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Effect of Dietary Fiber on the Induction of Colorectal Tumors and Fecal β-Glucuronidase Activity in the Rat[1]

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ABSTRACT

The purpose of the present study was to investigate whether three different types of dietary fiber, wheat bran, carrot fiber, and citrus pectin, influenced the induction of colorectal tumors produced by 1,2-dimethylhydrazine in rats.

In all groups, the tumor yield was high (87 to 97%). In the wheat bran and carrot fiber groups, the incidence of colorectal tumors was not significantly different from that of the group fed on the fiber-free basic diet. The citrus pectin group, however, had a significantly higher incidence of colorectal tumors ($p < 0.001$). An increased number of auditory duct tumors was also noted in this group. In a separate experiment, dietary pectin induced a 10-fold increase in fecal β-glucuronidase activity but did not alter this activity in the bowel wall.

It has been suggested that dietary fiber protects against the induction of colorectal tumors, but this was not the case in this experiment. It is possible that the high tumor yield made the demonstration of a weak protective effect of wheat bran impossible. The reason for the increased occurrence of tumors in the citrus pectin group is obscure and will be subjected to further investigation. Fecal β-glucuronidase activity might be one factor of importance in the activation of the carcinogen.

INTRODUCTION

Colorectal cancer is one of the most common forms of malignant tumors in humans, and its incidence is increasing. Much emphasis, therefore, is placed upon the research concerning its etiology, prevention, and treatment. The incidence of colorectal cancer is high in the United States, Canada, and Western Europe but low in parts of South America, Africa, and Asia. Migration studies indicate that it takes only one to 2 generations until migrants adapt to the incidence of the cancer in the new country. These and other epidemiological data strongly indicate the importance of environmental factors in the etiology of colorectal cancer (1, 16, 18).

Food is the environmental factor to which the most attention is paid in this context. Excess fat, especially in the form of beef, and a low intake of dietary fiber are the factors especially considered (1, 2, 7, 18).

It has been suggested that the intake of some dietary components may cause a high excretion of bile acids and cholesterol, which are converted by colonic bacteria to secondary bile acids and fecal sterols. These compounds may be further metabolized by the colonic flora to steroid carcinogens (8). A positive correlation between fat intake and colon cancer has been demonstrated in experimental studies (13). Dietary factors may also alter the bacterial flora of the intestine and its enzymatic activity (nitroreductase, azoreductase, and β-glucuronidase) and thereby influence the metabolism of fecal sterols or exogenous carcinogens (6, 8, 12).

A low dietary fiber content may give a small colonic bulk and a long transit time through the colon, possibly resulting in a high concentration of carcinogens in the colonic content and a long exposure time of the colonic mucosa to these carcinogens (1). Recently, several investigations have been conducted to study the effect of defined dietary fiber on the induction of experimental colorectal tumors which suggested a protective effect of dietary fiber in the development of colonic tumors (4, 5, 17).

The carcinogen DMH[3] can induce colorectal adenocarcinoma in rats with a high incidence and a great specificity, especially when administered s.c. Both the macroscopic and microscopic appearance of these tumors is quite similar to that of human colorectal cancer (3, 10). The purpose of the present work was to investigate whether 3 different types of dietary fibers, wheat bran, carrot fiber, and citrus pectin, influenced the induction of experimental colorectal cancer in rats. Further, it was investigated whether these diets influenced β-glucuronidase activity in the bowel wall or feces.

MATERIALS AND METHODS

Animals. One hundred sixty male Sprague-Dawley rats (Anticimex, Stockholm, Sweden) were used. They were randomly divided into 4 groups of 40 animals each and fed on the different diets described below.

The animals were housed individually in steel wire cages to prevent coprophagia, and they had free access to water. The room was air conditioned at 22–23° with a relative humidity of 56 to 60%. The light was switched on at 6 a.m. and off at 6 p.m.

The food with the different types of dietary fiber was given *ad libitum* in individual containers holding about 90 g of diet. The rats were weighed weekly at the same time of the day, just before they were given the DMH injection.

Diets. In order to simulate a Wester diet with high protein and fat content, a basic diet was prepared with 20% casein, 20% oil, 10% sucrose, 44% wheat starch, 5% mineral mixture, 0.8% vitamin mixture, and 0.1% choline chloride (Table 1).

Group 1 (control group) was fed the basic diet. Group 2 was fed the basic diet and wheat bran (20%); Group 3 was fed the basic diet and carrot fiber (20%); and Group 4 was fed the basic diet (90%), citrus pectin (6.5%), and sucrose (3.5%). Analytical data of the fiber preparations (Tables 2 and 3) show the elemental composition of the experimental diets. The diets

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[3] The abbreviation used is: DMH, 1,2-dimethylhydrazine.

Table 1

Components used in the basic diet mixture and their sources

Component	% in diet	Source
Casein	20	Kebo-Grave AB
Peanut oil	20	Karlshamns Oljefabriker AB
Sucrose	10	Svenska Socker AB
Wheat starch	44.1	AB Stadex
Mineral mixture[a]	5	
Vitamin mixture[b]	0.8	Purchased through hospital
Choline chloride	0.1	Pharmacy
	100	

[a] $CuSO_4 \cdot 5\ H_2O$ (8.6 g); $ZnSO_4 \cdot 7\ H_2O$ (32.0 g); KH_2PO_4 (7780 g); $NaH_2PO_4 \cdot 2\ H_2O$ (4024 g); $CaCO_3$ (7600 g); KI (1.6 g); $MgSO_4 \cdot 7\ H_2O$ (2000 g); $FeSO_4 \cdot 7\ H_2O$ (180 g); $MnSO_4 \cdot H_2O$ (80 g); $CoCl_2$ (0.46 g); NaCl (2382 g).

[b] Menadione (2.5 g); thiamin hydrochloride (10.0 g); riboflavin (10.0 g); pyridoxin hydrochloride (5.0 g); calcium pantothenate (25.0 g); nicotinic acid (25.0 g); folic acid (1.0 g); inositol (50.0 g); *p*-aminobenzoic acid (5.0 g); biotin (0.2 g); vitamin B_{12} (0.015 g); vitamin A (2,500,000 IU); vitamin D (1,000,000 IU); vitamin E (100,000 IU); wheat starch (up to 4.000 g).

Table 2

Dietary fiber preparations and their sources

		% of dry wt			
Diet	Source	Neutral detergent fiber[a]	Crude protein[b]	Total fat[c]	Ash (11)
Wheat bran	Kungsörnen AB	37	13	6	5
Carrot fiber	Nordreco AB	40	9	3	5
Citrus pectin	KEBO/Grave		1	2	1

[a] Preincubation with α-amylase was performed. The neutral detergent fiber method does not measure water-soluble dietary fiber components and therefore cannot be used for analysis of pectin (15).

[b] Kjeldahl nitrogen × 6.25.

[c] Chloroform-extractable material.

Table 3

Composition of experimental diets

	% of dry wt				
Diet	Protein[a]	Fat	Starch	Sucrose	Minerals
Basic diet	17	20	40	10	5
20% wheat bran	16	17	34	9	5
20% carrot fiber	15	17	32	8	5
6.5% citrus pectin	15	18	36	14	5

[a] Kjeldahl nitrogen × 6.25.

were given from 3 days before the first injection of the carcinogen until 14 days after the last injection, *i.e.*, in all for about 15 weeks. All the rats were then given standard rat pellets (Astra Ewos, Sweden) *ad libitum*.

Collection of Feces. During 3 days at the end of the period with the experimental diets, feces were collected from 8 rats in each group once a day and frozen at −40°. They were later lyophilized, weighed, and ground for analysis.

Administration of the Carcinogen. A solution of DMH, purchased from EGA-Chemie, West Germany, in the form of DMH dihydrochloride, was prepared immediately prior to injection. The solution contained DMH (7.0 mg/ml) and EDTA (0.5 mg/ml) for stabilization, and the pH was adjusted to 6.5 with sodium hydrogen carbonate. All the rats were given s.c. injections of DMH (15 mg/kg body weight) in the groin once a week for 12 consecutive weeks. The total dose given was 180 mg/kg body weight, calculated as DMH base.

Autopsy. The animals were killed randomly with diethyl ether 12 to 14 weeks after the last DMH injection, *i.e.*, 24 to 25 weeks after the start of the experiment. Each rat was subjected to a complete autopsy with macroscopic examination of the ear ducts, lungs, liver, kidneys, spleen, pancreas, stomach, duodenum, and small and large bowel, including the rectum. The entire intestinal tract was cut open and examined through a magnifying glass. Colorectal tumors were localized by measurement of the distance from the ileocecal valve. The size and appearance of the tumors were recorded, and in 25% of the animals, *i.e.*, in 10 randomly chosen rats in each group, the tumors were fully investigated histologically. Tissues were fixed in 10% formalin and embedded in paraffin. The sections were stained with hematoxylin and eosin.

β-Glucuronidase Assay. Four separate groups of 6 Sprague-Dawley rats each were fed the basic, wheat bran, carrot fiber, and citrus pectin diets, respectively. The rats were 6 to 7 weeks old at the start of the experiment. They were fed on the diets for 6 weeks and then killed. Weight gain and food consumption were measured weekly. Feces were collected during a 24-hr period every second week, frozen, and ground for later analysis. When rats were killed under ether anesthesia, bowel wall samples were immediately taken from the distal ileum and the proximal and distal colon, and at the same time feces were collected from the cecum and the distal colon. Bowel wall and fecal samples were processed as described by Reddy *et al.* (12), and β-glucuronidase activity was assayed. The protein concentrations in the samples were determined by the method of Lowry *et al.* (9).

Student's *t* test was used to determine the significance of the results.

RESULTS

Food Intake and Growth in the Main Experiment. During the first 2 weeks, food intake was about 10% lower in the group fed on carrot fiber than in the other groups. In the next 2-week period, however, food intake was the same in the groups fed on the basic, wheat bran, and carrot fiber diets, whereas the group fed on the citrus pectin diet consumed about 10% more food than the others did (Table 4).

Body weights at the start of the experiment and after 1 and 5 months are also shown in Table 4. There was no statistically significant difference in body weight after 5 months between any of the groups fed the fiber diets and the rats fed the basic diet, but the wheat bran group had a higher body weight when compared to the other fiber groups ($p < 0.01$).

Fecal Weight and Composition. The rats fed on the carrot fiber and the citrus pectin diets had a slightly greater fecal dry weight than those fed on the basic diet alone (Table 5). The rats fed on the wheat bran diet, however, had approximately twice the fecal weight compared to the rats fed on the other diets. All types of fiber increased the fecal loss of nitrogen.

Tumors. The incidence of colorectal tumors in all groups was high. Tumors could be detected in 87 to 97% of the rats. The total and maximum number of colorectal tumors in each group and the average number of tumors per rat can be seen in Table 6. There was a significantly higher frequency of tumors in the group fed on the citrus pectin diet. During the experiment, only 3 rats died spontaneously, 2 in the control group and one in the pectin group; all 3 had colonic tumors. In all the groups, the diets were given for 15 weeks out of a total experimental period of 24 to 25 weeks.

In about 25 to 30% of the cases, the tumors were situated in the proximal part of the colon, *i.e.*, in the first 10 to 15 cm from

Table 4

Food intake during the first 4 weeks and rat growth

Diet	Food intake (g)		Rat growth (g)		
	Wk 1–2[a]	Wk 3–4[b]	Start[c]	1 mo.[c]	5 mos.[d]
1. Basic diet	213 ± 21[e]	238 ± 45	105 ± 5	248 ± 20	484 ± 38
2. Wheat bran	215 ± 38	243 ± 27	95 ± 11	247 ± 14	487 ± 22
3. Carrot fiber	189 ± 25	244 ± 24	107 ± 6	241 ± 14	470 ± 31
4. Citrus pectin	209 ± 25	269 ± 38	105 ± 7	249 ± 16	471 ± 29

[a] Group 3 *versus* Group 1, $p < 0.001$; Group 3 *versus* Group 2, $p < 0.001$; Group 3 *versus* Group 4, $p < 0.001$.
[b] Group 4 *versus* Group 1, $p < 0.001$; Group 4 *versus* Group 2, $p < 0.001$; Group 4 *versus* Group 3, $p < 0.001$.
[c] No difference.
[d] Group 2 *versus* Group 3, $p < 0.01$; Group 2 *versus* Group 4, $p < 0.01$.
[e] Mean ± S.D.

Table 5

Fecal dry weight and nitrogen loss in feces

Diet	Fecal dry wt (g/day/rat)[a]	Nitrogen loss (g/day/rat)[b]
Basic diet	0.7	2.7
Wheat bran	1.6	3.7
Carrot fiber	0.9	4.9
Citrus pectin	0.9	3.8

[a] Feces collected during 3 days from 8 rats in each group. The samples from each group were pooled and then analyzed.
[b] Kjeldahl nitrogen.

Table 6

Colorectal tumors and tumors in the ear duct in each experimental group of 40 rats

Diet	No. of rats with tumors	Total no. of tumors	Maximum no./rat	No. of tumors/rat[a]	No. of rats with tumors in the ear duct[b]
1. Basic diet	35	79	7	2.0 ± 1.6[c]	14
2. Wheat bran	36	83	6	2.1 ± 1.6	16
3. Carrot fiber	36	103	8	2.6 ± 1.9	19
4. Citrus pectin	39	139	9	3.5 ± 2.0	29

[a] Group 4 *versus* Group 1, $p < 0.001$; Group 4 *versus* Group 2, $p < 0.001$; Group 4 *versus* Group 3, $p < 0.05$.
[b] Group 4 *versus* Group 1, $p < 0.01$.
[c] Mean ± S.D.

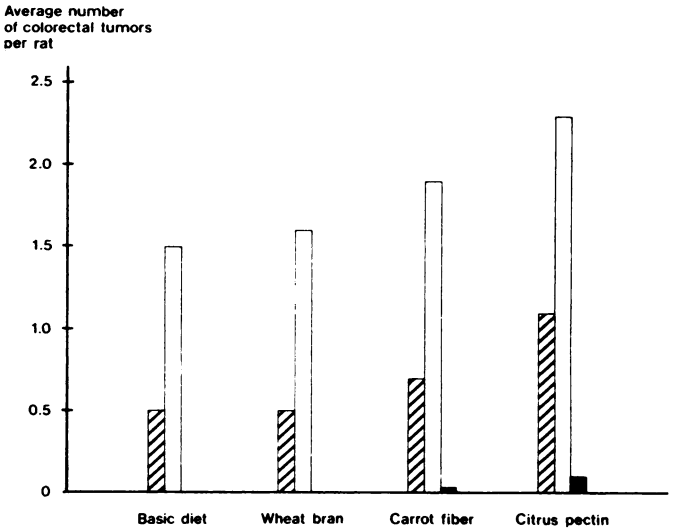

Chart 1. Tumor localization in large bowel (*hatched bar*, proximal colon; *open bar*, distal colon; *solid bar*, rectum) and the average number of colorectal tumors per rat in the different fiber groups.

the ileocecal valve. Most of the tumors (70 to 75%) were situated about 15 to 25 cm from the ileocecal valve, and only 1% was found in the rectum (Chart 1). The tumor sizes ranged from 2 mm to 2 cm in diameter in all groups.

For histopathological classification of the tumors, we have used the same definitions as has Rosengren (14). The majority of colorectal tumors were infiltrating adenocarcinomas. Two types of tumor growth were observed: an exophytic type, *i.e.*, a tumor usually protruding into the lumen; and an endophytic type, *i.e.*, a plateau-like or ulcerating tumor with slight or no tendency to protuberation into the lumen. This type was often constricting the lumen. Macroscopically, the tumors were usually well-differentiated colloid carcinomas. A number of mucus-producing signet ring cell carcinomas were seen. In many cases, the cancer infiltrated and involved all the layers of the intestinal wall, including the serosa. Metastases were few and, when present, had usually occurred by way of i.p. dissemination.

Adenocarcinomas *in situ* (mucosal cancers) were also observed. They were adenomatous tumors with pronounced epithelial or glandular atypia and not infiltrating the muscularis mucosae. Finally, a few adenomas were seen that varied in size from microscopic foci up to 2–3-mm-large sessile or pedunculated tumors.

In each group, a total number of about 20 infiltrating adenocarcinomas in the small intestine was diagnosed. The tumors were often localized in the duodenum 4–6 cm from the pylorus or in the upper part of jejunum.

Tumors in front of the outer orifice of the ear duct were seen in about 15 to 30 rats in each group (Table 6), and about 20% of these tumors were bilateral. The frequency of occurrence was significantly higher in the group fed on the citrus pectin diet than in the other groups. Histopathological examinations showed well-differentiated papillomatous squamous cell carcinomas in 60% of the cases. The other tumors were papillomas or sebaceous adenomas.

Gross examination of lungs, liver, kidneys, spleen, stomach, and pancreas showed no primary or secondary tumors. No sarcomas or other tumors were observed in the skin at the site of the injection of DMH. Thus, the tumor induction was restricted to the large and small bowel and the ear duct.

Results of β-Glucuronidase Assay. Weight gain and food consumption were the same in all the groups. In samples of bowel wall from the distal ileum and the proximal and distal colon, there were no differences in β-glucuronidase activity either within each group or among the groups, and the activity was low.

In contrast, the β-glucuronidase activity in feces from cecum and distal colon in killed animals from all the groups had nearly the same high activity. Feces from rats in the citrus pectin group, however, had a significantly higher β-glucuronidase

Table 7

Bacterial β-glucuronidase activity in feces from distal colon in 24 rats fed on different fiber diets

Diet	Activity/g protein[a, b]
1. Basic diet	139 ± 59[c]
2. Wheat bran	168 ± 69
3. Carrot fiber	256 ± 115
4. Citrus pectin	915 ± 534

[a] μg phenolphthalein liberated per 4 hr at 38° (12); protein determined according to the method of Lowry *et al.* (9).
[b] Group 4 *versus* Group 1, $p < 0.01$; Group 4 *versus* Group 2, $p < 0.01$; Group 4 *versus* Group 3, $p < 0.01$; Group 3 *versus* Group 1, $p < 0.05$.
[c] Mean ± S.D.

activity than did the colonic content from the other groups (Table 7). The enzymatic activity in feces collected every second week when rats were alive showed no significant difference among the groups.

DISCUSSION

In this model for experimental colorectal cancer in rats, the incidence of tumors was high, and the induction time was relatively short. The incidence of tumors at other locations was low, except for tumors in the ear duct and small intestine. Nearly 50% of the rats in each group developed tumors in the ear duct, and 20% developed tumors in the small intestine. The reason for the high incidence of ear duct tumors is unknown.

Since the fiber-containing diets were prepared by mixing the basic diet with various fiber preparations, the experimental diets contained slightly variable amounts of various nutrients, as shown in Table 3. The protein level used (15 to 17%) ensured a surplus of all amino acids so that neither total protein nor any specific amino acid was a limiting factor for growth. The peanut oil used as fat source (17 to 20%) had about 20% polyunsaturated fatty acids, ensuring an ample supply of essential fatty acids. The vitamin and mineral mixtures (Table 1) contained a surplus of these nutrients, ensuring adequate nutrient levels in the fiber-containing diets.

Calculation of the energy content in fiber-containing diets is a matter of discussion, since fiber broken down by colonic bacteria is to some extent available through absorption of intermediary breakdown products. The similar growth curves and food intake in the groups in the present investigation show that the diets were in fact quite comparable regarding the content of available energy as well as their essential nutrients.

The increased fecal bulk and reduced transit time on a diet rich in fiber has been suggested by Burkitt and Trowell (2) and others as a possible protective factor against colorectal cancer. In spite of the fact that the rats fed on the wheat bran diet in our experiment had more than twice the fecal dry substance weight than that of the rats fed on the basic diet, no protective effect of wheat bran against the development of colorectal tumor was found. However, the fiber-containing diets were fed only for 15 weeks out of a total experimental period of 24 to 25 weeks.

Wilson *et al.* (17) demonstrated a significantly lower incidence of benign colonic tumors in rats fed a diet containing 20% wheat bran. These authors, however, administered the carcinogen p.o. and used dose levels other than those in our experiment. The number of rats with tumors and the number of tumors per rat were smaller than in our experiment. It is possible, therefore, that the high tumor yield in our investigation made the demonstration of a weak protective effect of wheat bran impossible.

Recently, 2 studies have been published in which the same experimental approach as in our investigation was used and in which a protective effect of dietary fiber against the development of colonic tumors was demonstrated (4, 5). In the study by Fleiszer *et al.*, the fiber diets differed greatly with respect to both protein and fat content, and rat growth was highly varied among the groups, so that interpretation of the results seems to be difficult. In the other study by Freeman *et al.*, a diet containing a purified fiber component, microcrystalline cellulose, was used. The protective effect of this type of fiber, as opposed to the enhanced carcinogenesis with pectin in our investigation, points out the importance of defining the fiber component used in the experimental diets. Various types of fiber may have different physiological effects.

The quite unexpected finding in our experiment was the significantly higher incidence of both colonic and ear duct tumors in the rats fed on the diet with 6.5% citrus pectin. The reason for this greater tumor incidence in the pectin group is obscure, but different mechanisms of interaction are conceiveable. Pectin or some impurity in the pectin preparation may be carcinogenic or cocarcinogenic. Pectin may influence the final metabolism of the carcinogen DMH in the intestinal mucosa. The activation of DMH may be linked to an increased enzymatic activity of the intestinal microflora, for example, β-glucuronidase activity. This may explain the increased β-glucuronidase activity of the colonic content in rats fed on a pectin diet and the increased tumor incidence in the citrus pectin group in our investigation. Pectin may also induce hyperplasia of the colonic mucosa, and through this mechanism an increased sensitivity to carcinogens may result. Pectin may further, like a fat-rich diet and like cholestyramine (16), increase the excretion of neutral sterols, bile acids, and metabolites, which could act as carcinogens or cocarcinogens. The common factor may even here be mucosal hyperplasia, as opposed to the effect of an elementary diet, which may induce hypoplasia with a decreased sensitivity to carcinogenic factors.

To further elucidate the interplay between pectin and the carcinogenic effect of DMH and its metabolites, new experiments are planned with other sources and doses of pectin, lower doses of DMH, and a study of fecal β-glucuronidase activity.

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