucosal-to-serosal transfer rates were determined as described previously (1). Each experiment was carried out with two consecutive 10-cm segments of intestine taken 15 cm from the pylorus. All solutions were adjusted to 150 m*M* Na^+ by addition of NaCl.

Results and Discussion. The results presented in Table I indicate that the addition of phospholipid or fatty acid and monoglyceride to the incubation medium produces a pronounced decrease in the permeability of the everted rat intestine to salicylate. Typical plots of the cumulative amount of salicylate transferred *versus* time for each experimental condition are shown in Fig. 1. Also included in Table I and Fig. 1 are the salicylate transfer data from control experiments (incubation medium, Krebs phosphate buffer, pH 6.0).

Striking differences were evident in the gross appearance of intestinal segments incubated in STDC and STDC + lecithin or STDC + oleic acid + glyceryl monooleate.

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[3] Chromatographically pure, obtained from Maybridge Chemical Co., Ltd. North Cornwall, England.

[4] Nutritional Biochemicals Corp., Cleveland, Ohio.

[5] Purified form from Fisher Scientific Company.

[6] Myverol (Type 18-71-E) from Distillation Products Industries, Rochester, New York.

TABLE I. Influence of Egg Lecithin, Oleic Acid and Glycerylmonooleate (GMO) in Modifying the Effect of 10 m*M* Sodium Taurodeoxycholate (STDC) on the Transfer Rate of Salicylate Across the Everted Rat Small Intestine at pH 6.0.

Incubation media	No. of intestinal segments	Mean transfer rate ± SD (μg/min)
Control	6	30 ± 3
STDC	15	78 ± 8[b]
+ lecithin, 5 m*M*	4	55 ± 9[ab]
10 m*M*	4	51 ± 3[ab]
+ oleic acid, 3 m*M* + GMO, 1 m*M*	4	72 ± 5[ab]
6 m*M* + GMO, 4 m*M*	2	64 (63, 66)

[a] Results significantly different from STDC alone ($p<0.05$, Student's t-test, method of paired comparisons).

[b] Results significantly different from controls ($p<0.05$, Student's t-test).

After incubation in 10 m*M* STDC the mucosal surface was blanched and somewhat translucent compared to the appearance of segments incubated in buffer alone. This is consistent with the observations of Fry and Staffeldt (8) who reported that the upper intestine of mice fed a diet containing 2% sodium deoxycholate for 2 days was more translucent and thinner than normal. In contrast, intestinal segments which were incubated with STDC together with lecithin or monoglyceride and fatty acid appeared indentical to control segments. Nevertheless, all experiments with solutions containing STDC yielded salicylate transfer rates which were significantly greater than control values.

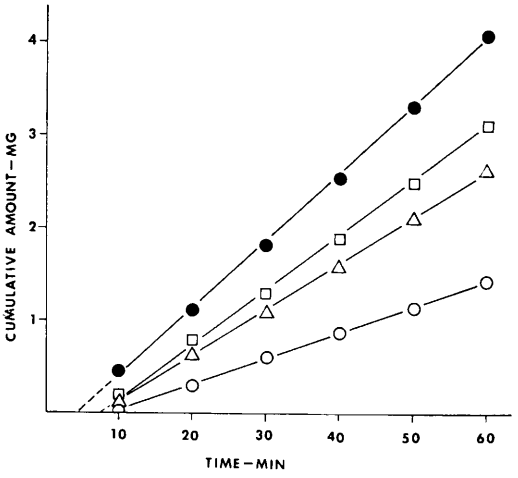

FIG. 1. Representative plots of salicylate transfer (mucosal to serosal) after 1-hr incubation. Incubation media: (○), Krebs phosphate buffer, pH 6.0; (●), 10 m*M* sodium taurodeoxycholate (STDC) in buffer; (□), 10 m*M* STDC + 3 m*M* oleic acid + 1 m*M* glyceryl monooleate; (△), 10 m*M* STDC + 5 m*M* egg lecithin.

Dietschy (9) found that addition of phospholipid to solutions containing sodium taurocholate at levels exceeding the critical micelle concentration (CMC) caused a decrease in the rate of transfer of the bile salt across the rat jejunum. In these experiments, the addition of phospholipid completely prevented a rather marked increase in the permeability coefficient of the membrane which occurred at taurocholate concentrations exceeding the CMC. In a previous report (1), we proposed that the change in the permeability coefficient is due to an alteration of the membrane structure by the taurocholate micelles. It is likely that incorporation of phospholipid in the bile salt micelle reduces this effect. This suggestion is consistent also with the results of the present study.

The manner in which incorporation of phospholipid or fatty acid and monoglyceride reduce the ability of the bile salt micelle to alter membrane permeability is not clear nor is the effect of the micelle itself on membrane structure well understood at present. Small (10) suggests that the latter effect may involve penetration into the membrane and formation of mixed micelles with the phospholipds of the membrane. The incorporation of lipids in the bile salt micelle may therefore reduce the ability of the micelle to solubilize lipid components of the membrane.

The possibility exists that phospholipid in bile and fat digestion products in the digestive tract prevent the membrane damage by bile salts which is observed in *in vitro* experiments.

Summary. Physiologic concentrations of the conjugated bile salt, sodium taurodeoxycholate, markedly increased the permeability of the everted rat small intestine to salicylate ion. Addition of egg lecithin or oleic acid and glyceryl monooleate to the medium diminished this effect and prevented changes in the gross appearance of the intestinal mucosa which occurred when the isolated intestine was exposed to the bile salt alone.

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