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Effect of Perilla Oil Rich in α-Linolenic Acid on Colon Tumor Incidence, Plasma Thromboxane B_2 Level and Fatty Acid Profile of Colonic Mucosal Lipids in Chemical Carcinogen-Treated Rats*

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ABSTRACT

This study was designed to compare the effect of different dietary fats on the incidence of colorectal tumor, the level of plasma thromboxane B_2(TXB_2) and fatty acid profiles of platelet and colonic mucosal lipids in N-methyl-N'-nitro-N-nitrosoguanidine(MNNG)-treated rats. Male Sprague Dawley rats, at 8 weeks old, were divided into 2 groups and infused intrarectally with saline(control group) or with 2mg MNNG(carcinogen-treated goup) twice a week for 3 weeks. Each group was again divided into 4 groups and fed one of four diets(BT, CO, PO, FO) containing dietary fat at 9%(w/w) level for 37 weeks. Dietary fats were beef tallow(7.2%)+corn oil(1.8%) for BT, corn oil(9.0%) for CO, perilla oil(9.0%) for PO, fish oil(6.5%)+corn oil(2.5%) for FO diets. MNNG-treated rats had colonic tumor, while no tumor was found in control group. BT-NMMG rats had a higher incidence of colon tumors(adenocarcinoma and adenoma) than others. Tumor sizes in BT-MNNG rats ranged from 2mm papillary form to 15mm of polypoid. However, the size of tumors in PO-MNNG or FO-MNNG rats could not be measured by gross examination. BT-MNNG and CO-MNNG groups were higher in the level of plasma TXB_2 and the ratio of c20 : 4/c20 : 5 in platelet. PO-MNNG groups were lower in the ratio of c20 : 4/c20 : 5($p<0.05$) in fatty acid of colonic mucosal lipids suggesting that perilla oil and fish oil could reduce the level of PGE_2 and TXB_2 by modifying its precursor content and restrain tumor promotion in colon. Effect of perilla oil rich in α-linolenic acid on colon carcinogenesis was similar to that of fish oil and thus perilla oil could have a protective effect against colon cancer possibly by inhibiting the production of arachidonic acid metabolite.

KEY WORDS : colon tumor · n-3 fatty acids · perilla oil · fish oil · MNNG.

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Introduction

Epidemiological studies have demonstrated a strong association between high fat intake and an increased risk of colon cancer[1]. Studies on animal models have made clear that diets high in fats derived from either animal or vegetable source enhance the development of chemical carcinogen-induced colon cancer[1]. However, some fats(coconut oil and olive oil) low in linoleic acid (18 : 2n-6 ; LA) did not enhance the carcinogenic effect of a chemical and fish oil diet high in n-3 fatty acids inhibited colon cencer development in rats[2)3)].

Prostaglandin(PG) synthesis was reported to be closely related to the type of dietary fat. Linoleic acid is desaturated and provides arachidonic acid(20 : 4n-6, AA) in cellular phospholipids which is the precursor of 2-series PG such as prostaglandin E_2(PGE_2) and thromboxane A_2(TXA_2). However, dietary eicosapentaenoic acid(20 : 5 n-3 ; EPA) inhibits not only the metabolism of AA via cyclooxygenase but also the conversion of LA to AA. Another essential fatty acid(EFA), α-linolenic acid(18 : 3n-3, LNA), is converted to EPA and docosahexaenoic acid(22 : 6n-3, DHA) in the liver, and these n-3 fatty acids replace n-6 fatty acid in membrane phospholipid pools in various types of cells[4]. Thus, perilla oil rich in n-3 LNA might decrease synthesis of 2-series of PGs.

PG level could be modified by carcinogenic process. High level of PGs have been found in the blood or urine of tumor-bearing animals. Increased levels of eicosanoids could be seen in malignant tumors of the breast and gastrointestinal tract[3)5)6)]. Since TXA_2 act as a cocarcinogen of colon cancer, any modification of AA substrate by the type of dietary fat might influence the colon carcinogenesis[7)]. The main purpose of the present study was designed to compare the effect of perilla oil on the frequency of colorectal tumor and plasma TXB_2 and fatty acid profiles of platelet and colonic mucosal lipid to other dietary fats in MNNG-treated rats.

Materials and Methods

1. Treatments

Male Sprague Dawley rats were fed chow diet until the end of 8 weeks old and were then randomly divided into 2 groups. Forty rats were assigned to 4 dietary groups of control and 145 rats for 4 dietary groups of NMMG-treated rats. Each rat was infused intrarectally with 2mg MNNG twice a week for 3 weeks and with saline for control groups. A relatively low amount of dietary fat was selected to have the same level of recommended dietary allowance for Korean and a low dose of MNNG was given to avoid the production of large number of colon tumors. After last infusion, each group was again divided into four groups and were fed one of four experimental diets(BT, CO, PO, FO) for 37 weeks. Different dietary fats were given at the level of 9%(w/w) of diet.

2. Experimental Diets

Experimental diets were composed of protein 20%, carbohydrate 60.2% fat 19.8% by calorie and were different only in the composition of dietary fatty acids. The dietary fats were beef tallow (BT), corn oil(CO), perilla oil(PO) and fish oil (FO) as a source of saturated fatty acid(SFA), LA, LNA, and EPA plus DHA, respectively. In order to compare the effect of dietary n-6 LA, n-3 LNA and n-3 EPA+DHA, small amount of corn oil was added to BT and FO diets to give the constant level of LA(2.7−3.4% kcal)(Table 1 and 2).

3. Colon Tumor Examination

All rats were autopsied after 37 weeks of experimental feeding period and the organs(liver, lung, heart, intestine) were examined grossly and histologically for the number and type and the size of tumors. About 1.5cm-sections of colon were fixed in 10% formalin and embedded in paraffin, and the sections were stained with hematoxylin and eosin.

Table 1. Composition of experimental diet

Ingredients (g/100g diet)		Dietary groups BT	CO	PO	FO
Corn starch		61.6	61.6	61.6	61.6
Casein		20.4	20.4	20.4	20.4
Fat or oil[1]	bt	7.2	—	—	—
	co	1.8	9.0	—	2.5
	po	—	—	9.0	—
	fo	—	—	—	6.5
DL-Methionine		0.3	0.3	0.3	0.3
Salt mixture[2]		3.2	3.2	3.2	3.2
Zinc mixture[3]		0.8	0.8	0.8	0.8
Vitamin mixture[4]		1.0	1.0	1.0	1.0
α-cellulose		3.7	3.7	3.7	3.7

[1]3mg vitamin A and 1.5mg vitamin D were dissolved in 150g oil.
[2]Hubble Mendel Wakeman mixture(per 100g)(ref 10)
[3]Zinc mixture : 1.67g Zn-acetate/kg corn starch
[4]Vitamin mixture : see ref 10.
bt : beef tallow co : corn oil po : perilla oil
fo : fish oil

4. Biochemical Analysis

Platelet was collected from aliquot of platelet rich plasma(PRP) as described in Park and Kim [8] and colonic mucosal layer was scraped off with spatula from large intestine. Lipid was extracted from platelet and colonic mucosal layer by the method of Folch et. al[9]. Phospholipid(PL) was separated from the lipid extract of platelet by thin layer chromatography[10] and the fatty acid profiles of platelet PL and total lipid extract of colonic mucosal layer were obtained by gas chromatography[11] and the relative percentage of each fatty acid was compared. Stable form of TXB_2 in plasma collected from collagen treated PRP was assayed by the mothod of radioimmunoassay[8][12].

Results

1. Body Weight Change

Table 3 shows that there was no significant difference in body weight gain among experimental groups even though the body weight gain of PO group was higher than those of any other groups.

2. Tumor Incidence

No tumor were found in the colon or other organs of rats without carcinogen. Table 4 summarizes the incidence of colon tumors in MNNG-treated rats. Rats fed dietary fats with MNNG

Table 2. Contents of n-6 and n-3 fatty acids in experimental diets

Diet groups	Fat (g/100g diet)	n-6 LA (% kcal)	n-3 LNA (% kcal)	n-3 EPA+DHA (% kcal)
BT	bt 7.2+co 1.8	3.2	0.1	—
CO	co 9.0	11.4	0.2	—
PO	po 9.0	2.7	12.2	—
FO	fo 6.5+co 2.5	3.4	0.2	6.2

bt : beef tallow
co : corn oil
po : perilla oil
fo : fish oil concentrate
LA : linoleic acid(c18 : 2)
LNA : α-linolenic acide(c18 : 3)
EPA : total of eicosapentaenoic acid(c20 : 5) and docosahexaenoic acid(c22 : 6)

Table 3. Body weight change of experimental groups

Groups	Times(weeks)										
	8	12	16	20	24	28	32	36	40	44	48
BT(10)	279.9	352.5	424.0	472.0	513.4	534.6	545.3	554.0	552.7	564.2	550.5
CO(10)	300.3	374.1	442.9	496.6	537.4	566.6	568.8	569.4	581.8	595.5	586.2
PO(10)	297.5	370.6	438.5	509.2	549.4	568.8	577.7	571.7	592.3	602.1	602.6
FO(10)	301.1	360.6	431.0	491.2	529.3	538.6	544.3	546.1	554.6	561.7	558.4
BT-MNNG(30)	287.6	370.0	449.9	506.8	543.1	566.0	559.0	556.7	561.5	560.2	560.8
CO-MNNG(55)	295.7	367.0	461.5	521.4	562.4	579.5	569.5	546.7	549.9	548.2	550.9
PO-MNNG(30)	298.1	380.6	445.7	513.7	556.2	586.4	581.9	561.2	580.7	590.4	585.1
FO-MNNG(30)	291.4	375.5	450.3	515.4	555.4	577.4	553.6	554.2	565.3	558.2	556.1

All rats were fed chow diet until the end of 8 weeks old and received saline or MNNG.
MNNG : N-methyl-N'-nitro-N-nitrosoguanidine(dissolved in saline to give 4mg/ml).
( ) : Number of rats

Table 4. Effect of dietary fats on colon tumor incidence in rats treated with saline or MNNG

	Rat Number with tumor	Total no tumor	Adeno-carcinoma	Adenoma
Control(40)	0	0	0	0
BT-MNNG(30)	10(33.3%)	13	6	7
CO-MNNG(55)	8(14.5%)	9	4	5
PO-MNNG(30)	3(10.0%)	3	—	3
FO-MNNG(30)	2(6.7%)	2	—	2

MNNG : N-methyl-N'-nitro-N-nitrosoguanidine 12mg infused i.r.
Control : All groups of BT, CO, PO, FO diets with saline infusion.
( ) : Number of rats

treatment had colonic tumors in the distal part of the large bowel. Rats fed BT diet with MNNG treatment(called as BT-MNNG) had a higher incidence of colon tumors(33.3%) than did those of CO-MNNG(6.7%) groups. BT-MNNG group developed more adenocarcinoma and adenoma than did PO-MNNG or FO-MNNG group. CO-MNNG group also produced less incidence of tumors than did BT-MNNG group but higher incidence of adenocarcinoma and adenoma than did PO-MNNG and FO-MNNG groups. Most of the lesion in colon was diagnosed microscopically as adenoma and a few cases developed into adenocarcinoma. Tumor sizes in BT-MNNG and CO-MNNG groups ranged from 2mm of papillary form to 15mm of polypoid. However, the size of tumors in PO-MNNG and FO-MNNG groups could not be measured by gross examination.

Table 5. Effect of dietary fats on plasma thromboxane B_2 level in MNNG-Treated rats

Groups	TXB_2(ng/ml)
BT-MNNG	$6.85\pm 1.93(10)^a$
CO-MNNG	$4.23\pm 1.20(10)^a$
PO-MNNG	$1.61\pm 0.36(10)^b$
FO-MNNG	$1.29\pm 0.29(9)^b$

Values with different superscript were significantly different at $P\leq 0.05$ by Duncan's multiple range test.

3. Thromboxane B_2

As shown in Table 5, the levels of plasma TXB_2 in BT-MNNG and CO-MNNG groups were higher than those in the groups of PO-MNNG and FO-NMMG($p<0.05$). The level of TXB_2 in

BT-MNNG group was greater than that in CO-MNNG group but not significant. The effect of perilla oil was not significantly different from that of fish oil.

4. Fatty Acid Profile

As shown in the fatty acid profile of platelet PL(Table 6), the relative proportion of c18 : 2 was siginificantly higher in the groups of BT-MNNG and CO-MNNG than in those of PO-MNNG and FO-MNNG. The proportion of c20 : 4 in the groups of BT-MNNG and CO-MNNG was also relatively higher than that in PO-MNNG and FO-MNNG, but the value of BT-MNNG group was only significantly higher than that of FO-MNNG group. The proportions of c20 : 5 and c22 : 5 of FO-MNNG group were higher than that of CO-MNNG group and c22 : 6 was higher in FO-MNNG group as compared to others($p<0.05$). Thus, total amount of n-6 series of fatty acids of BT-MNNG group was higher than those of PO-MNNG and FO-MNNG groups, but total amount of n-3 series of fatty acids of PO-MNNG and FO-MNNG groups was higher than that of CO-MNNG group and there was no significant difference between PO-MNNG and FO-MNNG group.

In the fatty acid profile of colonic mucosal lipid (Table 7), the proportions of c18 : 2 in PO-MNNG and FO-MNNG groups were higher than

Table 6. Effect of dietary fats on fatty acid profile of platelet phospholipid in MNNG-Treated rats

Fatty acids	BT-MNNG	CO-MNNG	PO-MNNG	FO-MNNG
c14 : 0	2.57± 1.63^{a}	2.36± 1.76^{a}	2.70± 0.84^{a}	2.45± 1.30^{a}
c16 : 0	21.32± 4.24^{ab}	25.46± 5.09^{b}	15.39± 2.33^{a}	16.56± 5.19^{ab}
c16 : 1	3.13± 1.17^{ab}	1.97± 0.91^{a}	4.30± 0.93^{b}	1.80± 0.56^{a}
c18 : 0	13.12± 1.75^{a}	14.45± 2.96^{a}	11.70± 2.26^{a}	14.39± 2.66^{a}
c18 : 1	7.23± 1.92^{b}	8.11± 4.01^{ab}	5.79± 0.91^{b}	3.72± 0.99^{a}
c18 : 2	8.48± 6.60^{ab}	8.49± 4.11^{b}	3.44± 0.80^{a}	3.72± 2.14^{a}
c18 : 3	3.30± 1.82^{a}	3.27± 1.78^{a}	4.92± 0.94^{a}	3.12± 1.39^{a}
c20 : 0	3.23± 2.28^{ab}	1.91± 1.41^{ac}	4.59± 0.76^{b}	2.41± 0.79^{a}
c20 : 2	3.67± 2.10^{a}	4.02± 1.64^{a}	4.06± 0.93^{a}	5.96± 2.89^{a}
c20 : 4	13.23± 2.52^{b}	11.18± 2.44^{a}	11.81± 1.90^{a}	7.32± 3.07^{a}
c20 : 5	3.97± 2.28^{ab}	3.56± 1.08^{a}	5.33± 1.51^{ab}	5.88± 1.28^{b}
c22 : 0	3.01± 1.68^{a}	4.26± 1.94^{a}	3.47± 0.66^{a}	3.89± 1.33^{a}
c22 : 1	1.77± 1.14^{a}	2.47± 1.81^{ab}	3.14± 1.29^{ab}	4.53± 1.44^{b}
c22 : 4	2.36± 2.70^{a}	trace	2.66± 1.11^{a}	trace
c22 : 5	3.88± 1.31^{ab}	3.30± 1.09^{a}	5.35± 1.59^{ab}	6.84± 1.92^{b}
c22 : 6	3.73± 1.32^{a}	3.68± 1.37^{a}	3.36± 2.05^{a}	5.50± 2.34^{a}
c24 : 1	3.66± 2.15^{a}	4.12± 1.36^{a}	5.84± 1.45^{a}	6.68± 2.00^{a}
$\sum$n-6	25.95± 3.72^{b}	22.12± 4.95^{ab}	20.20± 2.02^{ab}	16.63± 3.33^{a}
$\sum$n-3	13.74± 5.43^{ab}	13.41± 3.14^{a}	18.97± 2.11^{b}	21.34± 4.71^{b}
n-6/n-3	2.29± 1.41^{a}	1.73± 0.51^{a}	1.07± 0.13^{a}	0.83± 0.30^{a}
20 : 4/20 : 5	3.34± 1.11^{b}	4.02± 1.71^{b}	2.32± 0.56^{ab}	1.31± 0.64^{a}

Values sharing common superscripts in the same row were not significantly different at $p<0.05$ by Duncan's multiple range test.

Values are Mean± SD of 10 pooled samples of 3 rats.

Values are expressed as the relative % of total fatty acids.

Table 7. Effect of dietary fats on fatty acid profile of colonic mucosal lipids in MNNG-Treated rats

Fatty acids	BT-MNNG	CO-MNNG	PO-MNNG	FO-MNNG
c14 : 0	0.82± 0.80^{a}	0.64± 0.21^{a}	0.84± 0.23^{a}	2.54± 0.42^{b}
c16 : 0	19.37± 1.17^{b}	18.49± 1.77^{b}	15.34± 1.76^{a}	20.27± 1.08^{b}
c16 : 1	16.73± 3.73^{b}	12.33± 5.62^{ab}	11.34± 5.92^{a}	10.35± 2.71^{a}
c18 : 0	11.96± 0.53^{bc}	10.65± 2.27^{bc}	9.90± 9.82^{ab}	6.42± 1.40^{a}
c18 : 1	7.95± 0.82^{a}	9.44± 5.80^{ab}	15.07± 4.66^{b}	17.17± 4.52^{b}
c18 : 2	3.21± 0.36^{a}	8.33± 9.65^{ab}	9.73± 4.67^{b}	12.21± 3.74^{b}
c18 : 3	1.39± 0.29^{a}	1.01± 0.39^{a}	12.10± 8.17^{b}	2.39± 0.98^{a}
c20 : 0	0.84± 0.17^{a}	0.96± 0.60^{a}	–	1.27± 0.99^{a}
c20 : 4	29.62± 2.07^{b}	22.81± 7.01^{b}	13.63± 9.24^{a}	15.31± 6.54^{a}
c20 : 5	1.35± 0.61^{a}	1.34± 0.65^{a}	1.65± 0.36^{a}	2.50± 0.19^{b}
c24 : 1	4.10± 1.10^{a}	5.23± 1.85^{a}	3.03± 2.29^{a}	2.83± 0.92^{a}
c22 : 5	1.87± 0.80^{a}	2.30± 2.01^{a}	3.98± 2.41^{a}	1.60± 0.13^{a}
c22 : 6	trace	1.11± 0.47^{ab}	0.76± 0.17^{a}	2.32± 0.89^{b}
$\sum$n-6	32.83± 2.32^{bc}	31.14± 4.00^{ab}	23.36± 5.69^{a}	27.52± 2.87^{a}
$\sum$n-3	4.62± 0.90^{a}	4.87± 2.35^{a}	16.47± 3.88^{c}	8.80± 1.57^{b}
n-6/n-3	7.44± 1.98^{c}	7.80± 4.88^{bc}	1.56± 0.75^{a}	3.25± 0.78^{b}
20 : 4/20 : 5	22.01± 9.41^{bc}	18.21± 4.15^{c}	8.23± 5.78^{ab}	6.07± 2.48^{a}

Values are Mean± SD of 10 pooled samples of 3 rats and are expressed as the relative % of total fatty acids. Values with common superscripts in the same row were not significantly different at $p<0.05$ by Duncan's multiple range test.

that of BT-MNNG group but the c20 : 4 was lower than those of BT-MNNG and CO-MNNG groups, and the value of BT-MNNG was higher than that of CO-MNNG group($p<0.05$). FO-MNNG group showed higher level of c20 : 5 as compared to others($p<0.05$). The ratio of 20 : 4/20 : 5 in PO-MNNG and FO-MNNG groups was singificantly lowered as compared to those of BT-MNNG and CO-MNNG groups, but there was no significant difference between PO-MNNG and FO-MNNG. FO-MNNG group showed higher level of c22 : 6 compared to that of PO-MNNG and PO-MNNG showed higher level of c22 : 5 compared to others($p<0.05$). PO-MNNG and FO-MNNG groups were higher in the total amount of n-3 series of fatty acids compared to those of BT-MNNG and CO-MNNG groups, but BT-MNNG and CO-MNNG groups were higher in the total amount of n-6 series of fatty acids($p<0.05$).

Discussion

It was reported that linoleic acid might have promoting effect in colon carcinogenesis[2)13)], so that the present study was performed in the presence of adequate amount of EFA to observe the effec of dietary n-6 and n-3 fatty acids on colon tumor incidence and its relation to the variation in membrane arachidonic acid content and eicosanoid biosynthesis in colon and platelet. The main dietary fatty acid was SFA(7.7% kcal) for BT diet, n-6 LA(11.4% kcal) for CO diet, n-3 LNA(12.2% kcal) for PO diet and n-3 EPA+DHA(6.2% kcal) for FO diet and the content of LA was constant in the range of 2.7~3.4% by calorie in BT, PO and FO diets. Among those of MNNG-treated rats, BT-MNNG group had hi-

gher number of colon tumor compared to CO-MNNG group which suggests that the extra amount of n-6 LA given in CO-MNNG group over the level of BT-MNNG group did not produce more tumors in colon. However, PO- and FO-MNNG groups had lower incidence of colon tumor and smaller size of tumor compared to CO- and BT-MNNG groups. This result suggests that n-3 fatty acids, LNA and EPA+DHA rich in PO and FO diets, respectively, had an inhibitory effect on colon tumor development.

The mechanism by which n-3 fatty acids reduce tumor is still unknown. It is generally thought that n-3 fatty acid exert their physiological effects primarily through changes in arachidonic acid metabolism, specifically eicosanoid production. Yamaguchi et. al[6] reported that especially, PGE_2 may be implicated as a promoter in MNNG-induced carcinogenesis in the large bowel. Membrane lipid composition reflects, in part, dietary fat intake[14-16]. Since eicosanoid precursors are present in membrane, it has been hypothesized that variation in membrane lipid composition, mainly variation in membrane arachidonic acid content, will effect eicosanoid biosynthesis. It is important that n-6 and n-3 fatty acids compete for △5 and △6 desaturases and also for cyclooxygenase and lipoxygenase enzymes[17]. Therefore, membrane lipid composition and relative concentrations of substrates are also essential factors determining tissue eicosanoid profiles. Our result showed that beef tallow feeding significantly increased the proportion of c20 : 4 in platelet PL compared to fish oil and fish oil feeding increased the proportions of c20 : 5 and c22 : 6 compared to corn oil. Others reported that EFA deficient rats were sensitive to dietary linolenate[18]. However, our result in the presence of enough amount of EFA showed that the increased dietary linoleate level(CO group) over a threshold value did not lead to further increase in AA content of platelets and dietary n-3 fatty acids reduced AA contant in colonic mucosa in PO- and FO-fed groups. Similar result was reported such as LA intake greater than 1−2% of energy does not further increase c20 : 4 in platelet PL(19−21). Out study shows that the levels of plasma TXB_2 in BT-MNNG and CO-MNNG groups were significantly higher than those in the groups of PO-MNNG and FO-MNNG. This increased plasma TXB_2 levels correlated well with the higher content of AA in platelet PL and higher incidence of colon tumor by feeding beef tallow. Fish oil reduced both the content of AA in platelet and plasma TXB_2 and lower incidence of colon tumor. The level of plasma TXB_2 was positively correlated well with the content of AA in platelet PL. In a simillar fashion beef tallow feeding also increased the c20 : 4 content and the ratio of 20 : 4/20 : 5 in colonic mucosal lipid compared to perilla and fish oil and the effect of perilla oil was not significantly different from that of fish oil. This result suggests that beef tallow might have elevated capacity to synthesize 2-series of prostaglandin and thromboxane in colonic mucosa. Other reports[18)19)22-24] indicate that increased or decreased n-3 fatty acid intake respectively reduces or elevates capacity to synthesize PGE_2 and TXB_2 in plasma and tissue. Many investigators showed that certain means leading to reduction of prostaglandins production decreased the incidence of colon tumor[3)24)25]. Minoura et. al[3] reported that the contents of c20 : 4 and PGE_2 of colon tumor in the linoleic acid diet group were significantly higher than those of normal colon mucosa and colon tumors in the EPA diet group. Therefore, our result suggests that the growth-retarding effect of n-3 dietary fatty acids on colon tumor in PO- and FO-fed rats could be partially related to the variation in cellular membrane lipid composition

and reduction of precursor of PGE_2 and TXB_2 in colonic mucosa. Our results also suggest that perilla oil feeding was effective as much as fish oil in restraining colon tumor promotion possibly by inhibiting the synthesis of 2-series prostaglandin and thromboxane. Further research is needed to understand better the role of various eicosanoids in tumor growth and how individual dietary fatty acids may affect these processes.

Conclusions

In MNNG-treated rats, beef tallow feeding developed more adenocarcinoma and adenoma in colon compared to perilla oil or fish oil. Beef tallow and corn oil significantly increased plasma TXB_2 level compared to perilla oil and fish oil. Perilla oil was effective as much as fish oil in reducing plasma TXB_2 level. Beef tallow also increased signiicantly the content of c20 : 4 in platelet PL compared to fish oil. Beef tallow and corn oil feeding increased AA content in colonic mucosa($p<0.05$) compared to fish oil and perilla oil.

In conclusion, tumor promotion-inhibiting effect of fish oil and perilla oil rich in n-3 fatty acids in MNNG-induced colon carcinogenesis was possibly by inhibiting normal AA metabolism with modification of fatty acid profile in cellular membrane.

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Colon Tumor N-3 Fatty Acids Perilla Oil Fish Oil MNNG

= 국문초록 =

발암원을 투여한 쥐에서 α-linolenic Acid가 풍부한 들기름이 대장암 발생빈도와 혈장 Thromboxane B_2 및 대장 상피세포막의 지방산조성에 미치는 영향*

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본 연구에서는 발암원인 N-methyl-N'-nitro-N-nitrosoguanidine(MNNG)을 쥐에게 투여하여 대장암을 유발한 후 식이지방이 대장암 발생빈도와 혈장의 TXB_2와 혈소판과 대장 상피세포막의 지방산조성에 어떤 영향을 미치는지 보고자 하였으며, 특히 들기름의 효과를 다른 식이지방과 비교하고자 하는데 목적이 있다.

Sprague Dawley 종 수컷쥐가 생 후 8주 되었을 때 크게 두군 즉 대조군과 MNNG투여군으로 나누어 대조군에는 식염수, 실험군에는 2mg MNNG를 각각 항문으로 일주일에 2번씩 3주동안 주입한 후 각군을 다시 4군으로 나누어(모두 8군) 각 실험식이 4가지(BT, CO, PO, FO)로 37주동안 더 사육하였다. 각 실험식이의 지방의 수준을 9%(w/w)로 같게하고 지방산 조성만 다르게 하였다. 즉 BT diet에는 beef tallow(7.2%)와 corn oil(1.8%), CO diet는 corn oil(9.0%), PO diet는 perilla oil(9.0%), FO diet는 fish oil(6.5%)과 corn oil(2.5%)을 각각 첨가하여 필수지방산의 결핍이 없게 하였다.

대조군에는 대장에 종양이 없었으나 MNNG 처리군중에서는 BT-MNNG군에서 종양이 가장 많이 생겼으며, BT-MNNG와 CO-MNNG군의 종양의 크기는 2mm papillary형에서 15mm polypoid형의 adenoma와 adenocarcinoma가 가장 많이 발생했으며 PO-MNNG와 FO-MNNG군의 종양의 크기는 너무 적어 육안으로 측정하기는 어려웠다. BT-MNNG과 CO-MNNG군은 PO-MNNG와 FO-MNNG군에 비해 혈장의 TXB_2 수준이 증가되었고 혈소판의 arachidonic acid 함량과 c20 : 4/c20 : 5 비율이 증가되었다. 또한 PO-MNNG와 FO-MNNG군의 대장 상피세포막의 지방산조성에서도 c20 : 4/c20 : 5 비율이 감소되었다. 그러므로 perilla oil과 fish oil은 대장에서 2-series의 prostaglandin과 thromboxane의 전구체인 arachidonic acid 함량에 영향을 주어 대장암 발생을 지연시키는 효과가 있었다고 사려된다. 그리고 n-3 EPA의 전구체인 n-3 α-linolenic acid가 60% 정도 함유된 들기름의 효과도 어유와 거의 비슷하게 대장암 발생을 지연시키는 효과가 있었다.