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BRIEF COMMUNICATION

Effects of Acarbose in Rats are Influenced by the Type of Dietary Starch

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GLICK, Z., A. OSHIRO AND U. SOD-MORIAH. *Effects of acarbose in rats are influenced by the type of dietary starch.* PHARMACOL BIOCHEM BEHAV 25(2) 491–494, 1986.—When rats consume a high cornstarch (raw) diet containing the alpha glucosidase inhibitor acarbose, they transport a large portion of the undigested starch into the large bowel, causing massive distention of the lower GI tract. In the present study we compare the effects of acarbose (50 mg per 100 g diet) when mixed in a raw cornstarch diet to its effects when mixed in a cooked cornstarch diet of otherwise identical composition. Controls received the respective diets but without the drug. In contrast to its effects when mixed in the raw cornstarch, mixed in the cooked cornstarch diet, acarbose consumption was not accompanied by any significant fecal losses of dietary starch. The intestinal distention induced by the drug was also much smaller in the rats eating the cooked cornstarch than the raw cornstarch. When either diet contained acarbose, fat depot weights were significantly lower than when the diets did not contain the drug. However, the difference was consistently greater with the raw cornstarch diet.

Acarbose Dietary starch Intestinal distention

ACARBOSE inhibits intestinal alpha glucosidases which degrade starch sucrose and other sugars to absorbable monosaccharides. This drug results in reductions in serum glucose and insulin in man [4, 5, 10, 12] and animals [8–10].

In normal and obese rats, the feeding of acarbose is associated with a significant and dose dependent distention of the lower GI tract [2,3]. This distention is apparently caused by the transport of undigested starch into the lower bowel [3]. Some mortality occurred among the animals receiving the drug at concentrations of 15 and 50 mg per 100 g diet [3]. Though the cause of death has not been determined with any certainty, it could have resulted from complications associated with the distention and thinning of the intestinal wall (Howard and Glick, unpublished observations).

Since the effect of acarbose on starch digestion is evident in several types of rats tested [3], and since the same dietary level of acarbose (50 mg per 100 g diet) is without any effect on the GI tract (or on any parameter tested) when it is mixed into a high fat diet [2,3], the effect of the drug on the GI tract apparently results from its interaction with the dietary carbohydrate. Mixed in raw cornstarch the drug apparently blocks the intestinal digestion of the starch, rather than slowing down its rate of digestion.

In the present study we compare the effects of acarbose when it is mixed in raw cornstarch to its effects when mixed in cooked cornstarch, in diets of otherwise identical compositions. The rationale for the study is based on a reported observation that much smaller doses of acarbose are required to delay the digestion of raw starch than of cooked starch. The ED_{50} i.e., the dose of the inhibitor that will reduce the post prandial increments in blood glucose and insulin by 50%, is only 0.2 mg acarbose per kg body weight with raw starch, compared to 1.5 mg with cooked starch [11]. Since cooking results in major modifications of the starch granule [7] rendering it more accessible for enzymatic digestion, it was thought that the effects of acarbose on parameters of energy balance, and on distention of the lower GI tract, will vary with the type of the dietary starch.

METHOD

Animals, Diet and Drug

Sprague-Dawley female rats (Simonsen Laboratories, Gilroy, CA), weighing about 200 g at the start of the experiment, were used. The rats were housed individually and maintained at 24°C±2, with lights on from 0700 to 1800. Composition of the high carbohydrate diet expressed as a percentage was as follows: Casein (vitamin free) 22%; salt mix (Rogers-Harper) 4%; non-nutritive fiber 2%; vitamin mix (AoAc) 1%; dl methionine 0.1%; starch (corn) 67.9%; and Crisco fat 3%. All dietary components with the exception of Crisco fat and cooked cornstarch were purchased from Tek-

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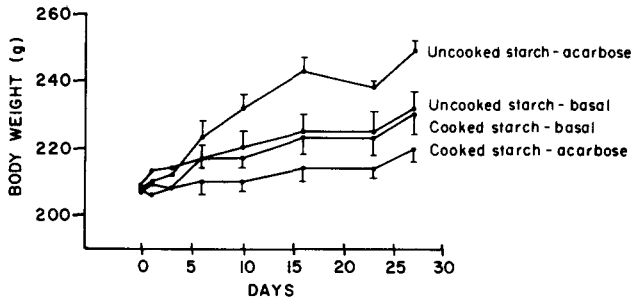

FIG. 1. Effect of acarbose on body weight, by the type of dietary starch. Data are mean±SE. Acarbose mixed in raw cornstarch caused a significant increase in body weight ($p<0.001$), and mixed in cooked cornstarch it caused a significant decrease ($p<0.01$) in weight.

TABLE 1

EFFECT OF THE DIETARY TREATMENT ON DAILY FOOD INTAKE AND WEIGHT OF THE GI TRACT WITH ITS CONTENTS

	Daily Food Intake (g)	Weight of GI Tract Plus Content (g)
Control, raw starch	14.2 ± 0.4 ***	10.6 ± 0.8 ***
Acarbose, raw starch	26.8 ± 0.8[a]	49.3 ± 3.7[a]
Control, cooked starch	13.3 ± 0.2 *	10.5 ± 0.7 **
Acarbose, cooked starch	12.1 ± 0.2[c]	17.9 ± 1.0[b]

Data are mean ± SE, asterisks denote level of significance between acarbose and respective control. *$p<0.05$, **$p<0.01$, ***$p<0.001$. Different superscripts denote level of significance between the effect of the drug when mixed in raw cornstarch vs. cooked cornstarch $^{ab}p<0.01$; $^{ac}p<0.001$.

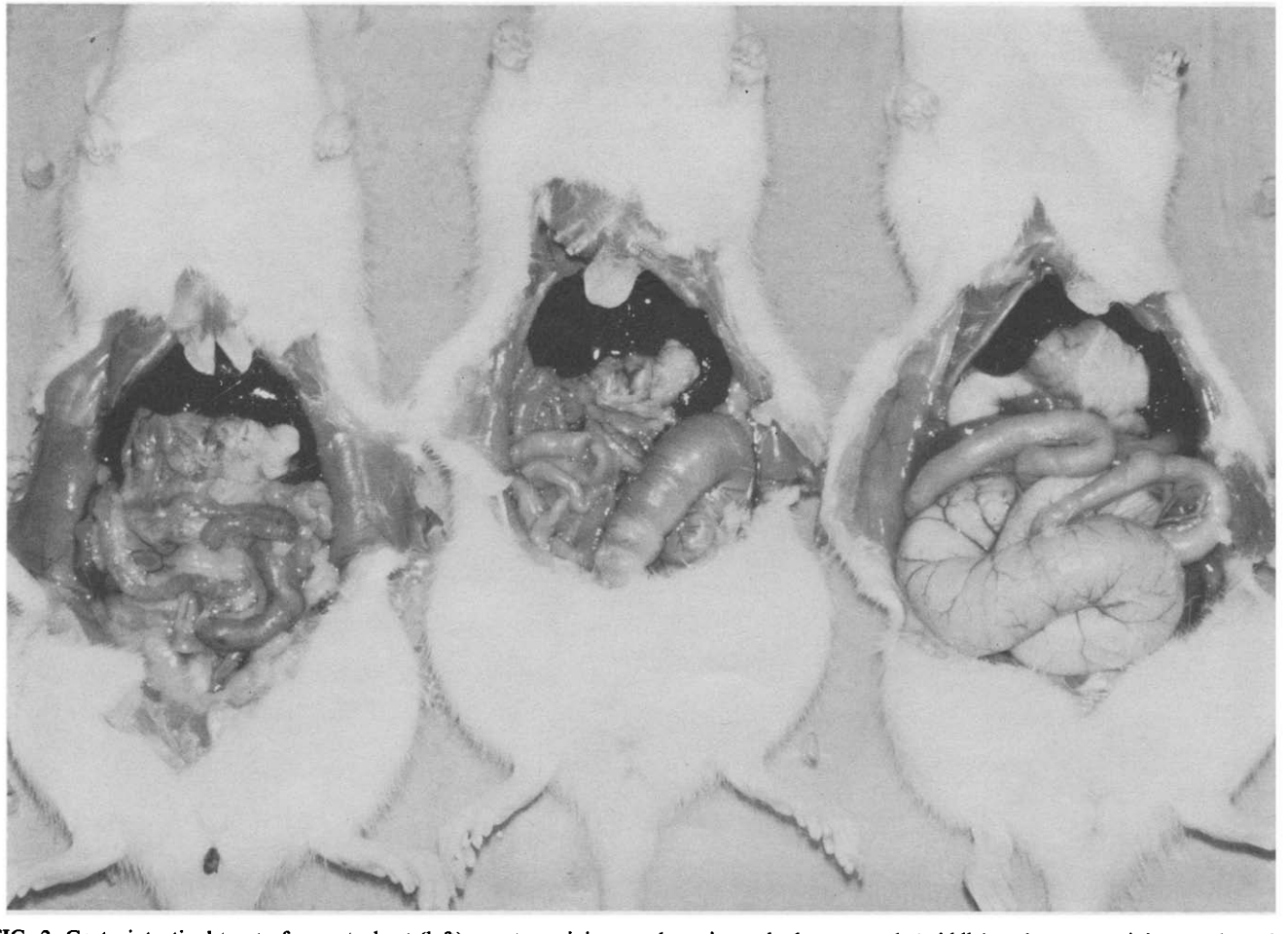

FIG. 2. Gastrointestinal tract of a control rat (left), a rat receiving acarbose in cooked cornstarch (middle) and a rat receiving acarbose in uncooked cornstarch (right).

TABLE 2

EFFECTS OF THE DIETARY TREATMENT ON WEIGHT OF FAT DEPOTS

	Fat Depots (mg)			
	Inguinal	Retroperitoneal	Perirenal	Parametrial
Control, raw starch	320 ± 15 ***	356 ± 46 ***	145 ± 30 **	1196 ± 170 ***
Acarbose, raw starch	114 ± 17	70 ± 17	39 ± 6	279 ± 59
Control, cooked starch	382 ± 94 ***	361 ± 31 ***	152 ± 19 **	1200 ± 128 **
Acarbose, cooked starch	174 ± 13	144 ± 50	71 ± 9	566 ± 72

Data are mean ± SE. Asterisks denote level of significance between acarbose and respective control. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

lad Test Diets, Madison, WI. Cooked cornstarch (Waxy cornstarch No. 12410, SA CPL, Westlake 119, San-Van-Gent, The Netherlands) was generously provided by Dr. W. Puls, Bayer AG Research Center, Wuppertal 1, West Germany. The Crisco vegetable shortening is produced by Proctor and Gamble, Cincinnati, OH. The glucosidase inhibitor acarbose (Bay g5421), an oligosaccharide containing an unsaturated cyclitol unit bound to an amino sugar [10], was provided through the generosity of Miles Laboratories (New Haven, CT).

Experimental Protocol

Twenty-four rats were divided into two groups closely matched for body weight (n=12 per group). The first group received a high carbohydrate diet made with raw cornstarch as the sole contributor of carbohydrate, and the second group received the same diet but with cooked cornstarch.

Each of the two groups was further subdivided into two (n=6 per group). One served as control and received no acarbose in the diet, and the second received acarbose mixed in the diet at 50 mg per 100 g diet. The rats received the respective dietary treatments for 27 days. Food intake was recorded every 3 to 4 days and body weight at least once weekly. After killing, the weight of four fat depots was determined, as well as the weight of the GI tract and its content (oesophagus to anus).

Data on the time course changes in body weight were analyzed by ANOVA. The rest of the comparisons were done by Student's "*t*" test, using the Bonferroni approach for multicomparisons between treatments [6].

RESULTS

Effect of acarbose on body weight, by the type of dietary starch is shown in Fig. 1. On its own the type of starch had no effect on body weight. The effects of the drug on weight changes were however statistically significant. Mixed in the raw starch, acarbose intake was associated with a larger body weight, $F(1,75)=20.8$, $p<0.001$, and mixed in the cooked starch with a smaller weight, $F(1,75)=11.2$, $p<0.01$, when compared to respective controls.

The weight of the GI tracts and their contents are shown in Table 1. Compared to respective control groups acarbose in the raw cornstarch diet resulted in about a 5 fold greater GI tract weight ($p<0.001$), as compared with only a 70% greater GI tract weight ($p<0.01$) in the rats receiving the drug in the cooked cornstarch diet. The magnitude of the difference in GI distention between the various dietary treatments is clearly demonstrated in Fig. 2.

Compared to respective control groups food intake was markedly greater ($p<0.01$) in rats consuming the drug with raw cornstarch, and it was smaller ($p<0.05$) when the drug was mixed in the cooked cornstarch (Table 1).

Fat depots were smaller in the rats fed the acarbose when mixed in either type of starch than in rats fed the respective control diets. These effects of the drug were consistently greater when acarbose was mixed in the raw than in the cooked cornstarch (Table 2). The excretion of a massive quantity of starchy feces was observed only in the group receiving acarbose mixed in the raw cornstarch diet.

DISCUSSION

Our data clearly show that the extreme distention of the lower GI tract, typically observed upon feeding acarbose mixed in a raw cornstarch diet [2,3], and which results from acarbose acting as a blocker, rather than as retardant of starch digestion, is largely alleviated when the raw starch is replaced by cooked starch (Fig. 2, Table 1). The greater exposure of starch molecules to amylase in the lumen, brought about by cooking of the starch [7], apparently results in the inhibitor reducing the rate of intestinal absorption, but by and large, not the quantity of the starch that is absorbed. Hence there is no evidence for excretion of dietary starch in the feces. Our data are compatible with a previous finding [11] that the ED_{50} for the effect of acarbose in reducing serum glucose is much smaller when mixed in uncooked, than in cooked starch.

It is not likely that the observed difference between the effects of acarbose when mixed in the raw and in the cooked cornstarch were due to the origins of the two starches (the raw starch derived from a regular type corn, and the cooked from a waxy type) rather than from the effect of cooking. Comparing the two control groups, no differences are observed in growth rate (Fig. 1), in weight of the GI tract and its content (Table 1), and in weight of the adipose tissue depots (Table 2). Therefore, by any measured criterion used in this study, the two types of starch were equally utilized. Moreover, it was reported that regardless of the origin of the starch, the effective dose (ED_{50}) of the glucosidase inhibitor in reducing serum glucose, was increased by about ten-fold upon cooking of the starch [11]. The starches tested were from a wide variety of origins, including wheat, potato, rice, and corn [11]. Therefore these data suggest that the predomi-

nant cause for the observed differential effects of the acarbose when mixed in the raw and in the cooked cornstarch diets were due to the cooking, and that the origin of the starch was of minor importance if at all.

The greater body weight of the rats consuming the acarbose mixed in the raw cornstarch diet, in the face of smaller fat depots (Fig. 1, Table 2), is explained by the larger weight of the GI tract and its content (Table 1). The undigested carbohydrate is apparently metabolized by the intestinal microflora, creating an osmotic effect and water sequestration. Subtracting the weight of the GI tract and its content from total weight, the rats receiving the acarbose display smaller weights whether the drug is mixed in raw or in cooked cornstarch, compared to their respective controls (Fig. 1, Table 1).

The hyperphagia observed in rats consuming the acarbose with the raw cornstarch diet (Table 1) [2,3] is apparently induced by starvation brought about by starch maldigestion. It is noteworthy that this hyperphagia was typically accompanied with large quantities of ingesta in the stomach, as well as large quantities of food passing through the small intestine. This would indicate that GI factors such as stomach distention, or cholecystokinin (expected to be released in larger quantities in response to the greater dietary protein and fat intake), are not important determinants of food intake under conditions of energy deprivation created in our study by starch maldigestion. The role of endogenously released cholecystokinin in determining food intake behavior has been questioned under a variety of feeding conditions [1].

When the raw was replaced by cooked starch the rats exhibited some hypophagia (Table 1). The reason for this reduction in food intake is not clear. In a state of nutrition balanced a reduced rate of starch digestion and absorption may be associated with the stimulation of an intestinal satiety mechanism, or alternatively, a reduced rate of absorption may prolong satiety through a post-absorptive mechanism.

A point of interest is our earlier finding that obese rats receiving acarbose in a raw cornstarch diet do not compensate for the energy losses in the feces by hyperphagia, as do lean rats. Depending on the type, and proportionate to the level of their obesity, they may display no change in food intake, or even a reduced intake [3]. This differential response to acarbose between lean and obese rats may be analogous to the greater sensitivity of the obese to other adulterants in the diet, which cause greater reductions in food intake in obese [3].

In summary, distention of the lower GI tract brought about upon consumption of acarbose mixed in a high starch diet is by and large alleviated when dietary raw cornstarch is replaced with cooked cornstarch. Though attenuated the beneficial effect of acarbose in regard to reduction in body fat are clearly evident when using the cooked instead of the raw starch.

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