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Dietary Effects on Chemical Carcinogenesis in Animal Models for Colon and Liver Tumors[1]

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Summary

Studies of dietary effects on chemical carcinogenesis in rats have demonstrated that colon tumor induction is enhanced by increased dietary fat intake or dietary deficiency of vitamin A in some but not all cases. The enhancing effect of a high-fat diet is augmented by lipotrope deficiency. Induction of hepatic tumors by several different carcinogens also is enhanced in rats fed a high-fat diet marginally deficient in lipotropes. The dietary effects may be exerted through alteration of metabolism of carcinogens, which has been demonstrated in lipotrope-deficient rats, through immunological mechanisms, which influence induction of colon tumors, or through effects on gastrointestinal bacteria and bile acid metabolism. Demonstration of dietary effects on carcinogenesis may require utilization of combined dietary stresses that alter metabolic loads but do not seriously impair growth.

Introduction

The development of animal models for carcinoma of the colon has proceeded rapidly, and the models are proving useful in studies of the development of the disease and of dietary and immunological effects on it. Application of carcinogens directly to the colon mucosa described by Weisburger *et al.* (26) is a valuable procedure for study of local interactions between fecal content and carcinogens that do not require activation or that can be activated by colon bacteria or mucosa. For studies of dietary effects that may not act locally or of carcinogens that require metabolic activation in the liver or elsewhere, i.g.[3] administration is useful and probably perferable to s.c. or i.v. injection, since it allows the detection of intralumenal interactions between diet and carcinogen and of specific nutrient effects on tissue responses to carcinogen.

A general anticarcinogenic effect in liver and other organs of stock diets compared to semisynthetic diets has been reported from several laboratories and reviewed recently (5, 29). Reddy *et al.* (27) and Weisburger *et al.* (26) reported a lower incidence of colon tumors induced by s.c. DMH in rats fed stock diet than in rats fed semisynthetic diet, but recent studies in their laboratory have shown no protection by stock diet against tumor induction by s.c. DMH or the i.r. administration of MNNG. In cases in which stock diets are protective, they may act by induction of the mixed-function oxidases (38).

Specific nutrients that influence chemical carcinogenesis in the gastrointestinal tract and liver of experimental animals are vitamin A, dietary fat, and a high level of dietary fat combined with a marginal deficiency of the lipotropes choline, methionine, and folic acid (21, 27-29, 32, 26).

Dietary Effects on Tumor Induction in Experimental Animals

Vitamin A. A history of decreased intake of vitamin A was found in patients with stomach or colon cancer, compared with normal controls in both the United States and Norway. Neither group was clinically deficient in vitamin A (2). Vitamin A controls differentiation to mucin-producing cells of the epithelial cells of the gastrointestinal tract (9). This differentiation is retarded or otherwise disturbed in premalignant and malignant changes in the colon in which polysaccharide and glycoprotein synthesis are abnormal, as demonstrated by histochemical staining or measurement of glycosyltransferases and blood group substances (11, 15, 16, 19). The transferases, which participate in synthesis of surface glycoproteins of intestinal and other mucosal cells, are abnormal in both tumors and intervening colon in DMH-treated rats and in people (15, 16). The effect of vitamin A on gastrointestinal transferases has not been demonstrated, but adequate dietary vitamin A is required for maintenance of galactosyltransferase in tracheal mucosa, and enzyme activity can be induced in tracheas from deficient animals *in vitro* by the addition of vitamin A (G. Wolf, personal communication).

In rats fed AFB_1, there was a positive association between the occurrence of colon carcinoma, marginal vitamin A intake, and decreased serum and tissue levels of vitamin A (21). Since spontaneous colon carcinoma is rare in rats, the development of colon tumors in the marginally vitamin A-deficient animals was significant, although the aflatoxins have been associated almost exclusively with hepatic and renal cancer in domestic and experimental animals (20).

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[3] The abbreviations used are: i.g., intragastric; DMH, 1,2-dimethylhydrazine; i.r., intrarectal; MNNG, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine; AFB_1, aflatoxin B_1; DMBA, dimethylbenz(a)anthracene; NNDA, *N*-nitrosodiethylamine; DBN, *N*-nitrosodibutylamine; BCG, *Bacillus Calmette-Guérin*.

AFB_1 administration at doses far below those which cause necrosis of hepatocytes significantly decreased hepatic vitamin A stores, which also suggested that there was an interaction between the 2 compounds. Hypervitaminosis A did not alter AFB_1 induction of hepatocarcinoma or colon tumors.

After Druckrey (10) reported that administration of DMH induced carcinomas of the small and large intestine in rats and mice, we utilized this model to investigate the effect of vitamin A on colon carcinogenesis. Three different doses of DMH were used in 3 experiments, and the effects of both severe dietary deficiency and dietary excess of vitamin A were studied. In contrast to AFB_1, DMH did not consistently affect hepatic content of vitamin A. In rats fed the diet deficient in vitamin A, hepatic vitamin A content was reduced essentially to zero and serum levels were significantly reduced; weight gain was retarded. Squamous metaplasia of the tracheal and bronchial epithelium was present in about one-third of the rats, as were testicular atrophy and arrest of spermatogenesis. The chronic severe deficiency of vitamin A did not significantly affect induction of colon tumors, although at the 2 higher doses of DMH, deficient rats had a slightly greater tumor incidence than did adequately fed rats, and the latent period for tumor development was somewhat reduced (Table 1) (31). Weisburger *et al.* (26) reported that vitamin A-deficient rats given i.r. MNNG developed fewer colon tumors than did adequately fed rats.

Hypervitaminosis A, documented by elevated hepatic and serum content of vitamin A and lipid accumulation in the liver, had no demonstrable effect on induction of tumors by DMH (Table 1) (31). In hamsters, hypervitaminosis A decreased induction of esophageal and gastric papillomas by benzo(*a*)pyrene or DMBA but did not consistently affect induction of respiratory tract tumors by benzo(*a*)pyrene (6, 34, 35). The vitamin may be anticarcinogenic only when applied locally in high concentration or in squamous epithelia; it has an anticarcinogenic action also in skin and cervix (3).

Since subclinical vitamin A deficiency is not uncommon in the western world, and dietary histories of patients with stomach or colon cancer have indicated chronically reduced intake of the vitamin, studies of the effect on tumor induction of marginal rather than severe deficiency may be productive. In our studies, marginal deficiency of vitamin A enhanced induction of colon tumors by AFB_1, while severe deficiency had little if any effect on DMH induction of colon tumors. Growth retardation and decreased caloric intake in the severely deficient rats may have retarded tumor development; the same factors may have inhibited tumor induction by MNNG.

Table 1

Incidence of colon tumors induced by DMH in rats fed high, adequate, or deficient levels of vitamin A (31)

Rats were autopsied 18 weeks or more after DMH treatment. Of 10 rats fed vitamin A, 10 μg/g diet, that died during DMH treatment, none had tumors; of 12 rats fed the deficient diet, 2 of 12 that died during treatment had tumors.

Diet (μg/g)	Vitamin A content: Serum (μg/100 ml)	Vitamin A content: Liver (μg/g)	% rats with colon carcinoma, given DMH: 420 mg/kg	275 mg/kg	195 mg/kg
175	97 ± 25[a]	683 ± 188	60	60	[b]
10	38 ± 5	67 ± 10	60	56	60
0–0.4	8.6 ± 1.5	0.4 ± 0.3	100	77	60

[a] Mean ± S.E.

[b] Not done.

Fat. Weisburger *et al.* (26) have reported increased colon tumor incidence and number in rats fed 20% corn oil or lard, compared with rats fed 5% of 1 of the 2 fats, and some increase in tumors in rats fed 5% corn oil, compared with rats fed 5% lard. Increased dietary fat was associated with increased fecal content of sterols, which may have a cocarcinogenic effect. In a pilot experiment, we fed rats an adequate semisynthetic diet that contained either 15% corn oil (19 rats) or 28% beef fat and 2% corn oil (19 rats) and gave them DMH, 30 mg/kg/week i.g. for 10 weeks. There was no significant different between the dietary groups in tumor incidence, number, or histological type (Table 2). The 2 studies differed in dose and route of administration of DMH and in the magnitude of the difference in lipid levels compared. In neither study was the expectation, derived from clinical studies, of finding an increased colon tumor incidence associated with increased intake of animal fat fulfilled. Correlation of tumor incidence with total fat intake was found when intakes were varied by a factor of 4 but not when varied by a factor of 2. In both studies, appropriate adjustments of nutrients were made by reciprocal alterations of carbohydrate content. The simple addition of fat to a complete diet, of course, dilutes all nutrients in the diet and reduces dietary intake because of the increased caloric density of the diet, so that observed results may depend on alteration of nutrients other than fat (24).

Fat and Lipotropes. Enhancement of hepatic tumor induction in lipotrope-deficient rats was reported 30 years ago (8). We have examined the effect of lipotrope deficiency on induction of tumors in liver and other organs by many different chemicals (22, 28, 29, 32). The experimental diet (Diet 2) is marginally, not severely, deficient in lipotropes and supports weight gain and longevity essentially equal to that supported by the adequate diet (Diet 1). Induction of hepatocarcinoma was increased or accelerated or both in rats fed Diet 2 and given AFB_1, NNDA, DBN, *N*-2-fluorenyl-acetamide, or 3,3-diphenyl-3-dimethylcarbomoyl-1-propyne (Table 3) (28, 29). The only hepatic carcinogen studied that was not more effective in deficient rats was DMN. NNDA induced more esophageal tumors also in deficient rats.

Induction of colon tumors by 2 different doses of DMH was enhanced in rats fed Diet 2 (Table 3) (32). Carcinogenesis in the stomach by MNNG or 3,3-diphenyl-3-dimethylcarbomoyl-1-propyne or in the urinary bladder by DBN or *N*-[3-(5-nitro-2-furyl)-2-thiazolyl]formamide was not affected by the dietary treatment (28).

One of the major ways nutritional condition may influence chemical carcinogenesis is by alteration of hepatic or

Table 2
Effect of varying dietary fat and fiber on DMH induction of colon tumors in rats

	% dietary		% of rats with carcinoma in		
	Fat	Cellulose	Colon	Small intestine	Zymbal's gland
Corn oil	15		84	21	37
Beef fat	28		58	11	11
+ Corn oil	2				
Corn oil	15	22.5	61	11	11

other microsomal mixed-function oxidases. Campbell and Hayes (5) recently reviewed and discussed the evidence for depression of the hepatic oxidases in experimental animals deficient in essential fatty acids, protein, lipotropes, vitamin A, riboflavin, ascorbic acid, vitamin E, selenium, calcium, magnesium, or zinc. Enzyme activity was increased by the addition of fat to adequate diets, but overall metabolism of foreign compounds may not have increased because fatty acids compete with other substrates for binding sites on the enzymes. In most of the studies cited, only hepatic enzymes were measured, but riboflavin deficiency reportedly depressed enzyme activity in fecal bacteria as well.

Rats fed Diet 2 had decreased levels of hepatic microsomal oxidases and did not alter their enzyme levels in response to AFB_1 treatment as did rats fed Diet 1 (29). The requirement for phosphatidylcholine in the microsomal enzyme system, possibly to maintain membrane integrity, may explain this dietary effect (5). We found a decreased rate of clearance of NNDA from the blood of rats fed Diet 2, no alteration of *N*-nitrosodimethylamine metabolism, and have in progress studies of metabolism of other carcinogens and studies to identify the dietary component(s) responsible for the effect on carcinogenesis (33). The addition of choline and methionine to lipotrope-deficient diets in earlier studies blocked AFB_1 carcinogenesis, but other components in the 2 diets may contribute also to the difference between them (8, 22). In particular, the enhancement by Diet 2 of DMH carcinogenesis may depend on the high-fat content of the diet. Similar combinations of dietary deficiencies and increased metabolic loads may be required to test the hypothesis that dietary abnormalities contribute to the causation of cancer.

The nutritional effects of nonnutrient substances added to the diet must also be considered. For example, addition of cholestyramine to the diet, which alters tumor number and site within the intestine, may reduce vitamin A absorption and storage (14, 23). The addition of cellulose to the diet may decrease dietary intake and retard growth. It did not alter the induction of colon tumors by azoxymethane given s.c. (37). In our preliminary study cited above, we examined the induction of colon tumors in a group of rats fed the 15% corn oil diet containing 22.5% cellulose. There was no difference in tumor incidence or number from the other 2 groups.

Studies of Immunological Effect on Colon Tumor Induction in Experimental Animals

The prognosis in colon cancer has been related to the intensity of the inflammatory response to the tumors (4). Nutritional condition may be important in this area, as well as in tumor induction, since both antibody formation and cell-mediated immunity are influenced by diet (7, 13). Immune responses in the gut are generally attributed to the scattered cells in the lamina propria rather than to the cells of the lymphoid aggregates. Reactivity to mitogens and staining reactions for surface immunoglobulins indicate that the scattered cells of the lamina propria of the small intestine are a mixture of T-, B-, and null cells, and that a similar mixture is found in the lymphoid aggregates (18). Colon lymphocytes have not been characterized but probably are similar to those of the small intestine.

We and others observed that, contrary to expectation, colon tumors induced in rats by DMH arose in mucosa lying over the lymphoid aggregates more frequently than would be expected to occur by chance (12, 36). The tumors that arose at those sites were the more malignant (by virtue of invasiveness and metastasis) mucinous adenocarcinomas. Second, we found that treatment of rats with BCG to increase the cellular immune response enhanced rather than

Table 3
Tumor incidence and latent period in rats fed adequate diet (Diet 1) or lipotrope-deficient, high-fat diet (Diet 2) (28, 29, 32)

Carcinogen	Target organ	% tumor incidence		Time to death (days)[a]	
		Diet 1	Diet 2	Diet 1	Diet 2
AFB_1, 375 μg	Liver	11	87[b]	392 ± 45[c]	388 ± 10
NNDA, 40 ppm, 18 wk	Liver	70	88	234 ± 10	204 ± 7[b]
NNDA, 40 ppm, 12 wk	Liver	24	60[b]	271 ± 35	244 ± 14
DBN, 3.7 g/kg	Liver	24	64[b]	238 ± 16	228 ± 7
N-2-Fluorenylacetamide, 0.02%, 0.0125%, 18 wk	Liver	19	41	247 ± 20	271 ± 16
DMH, 300 mg/kg	Colon	86	100	195 ± 6	172 ± 6[b]
DMH, 150 mg/kg	Colon	56	85	260 ± 20	249 ± 14

[a] Period between 1st dose of carcinogen and death with tumors in target organ.
[b] Compared to rats fed Diet 1; $p < 0.05$.
[c] Mean ± S.E.

reduced the induction of metastasizing mucinous adenocarcinomas (30).

Nonspecific stimulation of cellular immune reactions by bacteria or their products inhibits tumor development, growth, and metastasis under certain conditions in people and experimental animals (1). In rats, BCG given at the same time as an i.g. dose of DMBA significantly delayed mammary tumor development, but BCG injection after the appearance of the 1st tumor enhanced the further development of tumors (26). In mice, induction of sarcomas by methylcholanthrene was retarded by administration of BCG 2 weeks before or 2 to 6 weeks after carcinogen treatment, but, as with DMBA-induced mammary carcinoma, sarcoma development was enhanced if BCG was given only at the time tumors first appeared (17).

We studied the response of rats to injection of BCG into the colon immediately after DMH treatment and also of DMH-induced colon carcinomas to intratumor injection of BCG. The incidence of metastasizing mucinous adenocarcinoma of the colon was approximately 4 times greater in BCG-treated rats than in rats given a control injection into the colon (30). As in the previous studies, these tumors tended to occur in association with the lymphoid aggregates. The total incidence of colon tumors was not affected. Injection of BCG into primary, DMH-induced colon tumors had no discernible effect on tumor size over periods of observation ranging from 1 to 22 weeks.

As discussed above, rats fed Diet 2 were more susceptible to DMH carcinogenesis than rats fed Diet 1. Evidence for the immunological basis for this dietary effect was sought by examining the lymphoid tissue of the colon histologically, but we could detect no difference between rats fed Diet 1 or 2 in the size, distribution, or histological appearance of the lymphoid aggregates in the colon or the inflammatory infiltrate in the colon tumors (12). Lipotrope deficiency depresses cell-mediated immunity, and application of tests of T-cell function to the colon lymphocytes may demonstrate nutritional effects on their activity and response to tumors (13). We are adapting methods used to measure T-cell function in other tissues for use with lymphocytes derived from the colon aggregates and have found that the cells are stimulated by phytohemagglutinin to an uptake of [^{3}H]thymidine 4 to 6 times the unstimulated level; they do not respond to pokeweed mitogen.

In summary, studies in animal models of dietary interactions with colon tumor induction have demonstrated enhancement by increased dietary fat, particularly when coupled with lipotrope deficiency, but have not supported the epidemiological observation of enhancement by animal, compared with vegetable, fat. Vitamin A deficiency, also implicated by epidemiological studies, has given inconsistent results; tumor incidence has been increased, decreased, or not affected in deficient rats given different carcinogens. Hypervitaminosis A did not influence induction of colon tumors. Vitamin A has inconsistent effects also on induction of tumors of the respiratory tract but is anticarcinogenic in the skin and rodent forestomach. High local concentration may be required for an effect.

Lipotrope deficiency combined with increased dietary fat enhanced tumor induction by several hepatic carcinogens of different chemical classes and by DMH in the colon. The effect may be mediated through alteration of carcinogen metabolism, immunological responses, or target cell susceptibility. Both vitamin A and lipotropes exert their most significant effects on carcinogenesis in tissues which require them for maintenance of normal structure and function. Utilization of combined dietary stresses, *e.g.*, increased fat or protein and decreased vitamin A or lipotropes, which alter metabolic loads but do not seriously impair growth, may be necessary for demonstration of significant dietary effects on carcinogenesis.

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