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Effects of Dietary Carbohydrate on Sodium Cyclamate Toxicity in Rats Fed a Purified, Low-Fiber Diet (39605)

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Extensive literature is available indicating that a number of chemicals, drugs, and food additives, when incorporated in purified, low-fiber diets, induces toxic effects in rats and mice at dosages which have little if any adverse effect when fed with a natural food stock ration (1-5). Supplements of the known nutrients, either alone or in combination, when fed with the purified, low-fiber diets were without protective effect, but the toxic effects were largely counteracted by supplements of various dietary fiber-containing materials (3-6). Purified cellulose per se, however, when fed at a level comparable to the fiber content of the above supplements, had little if any protective effect. The above findings suggest that some dietary fibers present in a natural food stock ration were effective in counteracting the toxic effects induced by certain dosages of various chemicals, drugs, and food additives. Inasmuch as the purified diets indicated above contained dextrose or sucrose as the source of dietary carbohydrate, whereas the natural food stock ration contained starch and other complex polysaccharides as the major source of dietary carbohydrates, the question arose as to whether the type of carbohydrates present in a natural food stock ration may not have contributed to the protective effect of the latter ration in animals fed dosages of various chemicals, drugs, and food additives which were toxic when fed in conjunction with the purified, low-fiber diets indicated above. In the present communication, data are presented on the comparative effects of purified, low-fiber diets, containing sucrose, dextrose, dextrin, or cornstarch as the source of dietary carbohydrate, on the response of immature rats fed toxic amounts of the nonnutritive sweetener, sodium cyclamate.

Procedure and results. Sixty male rats of the Sprague-Dawley strain were selected at an average body weight of 52.7 g (range 49-56 g) and were divided into five comparable groups of 12 animals each. One group was fed a basal purified, low-fiber diet; the remaining groups were fed a similar diet + 5% sodium cyclamate[1] but differed as to the source of dietary carbohydrate. The composition of the experimental diets is indicated in Tables I and II. Animals were placed in metal cages with raised screen bottoms (three rats per cage) and were provided the test diets and water *ad libitum*. Animals were fed daily, and all food not consumed 24 hr after feeding was discarded. Body weight was recorded weekly. Feeding was continued for 14 days or until death, whichever occurred sooner.

In agreement with previous findings (3, 6), the addition of sodium cyclamate at a 5% level to the basal purified, low-fiber diet containing sucrose as the source of dietary carbohydrate (Diet II), resulted in a highly significant retardation in weight gain, lack of grooming, varying degrees of alopecia, and extensive diarrhea with watery and mushy stools. Of 12 rats fed the latter diet, 10 succumbed during the experimental period of 14 days. Similar findings were obtained in rats fed sodium cyclamate in conjunction with the dextrose-containing diet (Diet III), with 9 of 12 rats succumbing during the experimental period of 14 days. In contrast to the above, a marked improvement occurred in rats fed sodium cyclamate in conjunction with the dextrin- or cornstarch-containing rations. Ten of the 12 rats fed the dextrin-containing diet (Diet IV) and all 12 rats fed the cornstarch-containing diet (Diet V) survived the experimental period of 14 days. Gain in body weight (particularly dur-

[1] The sodium cyclamate employed in the present experiment was kindly provided by Dr. Ronald G. Wiegand of Abbott Laboratories, North Chicago, Illinois.

ing the first week of feeding) was significantly retarded in rats in all groups fed sodium cyclamate compared to those fed the basal purified diet (Diet I). During the second week of feeding, a marked increment in body weight occurred in all surviving rats fed the cyclamate-containing diets. This was particularly marked in rats fed the cornstarch-containing diet whose gain in body weight during the second week of feeding did not differ significantly from that of rats fed the basal-purified, cyclamate-free diet.

TABLE I. COMPOSITION OF EXPERIMENTAL DIETS.[a]

Dietary components	Diet (%)				
	I	II	III	IV	V
Sodium cyclamate	0	5	5	5	5
Sucrose	66	61			
Dextrose			61		
Dextrin				61	
Cornstarch					61
Casein[b]	24	24	24	24	24
Salt mixture[c]	5	5	5	5	5
Cottonseed oil	5	5	5	5	5

[a] To each kilogram of the above diets were added the following vitamins: thiamine hydrochloride, 5 mg; riboflavin, 5 mg; pyridoxine hydrochloride, 5 mg; calcium pantothenate, 50 mg; nicotinic acid, 100 mg; ascorbic acid, 200 mg; *para*-aminobenzoic acid, 200 mg; inositol, 400 mg; biotin, 1 mg; folic acid, 5 mg; vitamin B_{12}, 150 μg; 2-methyl,1,4-naphthoquinone, 5 mg; choline chloride, 2 g; vitamin A, 5000 U.S.P. units; vitamin D_2, 500 U.S.P. units; and alpha-tocopheryl acetate, 100 mg. The vitamins were added in place of an equal amount of dietary carbohydrate.

[b] Vitamin-Free Test Casein, Teklad Test Diets, Madison, Wisconsin.

[c] Mineral Mix, U.S.P. XVII, Teklad Test Diets, Madison, Wisconsin.

Extensive diarrhea and varying degrees of alopecia were manifest in rats fed the dextrin-containing diet. With the exception of a smaller size and slight diarrhea, rats fed the cornstarch-containing diet appeared grossly normal at the termination of the experiment. Food consumption was not determined for rats in the various groups for diarrhea in rats fed the cyclamate-containing diets contaminated the food and interfered with accurate determinations of food consumption data; the latter was particularly true for rats fed the sucrose- and dextrose-containing diets. It was readily apparent, however, from gross inspection of the food cups, that the amount of food consumed by rats fed the sucrose- and dextrose-containing rations (Diets II and III) was markedly less than that of rats fed the dextrin- and cornstarch-containing rations (Diets IV and V). Inasmuch as sodium cyclamate was present in all the above rations at a 5% level, animals with the largest food consumption also consumed the largest amount of sodium cyclamate. Findings indicate that the greater weight increment and lower mortality of rats fed the dextrin- and cornstarch-containing diets occurred despite the fact that these animals ingested more sodium cyclamate than did those on the sucrose- or dextrose-containing diets.

Discussion. Present findings indicate that the source of dietary carbohydrate significantly affected the response of immature male rats fed a purified, low-fiber diet containing 5% sodium cyclamate. When the source of dietary carbohydrate was sucrose

TABLE II. EFFECTS OF SOURCE OF DIETARY CARBOHYDRATE ON THE WEIGHT INCREMENT AND SURVIVAL OF IMMATURE MALE RATS FED A PURIFIED, LOW-FIBER DIET + 5% SODIUM CYCLAMATE.[a]

Dietary group	% Sodium cyclamate in diet	Dietary carbohydrate	Average gain (g) in body wt after following days of feeding:		% Survival after 14 days of feeding
			7 Days	14 Days	
I	0	Sucrose	35.8 ± 1.9[b]	78.6 ± 2.8	100
II	5	Sucrose	5.3 ± 2.1 (4)	18.5 ± 2.2 (2)	16.7
III	5	Dextrose	6.2 ± 4.8 (7)	32.3 ± 7.4 (3)	25
IV	5	Dextrin	4.2 ± 3.7	27.2 ± 8.0 (10)	83.3
V	5	Cornstarch	9.8 ± 3.5	48.7 ± 5.2	100

[a] The average initial body weight of rats in the various groups was 52.7 g. The values in parentheses indicate the number of animals which survived and on which data are based when this number is less than the original number per group. Twelve animals were in each group.

[b] Standard error of the mean.

or dextrose, animals fed the above diets exhibited a highly significant retardation in weight gain, lack of grooming, varying degrees of alopecia, extensive diarrhea, and high mortality within an experimental period of 14 days. With the exception of growth retardation during the first week of feeding, these effects, except for a slight diarrhea, were completely counteracted when the diet contained cornstarch as the source of dietary carbohydrate, and animals fed the latter diet appeared grossly normal in all respects. Intermediate results were obtained on a diet containing dextrin as the dietary carbohydrate. No data are available as to the *modus operandi* whereby cornstarch exerted its protective effect. It has been suggested that the activity of various dietary fibers in counteracting the toxicity of massive doses of sodium cyclamate and other food additives may be related to their effects on the kinds of organisms present and their metabolic activity in the intestinal tract (7). Further studies are indicated to determine to what extent diets containing cornstarch and other complex carbohydrates in a natural food stock ration may alter the intestinal flora in contrast to findings obtained with diets containing sucrose or dextrose as the source of dietary carbohydrate.

Available data indicate that the protective effects of dextrin and cornstarch in contrast to sucrose and dextrose as sources of dietary carbohydrate in rats fed a purified, low-fiber diet are not confined to rats fed toxic doses of sodium cyclamate. In preliminary studies conducted in this laboratory,[2] with six rats per group on diets identical to those employed above, except that FD & C Red No. 2 (amaranth) replaced sodium cyclamate in the diet, all rats fed the sucrose- or dextrose-containing diets succumbed within an experimental period of 14 days with a maximum weight increment during this period of 6 g. In contrast, four out of six rats on both the dextrin- and cornstarch-containing diets survived the experimental period of 14 days with an average weight increment of 41 and 35 g, respectively. The latter weight increment was considerably less than that obtained with various dietary fiber-containing materials when incorporated in a purified, low-fiber diet which contained 5% FD & C Red No. 2 and sucrose as the source of dietary carbohydrate (4). It was also significantly less than that obtained on a natural food stock ration supplemented with 5% FD & C Red No. 2 (4). The above findings suggest that the protective effects of a natural food stock ration in rats fed a diet containing 5% sodium cyclamate or 5% FD & C Red No. 2 were due in part to the kind of carbohydrates present in the natural food stock ration.

Present findings are in accord with the hypothesis initially proposed by Cleave (8), and subsequently elaborated upon by Cleave and associates (9, 10), that a number of disorders of Western man (including constipation, diverticular disease, irritable colon, diabetes, coronary disease, obesity, and others) is due in part to a marked change in the type of foods he eats compared to what he ingested in the past. During the past 200 years, a marked increase has occurred in Western societies in the per capita consumption of sugar. Associated with this change, due in large part to the introduction of roller milling between 1877 and 1880, a reduction occurred in the amount of dietary fiber ingested by Western man, particularly of the type present in cereal grains. Present findings indicating the marked toxicity of sodium cyclamate in rats fed a low-fiber diet containing sucrose as the source of dietary carbohydrate, and earlier findings indicating the absence of such toxicity in rats fed a similar amount of sodium cyclamate in conjunction with a natural food stock ration (which contained a number of diverse dietary fibers as well as complex polysaccharides as the prime source of dietary carbohydrate) (3), suggest that Cleave's hypothesis may also be applicable to other physiologic disturbances and to species other than man.

Summary. Immature male rats were fed a purified, low-fiber diet containing 5% sodium cyclamate but varying as to the source of dietary carbohydrate. On diets containing sucrose or dextrose as the dietary carbohydrate, animals exhibited a highly significant retardation in weight gain, lack of grooming, varying degrees of alopecia, extensive diarrhea, and high mortality within an experimental period of 14 days. With the ex-

[2] B. H. Ershoff, unpublished data.

ception of growth retardation during the first week of feeding, these effects except for a slight diarrhea were completely counteracted when the diet contained cornstarch as the source of dietary carbohydrate, and animals appeared grossly normal in all respects and comparable to those fed a purified, low-fiber, cyclamate-free diet. Intermediate results were obtained in rats fed sodium cyclamate in conjunction with a diet containing dextrin as the source of dietary carbohydrate.

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