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Effects of Acarbose on Food Intake, Body Weight and Fat Depots in Lean and Obese Rats

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GLICK, Z. AND G. A. BRAY. *Effects of acarbose on food intake, body weight and fat depots in lean and obese rats.* PHARMACOL BIOCHEM BEHAV 19(1) 71–78, 1983.—Effects of dietary acarbose at 0, 5, 15 and 50 mg per 100 g diet on food intake and body weight were studied for two months in female rats. The relationships between diet composition, the drug dose and the type of obesity were examined. In lean rats receiving the drug in a high carbohydrate diet (70 Cal.%), mean food intake was similar to control at 5 and 15 mg dietary levels, but was significantly increased at 50 mg. Body weight was significantly reduced only at the 15 mg level. In VMH obese rats receiving the drug in a high carbohydrate diet, it resulted in significant reductions in food intake at the 15 and 50 mg drug levels and in significant reductions in body weight at all three drug levels. In dietary obese rats receiving the drug in a high carbohydrate diet and also in a 32% sucrose drinking solution, food intake and body weight were significantly reduced at each of the drug levels. In dietary obese rats receiving the drug in a high fat diet (70 Cal.%), acarbose at all levels resulted in only small and usually not significant changes in either food intake or body weight. Weight of fat depots were significantly reduced at the 50 mg dietary level in all instances where a high carbohydrate diet was used while at the 5 mg level, fat depots were reduced only in the VMH obese, with the sucrose obese showing a trend for reduced depots. Acarbose in the high fat diet resulted in no significant changes in weight of fat depots. These data indicate that acarbose in a high carbohydrate diet is effective in reducing weight of rats, and that obese usually show a greater reduction in food intake and body weight than lean rats.

Acarbose α-Glucosidase inhibitor Dietary obese Hypothalamic-obese Food intake Adiposity

ACARBOSE is an α-glucosidase inhibitor which inhibits the intestinal digestion of starch, sucrose and other sugars [13]. Acarbose, as well as other inhibitors obtained from microbial sources, is an oligosaccharide containing an unsaturated cyclitol unit bound to an amino sugar [13,14]. In humans [5, 6, 11, 12, 13, 17] and in experimental animals [10, 11, 12, 13], α-glucosidase inhibitors given orally reduce serum glucose and insulin. These inhibitors also reduce serum triglycerides in humans [5,6] and in rats [12,13].

The effect of acarbose on energy balance has been studied using a high carbohydrate diet. Acarbose results in a dose dependent reduction in food intake, body weight and body fat of Zucker obese rats [13]. However, in normal rats, it results in a significant increase in food intake, but in a decrease in body weight [1,3]. These data suggest that host factors play an important role in the direction and the extent of the effect of acarbose on parameters of energy balance. In the present study, responses to various levels of dietary acarbose were examined in normal rats and in three types of obese rats: (1) In hypothalamic (VMH) obese rats, (2) In rats made obese, by consumption of a high sucrose diet, (3) In rats made obese by consumption of a high fat diet.

METHOD

Animals, Production of Obesities and Housing

A total of 96 female Sprague Dawley rats (Simonsen, Gilroy, CA), about 200 g initial weight, were used in four separate experiments. In each experiment, the effect of the drug was tested on one type of rat. Altogether four types of rats were tested: (1) normal (non-obese), (2) VMH-obese, (3) dietary-obese, where obesity was produced by consumption of a high sucrose diet (high sucrose diet-obese), (4) dietary-obese, where obesity was produced by consumption of a high fat diet (high fat diet-obese).

Hypothalamic obesity was proudced by knife cuts as described by Sclafani *et al.* [16]. Following lesioning, the rats were maintained on Purina Lab Chow (Ralston Purina) pellets for two months before the drug experiment began. One type of dietary obesity was produced by providing rats with a bottle containing a 32% sucrose solution in addition to the water bottle [7] for two months. The solid diet given to these rats was Purina Lab Chow. A second type of dietary obesity was produced by maintaining the rats for two months on a high fat diet. This diet was prepared by weighing into a food

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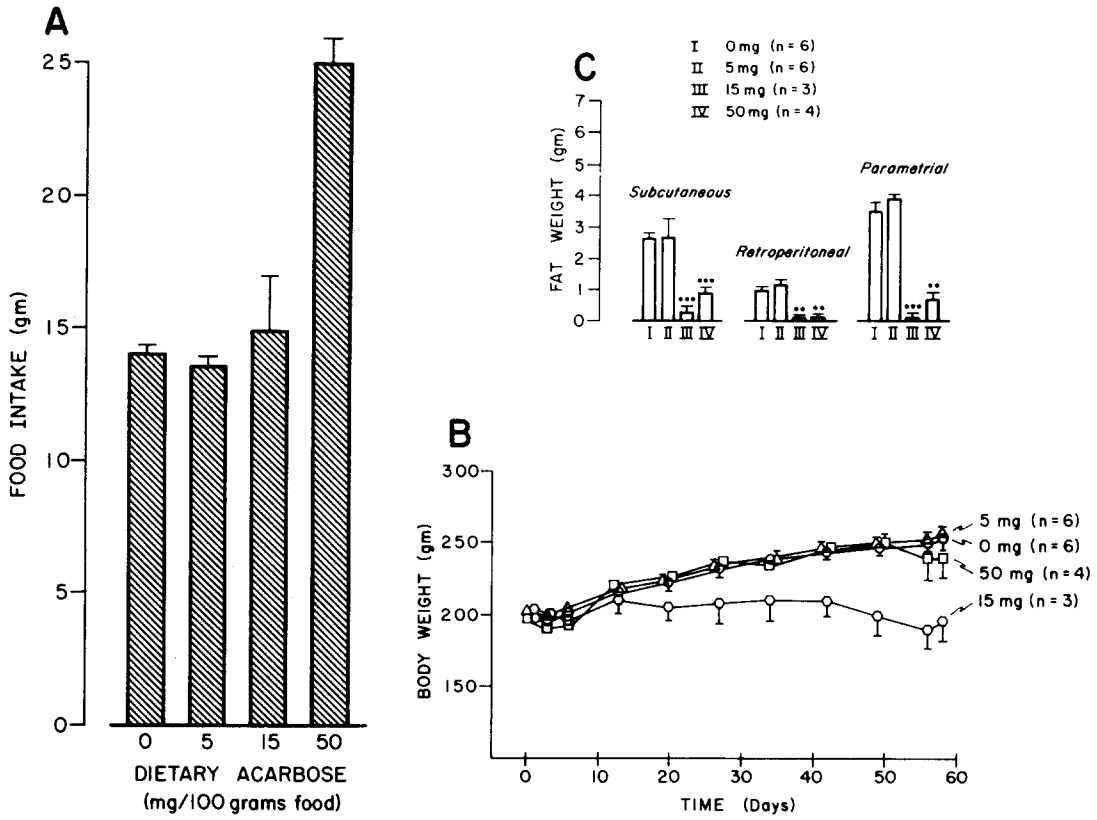

FIG. 1. Effect of dietary acarbose on mean daily food intake (1A), body weight (1B) and weight of fat depots (1C) of normal rats. Data are mean±SE. Asterisks indicate level of significance between treatment and control $^{**}p<0.01$; $^{***}p<0.001$. The increase in food intake at the 50 mg drug level is highly significant ($p<0.0001$). Only at the 15 mg drug level (1B) is body weight significantly reduced ($p<0.02$). Detailed analysis is shown in Table 2.

cup 100 g ground Purina Lab Chow, and 60 g (Crisco) hydrogenated oil. The food cups were put in the oven at 70°C until the Crisco melted evenly into the solid powder. During the development of obesity, all rats were caged in groups of four. The diets used to produce obesity were not the same diets used in the drug experiments. The latter diets will be described below.

Prior to the drug experiment, all rats were caged individually and were allowed to accustom themselves to their respective semi-synthetic basal diets for one week. Throughout the study, the rats were maintained at 24°C±2 with lights on from 0700 to 1800 hr.

Experimental Semi-Synthetic Diets

Two types of semisynthetic diets were used in the drug experiment: A high carbohydrate diet and a high fat diet. The composition of the diets is described in Table 1. The normal, the VMH obese, and the high sucrose diet obese rats, all received the high carbohydrate diet. The latter animals also continued to have access to a bottle containing a 32% sucrose solution. The rats whose obesity was produced on a high fat diet (made of Purina Lab Chow and Crisco), continued to receive a high fat diet whose composition is described in Table 1.

Dietary Level of Acarbose

Acarbose, provided through the generosity of Miles Laboratories (New Haven, CT), was mixed at levels of 5, 15 or 50 mg of drug per 100 g (high carbohydrate or high fat) diet. The drug was also dissolved in the 32% drinking solution in the same concentrations per g of sucrose as in the diet. The high-fat diet was prepared by first mixing the drug into the fat-free powder. This powder was then added to a mixer bowl containing an appropriate weight of Crisco, previously melted by gentle heating. The liquified Crisco was then mixed with the fat-free powder for about 5 minutes, the semi-solid mix cooled in a freezer, and then remixed to form a homogenous mixture of a semi-solid consistency.

Measurements

Food intake was measured to the nearest 0.5 g every 3–4 days and body weight was measured to the nearest gram once every week. Diarrhea was monitored throughout the study by expressing it as a percentage of soft or liquid stool in each rat. At the termination of each experiment, weight of right side fat depots were determined at three sites: subcutaneous (including inguinal and abdominal depots), retroperitoneal and parametrial.

Data Analysis

Data from each experiment were analyzed separately. Food intake and changes in body weight were analyzed by ANOVA for repeated measurements, and weight of the fat depots by a t-test, using the Bonferroni approach for multi-

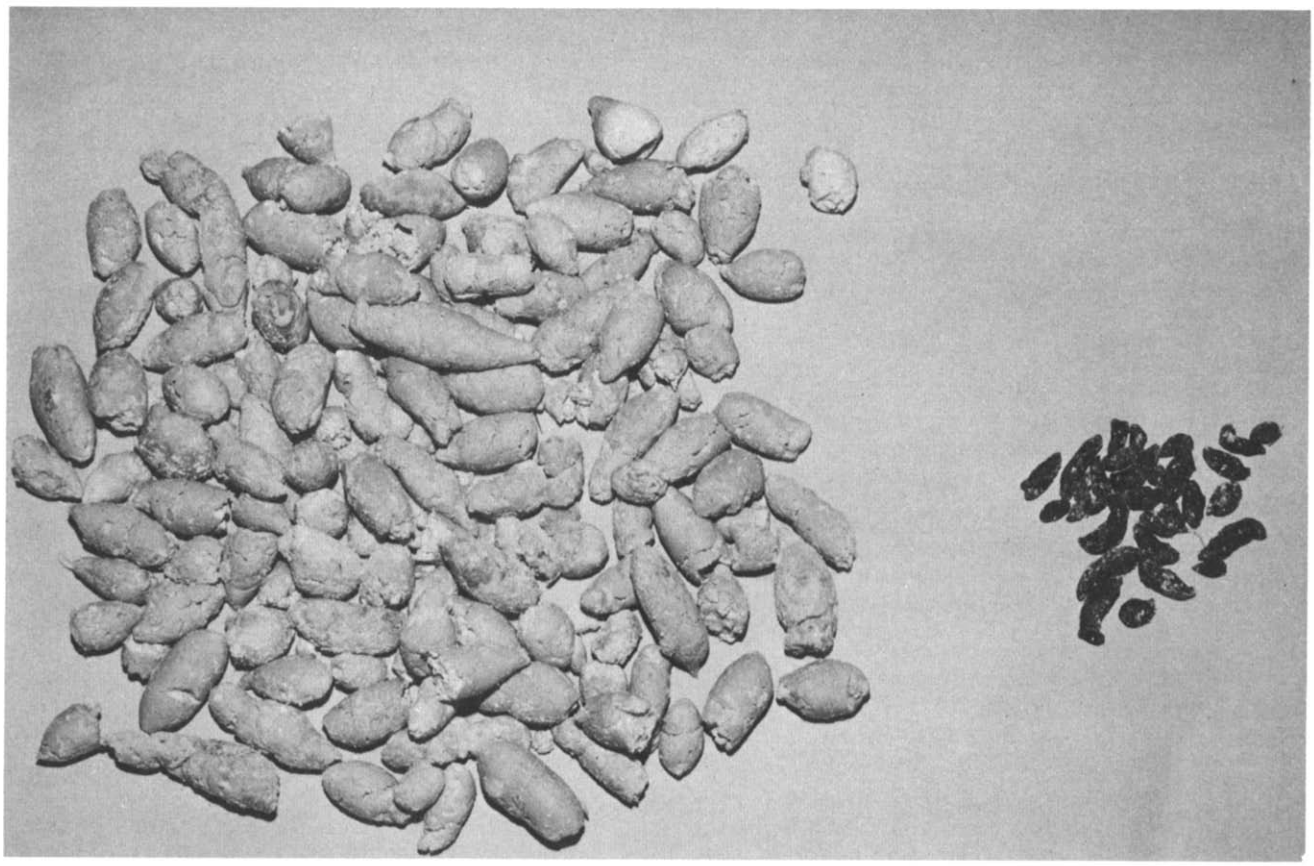

FIG. 2. A 60 hr fecal collection from a control and from a rat receiving 50 mg acarbose per 100 g diet. Both received a high carbohydrate diet.

TABLE 1
COMPOSITION OF THE DIETS*

	High Fat g/100 g diet	High Carbohydrate g/100 g diet
Casein (vitamin free)	32.80	22.00
Salt Mix (Rogers-Harper)	5.96	4.00
Non-nutritive bulk	2.98	2.00
Vitamin Mix (AOAC)	1.49	1.00
dl-Methionine	0.15	0.10
Starch (Corn)	12.66	67.90
Crisco (hydrogenated oil)	43.96	3.00

*All but the Crisco oil were purchased from Teklad Test Diets, Madison, WI.

comparisons between treatments [8]. Because mortalities were encountered that in some instances reduced the number of survivors to 3 or 4 rats per group, the data on food intake and body weight were also analyzed for the initial phase of these studies, i.e., the first 2 to 4 weeks, and (with one exception) before the first mortality occurred. These data have been summarized separately.

RESULTS

Experiment 1: Normal Rats–High Carbohydrate Diet

Food intake (Fig. 1A, Table 2). The overall effect of the drug treatment was significant ($p<0.0001$). Mean daily food intake of rats receiving 5 or 15 mg acarbose per 100 g diet was not significantly different from control, but at a 50 mg dietary level, acarbose resulted in a significant increase in daily food intake ($p<0.0001$).

Body weight (Fig. 1B, Table 2). The overall effect of the drug treatment was significant ($p<0.005$). Only at the 15 mg acarbose per 100 g diet was body weight significantly smaller than control ($p<0.02$). At the 5 and at the 50 mg dietary levels of the drug, body weight was very similar to control values throughout the study.

Body fat (Fig. 1C). The effect of acarbose on body fat was significantly different from control in rats fed both the 15 mg and the 50 mg acarbose per 100 g diet at each of the fat depots examined. However, the differences between the weight of depots at the 15 mg and at the 50 mg dietary levels of the drug were not statistically significant.

Among the rats fed 15 mg acarbose per 100 g diet, three rats died at days 23, 26 and 44. At the 50 mg dietary level, two rats died at days 10 and 47. Diarrhea was most frequent at the 15 mg level, while it was much less evident at the 50 mg level. The fecal pellets at the 50 mg level were very large, light in color and abundant (Fig. 2).

TABLE 2
ANALYSIS OF VARIANCE OF THE DATA ON THE EFFECTS OF ACARBOSE ON FOOD INTAKE AND ON CHANGES IN BODY WEIGHT PRESENTED IN FIGS. 1, 3, 4 AND 5

Type of rat		Effect of treatment	Comparisons by levels of acarbose: 0 mg vs. 5 mg	0 mg vs. 15 mg	0 mg vs. 50 mg
		Food Intake			
Normal	F	39.66			133.54
	df	(3,15)			(1,8)
	$p<$	0.0001	NS	NS	0.0001
VMH obese	F	7.11	4.28	33.46	10.48
	df	(3,15)	(1,10)	(1,8)	(1,7)
	$p<$	0.004	0.07	0.005	0.02
Dietary obese high sucrose diet	F	6.01	11.08	13.17	10.42
	df	(3,18)	(1,10)	(1,10)	(1,8)
	$p<$	0.006	0.01	0.005	0.02
Dietary obese high fat diet	F			20.43	
	df			(1,10)	
	$p<$	NS	NS	0.002	NS
		Body Weight			
Normal	F	6.65		10.44	
	df	(1,15)		(1,7)	
	$p<$	0.005	NS	0.02	NS
VMH obese	F	26.55	10.67	98.17	105.63
	df	(3,15)	(1,10)	(1,8)	(1,7)
	$p<$	0.001	0.009	0.0001	0.0001
Dietary obese high sucrose	F	15.49	5.22	17.18	34.37
	df	(3,18)	(1,10)	(1,10)	(1,8)
	$p<$	0.0001	0.05	0.003	0.005
Dietary obese high fat obese	F				
	df				
	$p<$	NS	NS	NS	NS

Experiment 2: VMH Obese Rats–High Carbohydrate Diet

Food intake (Fig. 3A, Table 2). The overall effect of the treatment was significant ($p<0.004$). Average daily food intake was significantly smaller than control at the 15 mg ($p<0.0005$) and at the 50 mg ($p<0.02$) drug levels. A trend for suppression of food intake at the 5 mg dietary level was also noted ($p<0.07$).

Body weight (Fig. 3B, Table 2). The overall effect of the treatment was highly significant ($p<0.0001$). Compared to controls, weights were significantly reduced at the 5 mg ($p<0.009$), at the 15 mg ($p<0.0001$) and at the 50 mg ($p<0.0001$) drug levels.

Body fat (Fig. 3C). Weight of the fat depots were significantly smaller than controls at each of the dietary drug levels. However, the differences among the various drug levels were not statistically significant in any of the three sites.

At the 15 mg acarbose per 100 g diet, two rats died at days 44 and 45. At the 50 mg level, three rats died at days 19, 26 and 30. Some diarrhea was evident at the 5 mg drug level, it was most evident at the 15 mg level, with some diarrhea again at the 50 mg acarbose level. Feces were light in color and abundant, especially at the 50 mg level.

Experiment 3: High Sucrose Diet Obese Rats–High Carbohydrate Diet + Sucrose Drinking Solution

Sum of food and sucrose intakes (Fig. 4A, Table 2). The overall drug effect on consumption of the sum of food and sucrose was significant ($p<0.006$). A significant reduction in intake was noted at each level of the drug, i.e., at the 5 mg ($p<0.01$), at the 15 mg ($p<0.005$) and at the 50 mg ($p<0.02$) drug levels. The differences among the various drug levels were not statistically significant.

Food intake (Fig. 4A). The overall effect of the treatment was not significant. Average daily food intake was not significantly different from control at any of the drug levels, though at the 15 mg level, there was a trend for a reduced food intake, $F(1,10)=4.59$, $p<0.06$.

Sucrose intake (Fig. 4A). There was a highly significant overall effect of treatment on sucrose intake, $F(3,18)=9.51$,

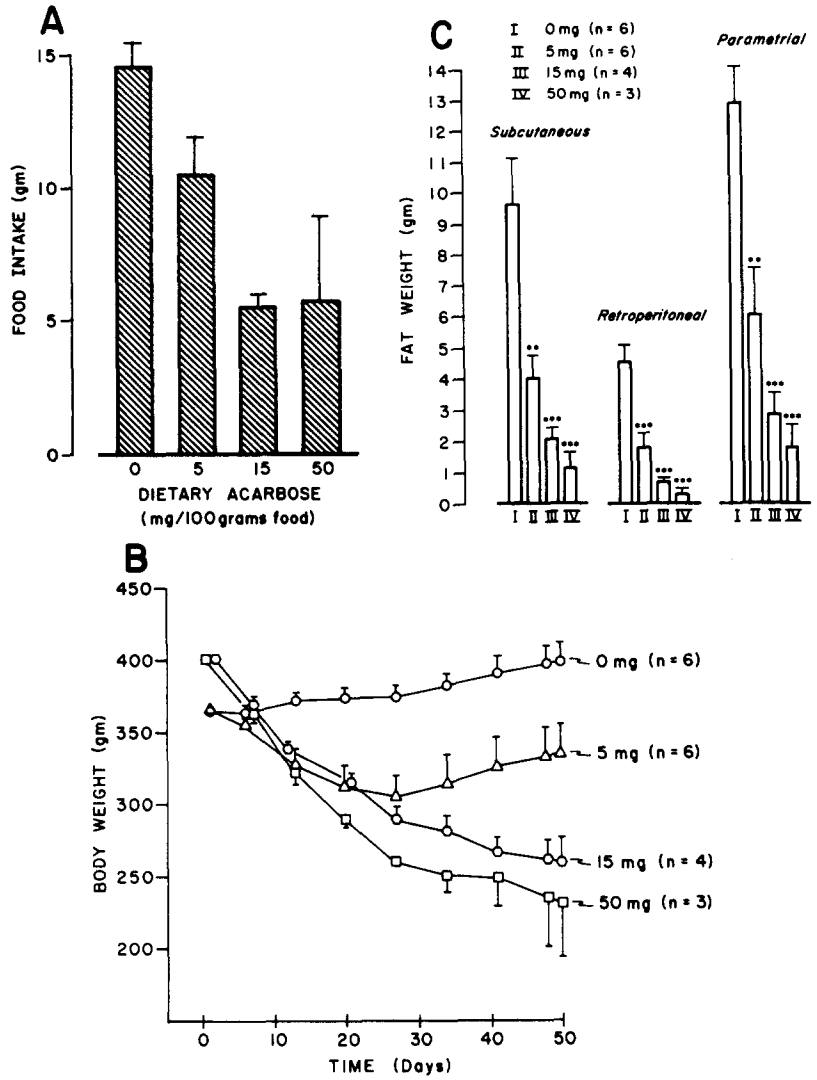

FIG. 3. Effect of dietary acarbose on food intake (3A), body weight (3B) and weight of fat depots (3C) of VMH obese rats. Data are mean±SE. $^{**}p<0.01$; $^{***}p<0.001$. Food intake is significantly reduced at the 15 mg ($p<0.005$) and at the 50 mg ($p<0.02$) dietary levels of acarbose. Body weights are significantly reduced at all three levels: $p<0.009$; $p<0.0001$; and $p<0.0001$ at 5 mg, 15 mg and 50 mg respectively. Detailed analysis is shown in Table 2.

$p<0.0006$. The effect was significant at the 15 mg, $F(1,10)=5.26$, $p<0.05$, and at the 50 mg, $F(1,8)=33.73$, $p<0.0005$, acarbose levels. The suppressive effect of acarbose on sucrose intake at the 50 mg level was also significantly greater than at the 15 mg drug level, $F(1,8)=30.31$, $p<0.0006$.

Body weight (Fig. 4B, Table 2). The overall effect of the treatment was highly significant ($p<0.0001$). Weight changes were significantly different from control at the 5 mg ($p<0.05$), at the 15 mg ($p<0.003$) and at the 50 mg ($p<0.005$) drug levels.

Body fat (Fig. 4C). Fat pad weights were significantly smaller than control in each of the three depots at the 50 mg drug level. The weight of the retroperitoneal fat pad was significantly smaller than in controls at the 15 mg drug level as well. There was a general trend towards a reduction in size of the three fat depots at all other drug levels.

At the 50 mg drug level, two rats died on days 28 and 38. Some diarrhea was evident at the 15 and 50 mg drug levels. Fecal pellets were light in color and abundant at the 50 mg drug level.

Typically, both lean and obese rats receiving acarbose in the high carbohydrate diet showed a dose dependent distention of the GI tract, especially the cecum and the colon. This distention was caused by accumulation of watery liquid.

Experiment 4: High Fat Diet Obese Rats–High Fat Diet

Food intake (Fig. 5A, Table 2). Average daily food intake was significantly greater than in controls only at the 15 mg

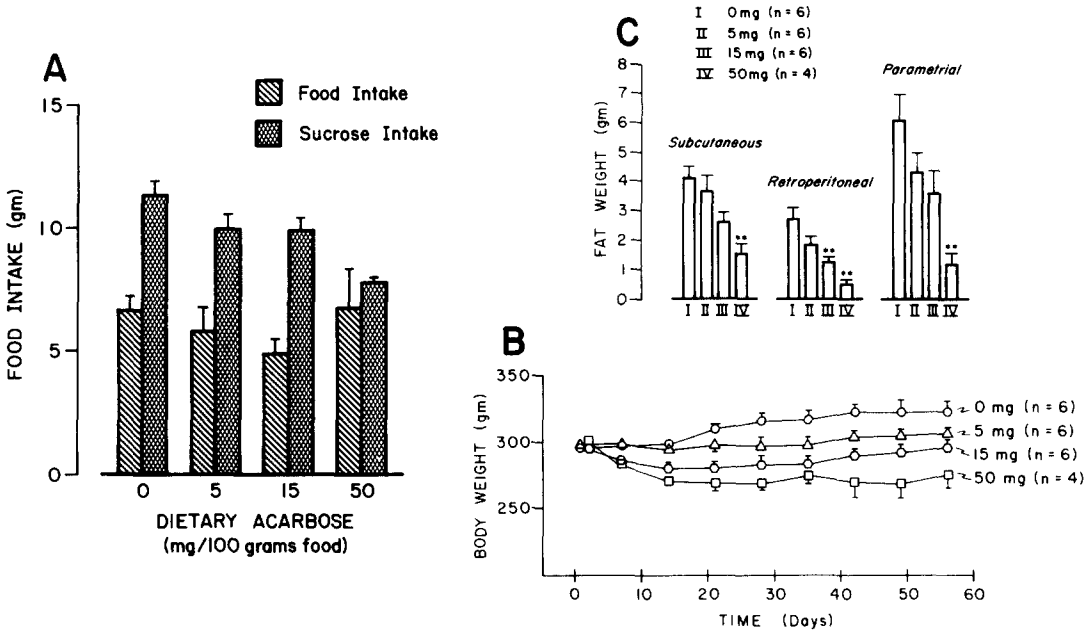

FIG. 4. Effect of dietary acarbose on food intake and sucrose intake (4A), body weight (4B) and weight of fat depots (4C) of high sucrose diet obese rats receiving the drug in the solid diet and in the 32% sucrose drinking solution. Data are mean±SE. $^{**}p<0.01$. Total caloric intake are significantly reduced at each of the three drug levels; $p<0.01$; $p<0.005$; $p<0.02$ at the 5, 15, and 50 mg drug levels respectively. Body weight is reduced at $p<0.05$; $p<0.003$; $p<0.005$ at the 5, 15, and 50 mg drug level respectively. Detailed analysis is shown in Table 2.

dietary level of acarbose ($p<0.002$). At the other levels, mean food intake was very similar to that of controls.

Body weight (Fig. 5B, Table 2). The changes in body weight were similar and not statistically distinguishable from controls at each of the three dietary levels of acarbose.

Body fat (Fig. 5C). None of the three fat depots was significantly different from controls at any of the dietary levels of acarbose. At the 50 mg drug level, there was a trend for a reduced depot size in each of the three depots measured.

No deaths occurred during the acarbose feeding experiment. One rat died before acarbose feeding had begun. Therefore, instead of six rats, five were used at the 50 mg drug level. Feces were normal at all drug levels.

Food Intake and Changes in Body Weight During the Early Phase

A summary of the data obtained during the early phases of the three experiments in which high carbohydrate diets were used and in which mortalities occurred is shown in Table 3. The pattern observed during the early phase of the study, usually in six rats per group, is similar to that observed throughout the study on the surviving rats.

DISCUSSION

Our data clearly demonstrate that the effect of acarbose is dependent on the composition of the diet and on the type of animal to which it is fed.

Mixed in a high carbohydrate diet, acarbose had a greater effect in obese than in normal rats. At the 5 mg dietary level, acarbose had no effect on any parameter of energy balance in the normal rats (Fig. 1), but it resulted in a significant reduction in both body weight and body fat in VMH obese rats (Fig. 3) and in a significant reduction in energy intake and in body weight in the high sucrose diet-obese rats (Fig. 4). At the 15 mg drug level, there was a significant suppression of food intake again in the VMH (Fig. 3) and in the high sucrose diet (Fig. 4) obese rats, but not in the normal rats (Fig. 1), however, body weight and body fat were reduced significantly in all three types of rats. The most intriguing difference between normal and obese rats occurred at the 50 mg level of the drug. While total food intake is significantly reduced in both the VMH and the high sucrose diet-obese rats (Figs. 3 and 4), it is significantly increased in the normal rats (Fig. 1). In the VMH and high sucrose diet-obese rats, the effect of acarbose on body weight and on weight of fat depots is dose-dependent, with these effects being highly significant at this 50 mg drug level. Body weight in the normal rats, however, is significantly reduced only at the 15 mg level, and fat depots, although significantly reduced, do not show dose-dependence. In fact, there is a trend for fat pads to be greater in the 50 mg than in the 15 mg drug level in the normal rats (Fig. 1). The compensatory increase in food intake observed in the normal rats receiving the high level of the drug may result in a more positive energy balance compared to the intermediate dose.

Based on our current findings, as well as on previous findings which showed that dietary acarbose resulted in decreased food intake in the Zucker obese [13], but in increased intake in lean rats [1,3], it is clear that the type of animal studied plays a key role in determining the direction and the intensity of the effects of acarbose on parameters of

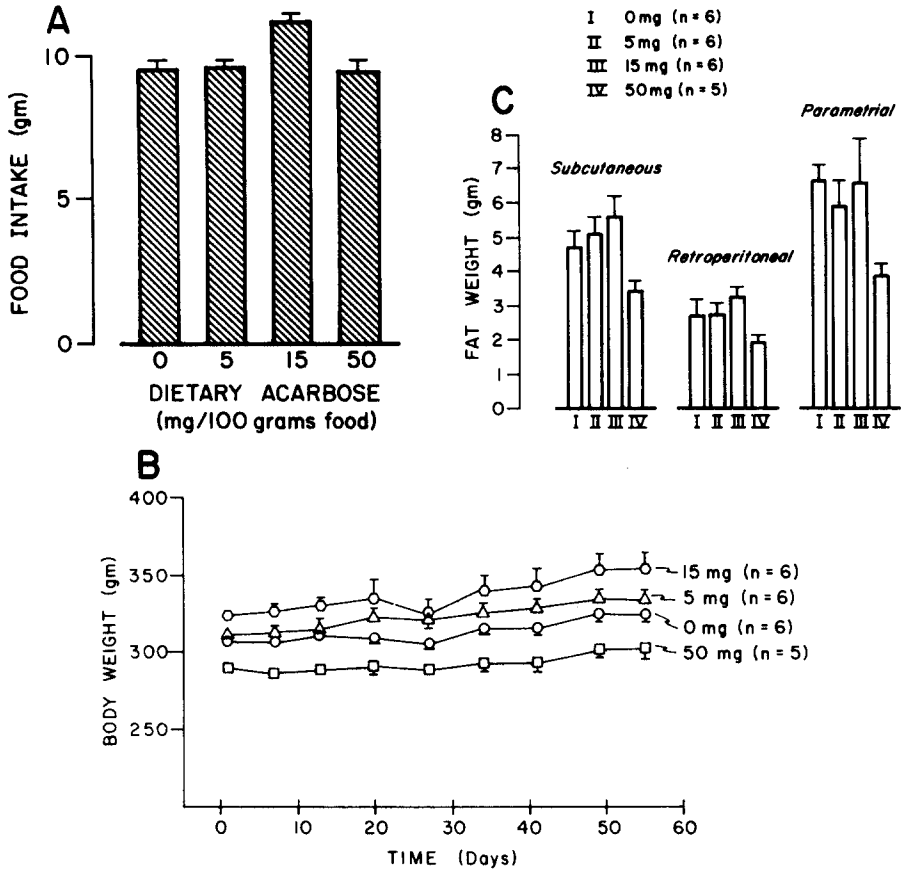

FIG. 5. Effect of dietary acarbose on food intake (6A), body weight (6B) and weight of fat depots (6C) of high fat diet obese rats receiving the drug in a high fat diet. Data are mean±SE. Food intake is significantly increased only at the 15 mg drug level ($p<0.002$). Detailed analysis is shown in Table 2.

TABLE 3

EFFECT OF DIETARY LEVEL OF ACARBOSE, BY TYPE OF RAT, ON MEAN DAILY FOOD INTAKE AND ON CHANGES IN BODY WEIGHT

Type of rats	Treatment Group	n	Mean daily food intake (g)	ANOVA* (p values)	Mean change in body weight (g)	ANOVA* (p values)
Normal	Control	6	14.1		+16.5	
(lean)†	5 mg	6	13.1	NS	+20.7	NS
	15 mg	6	13.3	NS	+ 3.8	$p<0.06$
	50 mg	5	21.9	$p<0.0001$	+17.8	NS
VMH obese‡	Control	6	17.3		+ 6.3	
	5 mg	6	11.3	$p<0.02$	−40.2	$p<0.03$
	15 mg	6	8.1	$p<0.0001$	−62.5	$p<0.0001$
	50 mg	6	9.0	$p<0.0007$	−67.8	$p<0.0001$
Dietary obese§	Control	6	17.9		+12.3	
high sucrose	5 mg	6	15.6	$p<0.02$	− 0.8	$p<0.03$
diet	15 mg	6	13.4	$p<0.001$	−17.5	$p<0.0005$
	50 mg	6	11.3	$p<0.0001$	−31.5	$p<0.0001$

Analysis of the data collected during the early phase of each study: before occurrence of mortality.

*p values obtained from analysis of variance for repeated measurements. In each type of rat p values indicate comparison between respective drug treament and control.

†Data on food intake represent the first 20 days and on body weight the first 13 days. Included in this study are data collected after the first mortality, but before the second mortality.

‡Data on food intake represent the first 16 days, and on body weight the first 12 days of the study.

§Data on food intake represent the first 24 days, and on body weight the first 20 days of the study.

energy balance. Our data, however, do not identify the factors involved in this differential response. The initial mean body weight of the VMH obese rats was about twice that of the lean. Therefore, it is not clear whether the differential response to the drug results from a specific effect of the lesions or merely from the associated gain in body weight. The sucrose obese rats with a mean initial body weight of about 300 g show rates of reduction in body weight which on the whole fall between a relatively small reduction in the lean (200 g initial weight) and a large reduction in the VMH obese (nearly 400 g initial weight), suggesting that initial body weight may determine the type of response to the acarbose. Adulteration of food by quinine [9] or by polyphenols [4] were shown to cause greater suppression of food intake in VMH obese than in lean rats. It was suggested that the increased body weight alone rather than other possible effects of VMH lesioning was the major cause for the increased sensitivity of these rats to quinine [2,15]. The differential response to acarbose observed in our study may be analogous to diet adulteration by other agents.

Mixed in a high fat diet acarbose had very little effect on parameters of energy balance (Fig. 5). Though we observed a significant increase in food intake at the 15 mg acarbose per 100 g high fat diet, this may be related to the fact that in this particular experiment, body weights were not matched at the start. The rats in this group were larger than in the other groups, perhaps reflecting a greater than normal food intake rather than a response to the drug treatment.

Acarbose mixed in the high carbohydrate, but not in the high fat diet, resulted in a dose-dependent distention of the lower GI tract. The undigested carbohydrate apparently metabolized by the intestinal microflora creating an osmotic effect that results in the accumulation of liquid there. The latter may have caused the apparent paradox of no change in body weight in the face of a significant reduction in the weight of fat depots observed in normal rats receiving 50 mg acarbose in the diet (Fig. 1). In the obese animals the increased weight due to the accumulation of liquids in the GI tract was evidently not sufficient to counteract the greater negative energy balance associated with the consumption of the drug (Figs. 3 and 4). Several deaths occurred in rats receiving the drug at the higher doses in the high carbohydrate diet only. In all cases death was associated with a marked distention of the lower GI tract. The nature of this association is not clear at the present.

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