Duodenal perfusion with sodium taurocholate inhibits biliary but not pancreatic secretion in man

Ó. G. BJÖRNSSON, D. R. FLETCHER, N. D. CHRISTOFIDES, S. R. BLOOM AND V. S. CHADWICK
Department of Medicine, Hammersmith Hospital, London

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Summary

1. A standard duodenal perfusion technique was used to study the effects of luminally perfused sodium taurocholate on basal and stimulated biliary and pancreatic secretion and gastrointestinal hormone release in man.

2. During duodenal perfusion with sodium taurocholate alone, both basal and caerulein/secretin-stimulated bilirubin secretion were suppressed. A successive perfusion with a mixture of the bile salt and essential amino acids in combination overcame the biliary suppression and biliary secretion rose above basal levels. A further increase in bilirubin secretion was not observed in a subsequent perfusion with essential amino acids alone in these studies.

3. No inhibitory effect on basal or caerulein/secretin-stimulated trypsin secretion was observed during the bile salt perfusion; basal trypsin secretion was in fact slightly increased during a prolonged (4 h) perfusion of the bile salt.

4. During bile salt perfusion, basal bicarbonate secretion remained unchanged but caerulein/secretin-stimulated bicarbonate secretion was slightly increased.

5. Plasma levels of pancreatic polypeptide, gastric inhibitory peptide and gastrin did not change significantly during duodenal perfusion with bile salt, but plasma levels of motilin were suppressed.

6. These results support the view that bile salts in the duodenum may regulate biliary and pancreatic secretion in man and affect plasma levels of motilin.

Key words: bicarbonate, bilirubin, caerulein, gastric inhibitory peptide, gastrin, motilin, pancreatic polypeptide, secretin, sodium taurocholate, trypsin.

Abbreviations: EAA, essential amino acids; GIP, gastric inhibitory polypeptide; PEG, polyethylene glycol; PP, pancreatic polypeptide; STC, sodium taurocholate.

Introduction

The effect on pancreatic secretion of introducing bile or bile salts into the duodenum has been studied by several workers [1–9], but the results have been conflicting. Some have found that bile salts stimulate pancreatic secretion [1, 3, 4, 6–9], whereas others have described no effect [2] or an inhibition [2, 3, 5, 6]. Much less attention has been paid to the effect of bile salts on biliary secretion. Forell et al. [4] reported that during duodenal infusion with sodium glycocholate in man, bilirubin was absent from the duodenal Auid, and Wormsley [3] noticed that although pancreatic secretion was stimulated by bile salts introduced into the duodenum in man, bilirubin secretion remained unchanged. These workers did not describe the effect of bile salts on biliary secretion further. Malagelada et al. [5, 6] found, however, that bile salts in the duodenum suppressed biliary secretion stimulated by amino acids or fatty acids, but no effect on basal or exogenously stimulated secretion was noticed [5].

In the present work we have studied the effect of the bile salt sodium taurocholate on biliary and pancreatic secretion in man, both in the basal state and during background stimulation with
either intravenous caerulein and secretin or luminal essential amino acids. Plasma levels of several gastrointestinal hormones, known to be released from the upper gastrointestinal tract and the pancreas, were monitored throughout the studies.

**Methods**

**Perfusion technique**

The duodenal perfusion technique has been described in detail before [10]. The recovery marker [polyethylene glycol: PEG 4000; 5 g/l in NaCl solution (150 mmol/l)] was infused into the duodenum opposite the ampulla of Vater at the rate of 10 ml/min. This solution was used as a vehicle for sodium taurocholate (STC) and essential amino acids (EAA) during different phases of the experiments. A continuous aspiration of the duodenal fluid was carried out close to the ligament of Treitz (18 cm perfusion segment) by using an aspiration tube with wide air ventile (2 mm inner diameter) to ensure efficient continuous suction. Gastric aspiration was carried out with a standard gastric aspiration technique with phenol red as a recovery marker [11]. Intravenous cannulae were positioned into antecubital veins of each arm for collection of blood and infusion of gastrointestinal hormones respectively. Fully informed, written consent was obtained from every volunteer and all human experiments were approved by the Royal Postgraduate Medical School Research Ethics Committee.

**Preparation of infusion and perfusion solutions**

Secretin and caerulein were diluted in sterile NaCl solutions (150 mmol/l), containing 200 µmol of human serum albumin/l, and infused intravenously at doses of 2.5 ng h⁻¹ kg⁻¹ (caerulein) and 0.025 clinical unit h⁻¹ kg⁻¹ (secretin) (for clinical units of secretin, see Instruments and chemicals, below). Perfusates of NaCl solution (150 mmol/l), STC (10 mmol/l), EAA (78 mmol/l) and a mixture of STC and EAA (10/78 mmol/l) were prepared immediately before use, made iso-osmolar (290 mosmol/kg) with NaCl solution and adjusted to pH 6.3 with NaOH or HCl and warmed to 37°C before use. All perfusates contained PEG 4000, 5 g/l, as a duodenal marker. Phenol red was dissolved and diluted in distilled water to final concentration of 1.5 g/l for gastric perfusion.

**Experimental design**

The experiments were planned to study the effect of duodenal perfusion with STC on basal and stimulated biliary and pancreatic secretion in man. The effects on plasma levels of gastrointestinal hormones were also studied. Duodenal perfusion with EAA was used to provide an endogenous stimulus for biliary and pancreatic secretion, and caerulein and secretin were administered by continuous intravenous infusion as exogenous stimuli for the secretion. The following series of studies were carried out.

**Effects of STC and EAA on basal secretion.**

The effects of STC and EAA on basal biliary and pancreatic secretion were studied in five healthy volunteers (ages 21–24 years). After 2 h duodenal perfusion with NaCl (150 mmol/l) (equilibration period), STC (10 mmol/l) was perfused for 4 h, followed by a perfusion of EAA (78 mmol/l) and STC (10 mmol/l) in combination for 1 h. In a separate group of studies, the prolonged effect of EAA (78 mmol/l) on basal secretion was studied in five volunteers (ages 20–24 years). The EAA perfusion lasted for 3 h and was preceded by an equilibration period of 2 h, where the duodenum was perfused with NaCl (150 mmol/l) alone. In a third group of studies (12 subjects, ages 20–25 years), the basal bilirubin and trypsin secretion were monitored for 6 h during duodenal perfusion with NaCl (150 mmol/l) alone.

**Effects of STC and EAA on exogenously stimulated secretion.**

The effects of STC and EAA on exogenously stimulated biliary and pancreatic secretion were studied in eight volunteers (ages 23–30 years), who received an intravenous infusion of caerulein (2.5 ng h⁻¹ kg⁻¹) and secretin (0.025 clinical unit h⁻¹ kg⁻¹) for 6 h. During this time the duodenum was perfused for the first 2 h with NaCl solution (150 mmol/l) alone (equilibration period). This was followed by a perfusion with STC (10 mmol/l) for 1 h, followed by a perfusion with EAA (78 mmol/l) and STC (10 mmol/l) in combination for 1 h, followed during the final hour with a perfusion of EAA (78 mmol/l) alone. As a control study, duodenal perfusion with NaCl (150 mmol/l) alone was carried out for 6 h in 12 volunteers (ages 20–25 years), who received the same caerulein/secretin stimulation as described above.

**Instruments and chemicals**

Aspiration pumps for gastric and duodenal aspiration were obtained from Air Shields Inc. (Hatboro, PA, U.S.A.). Intravenous infusion of caerulein and secretin and gastric perfusion of phenol red were carried out by Harvard pumps, model 975 (Harvard Apparatus Co. Inc., MA, U.S.A.). Peristaltic pumps from Scientific Supplies Co. Ltd, U.K., were used for duodenal
perfusion. Pure natural porcine secretin, 3500 clinical units/mg, stabilized in cysteine hydroperfusion. Stabilized in our laboratory as described by Lack Karolinska Institute, Sweden. Caerulein (Ceruletide, 5 μg/ml) (batches TF/20400, TF/20523 and TF/21257) was donated by Farmitalia Ltd, Milan, Italy. EAA were purchased from Sigma, London.

The EAA mixture was exactly the same as used by previous workers [5]. STC was synthesized in our laboratory as described by Lack et al. [12] with the following modifications: after refluxing the mixture of taurine (British Drug House Chemicals Ltd), cholic acid (Sigma, London) and EEDQ (N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline ethyl-1,2-dihydro-2-ethoxy-1-quinoline-carboxylate) (Aldrich Chemical Co. Inc., U.K.) for 24 h, ethanol was evaporated from the mixture in a rotary vacuum evaporator. The residue was transferred to a separating funnel, dissolved in water and washed three times with dichloromethane. The aqueous extract was freeze-dried. The freeze-dried material was dissolved in ethanol and precipitated by addition of ethyl acetate and finally allowed to crystallize over several days at −20°C. The product was tested by a thin-layer chromatography and proved to migrate as a single spot identical with an STC standard (Sigma T4009, London).

Sample processing and analytical methods

Blood samples for hormone measurements were collected at 10–20 min intervals into heparin-treated tubes containing aprotinin, centrifuged immediately (1500 g for 10 min) and the plasma was kept frozen at −20°C until assayed. Duodenal aspirates were pooled for 10 min on ice in darkness, and aliquots saved in dark-brown bottles for analysis of bilirubin, PEG 4000, trypsin, total bile salts and phenol red. A portion was collected separately into a narrow airtight container and sealed by a 1 cm layer of liquid paraffin for analysis of bicarbonate. Gastric aspirates were pooled on ice for 10 min, and the samples frozen until analysed for phenol red and PEG 4000. Bilirubin [13], trypsin [10], total bile salts [10, 14], PEG 4000 [15] and phenol red [11] were measured by methods described elsewhere. Bicarbonate was measured by addition of hydrochloric acid, boiling and back-titration. Calculation of total secretion of bilirubin, total bile salts and trypsin were based on standard equations for PEG 4000 recovery [16].

Motilin was measured with an N-terminal reacting porcine antiserum [17], which detected both large and small molecular forms of motilin in plasma [18] and showed no cross-reactivity with other hormones. Changes of 3 pmol of motilin/l of plasma could be detected with 95% confidence. Pancreatic polypeptide (PP) [10] was measured with an antiserum raised against bovine pancreatic polypeptide. The assay detected changes in PP concentration of 8 pmol/l with 95% confidence. Gastric inhibitory polypeptide (GIP) was measured with a C-terminal-reacting porcine antiserum, which detected large and small molecular forms of GIP in plasma without cross-reactivity with other hormones [19]. Changes of 2.5 pmol/l of plasma were detected with 95% confidence. Gastrin was measured with antiserum raised against human gastrin, which detected changes in gastrin plasma levels of 2 pmol/l with 95% confidence [20].

Statistical analysis was performed by using Student’s t-test for paired or unpaired data, as appropriate, or two-way analysis of variance. Since the data on biliary and pancreatic secretion and gastrointestinal hormones were not normally distributed, but approximately log normal, all statistical evaluation of these data was done on log values. The data are expressed in the text, Table and Figures as means (geometric mean) ± SEM (in parentheses), the geometric mean ± SEM being calculated on the log values and then transformed to a linear scale by taking anti-logs [21]. Except where otherwise stated the data on biliary and pancreatic secretion represent the mean (geometric mean)/10 min ± SEM of the hour or hours in question.

Results

Recovery of the gastric marker (phenol red) from the stomach and the duodenum

Studies with duodenal perfusion only. NaCl control group: recovery from the stomach 75.7% ± SEM 2.4 (n = 12) and the duodenum 13.8% ± 2.4 (n = 12); STC test group: recovery from the stomach 80.4% ± 6.1 (n = 5) and the duodenum 21.6% ± 4.5 (n = 5): EAA test group: recovery from the stomach 72.9% ± 4.9 (n = 5) and the duodenum 22.3% ± 5.8 (n = 5).

Studies with duodenal perfusion and caerulein/secretin stimulation. NaCl control group: recovery from the stomach 87.6% ± SEM 2.9 (n = 12) and the duodenum 11.6% ± 2.6 (n = 12); STC test group: recovery from the stomach 75.1% ± 5.3 (n = 8) and the duodenum 24.5% ± 3.2 (n = 8) (P < 0.01 compared with control group, 11.6% ± 2.6).
Effects of STC and EAA on basal secretion

Basal bilirubin secretion fell promptly from 389 μg/10 min (262–583, n = 5) during the hour immediately preceding STC perfusion to 23 μg/10 min (14–38, n = 5) (P < 0.001) during the second half of the first STC perfusion hour (Fig. 1a). During the following 3 h of STC perfusion, a progressive increase in bilirubin secretion was observed, the bilirubin secretion during the fourth hour of STC perfusion being 333 μg/10 min (195–578, n = 5) and not significantly different from the basal levels. During a subsequent perfusion for 1 h with EAA/STC in combination, bilirubin secretion rose markedly above these levels to 1195 μg/10 min (740–2095, n = 5) (P < 0.01) (Fig. 1a), suggesting that gallbladder

TABLE 1. Bicarbonate (μmol/10 min) in the duodenal fluid in basal and stimulated studies

<table>
<thead>
<tr>
<th>Perfusion fluid</th>
<th>NaCl (150 mmol/l)</th>
<th>STC (10 mmol/l)</th>
<th>EAA/STC (78/10 mmol/l)</th>
<th>EAA (78 mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal (n = 5)</td>
<td>77</td>
<td>128</td>
<td>252†</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>(45–139)</td>
<td>(86–196)</td>
<td>(220–290)</td>
<td>(85–256)</td>
</tr>
<tr>
<td>Basal (n = 5)</td>
<td>132</td>
<td>—</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(78–236)</td>
<td></td>
<td>(85–256)</td>
<td>(680–2683)</td>
</tr>
<tr>
<td>I.v. caerulein/secretin stimulation (n = 8)</td>
<td>1437</td>
<td>2848†</td>
<td>2213†</td>
<td>1351</td>
</tr>
</tbody>
</table>

* STC was perfused for 4 h in the basal studies. EAA was perfused for 3 h in the basal studies.
† P < 0.05 difference from NaCl control perfusion.
emptying had occurred. A slight increase in trypsin secretion was observed during the 4 h of STC perfusion (Fig. 1b), eventually reaching 1510 i.u./10 min (1210–1734, n = 5) (hour 4) versus 1250 i.u./10 min (992–1591, n = 5) basal (P = 0.05). When STC and EAA were perfused together, a marked increase above these levels was observed to 2455 i.u./10 min (1780–2965, n = 5) compared with 1250 i.u./10 min (992–1591, n = 5) basal (P < 0.01). Fig. 2 shows the mean duodenal recovery of bilirubin and trypsin secretion during perfusion of NaCl solution (150 mmol/l).

Bicarbonate secretion did not change during the 4 h of STC perfusion (Table 1) but, during the final hour when EAA and STC were perfused together, a trivial but statistically significant increase in bicarbonate secretion was observed (P < 0.05) (Table 1). The concentrations of total bile salts in the duodenum during the 4 consecutive hours of STC perfusion were 6.4 mmol/l (5.8–7.0), 6.4 mmol/l (6.3–6.5), 6.2 mmol/l (5.3–7.2) and 6.0 mmol/l (5.0–7.3) respectively, compared with 0.7 mmol/l (0.3–1.0) during the basal period when NaCl (150 mmol/l) was perfused alone. In the control group no abrupt changes in bilirubin secretion were observed, although there was a downward trend in secretion during the 6 h of NaCl (150 mmol/l) perfusion. However, a wide variation in basal bilirubin secretion was observed between the control group and the STC test group. Inherent individual variation in basal bilirubin secretion is a likely explanation to this rather than a difference in marker recovery.

**Effects of prolonged EAA stimulation**

Bilirubin secretion rose from 486 µg/10 min (257–927, n = 5) during the basal period to a peak value of 2727 µg/10 min (2428–3055, n = 5) 20 min after the beginning of EAA perfusion (P < 0.02). Subsequently, bilirubin secretion fell to a plateau of 1392 µg/10 min (1055–1716, n = 6) during the second and third hours of EAA perfusion (Fig. 3a) (P < 0.05, compared with basal). During the first 30 min of EAA perfusion peak output of trypsin was 4919
FIG. 5. Duodenal recovery of intravenous caerulein- (2.5 ng h⁻¹ kg⁻¹) and secretin- (0.025 clinical unit h⁻¹ kg⁻¹) stimulated bilirubin secretion (a) and trypsin secretion (b) during 6 h duodenal perfusion of NaCl solution (150 mmol/l saline). Geometric means ± SEM (bars) are shown (n = 12).

Effects of STC and EAA on exogenously stimulated secretion

Exogenously stimulated bilirubin secretion was 2628 µg/10 min (2179–3189, n = 8) during the hour immediately preceding STC perfusion (total bile salt concn. 1.1 mmol/l, 0.7–1.8, n = 8), but decreased to 393 µg/10 min (214–734, n = 8) (P < 0.01) during the STC perfusion hour (total bile salt concn. 6.8 mmol/l, 5.7–8.1, n = 8) (Fig. 4a). When EAA was added to the STC perfusate, bilirubin secretion reached a peak output of 6668 µg/10 min (4699–9462, n = 8) at 20 min (P < 0.01, compared with the pre-STC hour), after which bilirubin secretion fell towards initial levels. A subsequent perfusion with EAA alone did not increase bilirubin secretion further, which remained at 2747 µg/10 min (2328–3254, n = 8) (P > 0.05, compared with pre-STC hour).

Exogenously stimulated trypsin secretion did not change during perfusion with STC alone (3600 i.u./10 min, 3019–4303, n = 8, versus 3515 i.u./10 min, 2905–4261, n = 8, pre-STC hour, P > 0.05) (Fig. 4b). During the combined EAA/STC perfusion, trypsin secretion rose transiently at 20 min to 6295 i.u./10 min (5164–7674, P < 0.02, compared with pre-STC hour), falling before the EAA/STC perfusion was completed and failing to rise again during perfusion with EAA alone (Fig. 4b). A slight increase in bicarbonate secretion was observed during the perfusion of STC alone and EAA/STC in combination compared with the initial NaCl perfusion (P < 0.05) (Table 1).

In the control studies without STC perfusion, caerulein/secretin-stimulated bilirubin and trypsin secretion remained stable throughout 6 h (Fig. 5).

Plasma levels of gastrointestinal hormones

Plasma levels of gastrin, GIP and PP did not change during STC perfusion in either the basal or exogenously stimulated studies. However, EAA in combination with STC, or perfused alone, revealed an increase in plasma PP levels (Figs. 6 and 7) (P < 0.05). Plasma levels of motilin were significantly suppressed (P < 0.001) in both basal and exogenously stimulated studies during STC perfusion (Figs. 6 and 7); however, levels rose again when EAA were added to the perfusate.

Discussion

Perfusion of the duodenum with the bile salt STC suppressed the secretion of bilirubin into the duodenum, both in the basal state and during
exogenous stimulation of hepatobiliary secretion with caerulein and secretin. This suppression was overcome by simultaneous perfusion of the duodenum with EAA mixture, known to be a potent cholecystokininetic stimulus to the secretion of bile [5, 16, 22].

The anatomical location and mechanism of this inhibitory effect can only be explained in a limited way by our data. Bilirubin secretion into the duodenum depends on hepatic secretory rate, the fraction of bile entering the gallbladder and the amount of bile accommodated in the biliary tract. Inhibition of bile output was observed as early as 10–20 min after the beginning of the STC perfusion and is therefore unlikely to be caused by a direct action on the hepatic secretion by absorbed STC passing through the liver. Bile salts, including STC, are reported to act as choleretics in man [23], and indeed the gradual increase in bilirubin secretion after the initial inhibition in the prolonged (4 h) STC perfusion may reflect this. However, recent studies in cholecystectomized subjects suggest that hepatic secretion of bilirubin is not influenced by changes in hepatic bile salt flux within the 'physiological' range [24]. An inhibitory effect on the extrahepatic biliary tract and the gallbladder is a more likely explanation for reduced biliary output during STC perfusion. Although the sphincter of Oddi may play an important role in promoting gallbladder storage [25] STC does not apparently affect the sphincter, since the suppression of bile secretion was not accompanied by a parallel inhibition of pancreatic secretion. Other studies in cholecystectomized subjects suggest that in the absence of the gallbladder STC does not diminish bile output [26], which is consistent with an effect of STC on the gallbladder in normal subjects.

The mechanism by which bile salts in the duodenum may promote biliary inhibition remains obscure. Motility and secretory functions of the biliary tract and the pancreas are probably regulated by both hormonal and neural factors, evoked mainly by stimuli from inside the gastrointestinal tract [27, 28]. Although cholecystokinin and secretin may mediate enterobiliary and enteropancreatic responses, and certainly infusions of pure peptides are powerful stimuli, increases in cholecystokinin and secretin-like immunoactivity in the blood after luminal stimulation have not yet been shown to be adequate to account for the secretory responses to meals [29, 30]. Furthermore, the apparently selective inhibitory effect of STC on the biliary system demonstrated here would be unlikely to result from suppression of secretion of either of these hormones. Exclusively neural pathways for enterobiliary and enteropancreatic reflexes have not been defined though a rich autonomic innervation is evident and secretory functions of these organs can be stimulated or inhibited by this system [27, 28].

Of the gastrointestinal hormones measured during STC perfusion only motilin showed changes coincident with suppression of biliary output. Motilin enhances gastric emptying [31], activates duodenal motility [32] and increases gallbladder pressure [32, 33]. Suppression of plasma motilin levels may therefore be expected to facilitate gallbladder relaxation and promote gallbladder storage of bile. Motilin levels rise
modestly and transiently [34–38] during standard hospital meals and may be reduced below basal levels postprandially [35]. However, luminal bile salt concentrations have not been correlated with plasma motilin in these studies so that the potential significance of STC suppression of motilin levels observed in our studies to the postprandial events in the duodenum is not clear.

STC-induced inhibition of bilirubin output during caerulein/secretin stimulation was reversed by EAA perfusion, which caused a prompt increase in bilirubin output, suggesting gallbladder contraction. In contrast Malagelada et al. [5], using luminal EAA as a background stimulus, found that STC suppressed stimulated biliary and pancreatic secretion but that STC did not inhibit the biliary response to intravenous cholecystokinin, and concluded that STC may inhibit endogenous cholecystokinin release from the duodenum. Differences in the endogenous and exogenous stimuli doses probably account for these apparently contradictory results. The caerulein/secretin stimulus used in our studies could be expected to simulate the combined cholecystokinin [39] and choleretic [40] effects seen after a meal and these were inhibited by STC. The absence of any effect of STC on pancreatic secretion and the apparently normal biliary and pancreatic responses to luminal EAA during STC perfusion suggest that STC acts through a mechanism different from inhibition of cholecystokinin release.

The short-lived or phasic trypsin secretory response to EAA during STC perfusion was also observed during control studies with EAA perfusion alone. This pattern of enzyme response to EAA has been observed before and attributed to a ‘wash-out’ of stored enzymes [5, 16], or to a stimulation of glucagon release by absorbed EAA and a secondary inhibition of enzyme secretion [41]. Although frequently referred to, the ‘wash-out’ effect has never actually been proven to exist [42], and it is unlikely to explain the phasic enzyme response following the prolonged period of exogenous caerulein/secretin stimulation, which would have depleted enzyme stores (Fig. 4). It should also be pointed out in these studies that trypsin secretion during EAA/STC and EAA perfusion superimposed on caerulein/secretin stimulation never did fall below the plateau obtained by caerulein and secretin, which suggests that the mechanism of EAA and caerulein/secretin-induced secretion is different.

Although STC had no effect on pancreatic trypsin secretion, nor any effect on basal bicarbonate output, a modest increase in caerulein/secretin-stimulated bicarbonate output was observed. Other workers have shown that human bile [7] or pure bile salt mixtures simulating the composition of human bile [43] may increase bicarbonate secretion and plasma levels of secretin immunoreactivity and, in the cat, where STC is the major bile salt, an effect on bicarbonate secretion was observed [44]. Although our results do not support the idea that STC on its own stimulates bicarbonate secretion in man, it may act additively with the caerulein/secretin-stimulated bicarbonate secretion (Table 1), a concept which has support from previous work [3, 4, 44].

The selective inhibition of biliary secretion during duodenal perfusion with STC supports the concept that duodenal bile salt concentration may be one of the luminal factors regulating bile delivery to the duodenum. The role of motilin has not been defined in these studies though plasma levels of this hormone fell in parallel with the biliary inhibition.

Acknowledgments

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References

Biliary secretion inhibited by sodium taurocholate


