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Fermentable property of dietary fiber may not determine cecal and colonic mucosal growth in fiber-fed rats

Hiroshi Hara, Keiko Suzuki, Satomi Kobayashi, and Takanori Kasai

Department of Bioscience and Chemistry, Faculty of Agriculture, Hokkaido University, Sapporo, Japan 060

Differences in cecal and colonic mucosal weight, DNA, RNA, and protein content were observed after feeding fiber-free or cellulose, sugar-beet fiber (SBF), psyllium- and guar gum-containing diets in Sprague-Dawley male rats in regard to fermentable and physical properties of the dietary fiber. In rats fed a low fermentable viscous fiber, psyllium, protein, RNA, and DNA contents in the cecal mucosa were greater than those in the fiber-free and two insoluble fiber groups. The effects of psyllium feeding on the colonic mucosa were much greater than those of the other groups, except RNA and DNA content in the SBF group. In rats fed a highly fermentable viscous polysaccharide, guar gum, changes in the cecal protein, RNA and DNA content were very similar to those in the psyllium group. In contrast, guar gum feeding did not influence any indications of the colonic mucosa. The ingestion of cellulose did not affect the cecal and colonic mucosa. Effects of a highly fermentable insoluble fiber, SBF, on the cecal mucosa were intermediate between cellulose and soluble fiber groups. Colonic DNA pool in the SBF group was high and comparable to that in the psyllium group. The present study shows that fermentable property is not sole determinant of the mucosal growth of the large intestine by dietary fiber, and the effects of physical stress by dietary fiber on the cecal and colonic mucosa may be greater than stimulation of fermented products. © Elsevier Science Inc. 1996 (J. Nutr. Biochem. 7:549–554, 1996.)

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Introduction

Large intestinal mucosa adapts to ingested foods, especially dietary fibers, functionally and morphologically. The ingestion of many dietary fibers induces mucosal enlargement. The mucosa cell growth may be involved in water and ion transport and also in the development of colon cancer.

Fiber fermentation in the large intestine is related to the mucosal cell growth.[1] Short-chain fatty acids (SCFAs) produced by cecal fermentation of dietary fiber are absorbed and used as an energy source of cells,[2] and induce mucosal cell proliferation.[3] It was reported that physical properties were also involved in the mucosal growth using dietary fiber with different viscosity.[4] However, the relationship between the trophic effects and physical or fermentable property of dietary fiber is not clear. The aim of the present study was to examine mucosal alterations after feeding dietary fibers, cellulose, sugar-beet fiber, psyllium, and guar gum. These fibers have different fermentabilities and different physical properties.

The fermentability of dietary fibers was evaluated with the cecal concentration of SCFA and with fecal excretion of gross energy derived from ingested dietary fiber.[5] Sugar-beet fiber is a highly fermentable, insoluble dietary fiber as shown in this issue. Psyllium and guar gum are the most popular laxative and a widely used modifier of food texture, respectively, and these fibers are viscous non-starch polysaccharides.

Methods and materials

Animals and diets

Male Sprague-Dawley rats (Japan SLC, Hamamatsu, Japan), weighing about 100 g, were fed a semipurified powdered diet[6–9] containing 250 g casein/kg diet [fiber-free diet (basal diet), shown

Address reprint requests to Dr. Hiroshi Hara at Department of Bioscience and Chemistry, Faculty of Agriculture, Hokkaido University, Kita-9, Nishi-9, Kita-ku, Sapporo 060.
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655 Avenue of the Americas, New York, NY 10010

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in *Table 1*] for 7 days, and divided into five groups of six rats. One group was fed the fiber-free diet and the other four groups were fed test diets containing cellulose [Powdered cellulose PC-200, 100 g/kg diet (16.2 MJ), Pfizer Inc., New York, NY USA], sugar-beet fiber [SBF, 100 g/kg diet (16.2 MJ), Nippon Beet Sugar MFG. Co., Ltd., Obihiro, Japan], Psyllium [100 g/kg diet (16.2 MJ), Procter & Gamble Far East Inc., Kobe, Japan], or Guar gum [Guacol, 50 g/kg diet (17.1 MJ), Daiei Yakuhin Kogyo, Kanagawa, Japan] for 3 weeks. Digestible energy shown in parentheses (MJ/kg test diet) was calculated based on gross energy of a fiber-free (basal) diet measured by bomb calorimetry (18.0 MJ/kg basal diet, CA-3, Shimadzu Corporation, Kyoto, Japan). Body weight gain in rats fed diet containing guar gum, 100 g/kg diet was lower compared with that in rats fed fiber-free diet (unpublished observation). So, half amount of guar gum source was supplied to a test diet. The fiber sources contained 90.2%, 90% (arabinoxylan 85%) and 78.4% of total fiber in cellulose, psyllium, and guar gum sources, respectively (personal communications). A complex fiber source, sugar-beet fiber preparation contains 81.4% total dietary fiber that contains pectin (14%), hemicellulose (22%), cellulose (23%), and lignin (3%) (10). These fiber sources were added to a fiber-free diet at the expense of the whole diet not to change nutrient balance. Body weight and food intake were measured every day. Feces were collected from the 19th to the 21st day after feeding the test diets to measure gross energy excretion in feces. On the last day, aortic blood was withdrawn under pentobarbital anesthesia (Nembutal: sodium pentobarbital, 50 mg/kg body weight, Abbott Laboratories, North Chicago, IL, USA). The cecum and colon with their contents were removed. The cecal contents were collected and weighed. The cecal and colonic walls were washed with saline and weighed. These were stored at –40°C. Throughout the experiment, rats were housed in individual cages in a temperature controlled room at 22°C.

The study was approved by the Hokkaido University Animal Committee, and animals were maintained in accordance with the guidelines for the care and use of laboratory animals of Hokkaido University.

Table 1 Composition of fiber-free (basal) diet

	Fiber-free diet[a]
	g/kg diet
Casein[b]	250
Corn oil[c]	50
Mineral mixture[d]	40
Vitamin mixture[e]	10
Choline bitartrate	4.0
Sucrose	to make 1 kg

[a]Fiber sources were added to a fiber-free diet at the expense of the whole diet. Details were described in Methods and materials.
[b]Casein (ALACID; New Zealand Dairy Board, Wellington, New Zealand).
[c]Retinyl palmitate (7.66 μmol/kg diet) and ergocalciferol (0.0504 μmol/kg diet) were added to corn oil.
[d]The mineral mixture is prepared based on the AIN-76 Workshop held in 1989 (6). It provided (mg/kg diet): Ca, 4491; P, 2997; K, 3746; Mg, 375; Fe, 100; I, 0.32; Mn, 10.0; Zn, 34.7; Cu, 6.00; Na, 4279; Cl, 6542; Se, 1.05; Mo, 1.00; Cr, 0.50; B, 0.50; V, 0.25; Sn, 2.00; As, 1.00; Si, 20.0; Ni, 1.00; F, 2.72; Co, 0.20.
[e]The vitamin mixture without vitamin E was prepared in accordance with the AIN-76 mixture[7] except that menadione and L-ascorbic acid were added to make 5.81 μmol/kg[8], and 284 μmol/kg[9] diet, respectively.

Analyses

Frozen cecum and colon walls were thawed, and mucosa of each segment was pressed out from the side of the serosal membrane as described previously.[11] The mucosa was weighed and homogenized in a Teflon homogenizer at 500 rpm with three strokes. Concentrations of protein and DNA in the homogenates of the mucosa were evaluated by a modified Lowry method[12,13] and by the method of Brunk et al.[14] using 4′,6-diamidino-2-phenylindole, respectively. The concentration of total RNA was determined colorimetrically by the orcinol method[15] after treatment as described by Fleck and Munro.[16]

The feces were freeze-dried, weighed, and milled. Gross energy in fiber preparations and powdered feces were measured by bomb calorimetry (CA-3, Shimadzu Corporation).

The cecal contents were homogenized with 100 g/L of distilled water. SCFA concentrations in the homogenate were evaluated by a previously described method.[5] Individual SCFA were measured by gas-liquid chromatography [Shimadzu GC-14A] with a prepacked glass column [1600 mm × 3 mm, SP-1220 + H_3PO_4 (15% + 1%) on 80 to 100 mesh chromosorb W-AW DMCS, Shimadzu Corporation] after adding phosphoric acid (final concentration 0.67 mol/L).

Calculations and Statistics

The mucosal content of protein, RNA, and DNA are given as amounts per rats (pool).

Fermentable energy in dietary fiber sources in the test diets was evaluated with previous described method[5] applying the following equation:

$$\text{Fermentable energy in dietary fiber (DF) (\%)} = \frac{\text{[Energy in DF consumed (KJ/3d) − Fecal energy excretion derived from DF(KJ/3d)]}}{\text{Energy in DF consumed (KJ/3d)}} \times 100 \quad (1)$$

Fecal energy excretion derived from DF was estimated by subtracting the endogenous energy excretion in feces from the fecal energy of each rat in the fiber groups. The endogenous energy in feces was evaluated by applying the following equation:

$$\text{Endogenous energy in feces of rat fed a fiber-containing diet} = \text{Average of fecal energy in the fiber-free group} \times \frac{\text{Weight of diet consumed without fiber source in rat of the fiber group}}{\text{Average of food intake in the fiber-free group}} \quad (2)$$

Data were analyzed by one-way analysis of variance (ANOVA) and significant differences among diet groups were determined by Duncan's multiple range test ($P < 0.05$; SAS version 6.07, SAS Institute, Cary, NC, USA).

Results

Table 2 shows that the feeding of four fiber sources did not influence body weight gains, food intakes, and feed efficiency for 3 weeks.

As shown in *Table 3*, the sum of major SCFAs (acetic, propionic, and butyric acids) concentration in the cecal contents was higher in the guar gum and SBF groups and was lower in the psyllium group than that in rats fed fiber-free and cellulose diets. In vivo fermentable energy evaluated with gross energy excretion in feces was about 70% in guar

Table 2 Body weight gain, food intake and feed efficiency in rats fed test diets for 3 weeks*

Diet	Body weight gain	Food intake	Feed efficiency**
	g/3 weeks		g/g basal diet
Fiber-free	149 ± 5.2	392 ± 20.6	0.383 ± 0.010
Cellulose	148 ± 7.0	416 ± 18.4	0.398 ± 0.012
Sugar-beet fiber	143 ± 5.2	392 ± 20.3	0.408 ± 0.009
Psyllium	142 ± 3.7	368 ± 7.1	0.429 ± 0.017
Guar gum	138 ± 8.9	368 ± 26.1	0.397 ± 0.012
ANOVA (*P* value)			
Diet	0.6706	0.4154	0.1324

*Values are means ± SEM for six rats.
**Feed efficiencies were calculated with body weight gain and intake of basal diet in each test diet, which was multiplied by factors 1.0 for fiber-free, 0.95 for guar gum, and 0.9 for other groups to food intakes for 3 weeks.

gum and SBF, and was less than 10% in psyllium and negligible in cellulose.

The wet weight of cecal content was very high in the psyllium group, which was followed by those in the guar gum group, then in the SBF group as shown in *Table 4*. The value of the cellulose-fed rats was not different from that of rats fed fiber-free diet. Fecal dry weight for 3 days was higher in the cellulose and psyllium groups than the other groups.

Table 3 SCFA concentration in the cecal content in rats fed test diets for 3 weeks and fermentable energy of dietary fiber using rats fed fiber-containing diets*

Diet	Total SCFA concentration	Fermentable energy**
	mmol/g wet cecal content	%
Fiber-free	69.0 ± 6.05^{b}	
Cellulose	56.0 ± 1.65^{b}	−1.25 ± 5.69^{b}
Sugar-beet fiber	90.6 ± 6.00^{a}	70.8 ± 4.75^{a}
Psyllium	24.5 ± 3.84^{c}	8.10 ± 10.8^{b}
Guar gum	96.4 ± 8.23^{a}	74.5 ± 8.21^{a}
ANOVA (*P* value)	<0.0001	<0.0001

Diet	Acetic acid	Propionic acid	Butyric acid
	mmol/g wet cecal content		
Fiber-free	44.8 ± 4.25^{b}	18.1 ± 5.69^{b}	6.13 ± 1.10^{c}
Cellulose	33.4 ± 1.67^{c}	14.6 ± 0.75^{b,c}	8.02 ± 0.81^{b,c}
Sugar-beet fiber	63.5 ± 4.57^{a}	11.0 ± 0.79^{c}	16.1 ± 1.41^{a}
Psyllium	15.0 ± 2.19^{d}	4.35 ± 0.40^{d}	5.10 ± 2.28^{c}
Guar gum	57.6 ± 4.84^{a}	26.4 ± 3.43^{a}	12.4 ± 1.53^{a,b}
ANOVA (*P* value)	<0.0001	<0.0001	<0.0001

*Values are means ± SEM for six rats.
**In vivo fermentabilities of dietary fiber were estimated from energy intakes and excretion into feces of fiber preparations from the 19th day to the 21st day. Details are described in Methods and materials.
^{a,b,c,d}Values not sharing a common superscript letter differ significantly ($P < 0.05$).

Table 4 Wet weight of the cecal content in rats fed test diets for 3 weeks and fecal dry weight for 3 days (from the 19th to the 21st day after feeding the test diets)*

Diet	Cecal content	Fecal excretion
	wet g/rat	dry g/3 days
Fiber-free	1.71 ± 0.155^{d}	1.49 ± 0.067^{c}
Cellulose	2.19 ± 0.181^{d}	6.69 ± 0.404^{a}
Sugar-beet fiber	3.04 ± 0.286^{c}	3.20 ± 0.468^{b}
Psyllium	6.83 ± 0.135^{a}	7.60 ± 1.03^{a}
Guar gum	3.61 ± 0.177^{b}	2.70 ± 0.395^{b,c}
ANOVA (*P* value)		
Diet	<0.0001	<0.0001

*Values are means ± SEM for six rats.
^{a,b,c,d}Values not sharing a common superscript letter differ significantly ($P < 0.05$).

Cecal and colonic wall weights (open plus filled bars, statistical significance is shown with capital letters) and their mucosal weights (open bar) are shown in *Figure 1*. Cecal mucosal weight was the heaviest in rats fed guar gum, which was followed by that in rats fed psyllium, then SBF, and the weight was not influenced by cellulose feeding. Colonic mucosal weight in the psyllium group was significantly greater than those in the other fibers and fiber-free groups.

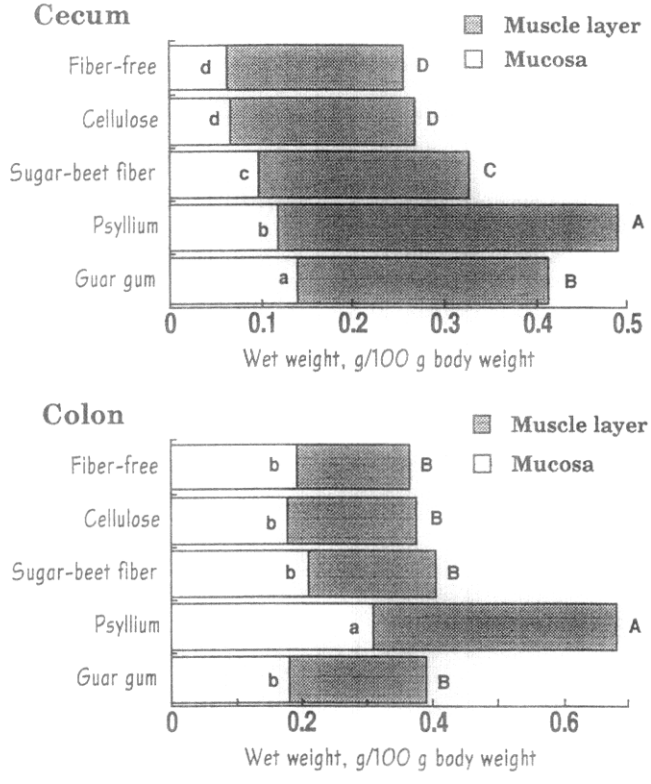

Figure 1 Differences in the cecal and colonic mucosal (open bar) and wall (mucosa + muscle layer) weights after feeding of test diets containing various dietary fibers for 3 weeks. Values are means for 6 rats. *P* values of one-way ANOVA in cecal and colonic mucosal and wall weight were <0.0001. Capital and small letters show statistical significance in the wall (total bar) and mucosal (open bar) weights ($P < 0.05$).

Differences in cecal mucosal protein, total RNA, and the DNA pools among all the groups were similar as shown in *Figure 2*. That is, these mucosal indications of both the soluble fiber groups and of the SBF group were 2 fold and 1.5 fold higher than those of the fiber-free and cellulose groups, respectively. Ingestion of cellulose did not have any effect on the cecal mucosa.

Colonic mucosal pools of protein, RNA, and DNA shown in *Figure 3* was higher in the psyllium group than in the fiber-free and cellulose groups. In rats fed SBF, the DNA pool was comparable to that in rats fed psyllium. The protein pool in the SBF group was higher than those in the fiber-free and cellulose groups and lower than that in the psyllium groups.

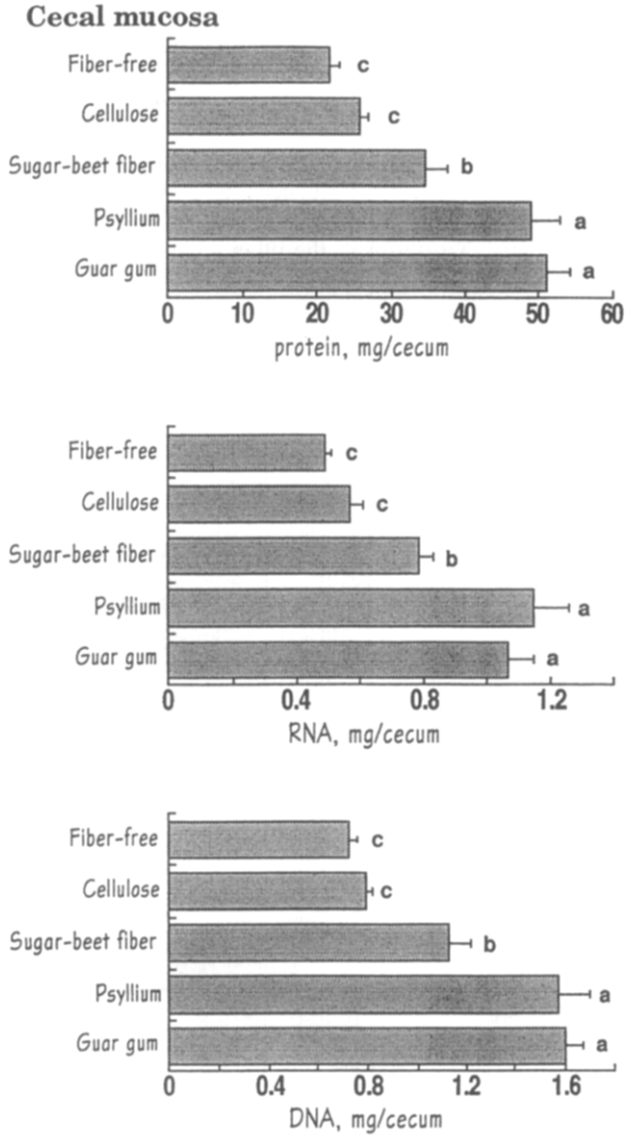

Figure 2 Differences in the cecal mucosal pools of protein, RNA and DNA after feeding of test diets containing various dietary fibers for 3 weeks. Values are means ± SEM for 6 rats. *P* values of one-way ANOVA in the protein, RNA, and DNA pools were <0.0001. Values not sharing a common superscript letter differ significantly ($P < 0.05$).

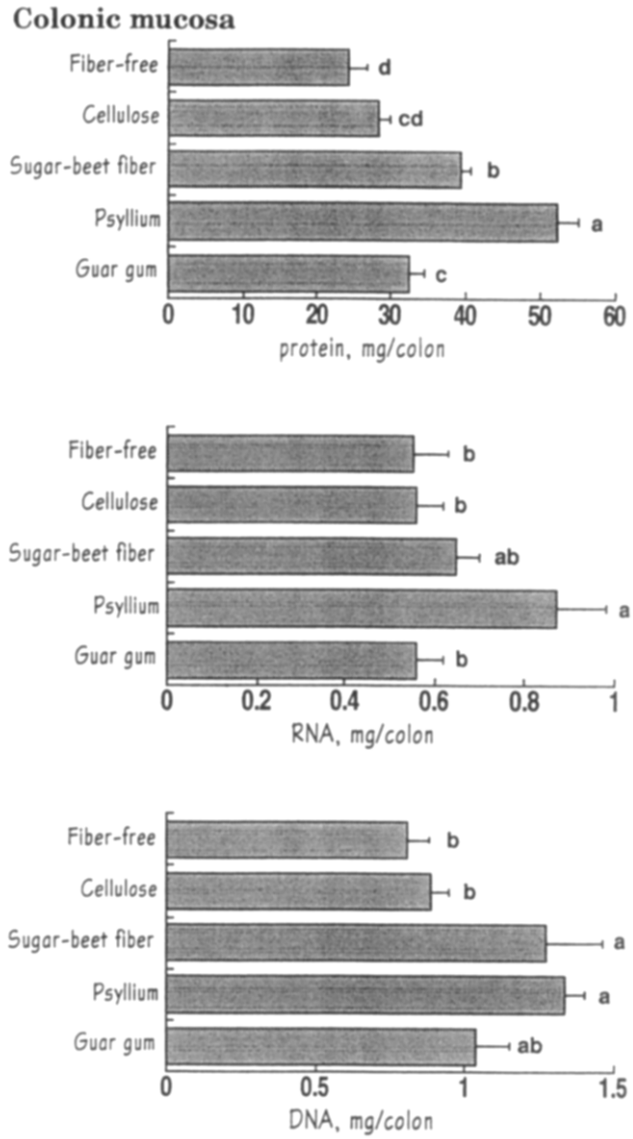

Figure 3 Differences in the colonic mucosal pools of protein, RNA and DNA after feeding of test diets containing various dietary fibers for 3 weeks. Values are means ± SEM for 6 rats. *P* values of one-way ANOVA in protein, RNA, and DNA pools were <0.0001, 0.0219, and 0.0076, respectively. Values not sharing a common superscript letter differ significantly ($P < 0.05$).

Discussion

In the cecal mucosa, protein, RNA and DNA pool size were greater in rats fed highly viscous, water-soluble dietary fibers, guar gum and psyllium than in rats fed insoluble fibers, cellulose and SBF (*Figure 2*). Chemical stimuli by fermented products, such as SCFA concentrations in the cecal content were increased in guar gum- or SBF-fed rats, but the concentration was very low in the psyllium group as shown in *Table 3*. The low fermentability of psyllium is also shown in *Table 3* by gross energy excretion into feces, and that is also shown in humans.[17] Thus, the fermentation of dietary fiber in the cecum may not predominantly contribute to the mucosal hypertrophy in the soluble fiber groups, especially in the psyllium group. Folino et al.[18] suggest that

fermentation of dietary fiber is not a key determinant of mucosal proliferation in the proximal colon.

The weight of cecal content in guar gum and psyllium fed rats was greater than those of the other fiber groups, but the weight of the guar gum group was lower than that of the psyllium group (*Table 4*). In the guar gum group, SCFA may affect the cecal mucosa in addition to the mechanical challenge. Zang and Lupton[19] showed that the concentration of SCFA and cell proliferation are positively correlated in the cecum but not in the colon. The mechanical stress-induced increment of the cecal mucosal DNA in the psyllium group shown in the present study is possibly due to prolongation of cell life span, not to enhancement of cell proliferation.

In the colon, effects of psyllium feeding on the mucosa were the greatest. The fermentability of psyllium was very low, so most of the ingested psyllium reached the colon. Also, feces in rats fed psyllium contained high water content.[22] These results suggest that physical stress to the colonic wall is high and that it is a major stimulus for the colonic mucosal hypertrophy in rats fed psyllium. Effects of guar gum on the colonic mucosa were very low. Cecal fermentation of guar gum is high, as shown in *Table 3* (SCFA concentration). Edwards and Eastwood[20] also demonstrated that guar gum is rapidly fermented in the cecum. The absence of a trophic effect in the guar gum group may be due to a decrease of the bulking effect with guar gum due to degradation of guar gum in the cecum. Pell et al.[21] showed that guar gum enhanced cell division of the cecal mucosa, but not of the colonic mucosa in rats.

In comparison between two insoluble fiber sources, cellulose and SBF, fermentability of SBF evaluated with gross energy excretion in feces was much higher than that of cellulose, and was comparable with that of guar gum (*Table 3*). Johnson et al.[22] reported that the digestible energy of SBF was 64%, which was similar to our estimation. The enhancement of cecal fermentation in rats fed SBF may cause mild increases in the protein, RNA, and DNA pool sizes in the cecal mucosa. In the colonic mucosa, the DNA pool was much higher in the SBF-fed rats than in the cellulose-fed rats, and was comparable to that in the psyllium group. The bulking effect of SBF in the colon may not be higher than that of cellulose because fecal weight was lower in the SBF group as shown in *Table 4*. Possibly, SBF was degraded and fermented not only in the cecum, but also in the colon because insoluble fiber, SBF, may be fermented slowly. We observed that the SCFA pool of the colon were about 20 fold higher in rats fed SBF diet than in rats fed fiber-free diet (unpublished data). The enlargement of the DNA pool size in the colonic mucosa in the SBF group may be involved in the SCFA production by the colon.

No effects of cellulose feeding on the mucosa were observed. In the colon of rats fed cellulose, bulking effects of cellulose may be rather high (high fecal output shown in *Table 4*), but water-holding capacity of cellulose may be very low because wet weight of the cecal contents was the lowest among the fiber-fed groups. Mechanical challenge to the colon in rats fed cellulose may be low.

Dimethylhydrazine-induced colon cancer is depressed by SBF feeding.[23] The suppression of colon cancer may be responsible for faster transit and SCFA, especially butyrate, production in the colonic lumen.[24,25] Enhancement of mucosal cell proliferation is a possible mechanism for the expansion of colonic mucosal DNA pool size shown in the SBF and psyllium groups (*Figure 3*). The increase in cell proliferation may lead to an increase in the incidence of colonic tumorigenesis. Psyllium also suppresses colon cancer.[26,27] These results suggest that increase in DNA pool size is not due to cell proliferation, but to prolongation of cell life span in the psyllium group, as discussed in a case of the cecal mucosa. Another possibility is that changes in the colonic environment with psyllium feeding suppress colon cancer.

The present study shows that mechanical challenge with fiber feeding is a determinant of the trophic effects on the cecal and colonic mucosa, which was demonstrated with the greatest effects on the mucosa in the psyllium group. Chemical stimuli by fermented products may be also involved in the mucosal trophic effects by dietary fiber, which is showed by great effects of SBF on the colonic mucosa and the greatest effects of guar gum feeding on the cecal mucosa.

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