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Treatment of the enhanced intestinal uptake of glucose in diabetic rats with a polyunsaturated fatty acid diet

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Intestinal absorption of most nutrients is enhanced in diabetic rats. We wished to test the hypothesis that manipulation of dietary fatty acids will modify enhanced uptake of glucose in rats with established streptozotocin-diabetes. Chow-fed control rats or animals with one week of streptozotocin-diabetes were continued on chow or were fed ad libitum for three weeks with semisynthetic isocaloric diets containing a high content of either essential polyunsaturated or non-essential saturated fatty acids. The jejunal and ileal in vitro uptake of varying concentrations of glucose was much higher in diabetic than control rats fed chow or the saturated fatty acid diet. In contrast, the enhanced uptake of this sugar was reduced or normalized in diabetic rats fed the polyunsaturated fatty acid diet. Feeding the polyunsaturated fatty acid diet was associated with increased brush-border membrane activity of alkaline phosphatase in diabetic jejunum and ileum, but neither the saturated fatty acid diet nor the polyunsaturated fatty acid diet altered brush-border membrane cholesterol or phospholipids in control or in diabetic rats. Mucosal surface area was similar in diabetic rats fed the saturated fatty acid diet or the polyunsaturated fatty acid diet. Thus, (1) feeding the polyunsaturated fatty acid diet diminishes the enhanced jejunal and ileal uptake of glucose in diabetic rats, and (2) the influence of the polyunsaturated fatty acid diet on uptake in diabetic rats was not explained by alterations in intestinal morphology or brush-border membrane content of cholesterol or phospholipids. This study suggests that manipulation of dietary lipids may play a role in the normalization of the enhanced intestinal glucose uptake in rats with established diabetes.

Introduction

A diet high in non-essential fatty acids (palmitic, stearic and oleic acids) is associated with altered intestinal transport which is not explained by variations in the animals' food intake, body weight gain, intestinal weight, effective resistance of the intestinal unstirred water layer, intestinal morphology, brush-border membrane cholesterol or phospholipid composition [1]. However, dietary changes may be associated with alterations in the phospholipid fatty acid composition of the brush-border membrane [2,3]. In streptozotocin-diabetic rats, there is enhanced intestinal uptake of many

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solutes, including sugars, amino acids and lipids [4–6]. This increased intestinal uptake can be modified by manipulation in dietary macronutrients [7,8], and by the injection of insulin or islet cell transplantation [9]. Feeding a diet high in essential polyunsaturated fatty acids prevents the enhanced uptake of glucose in diabetic rats when the dietary manipulation was performed before the animals were rendered diabetic with streptozotocin [10]. The present study was undertaken to test the hypothesis that variations in the fatty acid composition of the diet (a high essential polyunsaturated fatty acid diet versus a diet high in non-essential fatty acids) may be useful to treat the enhanced intestinal uptake of glucose in rats previously rendered hyperglycemic with streptozotocin.

Materials and Methods

1. Animals and diets

Guiding principles in the care and use of laboratory animals, approved by the Canadian Federation of Biological Societies and by the Council of the American Physiological Society, were observed in the conduct of this study. Female Wistar rats weighing 220–250 g were allowed ad libitum access to water and food until the morning of study. Drug-induced glucose intolerance was produced in the first group of rats by the intravenous administration of the β-cell cytotoxic agent streptozotocin (65 mg/kg). The second group served as non-diabetic controls and these animals were subjected to intravenous administration of bacteriostatic saline. The induction of glucose intolerance was assessed 3–4 days post-streptozotocin injection by the presence of hyperglycemia and glucosuria, using the glucose oxidase method. Control animals did not exhibit hyperglycemia or glucosuria. Blood glucose was repeated immediately before sacrificing the animals.

Animals were fed chow for one week, then fed one of three diets for a further three weeks: standard Purina® rat chow, or a semi-purified diet containing 20% (w/w) fat of either a high or low polyunsaturated-to-saturated fatty acid ratio [1]. The isocaloric semi-purified diets were nutritionally adequate, providing for all known essential nutrient requirements. The diet high in polyunsaturated fatty acids provided approx. 22% of calories and 55% of total fatty acids (% w/w) as C18 : 2($n-6$), whereas the diet high in saturated fatty acids provided approx. 2% of calories and 5% of total fatty acids as C18 : 2($n-6$). Animals were weighed at the beginning of the study, at the time of injection with streptozotocin, and just before the in vitro uptake studies were performed.

2. Probe and marker compounds

[^{3}H]Insulin (mol. wt. approx. 5000) was used as supplied by the manufacturer (ICN Biomedical Inc., Montreal, Quebec) to measure the adherent mucosal fluid volume. The concentration of ^{14}C-labelled probes D-glucose and D-galactose (Amersham Canada ltd., Oakville, Ontario) was varied from 1 to 20 mM.

3. Tissue preparation

Animals were killed by intraperitoneal injection of ketamine (500 mg/kg). A 15 cm length of proximal jejunum and distal ileum was rapidly removed and gently rinsed with 150 ml of cold saline, as described in detail elsewhere [4,6,11,12]. The intestine was opened along its mesenteric border, and the mucosal surface was washed carefully with cold saline to remove visible mucus and debris. Pieces of intestine were cut from the segments and tissue was mounted as flat sheets in the transport chambers. The chambers were placed in preincubation beakers containing oxygenated Krebs-bicarbonate buffer (pH 7.4) at 37 °C, and tissue discs were preincubated for 15 min to allow the tissue to equilibrate at this temperature. The transport chambers were then transferred to other beakers for specific experiments. These incubation beakers contained various concentrations (0.5–20 mM) of radiolabelled D-glucose. Preincubation and incubation solutions were mixed with circular magnetic bars at identical stirring rates which were precisely adjusted by means of a strobe light. Stirring rates were reported as revolutions per minute at which the stirring bar was driven. A stirring rate of 600 rpm was selected to achieve low effective resistance of the intestinal unstirred water layer [11,12].

4. Determination of uptake rates

After preincubation, the chambers were trans-

ferred to other beakers containing [^{3}H]inulin and various ^{14}C-labelled probe molecules in oxygenated Krebs bicarbonate (pH 7.4 at 37°C). After incubation of the discs in labelled solutions for 6 min, the experiment was terminated by removing the chamber and rinsing the tissue in cold saline for approx. 5 s. The exposed mucosal tissue was then cut out of the chamber with a circular steel punch, placed on glass slides and dried overnight in an oven at 55°C. The dry weight of the tissue was determined and the tissue was transferred to counting vials. The samples were saponified with 0.75 M NaOH, scintillation fluid was added and radioactivity was determined by means of an external standardization technique to correct for variable quenching of the two isotopes. The rate of glucose uptake was expressed as nmol/100 mg per min. Seven to ten animals were studied in each group. The significance of the difference between mean values was determined by analysis of variance and the unpaired *t*-test of diabetic versus control animals in each diet group.

5. Brush-border membrane lipid analyses

Published methods were used to measure the mucosal surface area, to isolate and purify brush-border membranes, and to assess their content of cholesterol, phospholipids, free fatty acids and bile acids [14–17].

Results

1. Characteristics of the animals

Control and diabetic animals fed the semisynthetic diets ate less than those fed chow (Table I). Diabetes was associated with an increase in food consumption regardless of diet. Diabetic animals on either semisynthetic diet lost weight when compared to control animals fed the same diets. Blood glucose levels were increased in the diabetic

TABLE I

EFFECT OF ALTERING DIETARY FAT COMPOSITION ON CHARACTERISTICS OF CONTROL AND DIABETIC RATS

	Control			Diabetic		
	chow diet	high polyunsaturated fatty acid diet	high saturated fatty acid diet	chow diet	high polyunsaturated fatty acid diet	high saturated fatty acid diet
Food consumption (g/day)	16.6 ±0.4	12.7 ±0.2 [a]	13.5 ±0.3 [a]	32.4 ±1.2 [c]	20.5 ±1.0 [a,c]	17.5 ±0.4 [a,b,c]
Body weight change (g/day)	0.80±0.08	0.89±0.08	0.93±0.06	0.42±0.14	−0.50±0.15 [c]	−0.31±0.19 [c]
Fasting blood glucose (mg/dl)	109 ±9	102 ±7	11 ±4	463 ±13 [c]	444 ±9 [c]	449 ±11 [c]
Jejunal dry weights (mg/unit serosal surface area)						
Mucosa	4.9 ±0.5	9.9 ±0.7 [a]	9.2 ±0.6 [a]	13.0 ±0.7 [c]	14.5 ±0.8 [c]	8.6 ±0.5 [a,b]
Submucosa	4.1 ±0.2	3.6 ±0.3	3.3 ±0.3	3.8 ±0.3	2.9 ±0.2	4.2 ±0.4
Total	9.0 ±0.5	13.4 ±0.7 [a]	12.2 ±0.6 [a]	14.2 ±1.7 [c]	17.4 ±0.9 [c]	13.1 ±0.7 [b]
Mucosa/Total intestinal wall	0.57±0.04	0.73±0.02 [a]	0.72±0.02 [a]	0.77±0.02 [c]	0.83±0.01 [a,c]	0.68±0.01 [a,b]
Ileal dry weights (mg/unit serosal surface area)						
Mucosa	1.7 ±0.3	2.4 ±0.3	1.9 ±0.3	3.4 ±0.4 [c]	2.3 ±0.3	5.1 ±0.6 [a,b,c]
Submucosa	1.5 ±0.1	2.4 ±0.3	1.5 ±0.1	1.7 ±0.2	1.9 ±0.1	2.2 ±0.1
Total	3.3 ±0.4	4.8 ±0.4 [a]	3.4 ±0.4 [b]	4.9 ±0.5 [c]	4.2 ±0.3	7.3 ±0.6 [a,b,c]
Mucosa/Total intestinal wall	0.51±0.03	0.50±0.05	0.53±0.03	0.65±0.07 [c]	0.55±0.03 [a]	0.68±0.03 [b,c]

[a] $P < 0.05$, high polyunsaturated fatty acid diet versus chow; high saturated fatty acid diet versus chow.
[b] $P < 0.05$, high saturated fatty acid diet versus high polyunsaturated fatty acid diet.
[c] $P < 0.05$, diabetic versus control.

animals, but not influenced by diet in either control or diabetic animals. The ratio of jejunal mucosa to entire intestinal wall of control animals was increased in animals fed the polyunsaturated fatty acid diet or the saturated fatty acid diet as compared to control animals fed chow. In diabetic animals, the ratio of jejunal mucosa/intestinal wall was increased and ileal percent mucosa was decreased in animals fed the polyunsaturated fatty acid diet as compared to those fed chow. The jejunal ratio of mucosa/intestinal wall was decreased in animals fed the saturated fatty acid diet as compared to those fed chow. Feeding the saturated fatty acid diet significantly decreased this ratio in the jejunum and increased the ratio of ileal mucosa/intestinal wall when compared to animals fed the polyunsaturated fatty acid diet.

The mucosal surface area was unaffected by diet in control animals. Jejunal and ileal mucosal surface area was decreased in diabetic animals fed the polyunsaturated fatty acid diet as compared to those fed chow (8.5 ± 0.9 versus 11.6 ± 0.9 mm^2/mm^2 serosal, respectively), but there was no difference in the jejunal mucosal surface area in diabetic animals fed the polyunsaturated fatty acid diet or the saturated fatty acid diet. The ileal mucosal surface area was also decreased in diabetic animals fed the saturated fatty acid diet as compared to those fed chow (data not shown), but again there was no difference between diabetic rats fed the saturated fatty acid diet or the polyunsaturated fatty acid diet (5.1 ± 0.3 versus 5.8 ± 0.3 mm^2/mm^2 serosal).

2. Composition of brush-border membranes

The jejunal and ileal brush-border membrane

TABLE II

EFFECT OF ALTERING DIETARY FAT SATURATION ON BRUSH-BORDER MEMBRANE MARKERS OF RAT JEJUNUM AND ILEUM

Marker assay	Control			Diabetic		
	chow diet	high polyunsaturated fatty acid diet	high saturated fatty acid diet	chow diet	high polyunsaturated fatty acid diet	high saturated fatty acid diet
Jejunum						
Wet weight (mg/cm length)	5 ± 7	37 ± 2 [a]	33 ± 2 [a]	66 ± 3 [c]	48 ± 4 [a,c]	41 ± 5 [a]
Protein (mg/g wet wt.)	1.81 ± 0.08	1.84 ± 0.09	1.78 ± 0.21	1.53 ± 0.16	1.85 ± 0.32	1.78 ± 0.14
Alkaline phosphatase						
U/g protein	1609 ± 157	1696 ± 177	1610 ± 202	1950 ± 124	2905 ± 203 [a,c]	2135 ± 170 [b]
Purification	6 ± 1	7 ± 2	7 ± 3	5 ± 1	7 ± 1	5 ± 1
Sucrase						
U/g protein	968 ± 32	678 ± 37 [a]	761 ± 44 [a]	1088 ± 109	967 ± 87 [c]	911 ± 56 [c]
Purification	15 ± 2	15 ± 2	18 ± 3	16 ± 3	14 ± 2	14 ± 4
Ileum						
Wet weight (mg/cm length)	38 ± 6	25 ± 1	24 ± 1 [a]	49 ± 2	38 ± 2 [a]	31 ± 1 [a,b,c]
Protein (mg/g wet wt.)	1.64 ± 0.08	1.80 ± 0.15	1.73 ± 0.13	1.75 ± 0.14	2.13 ± 0.58	2.24 ± 0.21 [c]
Alkaline phosphatase						
U/g protein	93 ± 10	229 ± 28 [a]	154 ± 15 [a]	140 ± 20 [c]	350 ± 68 [a]	311 ± 29 [a,c]
Purification	6 ± 1	7 ± 2	5 ± 2	4 ± 2	6 ± 2	6 ± 1
Sucrase						
U/g protein	358 ± 40	387 ± 37	398 ± 42	782 ± 60 [c]	691 ± 32	661 ± 67 [c]
Purification	20 ± 3	21 ± 5	23 ± 3	20 ± 4	17 ± 3	14 a± 6

[a] $P < 0.05$, high polyunsaturated fatty acid diet versus chow; high saturated fatty acid diet versus chow diet.

[b] $P < 0.05$, high saturated fatty acid diet versus high polyunsaturated fatty acid diet.

[c] $P < 0.05$, diabetic versus control.

TABLE III

EFFECT OF ALTERING DIETARY FAT SATURATION ON BRUSH-BORDER MEMBRANE LIPID COMPOSITION OF RAT JEJUNUM

Lipid (nmol/mg protein)	Control			Diabetic		
	chow diet	high polyunsaturated fatty acid diet	high saturated fatty acid diet	chow diet	high polyunsaturated fatty acid diet	high saturated fatty acid diet
Total free fatty acids	414 ±31	506 ±43	438 ±30	269 ±23 [c]	435 ±34 [a]	305 ±23 [b,c]
Total bile acids	0.6± 0.2	0.4± 0.9	0.8± 0.3	0.7±0.2	0.7± 0.3	1.3± 0.3
Total phospholipid	254 ±30	276 ±33	331 ±27	299 ±31	357 ±45	355 ±42
Cholesterol						
Total	279 ±16	280 ±14	280 ±19	282 ±15	288 ±35	266 ±19
Free	262 ±15	256 ±12	264 ±14	262 ±12	276 ±34	239 ±20
Esters	26 ± 4	18 ± 3	19 ± 9	25 ± 5	21 ± 17	24 ±12
Phospholipid/ Cholesterol	0.9± 0.1	1.0± 0.1	1.2±0.1	1.0± 0.1	1.3± 0.2	1.3± 0.2

[a] $P < 0.05$, high polyunsaturated fatty acid diet versus chow; high saturated fatty acid diet versus chow.
[b] $P < 0.05$, high saturated fatty acid diet versus high polyunsaturated fatty acid diet.
[c] $P < 0.05$, diabetic versus control.

alkaline phosphatase and sucrase specific activities were higher in diabetic as compared with control animals fed the polyunsaturated fatty acid diet, saturated fatty acid diet or chow (Table II). Comparable purity of the brush-border membranes in the different treatment groups is suggested by the

TABLE IV

EFFECT OF ALTERING DIETARY FAT SATURATION ON BRUSH-BORDER MEMBRANE LIPID COMPOSITION OF RAT ILEUM

Lipid (nmol/mg protein)	Control			Diabetic		
	chow diet	high polyunsaturated fatty acid diet	high saturated fatty acid diet	chow diet	high polyunsaturated fatty acid diet	high saturated fatty acid diet
Total free fatty acids	509 ±38	446 ±62	427 ±26	464 ±37	420 ±40	344 ±33
Total bile acids	0.7± 0.3	1.1± 0.5	0.9± 0.4	1.0± 0.4	1.4± 0.5	1.2± 0.4
Total phospholipids	172 ±18	168 ±27	156 ±27	279 ±29 [c]	277 ±54	234 ±43
Cholesterol						
Total	315 ±22	289 ±24	260 ±34	340 ±17	283 ±15	300 ±29
Free	295 ±20	257 ±24	262 ±22	314 ±18	258 ± 9	286 ±30
Esters	26 ± 7	21 ± 7	29 ± 8	27 ± 8	29 ±11	17 ±10
Phospholipid/ cholesterol	0.6± 0.1	0.6± 0.1	0.6± 0.1	0.8± 0.1	1.0± 0.2	0.8± 0.1

$P > 0.05$, high polyunsaturated fatty acid diet versus chow; high saturated fatty acid diet versus chow.
$P > 0.05$, high saturated fatty acid diet versus high polyunsaturated fatty acid diet.
[c] $P < 0.05$, diabetic versus control.

finding that the change in specific activity of these enzymes with purification of the brush-border membranes was similar in the control and the diabetic animals and in the three dietary treatment groups (Table II) and by the finding of the similar absence of DNA (none detected) and β-glucuronidase activity (< 1 U/g protein) in the preparations. In the jejunum the brush-border membrane content of total free fatty acids were lower in diabetic than in control rats fed the polyunsaturated fatty acid diet, saturated fatty acid diet or chow (Table III). The brush-border membrane total free fatty acids was higher in diabetic rats fed the polyunsaturated fatty acid diet than in those fed the saturated fatty acid diet or chow. Neither diet nor diabetes significantly influenced the jejunal brush border membrane content of total phospholipid, cholesterol or the ratio of phospholipid/cholesterol. Ileal brush-border membrane lipid content was not influenced

TABLE V

EFFECT OF ALTERING DIETARY FAT SATURATION ON BRUSH-BORDER MEMBRANE PHOSPHOLIPID COMPOSITION OF RAT JEJUNUM

Phospholipid	Control			Diabetic		
	chow diet	high polyunsaturated fatty acid diet	high saturated fatty acid diet	chow diet	high polyunsaturated fatty acid diet	high saturated fatty acid diet
Choline						
Sphingomyelin (%)	17.8± 2.0	19.4± 1.8	18.3± 1.6	21.6± 1.3	20.4± 2.2	19.8± 2.2
nmol/mg protein	40.6± 6.0	38.0± 5.1	54.2± 7.1	60.8± 6.9 [c]	58.2± 9.2	60.2± 7.7
Lysolecithin (%)	1.5± 0.8	0.9± 0.3	1.6± 0.6	0.6± 0.3	0.1± 0.1	0.5± 0.3
nmol/mg protein	2.4± 1.2	1.6± 0.7	3.2± 0.3	1.8± 0.9	0.4± 0.4	2.0± 1.2
Lecithin (%)	50.2± 1.9	50.6± 1.5	49.3± 2.9	46.4± 2.4	45.1± 1.9 [c]	47.1± 2.1
nmol/mg protein	127.9±14.3	126.0±16.7	161.9± 20.2	155.0±19.0	147.7±20.6	168.2±21.1
Total choline (%)	69.0± 3.9	70.8± 2.8	69.2± 3.9	68.6± 2.9	65.6± 3.6	67.4± 2.9
nmol/mg protein	163.9±19.3	170.3±22.6	227.0±27.6	191.9±20.2	214.0±30.1	240.0±30.2
Amine						
Phosphatidyl-serine (%)	2.4± 0.6	1.6± 0.6	2.2± 0.6	2.2± 0.4	2.9± 0.8	0.9±0.4 [b]
nmol/mg protein	6.4± 1.7	3.5± 1.4	6.7± 1.9	7.0± 1.8	7.4± 2.5	3.8± 1.8
Lysophosphatidyl-ethanolamine (%)	3.0± 0.6	5.0± 0.9	2.2± 0.5 [b]	3.5± 0.8	2.4± 0.7	6.0± 1.5 [c]
nmol/mg protein	8.9± 2.4	13.6± 3.0	7.2± 1.8	9.0± 2.0	7.4± 2.5	17.2± 5.3
Phosphatidyl-ethanolamine (%)	24.4± 2.9	18.2± 2.8	19.6± 2.6	22.4± 3.0	22.9± 3.5	21.5± 2.6
nmol/mg protein	64.3±13.3	54.7±12.2	60.7± 6.5	60.9±15.0	86.9±12.1	68.5±11.0
Total amine (%)	27.2± 3.9	24.8± 2.8	24.0± 2.8	28.2± 3.0	28.2± 3.4	28.3± 2.5
nmol/mg protein	73.5±15.3	67.3±14.0	74.6± 7.2	87.2±18.6	106.5±12.7	117.2±15.9 [c]
Other						
Phosphatidic acid (%)	0.4± 0.3	0.6± 0.4	1.1± 1.0	0.3± 0.3	n.d.	0.2± 0.2
nmol/mg protein	1.7± 1.3	1.4± 1.0	0.5± 0.4	1.1±1n2.2	n.d.	0.7± 0.7
Phosphatidyl-inositol (%)	2.7± 0.9	3.4± 0.7	6.2± 1.0 [a,b]	2.8± 1.0	3.4± 0.8	4.2± 0.6
nmol/mg protein	4.2± 1.4	7.7± 1.9	17.4± 2.9 [a,b]	7.6± 2.3	12.2± 3.8	16.6± 3.1
Choline/Amine	2.6± 0.4	3.0± 0.4	2.5± 0.4	2.4± 0.3	2.5± 0.4	2.6± 0.3

[a] $P < 0.05$, high polyunsaturated fatty acid diet versus chow; high saturated fatty acid diet versus chow.
[b] $P < 0.05$, high saturated fatty acid diet versus high polyunsaturated fatty acid diet.
[c] $P < 0.05$, diabetic versus control
[d] n.d., not detected.

by diet or diabetes except for a diabetes-associated increase in total phospholipids in animals fed chow (Table IV). Jejunal brush-border membrane phosphatidylinositol content was increased in control animals fed the saturated fatty acid diet as compared with those fed the polyunsaturated fatty acid diet or chow (Table V). Diet did not influence phospholipid composition of jejunal or ileal brush-border membrane of diabetic animals (Tables V and VI). Diabetes was associated with an increase in jejunal brush-border membrane total phospholipids in animals fed the saturated fatty acid diet but this did not affect the choline/amine phospholipid ratio. Ileal brush-border membrane total choline content was increased in diabetic animals fed chow due to an increase in phosphatidylcholine (PC). This increase did not, however, significantly affect the ratio of choline/amine phospholipids. An increase in ileal brush-border membrane amine phospholipids observed in diabetic animals fed S resulted in a significantly reduced choline/amine phospholipid ratio.

TABLE VI

EFFECT OF ALTERING DIETARY RAT SATURATION IN BRUSH-BORDER MEMBRANE PHOSPHOLIPID COMPOSITION OF RAT ILEUM

Phospholipid	Control			Diabetic		
	chow diet	high polyunsaturated fatty acid diet	high saturated fatty acid diet	chow diet	high polyunsaturated fatty acid diet	high saturated fatty acid diet
Choline						
Sphingomyelin (%)	10.2± 2.3	19.0± 3.8	22.5± 2.4	24.7± 2.6	22.3± 2.2	20.7± 1.0
nmol/mg protein	34.0± 4.3	30.3± 7.7	36.9±13.1	53.0± 7.2	49.7± 5.3	52.3±10.8
Lysolecithin (%)	1.6± 0.6	0.9± 0.9	1.6± 0.6	2.5± 1.0	1.8± 0.7	1.4± 0.9
nmol/mg protein	3.1± 1.0	1.8± 1.2	4.1± 1.7	6.4± 2.2	4.1± 1.7	1.8± 1.1
Lecithin (%)	45.2± 4.3	47.2± 7.1	43.4± 3.0	38.1± 1.6	36.7± 2.3	38.3± 2.4
nmol/mg protein	65.6± 6.4	94.5±13.4	78.5±13.1	95.5± 4.7 [c]	82.3± 8.7	97.3±11.3
Total choline (%)	66.0± 5.0	67.1± 6.3	67.8± 1.6	65.3± 4.1	60.7± 4.5	60.4± 1.8 [c]
nmol/mg protein	98.8±11.5	132.6±14.5	129.6±23.8	161.6± 5.6 [c]	136.1±14.4	156.7±22.5
Amine						
Phosphatidyl-serine (%)	3.7± 1.3	2.9± 1.2	3.3± 1.8	3.1± 0.6	5.8± 1.5	4.2± 1.0
nmol/mg protein	3.5± 1.4	4.4± 2.1	3.2±1.6	7.9±1.6	8.6± 3.6	7.4± 2.5
Lysophosphatidyl-ethanolamine (%)	4.1± 1.7	2.2± 2.2	2.5± 1.0	2.4± 1.6	2.6± 1.0	4.3± 1.6
nmol/mg protein	3.1± 1.44	9.0± 5.8	2.9± 1.2	2.5± 1.0	5.6± 2.3	4.9± 3.1
Phosphatidyl-ethanolamine (%)	17.3± 1.9	17.2± 3.8	19.4± 1.8	24.8± 3.3	23.3± 2.7	28.1± 2.5 [c]
nmol/mg protein	35.6±10.9	36.2± 7.0	30.8± 9.3	62.7±10.5	60.7±10.9	73.9±13.7 [c]
Total amine (%)	28.4± 4.5	27.5± 7.0	25.2± 2.6	30.3± 4.1	35.3± 4.0	36.6± 2.3 [c]
nmol/mg protein	49.0±14.3	56.2±11.7	38.6± 8.8	87.3±11.0	79.2±11.4	85.3±19.4
Other						
Phosphatidic acid (%)	1.4± 0.9	2.2± 0.6	1.4± 1.0	1.5± 0.7	0.9± 0.6	0.8± 0.8
nmol/mg protein	2.5± 2.3	3.1± 1.1	3.2± 2.4	5.2± 2.3	2.4± 1.6	2.5± 1.7
Phosphatidyl-inositol (%)	4.1± 1.2	3.3± 1.5	5.6± 1.5	2.0± 0.7	3.1± 1.5	2.2± 0.6 [c]
nmol/mg protein	3.8± 1.0	6.4± 2.0	11.0± 4.7	5.1± 2.0	3.7± 1.2	4.4± 1.8
Choline/Amine	2.4± 0.4	2.2± 0.5	2.8± 0.3	2.0± 0.2	1.9± 0.3	1.8± 0.2 [c]

$P > 0.05$, high polyunsaturated fatty acid diet versus chow; high saturated fatty acid diet versus chow.
$P > 0.05$, high saturated fatty acid diet versus high polyunsaturated fatty acid diet.
[c] $P < 0.05$, diabetic versus control.

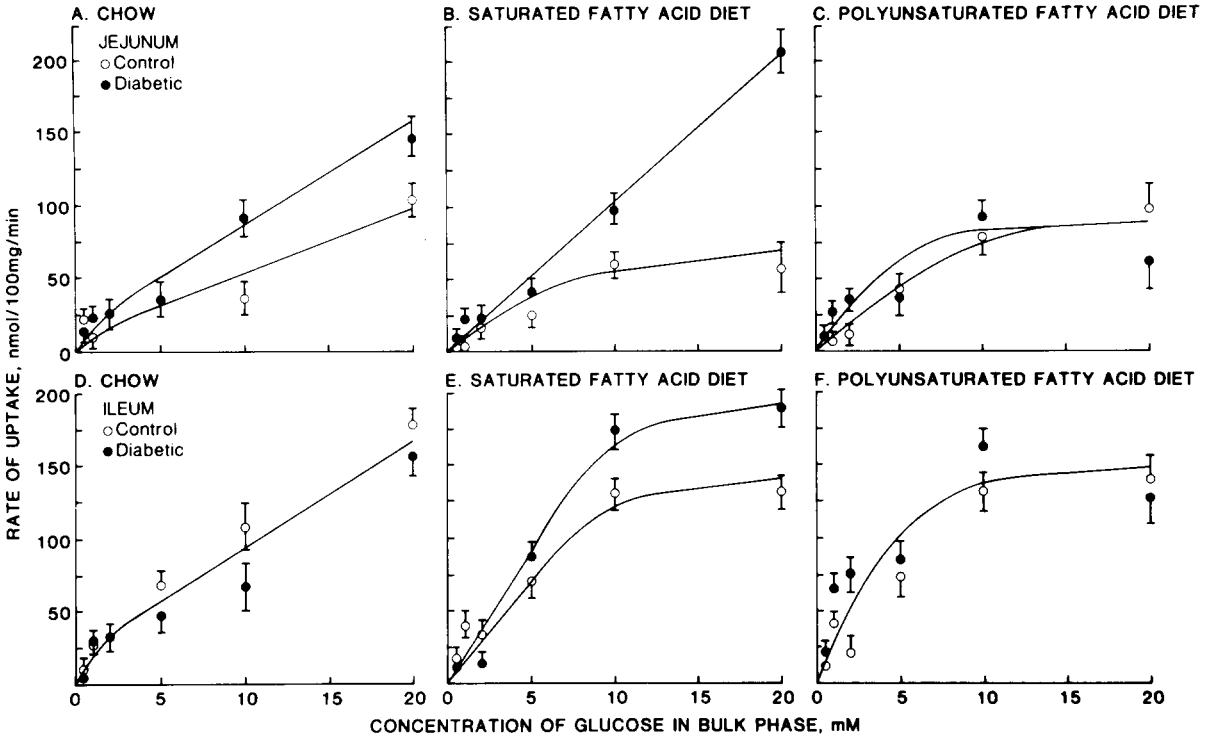

Fig. 1. Effect of dietary fatty acid saturation on jejunal and ileal uptake of glucose in diabetic rats. The bulk phase was stirred at 600 rpm to reduce the effective thickness of the intestinal unstirred water layer. The concentration of sugar was varied from 1 to 20 mM. Each point represents the mean ± S.E. of the results from 7–10 animals.

3. Uptake

In rats fed chow, glucose uptake in the jejunum was greater in diabetic than in control rats (Fig. 1A). The discrepancy between diabetic versus non-diabetic control rats was even greater for animals fed the saturated fatty acid diet (Figs. 1B and 1E), whereas no difference in glucose uptake was noted between diabetic and control rats fed the polyunsaturated fatty acid diet (Figs. 1C and 1F).

Discussion

Despite the presence of established and pre-existing intestinal functional abnormalities, the polyunsaturated fatty acid diet was capable of normalizing the jejunal and ileal uptake of glucose (Fig. 1). Feeding the polyunsaturated fatty acid diet also prevented the subsequent development of intestinal transport abnormalities in diabetic rats [10]. Changes in the animals' food intake, weight gain, or intestinal morphology did not explain this improved intestinal transport in animals fed the polyunsaturated fatty acid diet (Table I). Cholesterol/phospholipid ratio of the jejunal and ileal brush border membrane did not differ between control animals fed chow, the saturated fatty acid diet or the polyunsaturated fatty acid diet (Tables III and IV). This confirms an earlier study in non-diabetic animals [1]. Diabetes itself did not alter the brush border membrane lipid composition: no change in the choline/amine phospholipid ratio was observed in control and diabetic animals fed the polyunsaturated fatty acid diet or chow. When animals were fed the saturated fatty acid diet only the ileal choline/amine phospholipid ratio was reduced with diabetes. Thus, successful treatment of the enhanced intestinal uptake of glucose with the polyunsaturated fatty acid diet was unlikely to be due to changes in brush-border membrane amount or type of phospholipids, or the ratio of cholesterol to phospholipids. Modifying the dietary content of lipid is associated with altered brush-border membrane

phospholipid fatty acyl components in non-diabetic rats [2,3].

There appears to be an association between alterations in membrane lipid fluidity with changes in transport functions although this association is variable [3,7,8,10,18–22]. The results of present experiments, taken together with prior data support the contention that dietary lipid manipulations can influence important intestinal functions, including transport processes, but the mechanism of this effect remains to be established. It remains to be determined whether the therapeutic effect of feeding the polyunsaturated fatty acid diet to diabetic rats is achieved by alterations in the fatty acyl components of the brush border membrane phospholipids. This is a possibility, since studies using other membrane systems have suggested that deficiency of membrane arachidonic acid occurs in diabetes, possibly due to the impaired conversion of linoleic acid to arachidonic acid as a result of depressed desaturase enzyme activity [23,24]. Thus, manipulations in the dietary content of essential fatty acids may be useful to prevent or to treat the altered intestinal transport function in diabetic rats, but the exact mechanism(s) involved in these alterations remain unclear and appear complex. It is now necessary to perform long-term studies of the effect of feeding the polyunsaturated fatty acid diet in diabetic rats. If such studies demonstrate superior control of hyperglycemia or clinical complications, then it would be appropriate to consider the design of analogous dietary studies in diabetic patients.

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