Effect of sub-diaphragmatic vagotomy on gastric ulcer produced by pylorus ligation in albino rats

Experimental situation and No. of rats	Part of the gastric mucosa involved in ulceration (No. of rats)				Ulcer index	Gastric content (ml)	Free acidity (U)	Total acidity (U)
	Fundus alone	Fundus + body	Body alone	Body + fundus				
Pylorus ligation with vagus nerve intact (7)	5	2	–	–	0.40 ± 0.36	7.64 ± 1.84	22.14 ± 24.62	74.57 ± 23.35
Pylorus ligation with confirmed vagotomy (9)	–	–	6	1	0.039 ± 0.035	3.43 ± 1.63	2.44 ± 7.33	34.33 ± 21.41

Statistical analysis (t-values)

	Ulcer index	Gastric content	Free acidity	Total acidity
Between pylorus ligation with vagus-intact rats and pylorus-ligation with vagotomized rats	3.04[a]	4.89[a]	2.31[b]	3.70[a]

[a] Significant at 1% level; [b] Significant at 5% level.

Pylorus ligation was performed after the method of SHAY et al.[8]. Prior to operation, food was withheld for 40–48 h and following operation water was also withheld; 10 cm³ of 25% glucose was allowed after 24 h of fasting to prevent hypoglycemia of fasting. Then 19 to 22 h after pylorus ligation, the stomach was removed with a clamp on the lower oesophagus. Gastric content was collected, volume was noted and free and total acidity were determined by using Töpfer's reagent and alcoholic phenolphthalein as indicators.

Ulcers were stained by ROBERT and NEZAMIS' method[9]. The stomach was carefully opened along the greater curvature, cleaned in running water, spread on a cardboard with mucus surface upwards. The total area of stomach mucosa and that of ulcers were taken into consideration for determining the ulcer index[10]. A transparent perspex plate, with mm² rulings on it over an area of 4 square inches, was positioned over the mucosa for determining the area of stomach and that of ulcers. The ulcer index was expressed as 10/X, where X was taken as the ratio between the total area of stomach mucosa and that of ulcers[6].

Results. The results are summarized in the Table which shows that after complete subdiaphragmatic vagotomy, the ulcer index is reduced from 0.40 to 0.039 in pylorus-ligated rats. The volume and free and total acidity of the gastric content are also significantly lower in the vagotomized group. The Table also shows that the main area of involvement is the fundus of the stomach in the vagus-intact group, whereas it is the glandular portion in the case of vagotomized rats.

Discussion. The reduction of mean ulcer index from 0.40 in vagus-intact pylorus ligated rats to 0.039 in vagotomized pylorus-ligated rats with concomittant reduction of volume, free and total acidity of gastric content clearly shows that the beneficial effect of vagotomy against development of ulcers must be due to the reduction in vagus and gastrin-mediated gastric secretion. So far as the site of ulceration is concerned, it can easily be explained how ulcers develop in the unprotected fundus in vagus-intact rats due to accumulating acid[8], whereas in vagotomized group, the fundic area escapes from ulceration due to low volume and acidity of gastric content. But it is not clear why there should be a development of ulcers in the glandular part following vagotomy, whereas in the vagus-intact group glandular part of the stomach is involved only to a minor extent.

Although the volume and acidity is reduced to a great extent after vagotomy, it is possible that adrenal pathway becomes active during the stress of pylorus ligation and corticosteroids, or that vagotomy by itself weakens the mucosal barrier in the glandular part of the stomach, thus making the area susceptible for development of ulcers.

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Effect of Cholestasis and Biliary Diversion on the Absorption of Na Octanoate in the Rat[1]

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Summary. The intestinal absorption and portal vein transport of Na octanoate by isolated jejunal segments perfused in vivo were unchanged in rats studied 48 h after bile duct ligation or fistula.

Medium chain fatty acids (MCFA) are rapidly taken up by enterocytes and pass directly into the portal circulation without forming chylomicrons[2]. Administered as medium chain triglycerides (MCT), they are useful in clinical situations where the digestive and transport phase of fat absorption are defective[3]. Having shown previously

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Table I. Weight loss, lyophilized weight of jejunal segments and portal blood flow

	Wt loss (%)	Dry wt of segments (mg)	Portal blood flow (ml/min)
Controls (8)	1.4 ± 0.3	270.2 ± 18.2	22.1 ± 1.2
Bile duct ligation (10)	3.0 ± 0.9	263.8 ± 22.3	22.6 ± 1.9
Bile duct fistula (8)	3.2 ± 0.5	267.7 ± 26.1	21.7 ± 1.3

Figures in parentheses correspond to the number of animals studied. Results shown represent mean ± SE. The mean portal blood flow for each group was obtained by averaging 8 to 10 measurements from each animal.

Table II. Net absorption of octanoate, sodium and water from the intestinal lumen

	Octanoate (μ*M*)	Sodium (μEq)	Water (ml)
Controls (8)	15.6 ± 1.3	233 ± 36	0.93 ± 0.2
Bile duct ligation (10)	12.6 ± 1.1	163 ± 31[a]	0.91 ± 0.2
Bile duct fistula (8)	13.2 ± 1.5	313 ± 37	0.86 ± 0.2

Figures in parentheses correspond to the number of animals studied. Results shown represent mean ± SE/h/100 mg dry weight of upper jejunum. [a] $p < 0.01$ vs bile duct fistula.

Table III. Absorption of octanoate from the lumen in relation to tissue uptake and net portal transport

	DPM × 10^3/100 mg dry wt of jejunum			
	Absorption (min)	Tissue uptake	Net portal transport/min	
			^{14}C in plasma	$^{14}CO_2$ in blood
Controls (8)	9.3 ± 0.9	42.2 ± 2.7	5.3 ± 0.9	4.2 ± 1.3
Bile duct ligation (10)	6.7 ± 0.9	43.9 ± 1.2	4.8 ± 0.7	4.4 ± 0.5
Bile duct fistula (8)	8.1 ± 1.2	44.1 ± 2.6	5.2 ± 0.9	3.9 ± 0.6

Figures in parentheses correspond to the number of animals studied. Results shown represent mean ± SE. Net portal transport of plasma ^{14}C and whole blood $^{14}CO_2$[8] was estimated by using the difference between the portal and aortic concentration measured twice in each animal, the portal blood flow (ml/min) and the hematocrit.

that the absorption of an actively transported substrate (3-*O*-methyl glucose) is increased following a 48 h period of biliary diversion[4] and impaired after a comparable period of cholestasis[5], the present study was carried out to see if the absorption of octanoate, a passively transported molecule and the main constituent fatty acid of MCT, is similarly affected.

Material and methods. Following the creation of a bile fistula, the ligation of the common duct or a sham operation, 3 groups of male Sprague-Dawley rats weighing 300 to 350 g were placed in restraining cages. Through a gastrostomy tube placed in the first part of the duodenum, they were given at a constant rate of 4.7 ml/h a mixture of 2% casein hydrolysate, 3% Na caseinate and 13% dextrimaltose in an electrolyte solution containing 35 and 9 mEq/l of Na and K respectively. After 48 h, the absorption of Na octanoate was studied in 20 cm segments of proximal jejunum perfused in vivo at a rate of 0.26 ml/min for a 30 min period necessary to obtain a steady rate of intestinal absorption followed by an experimental period of 60 min. The perfusate consisted of an 11 m*M* solution of Na octanoate (Biochemical Laboratories, California) in a 5% fatty acid free bovine albumin solution to which was added 3.6 μCi of Na octanoate-1-^{14}C (New Engl. Nuclear Corp., 5.0 mCi/mMole) and 8.4 μCi of ^{3}H-labeled dextran (New Engl. Nuclear Corp., 70.4 mCi/g). The pH of the solution was adjusted to 7.4. Its osmolality was 288 mosm/kg and its Na content 164.5 mEqu/l. The rate of absorption from the lumen was determined by the measurement of concentration differences of octanoate, Na and dextran in the perfusate entering and in the fluid leaving the segment. The usual calculations were applied[6]. During the course of preliminary experiments with control animals, increasing concentrations of octanoate (0.75, 1.5, 3.0, 6.0 and 11 m*M*) were used. Absorption was related linearly to the concentration of substrate. Portal vein blood flow was monitored with a 2 mm electromagnetic flow probe (Model SP 2202 Statham Instruments, Inc., California). Samples of portal blood were obtained at 30 min intervals[7]. A femoral catheter through which normal saline was given at a rate of 4 ml/h permitted simultaneous sampling of aortic blood. At the end of each experiment, the perfused intestinal segment was promptly removed from the animal, lyophilized for determination of dry weight and then dissolved in NCS for counting of tissue ^{14}C radioactivity.

Results. As seen in Table I, the weight loss suffered by the animals during the 48 h. period following biliary diversion or ligation was negligible. Because of difficulties inherent to the in situ measurement of the length of jejunal segments, lyophilized weights were recorded and found to be the same for the 3 groups. Portal blood flows recorded 8 to 10 times during the 60 min experimental period were remarkably constant in each animal. Although the disappearance of octanoate from the lumen of jejunal segments taken from cholestatic and bile diverted animals was somewhat lower, the difference with the controls was not significant (Table II). There was net absorption of both sodium and water in all segments. Although more Na was absorbed in bile fistula animals than in the two other groups, the difference with the bile ligated rats was the only one to reach statistical significance (Table II). The ^{14}C radioactivity in portal plasma was usually more than twice that found in aortic plasma and accounted roughly for $^{2}/_{3}$ of the counts absorbed over the 60 min experimental period. At the end of the perfusion, the ^{14}C uptake by jejunal segments represented less than 10% of the octanoate radioactivity which had disappeared from the lumen. No difference could be

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found between the 3 groups for tissue uptake and net portal transport (Table III).

Discussion. In the absence of pancreatic lipase, MCT undergo extensive hydrolysis by the intestinal mucosa[2]. However, because their maximum absorption rate is 4-fold less than for their constituent MCFA[9], it was elected to use the sodium salt of octanoic acid. Initial experiments showed that the probe molecule exhibited the transport characteristics of a passively absorbed substrate; as the concentration of Na octanoate was increased, the rate of absorption increased proportionately[10]. In order to minimize the detrimental effects of undernutrition[11] on absorption and more specifically on the activation of MCFA[12], adequate calories were provided during the 48 h period between the initial surgical procedure and the study of absorption. As a result, the average weight loss was negligible.

The disappearance rate of Na octanoate from the lumen was unchanged in the absence of bile for 48 h from the intestine of bile fistula and bile duct ligated animals. However, the fact that Na was better absorbed in the bile diverted than in the cholestatic group tends to support our previous observations[4,5]. Two major resistances to the flux of lipid into enterocytes are now recognized, a diffusion barrier due to an unstirred aqueous layer and the resistance to translocation through the cell membrane itself[13]. Since the resistance to diffusion of octanoic acid across the unstirred water layer does not represent a substantial fraction of the total resistance[14], the present results suggest that the permeability characteristics of the lipid membrane to octanoate were unaffected by the absence of bile. In contrast to LCFA which, on entering the mucosa from the lumen, are mainly esterified to triglycerides[15], a significant proportion of absorbed octanoic acid, once activated, is oxidized[16]. Therefore, the equally large net portal transport of $^{14}CO_2$ in the 3 groups of animals could suggest that mucosal metabolism of octanoate subsequent to its transport was unchanged. However, this interpretation may not be totally valid because oxidation may go on in the intestinal lumen and account for a small but significant % of the CO_2 in the portal vein[17]. The net portal transport of ^{14}C radioactivity in plasma and the counts in the tissue of the perfused segments were the same in the 3 groups. Since the absorption of octanoate in lymph is negligible[18], it can be concluded that extrusion from the enterocytes and subsequent transport were unaffected by biliary diversion and by experimental cholestasis.

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The (Na^+ + K^+)-ATPase Activity in Brain of Quaking Mice

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Summary. The (Na^+ + K^+)- and Mg^{2+}-dependent ATPase distribution in several brain areas has been investigated in Quaking mutant mice characterized by myelin deficiency. A marked decrease of (Na^+ + K^+)-ATPase activity has been found in limbic structures, hypothalamus and cerebellum. The Mg^{2+}-dependent activity did not change. A possible involvement of the impairment of the (Na^+ + K^+)-ATPase activity in the seizure susceptibility of this mice is discussed.

Sidman et al.[2] described Quaking mutation characterized by myelin deficiency on the central nervous system. The disease is autosomal recessive and animals can survive for several months. Mutant mice can be recognized at about the 12th day after birth and the disease reaches its full expression by about 3 weeks. Besides marked tremor of the hindquarters, epileptic fits can be induced in the adult by sensory stimulations.

There is a substantial amount of data indicating that the mutation could be related to a deficiency of myelination caused by a lowering of the rate of synthesis of several enzymes involved in biosynthesis of myelin constituents[3-7]. On the other hand, little has been done on the molecular basis of seizure susceptibility in mutant mice.

It was shown previously that slices of human epileptic brain tissue cannot take up potassium nor extrude sodium as well as normal human brain slices[8]. Moreover, sodium and potassium transport seems to be involved in the mechanism of the anticonvulsant action of diphenylhydantoin[9]. Due to the work of Skou et al.[10], an identity has been established between the sodium pump and an enzyme, the (Na^+ + K^+)-ATPase activity. Thus, in the present study we were concerned primarily with the

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