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Effects of Dietary Lipids and Dexamethasone on Mucosal Hyperplasia after 70% Jejunoileal Resection in Rats

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ABSTRACT

Dietary mehaden oil enhances mucosal hyperplasia that normally occurs after massive small bowel resection. In contrast, dexamethasone and aspirin inhibit the adaptation response. In order to gain insight on the mechanism of these effects, male Sprague-Dawley rats weighing approximately 150gram were randomly divided into two groups and fed diet containing either 15% safflower oil or 14% menhaden oil and 1% safflower oil. Ten days later they were subjected to 70% jejunoileal resection. Immediately after surgery each group was further divided into two groups and received either vehicle or 125μg/kg/day dexamethasone subcutaneously. All animals were sacrificed seven days after the surgery, and the remaining intestine was removed and divided at the anastomotic site. Dexamethasone, which decreased gut hyperplasia in both dietary groups, decreased both serum IGF-I levels and ileal PGE_2 synthesis. Menhaden oil enhanced gut hyperplasia, but did not increase IGF-I or IGF-II levels in serum. PGE_2 synthesis was lower in the ileum of menhaden oil-fed rats compared to that of safflower oil-fed rats. The effects of menhaden oil on adaptation did not appear to be mediated either through IGFs or PGE_2 synthesis. Other factors could have played a role in enhancing adaptation following menhaden oil feeding.

KEY WORDS : insulin-like growth factors · dexamethasone · jejunoileal resection · rats · prostaglandin E_2.

Introduction

Malabsorption resulting from massive resection of the small intestine is known as short bowel syndrome[1]. Resection is performed for numerous conditions, with necrotizing enterocolitis and congenital anomalies being the most common in infants. Prolonged therapy with total parenteral nutrition is often necessary in such patients and the gradual introduction of enteral feedings, either orally or by tube feeding, will often eventually replace the need for parenteral nutrition. The degree to which enteral nutrition can be successfully administered to patients with short bowel syndrome is heavily dependent upon the process of mu-

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cosal adaptation. This involves hyperplasia of the absorptive epithelium in the small intestine resulting in the gradual lengthening of the villi and increased absorptive surface area[2]. Therefore, stimulation of intestinal adaptation, a process highly dependent upon the presence of enteral nutrition, is a key factor in the successful treatment of short bowel syndrome[3-7].

The mechanism by which enteral nutrients stimulate intestinal adaptation is not known. Long-chain triglycerides are important trophic factors in the stimulation of intestinal adaptation[8)9)]. Among various oils containing long-chain triglycerides, highly unsaturated marine oils such as menhaden oil are especially potent stimulators of adaptation[10)]. We have previously attempted to relate the stimulatory effects of enteral nutrition, especially lipids, to changes in gastrointestinal hormones and arachidonic acid metabolism, in particular, prostaglandin E_2(PGE_2)[11)].

We have previously shown that exogenous 16,16-dimethyl-PGE_2 augments mucosal hyperplasia after 70% jejunoileal resection[12)]. Other studies have shown that the adaptation response is inhibited by corticosteroids [13)], substances that are acknowledged to reduce the synthesis of prostaglandin E_2. Inhibition of prostaglandin synthesis by aspirin also reduces the adaptation response[14)].

An alternate explanation for the inhibitory effects of corticosteroids on adaptation relates to their effect on insulin-like growth factor(IGF) metabolism. It has been shown that dexamethasone infusion decreases serum IGF-I and IGF-II levels[13)15)]. IGF-I and IGF-II are important regulators of somatic growth[16)]. In vitro studies indicate that insulin, IGF-I and IGF-II stimulate proliferation of intestinal epithelial cells[17)]. In vivo, administration of IGF-I and its truncated analog, des-(1-3)-IGF-I, has both been shown to enhance mucosal hyperplasia that normally occurs after massive small bowel resection[18)]. In a study of osteoblast-enriched cultures from fetal rat bone, McCarthy et al[19)] have shown that PGE_2 is a potent activator of IGF-I expression.

The present study was conducted to explore the interrelationship between corticosteroids, menhaden oil, and adaptation. Specifically, we wanted to assess how various therapeutic manipulations alter prostaglandin and IGF-I metabolism, hopefully to gain greater insight into the importance of prostaglandins in intestinal adaptation.

Materials and Methods

1. Materials

Recombinant human IGF-I and IGF-II were generously provided by Lilly Research Laboratories, Indianapolis, IN. Dexamethasone sodium phosphate, a synthetic glucocorticoid, was purchased from American Regent Laboratories(Shirley, NY). ^{125}I-IGF-I and ^{125}I-IGF-II(sp act 2,000 Ci/mmol) were purchased from Amersham(Arlington Heights, IL). Rabbit IGF-I antiserum(UB3-189) was a gift from Drs. L. E. Underwood and J.J Van Wyk(University of North Carolina, Chapel Hill, NC) through the National Hormone and Pituitary Program of National Institute of Diabetes and Digestive and Kidney Diseases (Baltimore, MD). This antibody has wide species cross-reactivity and has been used successfully in studies with rats[16)]. Recombinant rat IGF-I has been shown to be 90% cross-reactive with this antiserum compared with recombinant human IGF-I(personal communication, Dr. L.E. Underwood). Unless otherwise stated, all other chemicals were obtained from Sigma Chemical(St. Louis, MO).

2. Animals, Diets, and Study Protocol

The animals used in this study were cared for according to the guidelines of the Animal Review Committee at the University of Nebraska Medical Center. Forty male Sprague-Dawley rats, weighing approximately 150grams(Sasco, Omaha, NE), were housed individually in stainless steel hanging cages. They were fed Purina Rat Chow(Ralston Purina, St. Louis, MO) and tap water *ad libitum* to be acclimated to laboratory conditions over a three-day period. Subsequently, the animals were randomly divided into two groups and fed a modified AIN-76 diet obtained from Tech Lab(Madison, WI, USA) containing one

of the following dietary lipids. One group received 14%(w/w) menhaden oil and 1% safflower oil, while the other group received 15% safflower oil. The dietary menhaden oil contained the following fatty acids(weight % of total fatty acids) : 14 : 0, 8.95% ; 15 : 0, 0.72% ; 16 : 0, 17.08% ; 16 : 1, 12.52% ; 16 : 2, 1.66% ; 16 : 3, 1.71% ; 16 : 4, 1.83% ; 18 : 0, 2.81% ; 18 : 1, 11.38% ; 18 : 2, 1.54% ; 18 : 3, 1.61% ; 18 : 4, 3.45% ; 20 : 0, 0.2% ; 20 : 1, 1.56% ; 20 : 4, 2.03% ; 20 : 5, 15.51% ; 21 : 5, 0.79% ; 22 : 5, 2.42% ; and 22 : 6, 9.13%. The composition of the safflower oil was as follows : 16 : 0, 6.6% ; 18 : 0, 2.4% ; 18 : 1, 12.5% ; 18 : 2, 77.4% ; and 18 : 3, 0.3%. Rats were fed these diets for 10 days and then underwent 70% jejunoileal resection. The operation resulted in removal of all of the small intestine from 4 cm distal to the ligament of Treitz to a point 12 cm proximal to the ileocecal valve. Surgery was performed under pentobarbital anesthesia(40 mg/kg). Animals were given D-glucose(5%, w/v) and oxytetracycline hydrochloride(0.0225%) in their drinking water for 36 hours pre- and postoperatively, and then fed their respective study diets. Throughout the pre- and postoperative period, food intake from the menhaden oil group was measured daily and the other group was pair-fed based upon this amount as our previous experience indicated that the menhaden oil group commonly consumes a lesser amount of food during any 24-hour period. The diets were freshly prepared each week and stored in tightly sealed bags in the freezer. The animals received fresh food every day.

Immediately after surgery, each dietary group was further divided into two groups. A mini-osmotic pump(Alzet Model 2001, Palo Alto, CA) was placed subcutaneously to administer either dexamethasone (125μg/kg/day) or a placebo(25 mM sodium phosphate, pH 7.4).

Seven days following surgery, the animals were sacrificed. The small intestine from the pylorus to ileocecal valve was removed and divided at the anastomosis. Portions of the intestine one centimeter on either side of the anastomosis were discarded because of surgically induced hyperplasia occurring in the region. The duodenojejunal and ileal length were measured, specimens were weighed, and mucosa was subsequently scraped from the underlying tissue with a glass slide.

3. Mucosal DNA, Protein, and Enzyme Assays

The status of mucosal hyperplasia was assessed by measuring mucosal weight, DNA, and protein. Mucosal samples were homogenized in ice-cold deionized water. DNA was extracted by the method of Munro and Fleck[20], and the resulting DNA fractions were assayed according to method of Giles and Myers [21]. Protein concentration was determined by the method of Lowry et al[22] and expressed as milligrams of protein per centimeter of bowel. Disaccharidase activities were measured according to the method of Dahlqvist[23] as one measure of mucosal function.

4. Determinations of IGF-I and IGF-II

Blood was drawn from the aorta at the time of death and serum was prepared for determination of IGF-I levels. Before assaying for IGFs, IGF binding proteins were removed from serum by the acid-gel filtration method[24]. IGF-I levels were estimated by radioimmunoassay as described previously using ^{125}I-IGF-I and rabbit anti-IGF-I serum[17]. Recombinant human IGF-I was used as an unlabeled standard. The levels of IGF-II were determined by the double antibody immunoassay method with a monoclonal antibody highly specific for IGF-II(Amano International Enzyme, Troy, VA) as described previously[17].

5. Prostaglandin Analysis

PGE_2 synthesis was assessed by organ culture technique[25]. One cm segment of the distal ileum was flushed with ice-cold saline to remove any intestinal contents, and then placed in cold Dulbecco's modified Eagle medium : Ham's F-12 nutrient mixture (DMEM/F12 ; GibcoBRL, Gaithersburg, MD) supplemented with 200 units/ml penicillin and 200μg/ml streptomycin prior to further processing. The tissue was split longitudinally and then into 1.5×1.5 mm full thickness explants with a razor blade. Ten tissue explants were placed directly onto Falcon stainless

Table 1. Effects of fatty acid and dexamethasone on duodenojejunal mucosal parameters

	Menhaden	Menhaden-DEX	Safflower	Safflower-DEX
Body weight(g)	206 ± 5^{a}	162 ± 5^{b}	193 ± 4^{c}	152 ± 4^{b}
Mucosal weight(mg/cm)	160 ± 4.4^{a}	136 ± 5.8^{b}	134 ± 5.0^{b}	125 ± 5.1^{b}
Protein(mg/cm)	17.5 ± 0.7^{a}	16.8 ± 0.6^{ac}	15.2 ± 0.6^{bc}	13.3 ± 0.8^{b}
DNA(μg/cm)	197 ± 9.2^{a}	162 ± 6.6^{b}	166 ± 5.1^{b}	134 ± 4.5^{c}
Maltase(μmol/g prot/min)	355 ± 23^{ac}	402 ± 10^{ad}	338 ± 36^{bc}	469 ± 28^{d}
(nmol/cm/min)	6097 ± 266^{a}	6751 ± 272^{a}	5172 ± 316^{b}	6097 ± 291^{a}
Sucrase(μmol/g prot/min)	55 ± 4^{a}	62 ± 3^{a}	62 ± 3^{a}	94 ± 8^{b}
(nmol/cm/min)	945 ± 58^{a}	1037 ± 46^{a}	941 ± 59^{a}	1229 ± 53^{b}
Lactase(μmol/g prot/min)	4.46 ± 0.12^{a}	5.98 ± 0.99^{a}	4.33 ± 0.41^{a}	9.82 ± 0.92^{b}
(nmol/cm/min)	78 ± 3.5^{a}	97 ± 12.5^{ac}	67 ± 7.7^{a}	128 ± 10.7^{bc}

Values are means ± SEM. Values within rows with different superscripts differ($p < 0.05$).

steel grids, with one grid placed per well in Falcon 6-well, cell-culture plates(Becton Dickinson, Lincoln Park, NJ) and rinsed twice with DMEM/F12. The explants were placed at the air-fluid interface with 1.4 ml DMEM/F12. The 6-well plates were put into modular airtight incubators from Billups-Rothenberg(Del Mar, CA) which were filled with 5% CO_2/95% O_2, and then placed in an incubator at 37℃ for 1.5 h. Our preliminary experiments had shown that PGE_2 secretion was linear up to 6 h under these experimental conditions. The medium and tissue were collected after 1.5 h of incubation. The PGE_2 released into the medium was extracted immediately using ethyl acetate (4 : 1, v/v) after acidifying the medium with glacial acetic acid at pH 4.0. The upper organic phase was saved and dried under N_2. PGE_2 was quantified by utilizing an enzyme immunoassay kit(Advanced Magnetics, Cambridge, MA). The protein contents of tissues were determined by the method of Lowry et al[22], and the data were expressed as ng PGE_2 released per h per g of protein.

6. Statistical Analysis

All data were calculated as mean ± standard error of the mean. Statistically significant differences among group means were determined by analysis of variance and Duncan's New Multiple Range Test[26].

Results

Of the rats that were not given dexamethasone, those fed menhaden oil were significantly heavier than the ones fed safflower oil. Dexamethasone infusion resulted in marked decreases in body weight regardless of whether rats were fed menhaden oil or safflower oil. In fact, there was no difference in body weight between the two dietary groups infused with dexamethasone(Table 1).

Duodenojejunal mucosal characteristics are shown in Table 1. Administration of menhaden oil significantly enhanced mucosal weight when compared to the animals fed safflower oil. Dexamethasone appeared to inhibit the response, reducing adaptation in menhaden oil-fed rats to a level equal to that achieved with safflower oil. As mucosal DNA and protein responded similarly, the hyperplasia process itself appeared to be altered, causing the changes in mucosal weight. Disaccharidase activities were enhanced significantly in safflower oil-fed animals treated with dexamethasone, but differences were not significant in menhaden oil-fed animals, although similar trends were apparent. These changes were generally apparent regardless of whether the data were expressed per gram of protein or per centimeter of bowel. There were no differences in disaccharidase activities between the menhaden oil and safflower oil groups infused with vehicle.

Data from the ileum are shown in Table 2. Comparable findings were observed. Mucosal weight was greatest in the animals fed menhaden oil, whereas treatment with dexamethasone reduced the adaptive

response of the menhaden oil-fed animals to the level seen with safflower oil. Dexamethasone further reduced the adaptation response in safflower oil-fed animals. DNA and protein levels generally demonstrated similar changes. In contrast to the jejunum, disaccharidase levels were not enhanced in response to corticosteroid administration. Menhaden oil administration again appeared to have either no effect or a negative effect on disaccharidase levels.

Prostaglandin E_2 production in the ileum was markedly elevated in animals fed safflower oil when compared to menhaden oil-fed animals, as linoleic acid present in safflower oil is a substrate for the PGE_2 synthesis. Dexamethasone reduced prostaglandin E_2 production in both dietary groups, although it had a smaller effect on menhaden oil-fed animals(Table 2).

Menhaden oil did not significantly elevate either IGF-I or IGF-II levels in the serum relative to safflower oil. Dexamethasone administration, however, reduced the levels of both the IGF-I and IGF-II in the serum of animals fed either lipid(Table 3).

Discussion

The stimulatory effect of menhaden oil on intestinal adaptation is consistent with data previously described in our laboratory[10]. These results suggest that menhaden oil have potential as a therapeutic agent for patients with short bowel syndrome or with a limited absorptive surface area. Prior attempts to relate this observation to changes in potentially trophic gastrointestinal hormone levels have been largely unsuccessful. We found a small but statistically significant elevation in peptide YY levels in animals fed menhaden oil, an observation which prompted us to suggest the possibility that peptide YY could have reduced intestinal motility, thereby increasing nutrient contact with the mucosal epithelium. As nutrient contact is known to stimulate intestinal adaptation, this might be one potential mechanism whereby menhaden oil could stimulate mucosal hyperplasia in the small bowel. Our preliminary studies were not, however, able to demonstrate an elevation in enteroglucagon levels, but rather a decrease in enteroglucagon, a hormone which was previously thought to be important in stimulating intestinal adaptation.

At least in the proximal small intestine, dexamethasone appeared to also increase the specific activity of disaccharidases. As dexamethasone also reduc-

Table 2. Effects of fatty acids and dexamethasone on ileal mucosal parameters

	Menhaden	Menhaden-DEX	Safflower	Safflower-DEX
Mucosal weight(mg/cm)	168 ± 7.8^{a}	140 ± 8.8^{b}	134 ± 4.0^{b}	90 ± 5.1^{c}
DNA(μg/cm)	214 ± 5.1^{a}	182 ± 13.7^{bd}	192 ± 9.2^{ad}	123 ± 6.1^{c}
Protein(mg/cm)	17.9 ± 0.7^{a}	15.3 ± 0.7^{a}	14.8 ± 0.6^{b}	9.4 ± 0.5^{c}
Maltase(μmol/g prot/min)	170 ± 9^{a}	248 ± 13^{b}	248 ± 22^{b}	299 ± 17^{b}
(nmol/cm/min)	3048 ± 239^{ac}	3850 ± 350^{a}	3593 ± 260^{a}	2793 ± 202^{bc}
Sucrase(μmol/g prot/min)	14.9 ± 1.17^{a}	22.0 ± 2.24^{b}	25.7 ± 2.9^{b}	21.9 ± 2.47^{b}
(nmol/cm/min)	269 ± 28^{ac}	344 ± 45^{a}	365 ± 28^{b}	208 ± 28^{c}
Lactase(μmol/g prot/min)	2.69 ± 0.10^{a}	2.95 ± 0.14^{a}	3.13 ± 0.21^{a}	3.01 ± 0.01^{a}
(nmol/cm/min)	48 ± 2.06^{a}	45 ± 2.42^{a}	45 ± 1.67^{a}	28 ± 1.2^{b}
PGE_2(ng/hour/g prot)	297 ± 28^{a}	229 ± 24^{b}	777 ± 76^{c}	486 ± 48^{d}

Values are means ± SEM. Values within rows with different superscripts differ($p < 0.05$).

Table 3. Effects of fatty acids and dexamethasone on serum IGF-I and IGF-II

	Menhaden	Menhaden-DEX	Safflower	Safflower-DEX
IGF-I(ng/ml)	335 ± 19^{a}	222 ± 25^{b}	307 ± 23^{a}	224 ± 18^{b}
IGF-II(ng/ml)	9.42 ± 0.95^{a}	4.62 ± 1.29^{b}	9.35 ± 1.0^{a}	2.94 ± 0.37^{b}

Values are means ± SEM. Values within rows with different superscripts differ($p < 0.05$).

ed hyperplasia, these changes are typical for more functionally mature, but less rapidly dividing, mucosal cells. Dexamethasone inhibited mucosal hyperplasia in both dietary groups and inhibited IGF-I and IGF-II synthesis. IGF-I and IGF-II are stimulants of mucosal cell proliferation[17]. In addition, infusion of dexamethasone significantly inhibited PGE_2 synthesis in the ileum. From these results and those by McCarthy et al[19], one can hypothesize that dexamethasone inhibits IGF-I production by inhibiting PGE_2 synthesis. However, Feeding menhaden oil to animals given dexamethasone appeared to reverse the negative effects of dexamethasone seen in safflower oil-fed rats following resection, but these findings could not be explained by greater IGF-I production in menhaden vs. safflower oil-fed steroid-treated rats. Therefore, it is likely other factors were involved.

Previous studies in our laboratory have demonstrated that mucosal mass in rats following small bowel resection could be augmented by the administration of 16,16-dimethyl-prostaglandin E_2[12]. The reason for this positive effect is also poorly understood. Prostaglandins are known to increase mucosal blood flow in the small intestine, alter intestinal motility, and influence fluid secretion in the small bowel[27][28]. Previous studies from our laboratory have suggested that inhibition of prostaglandin synthesis with aspirin can reduce the intestinal adaptation response[14]. Dexamethasone appeared to be much more potent reducer of intestinal mass following intestinal resection. The corticosteroid reduced PGE_2 synthesis in the ileum of both safflower oil-fed and menhaden oil-fed animals(Table 2). However, animals fed menhaden oil regardless of corticosteroid therapy had markedly reduced prostaglandin E_2 synthesis and increased mucosal hyperplasia. It is likely that the omega-3 fatty acids present in menhaden oil acted as a substrate for synthesis of a structurally different group of prostaglandin compounds[29]. The physiologic activity of these substances might differ significantly from the 2-series prostaglandins. These compounds would not have been measured by our assay, and their effect on mucosal adaptation is unknown. In the colon, they appear to be associated with decreased cellular proliferation and decreased ornithine decarboxylase levels, an early indicator of cell proliferation[30]. Another possible explanation may have been changes in membrane compositions of enterocytes in menhaden oil fed rats. Previously we observed differences in fatty acid composition of intestinal mucosa between animals fed the two dietary lipids[31]. Because the life span of enterocytes is very short, it is reasonable to assume that such differences in fatty acid profile also existed in enterocyte membranes. These changes in the membrane may have resulted in alteration of tissue metabolism.

We have shown that menhaden oil enhances gut hyperplasia, but does not increase serum IGF-I or IGF-II levels. Dexamethasone decreases mucosal hyperplasia, IGF production, and prosatglandin E_2 synthesis. The stimulatory effect of menhaden oil on adaptation is in opposition to its negative effect on PGE_2 synthesis. Therefore, the effects of menhaden oil on mucosal hyperplasia are not likely mediated through effects on either growth factors such as IGF-I and IGF-II or PGE_2 synthesis.

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Literature cited

1) Vanderhoof JA, Langnas AN, Pinch LW, Thompson JS, Kaufman SS. Invited review. Short bowel syndrome. *J Pediatr Gastroenterol Nutr* 14 : 359-370, 1992

2) Dowling RH, Booth CC. Structural and functional changes following small intestinal resection in the rat. *Clin Sci* 32 : 139-149, 1967
3) Nygaard K. Resection of the small intestine in rats. III. Morphological changes in the intestinal tract. *Acta Chir Scand* 133 : 233-248, 1967
4) Hanson WR, Osborne JW, Sharp JG. Compensation by the residual intestine resection in the rat. I. Influence of amount of tissue removed. *Gastroenterology* 72 : 692-700, 1977
5) Hanson WR. Osborne JW, Sharp JG. Compensation by the residual intestine resection in the rat. II. Influence of postoperative time interval. *Gastroenterology* 72 : 701-705, 1977
6) Wilmore DW, Durdrick SJ, Daly JM, Vars HM. The role of nutrition in the adaptation of the small intestine after massive resection. *Surg Gynec Obstet* 1323 : 673-680, 1971
7) Hanson WR. Osborne JW. Epithelial cell kinetics in the small intestine of the rat 60 days after resection of 70 percent of the ileum and jejunum. *Gastroenterology* 60 : 1087-1097, 1971
8) Vanderhoof JA, Grandjean CJ, Kaufman SS, Burkley KT, Antonson DL. Effect of high percentage medium chain triglyceride diet on mucosal adaptation following massive bowel resection in rats. *JPEN* 8 : 685-689, 1984
9) Park JHY, Grandjean CJ, Hart MH, Baylor JM, Vanderhoof JA. Effects of dietary linoleic acid on mucosal adaptation after small bowel resection. *Digestion* 44 : 57-65, 1989
10) Vanderhoof JA, Park JHY, Herrington MK, Adrian TE. Effects of dietary menhaden oil on mucosal adaptation after small bowel resection in rats. *Gastroenterology* 106 : 94-99, 1994
11) Vanderhoof JA, Grandjean CJ, Baylor JM, Bailey J, Euler AR. Morphological and functional effects of 16, 16-dimethyl-prostaglandin E_2 on mucosal adaptation following massive small bowel resection in the rat. *Gut* 29 : 802-808, 1988
12) Vanderhoof JA, Eurler AR, Park JHY, Grandjean CJ. Augmentation of mucosal adaptation following massive small-bowel resection by 16, 16-dimethyl-prostaglandin E_2 in the rat. *Digestion* 36 : 213-219, 1987
13) Park JHY, McCusker RH, Mohammadpour H, Blackwood DJ, Hrbek M, Vanderhoof JA. Dexamethasone inhibits mucosal adaptation after small bowel resection. *Am J Physiol* 266(Gastrointest Liver Physiol 29) : G497-G503, 1994
14) Vanderhoof JA, Park JHY, Grandjean CJ. Reduced mucosal prostaglandin synthesis after massive small bowel resection. *Am J Physiol* 254(Gastrointest Liver Physiol 3) : G373-G377, 1988
15) Tomas FM, Knowles SE, Owens PC, Chandler CS, Francis GL, Read LC, Ballard FG. Insulin-like growth factor-I(IGF-I) and especially IGF-I variants are anabolic in dexamethasone-treated rats. *Biochem J* 282 : 91-97, 1992
16) Daughaday WH, Rotwein P. Insulin-like growth factor I and II. Peptide, messenger ribonucleic acid and gene structures, serum and tissue concentration. *Endocr Rev* 10 : 68-91, 1989
17) Park JHY, McCusker RH, Vanderhoof JA, Mohammadpour H., Harty RF, MacDonald RG. Secretion of insulin-like growth factor II(IGF-II) and IGF-binding protein-2 by intestinal cells : implication for autocrine growth regulation. *Endocrinology* 131 : 1359-1368, 1992
18) Vanderhoof JA, McCusker RH, Clark R, Mohammadpour H., Blackwood DJ, Harty RF, Park JHY. Truncated and native insulinlike growth factor I enhance mucosal adaptation after jejunoileal resection. *Gastroenterology* 102 : 1949-1956, 1992
19) McCarthy TL, Centrella M, Raisz LG, Canalis E. Prostaglandin E_2 stimulates insulin-like growth factor I synthesis in osteoblast-enriched cultures from fetal rat bone. *Endocrinology* 128 : 2859-2900, 1991
20) Munro HN, Fleck A. Recent developments in the measurement of nucleic acids in biological materials. *Analyst* 91 : 78-87, 1966
21) Giles KW, Myers A. Improved diphenylamine method for estimation of DNA. *Nature Lond* 206 : 93-4, 1965
22) Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. *J Biol Chem* 193 : 265-275, 1951

23) Dahlqvist A. Method for assay of intestinal disaccharidases. *Analyt Biochem* 7 : 18-25, 1964

24) Rivero F, Goya L, Pascual-Leone M. Comparison of extraction methods for insulin-like growth factor-binding proteins prior to measurement of insulin-like growth factor-I in undernourished neonatal and adult rat serum. *J Endocrinol* 140 : 257-263, 1994

25) Malo C, Arsenault P, Menard D. Organ culture of the small intestine of the suckling mouse in serum-free medium. *Cell Tis Res* 228 : 75-78, 1984

26) Steel RGD, Torrie JH. Principles and Procedures of Statistics, 2nd edn. New York : McGraw-Hill, 1980

27) Chapnick BM, Feigen LP, Human AL, Kadowitz PJ. Differential effects of prostaglandins in the mesenteric vascular bed. *Am J Physiol* 235 : H326-H332, 1978

28) Jackson DM, Malor R, Chesher GB, Starmer GA, Welburn PH, Bailey R. The interaction between prostaglandin E_1 and 9-tetrahydrocannabinol on intestinal motility and on the abdominal constriction response in the mouse. *Psychopharmacology* 47 : 187-193, 1976

29) Leaver HA, Howie A, Wilson NH. The biosynthesis of the 3-series prostaglandins in rat uterus after alpha-linolenic acid feeding : Mass spectroscopy of prostaglandins E and produced by rat uteri in tissue culture. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 42 : 217-224, 1991

30) Bartram HP, Gostner A, Scheppach W, Reddy BS, Rao CV, Dusel G, Richter F, Richter A, Kasper H. Effects of fish oil on rectal cell proliferation, mucosal fatty acids, and prostaglandin E_2 release in healthy subjects. *Gastroenterology* 105 : 1317-1322, 1993

31) Vanderhoof JA, Blackwood DJ, Mohammadpour H, Park JHY. Effect of dietary menhaden oil on normal growth and development and on ameliorating mucosal injury in rats. *Am J Clin Nutr* 54 : 346-350, 1991

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식이 지방과 Dexamethasone 주입이 소장절제후 소장 점막의 증식에 미치는 영향

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동물은 소장의 일부를 상실한 경우, 남아 있는 장 점막의 증식을 통해서 부족한 소화 흡수 표면적을 충당시키려한다. 따라서 소장 점막의 증식 분화를 연구하는 실험 model로서 공장 회장의 70-80%를 절제한 흰쥐가 자주 이용되어진다. 본인의 실험실에서는 여러 개의 이중결합을 보유하는 지방산으로 이루어져 있는 생선 지방이나 식물성 지방이 소장 절제후 남아있는 장 점막의 증식 과정을 증진시키는 것을 보고하였다. Menhaden oil은 omega-3 지방산을 고농도로 포함하고 있는 생선기름으로 소장 절제후 장 점막의 증식을 증가시키고 인공적으로 합성된 glucocorticoid인 dexamethasone은 감소시킨다. 본 연구에서는 이 두 가지 물질의 소장 점막에 미치는 영향이 prostaglandin(PG)이나 insulin-like growth factor(IGF)의 변화와 관계가 있는지 조사하였다. 수컷 흰 쥐(150±5g)를 두 군으로 나눠서 한 군은 15% safflower oil이 다른 군은 14% menhaden oil과 1% safflower oil이 포함된 식이를 먹였다. 식이를 시작한지 10일 후에 공장과 회장의 70%를 절제한 다음 각 식이 군들을 다시 둘로 나누어 dexamethasone을 하루에 몸무게 1 kg 당 125㎍씩 투여하거나 또는 buffer만을 투여하였다. 식이 섭취량을 측정하여 모든 군들이 같은 양의 식이를 섭취하게 pair-feeding을 하였다. Dexamethasone 투여는 두 가지 식이 군에서 모두 장 점막의 증식을 감소시켰고 혈청의 IGF-I 농도와 장 점막의 PGE_2 생성분비를 감소시켰다. 이 결과는 dexamethasone이 장 점막에 미치는 영향의 일부는 IGF나 prostaglandin에 의해 전달된다는 가설을 성립시킨다. 하지만 Menhaden oil을 먹인 쥐에서 장 점막의 증식이 대조군보다 증가했으나 혈청의 IGF-I과 IGF-II의 농도는 변하지 않았고 PGE_2 생성은 감소되었다. 따라서 장 점막 증식에 미치는 menhaden oil의 영향은 IGF-I, IGF-II 또는 PGE_2의 생성과는 관계가 없는 것으로 생각된다.