Total Gastrectomy and Small Intestinal Cholesterol Synthesis in Diabetic Rats

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Cholesterol synthesis is increased two- to threefold in the small intestine of diabetic rats. We have observed, in three separate experiments, that the characteristic increase in small intestinal cholesterol synthesis (SICS) in diabetic rats was prevented by total gastrectomy. Food intake was increased twofold, and the small intestine hypertrophied in the gastrectomized diabetic animals. In normal animals, total gastrectomy resulted in only a very small increase in intestinal cholesterol synthesis. In hyperphagic lactating animals, total gastrectomy did not prevent the characteristic increase in SICS that is usually observed in this hyperphagic model. These results indicate that the effects of total gastrectomy on preventing an increase in SICS are relatively specific for the diabetic state. The mechanism by which total gastrectomy prevents the increase in intestinal cholesterol synthesis in diabetic animals is unknown. Vagotomy did not prevent the typical increase in intestinal synthesis in diabetic animals. Additionally, selectively removing either the antrum or fundus of the stomach did not prevent the increase in SICS in diabetic animals, indicating that the inhibition requires the removal of the entire stomach. It can be speculated that the stomach produces a substance that induces the increase in SICS observed in diabetic animals and that total gastrectomy removes this stimulatory substance. *Diabetes* 38:219–24, 1989

Previous studies in our laboratory have demonstrated that ^3H_2O incorporation into cholesterol is increased two- to threefold in the small intestine of intact rats with steptozocin (STZ)-induced diabetes (1). Other laboratories, with different techniques to measure cholesterol synthesis, have also demonstrated an increase in small intestinal cholesterol synthesis (SICS) in diabetic rats (2–4). This enhancement of SICS occurs soon after the onset of diabetes and persists for at least 5 wk (1). Most important, insulin therapy that normalized serum glucose levels markedly decreased SICS in diabetic rats to a level similar to that observed in controls (1). We have also observed increases in SICS in other diabetic animal models (diabetic Chinese hamster), suggesting that stimulation of synthesis may be a general phenomenon (5).

Cholesterol synthesized in the small intestine has three main fates: it can be transported via the lymphatics to the bloodstream, it can be excreted in the feces, or it can be utilized in situ for the formation of cellular membranes. Studies from our laboratory with control and diabetic rats with thoracic duct cannulas have demonstrated that the transport of newly synthesized cholesterol from the intestine to the circulation is increased fourfold in diabetic animals (6). In both control and diabetic animals, most of the labeled cholesterol transported from the small intestine to the bloodstream is localized to the chylomicron lipoprotein fraction (6). The clearance from the circulation of diabetic chylomicrons is normal in diabetic animals, and thus the intestinally derived cholesterol is rapidly delivered to the liver (7). Using entirely different experimental methods, Young et al. (8) have shown that cholesterol synthesized in the small intestine is transported to the circulation to a greater extent in diabetic animals than in controls. These findings suggest that the increase in SICS observed in diabetic animals contributes to the total-body cholesterol pool and to the elevated plasma cholesterol levels that are observed in diabetes mellitus.

The mechanism by which insulinopenic diabetes increases SICS is unknown, but it has been proposed that the hyperphagia associated with poorly controlled diabetes is the chief stimulus. Experiments have demonstrated that limiting food intake by pair feeding can prevent the diabetes-induced increase in SICS (9,10). Moreover, it has been dem-

Glucose 1 mM = 18 mg/dl

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onstrated that other experimental situations that result in increased food intake also enhance SICS (11). Specifically, SICS is increased 30% in 3rd-trimester pregnant rats, 168% in 21-day-postpartum lactating rats, 73% in obese rats, and 64% in animals infused intragastrically with 16 vs. 8 g glucose/day (11). These findings provide further support for the hypothesis that the increased calorie intake associated with diabetes is the chief stimulus for the increase in intestinal synthesis.

We present data demonstrating that total gastrectomy prevents the characteristic increase in SICS that occurs in diabetic animals.

MATERIALS AND METHODS

Tritiated water (1 Ci/g) was purchased from ICN (Irvine, CA). [26-^{14}C]cholesterol (50–60 mCi/mmol) was purchased from New England Nuclear (Boston, MA). STZ was purchased from Sigma (St. Louis, MO). The thin-layer chromatography (TLC) polygram silica gel plates were purchased from Brinkmann (Westbury, NY). Ultrafluor scintillation fluid was purchased from National Diagnostics (Somerville, NJ). Ketodiastix were obtained from Ames (Elkhart, IN).

Procedures. Female Sprague-Dawley rats were purchased from Simonsen (Gilroy, CA). Animals were maintained on a reverse 12-h light cycle (0300–1500 dark, 1500–0300 light) and were fed Simonsen rat and mouse diet and water ad libitum. Food intake was periodically measured in some experiments.

The animals underwent one of four surgical procedures under isoflurane inhalation anesthesia. Total gastrectomy was carried out by transecting the esophagus just proximal to the esophageal gastric junction and transecting the duodenum just distal to the pylorus. The continuity of the gastrointestinal tract was preserved by end-to-end anastomosis of the esophagus to the duodenum. Total vagotomy was carried out by transecting the entire thickness of the muscular layer of the esophagus just proximal to the esophageal gastric junction. The transected muscular layer was then sutured end to end to maintain a patent esophagus. Removal of the antrum of the stomach was carried out after the animals had fasted overnight. In the rat, the division of the antrum from the fundus of the stomach is apparent on gross inspection of the mucosa. The duodenum was transected just distal to the pylorus. The continuity of the gastrointestinal tract was preserved by end-to-end anastomosis of the fundus of the stomach to the duodenum. Removal of the fundus was carried out after the animals had been fasted overnight. The stomach was transected at the antral-fundal junction, except that the portion of the fundus through which the esophagus enters the stomach was preserved (~95% of the fundus was removed). The antrum was then reanastomosed to the fundal cuff and esophagus.

Food was withheld postoperatively for 24 h. When the animals had recovered from the surgical trauma (~1 wk), diabetes was induced in one group of animals, and the remainder of the animals served as nondiabetic controls. Diabetes was induced by injecting the animals after an overnight fast with 40 mg/kg i.p. STZ in a 1 M sodium citrate buffer (pH 4.5). Control animals were injected with buffer alone. The urine of the animals administered STZ was periodically analyzed with Ketodiastix, and the animals were eliminated from the study if they did not have at least 1% glycosuria at all times or if they were ketotic.

Experimental protocol. Between 0800 and 1000, the rats were injected with ^3H_2O (50 mCi i.p.). One hour later, the animals were killed and weighed, and a blood specimen was obtained. The small intestine was removed, and the lipids were saponified by refluxing overnight in a solution of 45% KOH, water, and 70% ethyl alcohol (2:1:5). The flasks were cooled, and an internal standard of [^{14}C]cholesterol was added before extraction of the nonsaponifiable material 3 times with 25 ml of petroleum ether. The petroleum ether extract was dried, dissolved in chloroform, and then applied to TLC plates. The plates were developed in ethyl acetate and benzene (1:5) for 75 min, and the band corresponding to a standard of cholesterol was cut from the plate and counted. The window settings of the scintillation counter were adjusted so <0.2% of the ^3H_2O counts were recorded in the ^{14}C window, and ~10% of the ^{14}C counts were recorded in the ^3H_2O window. Calculations were corrected for the spillover of ^3H_2O and ^{14}C, for the background, and for the recovery of the internal standard. The specific activity of the ^3H_2O was determined individually for each animal by measuring disintegrations per minute per milliliter of plasma at the end of the experiment and dividing by millimoles of water per milliliter of plasma (52 mmol/ml plasma, assuming that plasma is 93% water). The validity of our methodology for measuring cholesterol synthesis has been demonstrated (1,12).

The results are expressed in both a per-total-organ basis and a per-gram basis. Data presented on a per-organ basis indicate the relative contribution of the small intestine to total-body cholesterol synthesis, whereas data presented on a per-gram basis address whether the increase or decrease in cholesterol synthesis was due to an increase or decrease in the rate of synthesis per weight of tissue.

Statistical significance was determined with a two-tailed Student's *t* test. As in our prior studies, we noted a variation in the rates of cholesterol synthesis from month to month and therefore only compare animals that were studied simultaneously under identical experimental conditions.

RESULTS

Table 1 exhibits the results of three separate experiments comparing cholesterol synthesis in control and diabetic animals that underwent total gastrectomies. As expected, serum glucose levels were increased in the diabetic animals compared with controls. Additionally, similar to our observations in nongastrectomized animals, food intake was increased in the diabetic animals, and the small intestine was hypertrophied. Surprisingly, in all three experiments, SICS expressed on a per-organ basis was not increased in diabetic animals compared with controls. This finding markedly differs from our current and previous studies in nongastrectomized animals, in which a two- to threefold increase in SICS in diabetic animals was a characteristic observation (1,5,6,10; Table 2). On a per-gram basis, SICS tended to be decreased in the gastrectomized diabetic animals, but this reached statistical significance in only one of the three experiments. In previous studies, SICS on a per-gram basis in diabetic animals was increased, decreased, or the same,

TABLE 1
Effect of total gastrectomy on small intestinal cholesterol synthesis

	n	Total body weight (g)	Small intestinal mass (g)	Serum glucose (mg/dl)	Food intake (g/day)	Small intestinal cholesterol synthesis	
						μmol · h^{-1} · organ^{-1}	μmol · h^{-1} · g^{-1}
Experiment 1							
Control	3	179 ± 1.9	6.48 ± 0.17	242 ± 21	14.0 ± 0.33	6.46 ± 1.58	0.98 ± 0.21
Diabetic	4	143 ± 6.5	15.0 ± 1.37	959 ± 74	24.9 ± 2.85	6.15 ± 0.63	0.41 ± 0.02
P		<.01	<.01	<.001	<.02	NS	<.02
Experiment 2							
Control	7	176 ± 7.4	7.11 ± 0.38	136 ± 6	13.6	14.8 ± 1.95	2.06 ± 0.24
Diabetic	7	161 ± 7.7	10.76 ± 0.89	585 ± 37	21.0	16.9 ± 1.08	1.61 ± 0.12
P		NS	<.01	<.001		NS	NS
Experiment 3							
Control	5	169 ± 7.3	6.28 ± 0.20	173 ± 7	12.9	11.5 ± 0.87	1.78 ± 0.17
Diabetic	6	172 ± 10.0	9.93 ± 0.78	367 ± 52	22.9	13.95 ± 2.66	1.37 ± 0.18
P		NS	<.01	<.01		NS	NS

Values are means ± SE. Food intake was measured for each individual animal (experiment 1) or per cage of animals and then divided by the number of animals in the cage (each group in experiments 2 and 3 was divided into 2 cages). In experiment 1, a total gastrectomy was performed, and when the animals were stable 7–9 days later, diabetes was induced by streptozocin administration in a subset of animals. Seventeen days later, the rats were injected with 50 mCi i.p. ^3H_2O. In experiment 2, diabetes was induced 9–10 days after gastrectomy, and cholesterol synthesis was measured 11 days after the onset of diabetes. In experiment 3, diabetes was induced 12–15 days after gastrectomy, and cholesterol synthesis was measured 11 days after the onset of diabetes. Animals were killed 1 h after ^3H_2O administration, and [^{3}H]cholesterol was assayed after saponification in a KOH-ethanol solution, extraction with petroleum ether, and thin-layer chromatography.

depending on the experiment (10). These results demonstrate that total gastrectomy prevents the characteristic increase in SICS observed in diabetic animals without preventing the increase in food intake or the increase in small intestinal mass that accompanies diabetes.

Total gastrectomy in normal animals does not result in any changes in either food intake or small intestinal size (Table 3). In animals gastrectomized 10 days before study, SICS is similar in gastrectomized normal animals and sham-operated controls. In animals gastrectomized 22 days before study, we observed a small increase in total SICS. This increase in synthesis is much less than the characteristic two- to threefold increase observed between control and diabetic animals (1,5,6,10; Table 2). These results indicate that the absence of the typical increase in SICS in diabetic animals that have undergone gastrectomy is not due to a similar stimulation of synthesis in the gastrectomized controls.

The effect of total gastrectomy on cholesterol synthesis in control and lactating animals is shown in Table 4 (experiment 1). Lactating rats were hyperphagic and had an increase in both small intestinal mass and SICS (11,13). Thus, the changes in lactating rats were similar to those seen in diabetic rats, and it was therefore of interest to determine whether total gastrectomy affected SICS in this hyperphagic animal model. Food intake and small intestinal mass were increased in gastrectomized lactating animals compared with gastrectomized controls (Table 4). However, in contrast to our observations in diabetic rats, SICS was increased

TABLE 2
Cholesterol synthesis in control and diabetic rats

	n	Total body weight (g)	Small intestinal mass (g)	Serum glucose (mg/dl)	Food intake (g/day)	Small intestinal cholesterol synthesis	
						μmol · h^{-1} · organ^{-1}	μmol · h^{-1} · g^{-1}
Experiment 1							
Control	4	188 ± 3.3	3.95 ± 0.11	140 ± 6	11.5 ± 0.29	2.33 ± 0.33	0.59 ± 0.08
Diabetic	4	190 ± 6.4	6.28 ± 0.37	446 ± 18	25.8 ± 1.25	6.38 ± 0.58	1.03 ± 0.11
P		NS	<.001	<.001	<.001	<.001	<.02
Experiment 2							
Control	5	227 ± 5.0	7.25 ± 0.23	136 ± 7		9.55 ± 0.68	1.33 ± 0.13
Diabetic	6	208 ± 2.4	11.7 ± 0.58	597 ± 28		18.65 ± 2.04	1.58 ± 0.14
P		<.01	<.001	<.001		<.01	NS
Experiment 3							
Control	5	226 ± 2.8	6.53 ± 0.37	129 ± 5.1	9.1 ± 4.2	4.56 ± 0.76	0.73 ± 0.16
Diabetic	5	195 ± 5.8	20.29 ± 0.97	744 ± 22	29.5 ± 2.02	10.70 ± 0.55	0.53 ± 0.02
P		<.01	<.001	<.001	<.001	<.001	NS

Values are means ± SE. In experiments 1 and 3, food intake was measured for each animal. In experiment 1, diabetes was induced by streptozocin administration 7 days before study. In experiments 2 and 3, diabetes was induced 10 and 16 days before study, respectively. On the day of study, the rats were injected with 50 mCi i.p. ^3H_2O. Animals were killed 1 h later, and [^{3}H]cholesterol was assayed after saponification in a KOH-ethanol solution, extraction with petroleum ether, and thin-layer chromatography.

TABLE 3
Effect of total gastrectomy on small intestinal cholesterol synthesis in normal rats

	Total body weight (g)	Small intestinal mass (g)	Food intake (g/day)	Small intestinal cholesterol synthesis	
				μmol · h^{-1} · $organ^{-1}$	μmol · h^{-1} · g^{-1}
Experiment 1					
Normal sham operated	226 ± 6.9	7.03 ± 0.29	12.67 ± 2.67	4.05 ± 0.67	0.570 ± 0.084
Normal total gastrectomy	179 ± 7.3	6.20 ± 0.68	12.75 ± 0.40	4.73 ± 0.82	0.782 ± 0.045
P	<.01	NS	NS	NS	NS
Experiment 2					
Normal sham operated	242 ± 5.4	8.69 ± 0.57	14.1 ± 2.1	4.75 ± 0.30	0.568 ± 0.038
Normal total gastrectomy	210 ± 5.4	7.86 ± 0.35	17.0 ± 4.0	6.74 ± 0.37	0.858 ± 0.031
P	<.01	NS	NS	<.01	<.01

Values are means ± SE; n = 5 for each group. Food intake was measured for each animal. In experiment 1, a total gastrectomy was performed, and 10 days later the rats were injected with 50 mCi i.p. ^3H_2O. In experiment 2, a total gastrectomy was performed 22 days before ^3H_2O administration. Animals were killed 1 h later, and [^{3}H]cholesterol was assayed after saponification in a KOH-ethanol solution, extraction with petroleum ether, and thin-layer chromatography.

twofold in gastrectomized lactating animals compared with controls. Total SICS was similar in gastrectomized lactating and sham-operated lactating animals (Table 4, experiment 2). These results indicate that the effects of total gastrectomy on preventing an increase in SICS are relatively specific for diabetic animals, and the surgery does not prevent the characteristic increase in SICS that normally occurs in lactating rats.

The purpose of the next series of experiments was to determine the mechanism by which total gastrectomy might prevent the characteristic increase in SICS in diabetic animals. When performing a total gastrectomy, a vagotomy also occurs, and therefore we determined the effect of vagotomy on SICS in control and diabetic animals. Diabetic animals who underwent a total vagotomy had an increased serum glucose level, consumed more food, and had an increase in intestinal mass compared with vagotomized controls (Table 5). Most important, SICS was increased twofold in diabetic animals compared with controls, indicating that incidental total vagotomy does not account for the inhibition of SICS observed in diabetic animals.

The effect of antrectomy on SICS in control and diabetic animals is shown in Table 6. As expected, food intake, serum glucose levels, and small intestinal mass were increased in diabetic animals compared with controls. SICS was also increased, indicating that removal of only the antrum of the stomach is not sufficient to prevent the increase in SICS in diabetic animals.

The effect of removal of the fundus of the stomach on SICS control and diabetic animals is shown in Table 7. Food intake, serum glucose levels, small intestinal mass, and, most significantly, SICS were increased in diabetic animals compared with controls. These results, in conjunction with the effects of antrectomy, indicate that a total gastrectomy is required to prevent the characteristic increase in SICS that occurs in diabetic animals.

TABLE 4
Effect of total gastrectomy on small intestinal cholesterol synthesis in lactating rats

	n	Total body weight (g)	Small intestinal mass (g)	Food intake (g/day)	Small intestinal cholesterol synthesis	
					μmol · h^{-1} · $organ^{-1}$	μmol · h^{-1} · g^{-1}
Experiment 1						
Control	7	211 ± 8.9	7.83 ± 0.54	11.2	6.52 ± 1.28	0.810 ± 0.120
Lactating	7	205 ± 12.8	14.15 ± 1.31	43.4	11.13 ± 1.13	0.785 ± 0.120
P		NS	<.001		<.02	NS
Experiment 2						
Lactating sham operated	5	314 ± 15.4	22.0 ± 1.33		12.8 ± 0.58	0.593 ± 0.046
Lactating total gastrectomy	5	251 ± 16.6	17.8 ± 2.17		13.4 ± 1.33	0.760 ± 0.029
P		<.05	NS		NS	<.02

Values are means ± SE. In experiment 1, food intake was measured per cage of animals and then divided by the number of animals per cage (3 or 4 animals per cage). A total gastrectomy was performed 4–7 days after parturition. A subset of animals continued lactating, and a subset was removed from contact with the pups. In experiment 2, gastrectomies or sham operations were performed 3–6 days after parturition, and all animals were allowed to continue lactating. Twenty days after parturition, the rats were injected with 50 mCi i.p. ^3H_2O. Animals were killed 1 h later, and [^{3}H]cholesterol was assayed after saponification in a KOH-ethanol solution, extraction with petroleum ether, and thin-layer chromatography.

TABLE 5
Effect of vagotomy on small intestinal cholesterol synthesis

	n	Total body weight (g)	Small intestinal mass (g)	Serum glucose (mg/dl)	Food intake (g/day)	Small intestinal cholesterol synthesis	
						μmol · h^{-1} · organ^{-1}	μmol · h^{-1} · g^{-1}
Control	7	214 ± 4.4	7.71 ± 0.39	182 ± 12	12.7 ± 1.23	7.6 ± 1.1	0.981 ± 0.133
Diabetic	5	197 ± 3.8	17.95 ± 0.99	695 ± 33	26.2 ± 2.21	13.8 ± 2.3	0.756 ± 0.110
P		<.02	<.001	<.001	<.001	<.05	NS

Values are means ± SE. Food intake was measured for each animal. Vagotomies were performed, and when the animals were stable 7 days later, diabetes was induced by streptozocin administration in a subset of animals. Fourteen days later, the rats were injected with 50 mCi i.p. ^3H_2O. Animals were killed 1 h later, and [^{3}H]cholesterol was assayed after saponification in a KOH-ethanol solution, extraction with petroleum ether, and thin-layer chromatography.

DISCUSSION

Previous studies have demonstrated that diabetes results in a two- to threefold increase in SICS (1–4). In animals with diabetes of relatively short duration (4 days), the small intestine hypertrophies only slightly, and SICS is increased on both a per-total-organ and per-gram basis (10). In animals with diabetes of a longer duration, the small intestine hypertrophies, and SICS is increased on a per-total-organ basis; however, on a per-gram basis, SICS is increased, remains the same, or even decreases compared with controls (10). Thus, in short-term diabetic animals, the increase in SICS is primarily due to an increased rate of synthesis per unit mass, whereas in long-standing diabetes, the increase in total SICS is primarily due to an increase in intestinal mass.

The mechanism by which diabetes leads to an increase in SICS is unknown, but it has been proposed that the increased food intake associated with poorly controlled diabetes is the chief stimulus. Pair-feeding experiments have demonstrated that limiting food intake in diabetic animals prevents the increase in SICS (9,10). Moreover, studies have demonstrated that in experimental situations in which food intake is increased, e.g., pregnancy, lactation, or obesity, SICS is also enhanced, supporting the hypothesis that hyperphagia is the stimulus for the increased SICS observed in diabetes (11).

The stimulation of SICS by increased food intake is not simply due to increased ingested food bulk. In both control and diabetic animals, when 50% Alphacel (a nonnutritive bulk) is added to the diet, the quantity of food intake approximately doubles, whereas the calorie intake remains constant (11). Despite the marked increase in ingested food bulk, SICS in control and diabetic animals is not altered (11). Studies have further shown that feeding either a glucose or fructose solution is sufficient to stimulate SICS in diabetic animals (14). These findings indicate that the increase in SICS in diabetic animals occurs in response to a single caloric source and that dietary fiber, complex carbohydrates, protein, or lipids are not requirements for this phenomenon. These observations suggest that an increase in the number of calories ingested per se is sufficient to increase SICS.

Our studies have also explored the possible mechanisms by which increasing calorie intake might stimulate SICS. Thiry fistulas were surgically constructed in normal rats so that the midportion of the small intestine was excluded from contact with the food stream. Diabetes was then induced in a subset of animals by STZ administration. In the diabetic animals, SICS was increased, and this increase was due to an increase in cholesterol synthesis in the segment of the intestine in contact with the food stream and the segment of intestine excluded from contact (296% increase) (11). In similar studies in which the proximal portion of the small intestine was excluded from contact with nutrients, we also observed that diabetes resulted in a 91% increase in cholesterol synthesis in the bypass segment (15). Moreover, in hyperphagic lactating animals, a 2.9-fold increase in cholesterol synthesis was observed in segments of the proximal intestine excluded from contact with the food stream and a 2.4-fold increase in bypassed mid-intestinal segments. These observations indicate that the hyperphagia-induced increase in SICS occurs in portions of the small intestine even when direct contact with calories is prevented, suggesting that the direct interaction of nutrients with the small intestinal mucosa is not the sole trigger for increasing SICS. Taken together these results suggest that a yet unspecified

TABLE 6
Effect of antrectomy on small intestinal cholesterol synthesis

	Total body weight (g)	Small intestinal mass (g)	Serum glucose (mg/dl)	Food intake (g/day)	Small intestinal cholesterol synthesis	
					μmol · h^{-1} · organ^{-1}	μmol · h^{-1} · g^{-1}
Control	222 ± 6.1	8.82 ± 0.59	154 ± 12	9.1 ± 0.49	6.67 ± 0.47	0.762 ± 0.051
Diabetic	216 ± 7.6	17.8 ± 0.37	631 ± 53	17.4 ± 2.49	15.52 ± 1.81	0.877 ± 0.107
P	NS	<.001	<.001	<.02	<.01	NS

Values are means ± SE; *n* = 5 for each group. Food intake was measured for each animal. An antrectomy was performed, and when the animals were stable 10 days later, diabetes was induced by streptozocin administration in a subset of animals. Fourteen days later, the rats were injected with 50 mCi i.p. ^3H_2O. Animals were killed 1 h later, and [^{3}H]cholesterol was assayed after saponification in a KOH-ethanol solution, extraction with petroleum ether, and thin-layer chromatography.

TABLE 7
Effect of fundus removal on small intestinal cholesterol synthesis

	Total body weight (g)	Small intestinal mass (g)	Serum glucose (mg/dl)	Food intake (g/day)	Small intestinal cholesterol synthesis	
					μmol · h^{-1} · $organ^{-1}$	μmol · h^{-1} · g^{-1}
Control	215 ± 5.1	7.0 ± 0.13	169 ± 3	12.2	6.50 ± 0.31	0.92 ± 0.04
Diabetic	195 ± 7.0	17.3 ± 1.21	724 ± 34	24.3	15.77 ± 2.17	0.90 ± 0.07
P	<.05	<.001	<.001		<.01	NS

Values are means ± SE; $n = 5$ for each group. Food intake was measured per cage of animals and then divided by the number of animals per cage (2 or 3 animals per cage). The fundus was removed, and when the animals were stable 7 days later, diabetes was induced by streptozocin administration in a subset of animals. Fourteen days later, the rats were injected with 50 mCi i.p. ^3H_2O. Animals were killed 1 h later, and [^{3}H]cholesterol was assayed after saponification in a KOH-ethanol solution, extraction with petroleum ether, and thin-layer chromatography.

circulatory and/or neurological factor induced by an increase in calories ingested plays a role in stimulating SICS in hyperphagic animals.

In this study we observed that total gastrectomy prevents the characteristic increase in SICS that occurs in diabetic animals. In three separate experiments we observed that SICS was similar in diabetic and control animals who had undergone total gastrectomies (Table 1). Note that in all three studies, food intake was increased approximately twofold in the gastrectomized diabetic animals, an increase similar in magnitude to that observed in our previous studies of unoperated diabetic animals. Moreover, in this study, the diabetes-induced increase in small intestinal mass was observed. Nevertheless, despite hyperphagia and hypertrophy of the small intestine, the characteristic increase in SICS in diabetic animals was prevented by total gastrectomy.

In contrast, in normal animals, gastrectomy resulted in only a slight increase in SICS (Table 3). In lactating animals with total gastrectomies, SICS was increased twofold compared with controls and was similar to that observed in sham-operated lactating animals (Table 4). This increase in lactating animals is similar to results observed in our previous studies (11,13), indicating that the inhibition of SICS observed in diabetic animals was specific to this metabolic state; it was not observed in normal animals or in other hyperphagic animals. The results also suggest that there are differences between the mechanism of stimulation of cholesterol synthesis in lactating and diabetic animals.

The mechanism by which total gastrectomy prevents the characteristic increase in SICS in diabetic animals is unknown. Vagotomy, which is a uniform incidental occurrence when the stomach is surgically removed, did not prevent the increase in SICS in diabetic animals (Table 5). Selectively removing either the antrum or the fundus of the stomach did not inhibit SICS in diabetic animals (Tables 6 and 7). These observations indicate that SICS inhibition in diabetic animals requires the removal of the entire stomach. It could be speculated that the stomach produces a circulatory and/or luminal substance that induces the increase in SICS observed in diabetic animals and that total gastrectomy removes this stimulatory substance.

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