The Effect of High NaCl Diet on Gastroduodenal Carcinogenesis in Sprague-Dawley Rats Induced by N-methyl-N'-nitro-nitrosoguanidine[†]

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= Abstract =The enhancement of dietary NaCl on the gastric carcinogenesis induced by N-methyl-N'-nitro-nitrosoguanidine (MNNG) was studied in male Sprague-Dawley rats. One hundred and sixty four rats were divided into seven groups. Rats in control group were given MNNG at a concentration of 150 μg/ml in their drinking water while on a normal diet for 28 weeks. In two experimental groups, the rats were given MNNG at a concentration of 100 μ g/ml in their drinking water and the diet was supplemented with 5% NaCl and 10% NaCl in each. Histopathologic exammination showed that the rates of tumorigenesis in the stomachs of 5% NaCl diet group and 10% NaCl diet group were 72.2% and 95.2%, respectively. Though the rates were considerably higher compared with that of control group (45.5%), significant statistical difference was evident only in 10% NaCl diet group. The MNNG for first 28 weeks and 10% NaCl diet for ensuing 12 weeks, was similar to that in the control group.

Cocarcinogenic effect of NaCl was more pronounced in the group fed a diet supplemented with a higher concentration (10%) than in that with a lower concentration (5%).

Key Words: *Carcinogenesis, Nitrosoguanidine, NaCl diet, Enhancement*

INTRODUCTION

In Korea, stomach cancer is the most common malignant tumor and the relative frequency is 23.9% of all malignant tumors for three years (14,370/60,093) according to Korean Central Cancer Registry (MOHSA* 1984). The incidence of stomach cancer is high in Korea, Japan, Finland, South and Central America (Hill 1984). Epidemiological observations (Higginson 1984) suggest that dietary habbit is a major environmental factor in gastric carcinogenesis.

The diet is a rich source of carcinogens, mutagens, and tumor promotors (Kamiyama and Michioka 1983; Sugimura and Sato 1983). It is clear that the stomach is subjected to a varied carcinogen load. The stomach is the first resting place for dietary carcinogens. The studies of Americans of Japanese descent living in Hawaii, and Americans of African descent (Lijinskii 1983) showed the close relationship between diet and cancer. Analysis of the main ethnic groups in Hawaii (Kolonel 1983) suggested an association of stomach cancer incidence with the consumption of salted fish, pickled vegetables and a lower intake of vitamin C.

Mutagens-carcinogens in food (Higginson 1984) are classified into three categories. The first category includes naturally occurring ones as exemplified by mycotoxins. The second category of mutagens-carcinogens contained those produced in food storage, food processing, and cooking. The third category is derived from pesticides, fungicides, and artificially added chemicals (Lyon 1983). The presence of opportunistic tumor initiators, promotors should also be seriously taken into consideration (Sugimura 1983). Many dietary

factors (Kolonel 1983) have been implicated in gastric carcinogenesis including vitamin A,C and E intake, high intake of cooked vegetables, consumption of smoked or salty foods, exposure to nitrate or nitrite in high amounts, and low intake of fat and meat. Red pepper (Park 1980), Maeoo-fermented food stuff used in Korea (Lee 1982), and ginseng (Han 1983) were studied in Korea.

Excess intake of highly salted food is a common characteristics of many countries where incidence of stomach cancer is high (Lyon 1983). The geographic comparison indicated that the incidence of stomach cancer paralleled the amount of salted foods consumed (Kamiyama and Michioka 1983). The origin of human custom of adding sodium chloride to food is still in prehistory (Meneely 1958). The most often estimate of recommended requirement of salt (Oak 1983) is 1 gm of NaCl per 1 liter of water intake. The weighed mean of NaCl content in Korean soybean sauce and salted fish is over 20%, and Koreans are frequently exposed to high NaCl environment (Park 1974; Oak 1983; Cha 1970). But little effort has been tried for investigations of the influence of sodium chloride on gastric carcinogenesis except epidemiological surveys. Tatematsu et al. (1975) suggested that intragastric administration of saturated NaCl solution simultaneously with carcinogens increased the incidence of tumors of rat stomach. Since then, a few authors (Takahashi et al. 1983; Kim et al. 1979) have undergone similar experiment. But there was no definite conclusion, probably because of inappropriate experimental designs and results (Ohgaki et al. 1984; Shirai et al. 1984; Takahashi et al. 1984).

The rat model for gastric carcinogenesis induced by N-methyl-N′-nitro-nitrosoguanidine (MNNG) established by Sugimura and Fugimura (1967) has provided a suitable system which evaluates the effect of sodium chloride on gastric carcinogenesis.

Therefore we conducted this experiment to evaluate the enhancement of dietary sodium chloride on the gastric carcinogenesis induced by MNNG in male Sprague-Dawley rats.

MATERIALS AND METHODS

Male eight-week-old Sprague-Dawley rats weighing about 130 to 150 gm (Seoul National University Laboratory Animals) were housed in plastic cages, six rats/cage in an animal room. MNNG (Aldrich Chemical Co., Milwaukee, Wisconsin) was dissolved in deionized water at the con-

centration of 1 mg/ml or 1.5 mg/ml and kept in the dark as a stock solution. The stock solution was diluted 10-fold with tapwater just before use and given to rats ad libitum. The diet of which sodium chloride content was less than 0.25% was purchased from Samyang Oil and Food Co. Ltd., Wonjoo, Korea. The NaCl was purchased from Hwasung Chemical Co., Seoul, Korea and the NaCl crystals were more than 99.5% pure.

One hundred and sixty four rats were divided into seven groups and treated as follows (Table 1). Rats in group S-1 were maintained on a normal

Table 1. Experimental group and their treatment

Group	No. of animal		Treatment	
	ED-1**	Examined	MNNG(μg/ml)	Diet
Control				
S-1	20	14	0	normal
S-2	24	20	100	normal
S-3	24	22	150	normal
Experiment				
S-4	24	18	100	5% NaCl diet
S-5	24	21	100	10% NaCl diet
S-6*	24	15	100	10% NaCl diet
S-7	24	20	0	10% NaCl diet

* In group 6, MNNG was given for first 28 weeks, and then NaCl diet was given next 12 weeks.
** ED-1, first day of experiment.

diet and MNNG-free water. Rats in group S-2 and S-3 were given MNNG at a concentration of 100 μg/ml and 150 μg/ml, respectively, in their drinking water while on a normal diet for 28 weeks. In group S-4 the rats were given MNNG at a concentration of 100 μg/ml in their drinking water and the diet was supplemented with 5% NaCl. Concentration of NaCl in group S-5 was increased to 10%. At the end of 28th week of experiment, all the animals except group S-6 and S-7 were put on a normal diet with MNNG-free water. The rats in group S-6 were given MNNG for first 28 week and 10% NaCl diet for the ensuing 12 weeks. In group S-7 MNNG-free water and 10% NaCl diet were given to the rats throughout the experimental period.

All the animals had free access to food and water. The experimental animals were weighed on monthly basis. Water consumption was also measured. At the end of 40th week, all the animals

Table 2. Average body weight of the animals

Group \ Week	0	4	8	12	17	27	35	40
S-1	137.4	261.6	291.3	304.3	377.9	419.3	450.0	408.2
	±24.4	±29.9	±32.3	±33.3	±35.2	±47.8	±37.7	±42.9
S-2	133.1	223.7	258.9	268.9	342.3	364.6	419.2	363.2
	± 5.9	±20.2	±33.8	±33.3	±46.3	±38.1	±30.6	±44.0
S-3	142.9	191.0	238.1	255.0	324.6	349.1	391.9	323.7
	± 8.7	±26.3	±31.3	±31.0	±38.0	±40.6	±41.7	±53.5
S-4	133.5	175.3	251.3	262.3	286.4	315.2	409.5	344.7
	± 6.5	±27.1	±42.3	±32.6	±47.4	±35.8	±41.2	±48.5
S-5	132.0	171.8	255.0	258.7	254.6	286.2	349.1	325.3
	± 6.3	±23.7	±37.3	±34.1	±30.9	±37.8	±40.1	±48.7
S-6	143.0	227.5	309.7	314.2	333.9	377.6	369.3	351.2
	±10.1	±28.8	±25.7	±20.4	±36.7	±49.4	±46.8	±68.6
S-7	132.4	208.3	244.0	264.0	337.0	410.0	442.2	396.7
	± 6.4	±32.7	±43.1	±39.6	±39.6	±65.0	±35.2	±70.0

were sacrificed and autopsied. Animals which survived for more than 30 weeks were included in effective numbers of rats. The stomach and other organs were subjected to careful macroscopic examination. The stomach was opened along the great curvature, pinned flat on a cork board and fixed with 10% neutralized formalin. Fixed stomachs were photographed and cut along the lesser curvature into strips (4 mm), embedded in paraffin, and then cut into 5-6 μm thick sections. The intestine was opened longitudinally and any lesions detected were sectioned. The sections were stained with hematoxylin and eosin, alcian blue-PAS and Masson trichrome.

The results were analyzed by means of chi-square test and/or student t-test. The word "significant" indicates a calculated p value of less than 0.05.

RESULTS

The average body weight in the MNNG treated group was less than that in the untreated group (p <0.005). Administration of NaCl to the MNNG treated group showed an additive effect on the weight of the rats in group S-5 (S-3 versus S-5: p< 0.005, S-2 versus S-4:p>0.1, Table 2 and Fig. 1). A few animals in each group dead in the early stages of the experiment were also autopsied. But there was no tumor in all animals but pneumonia. The number of effective animals which survived for more than 30 weeks but died during the experimental period were eight cases (S-2: 3 cases, S-4: 1 case, S-5: 2 cases, S-6: 2 cases). Drinking

water consumption measured during the first 28 weeks of experiment showed that daily average intake by NaCl treated group was 1.4 times that by control group (S-3 versus S-4: p<0.005, S-3 versus S-5: p<0.005, Table 3). The average total MNNG consumption per rat in S-3 group was more than other groups (840.8 mg), and S-3 group could be a control group. Polyuria and polydipsia disappeared after the NaCl treatment period.

Gastric tumors developed only in MNNG-treated groups. Tumors were predominantly located in stomach, especially glandular stomach and duodenum. No lesions in forestomach were observed. Almost all tumors of glandular stomach were observed in the lesser curvature of the pyloric region or of the antrum and their average size was 8.2±9.6 mm (ranging from 5.7±2.3 mm in group S-3 to 11.6±14.1 mm in group S-5, p<0.1, Fig. 2). The average size of small bowel tumors (18.2± 16.2 mm) was larger than that of glandular stomach (p<0.01, Fig. 2). Double tumors in glandular stomach were observed in 3 cases (S-2-12, S-4-6, S-5-21) and triple tumors in duodenum was observed in one case(S-4-3). Synchronous dual tumors in glandular stomach and small bowel were in 2 cases (S-4-4, S-4-6). The tumors appeared as smooth surfaced globules and varied in size; some formed umbilicated ulcerous lesions.

The microscopic findings which were observed from 130 animals which survived for more than 30 weeks were summarized in Table 4. Epithelial lesions of the glandular stomach classified into three types, regenerative hyperplasia 25 cases, adeno-
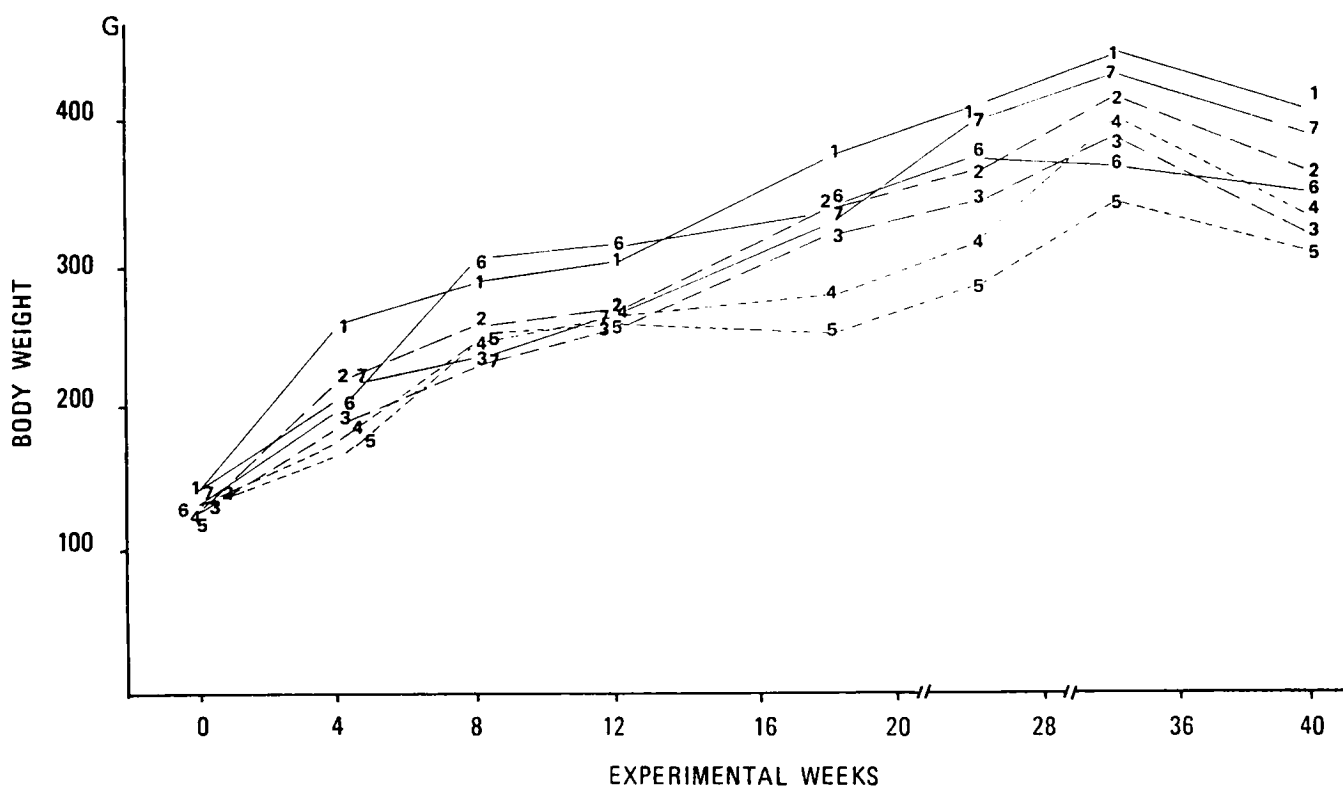
Fig. 1. Weight gain of the rats treated with MNNG in drinking water.

Table 3. The amount of drinking water and MNNG

Group	Amount of water (ml)/day	Total intake of MNNG (mg)
S-1	31.2±1.2	0
S-2	29.2±0.7	572.1±14.7
S-3	28.6±1.5	840.8±44.4
S-4	41.1±4.7	805.6±91.9
S-5	40.2±4.3	787.9±84.1
S-6	30.3±4.7	593.5±92.1
S-7	39.0±3.7	0

matous hyperplasia 18 cases, adenocarcinoma 33 cases. Regenerative glandular hyperplasia means irregular proliferation at the margin and base of the erosion of mucosa with little cellular atypism. Adenomatous hyperplasia means excessive glandular proliferation with scanty cellular atypism, with either peripheral growth into the stomach cavity or the growth into the submucosa. Adenocarcinoma was defined as excessive glandular proliferation with pronounced structural and cellular atypism invading the submucosa, the muscularis propria or the serosa. Some leiomyosarcomas, malignant schwanoma, malignant lymphomas and angiosarcomas were observed in high NaCl treated groups.

The incidence of tumors including regenerative hyperplasias, adenomatous hyperplasias, adenocar-
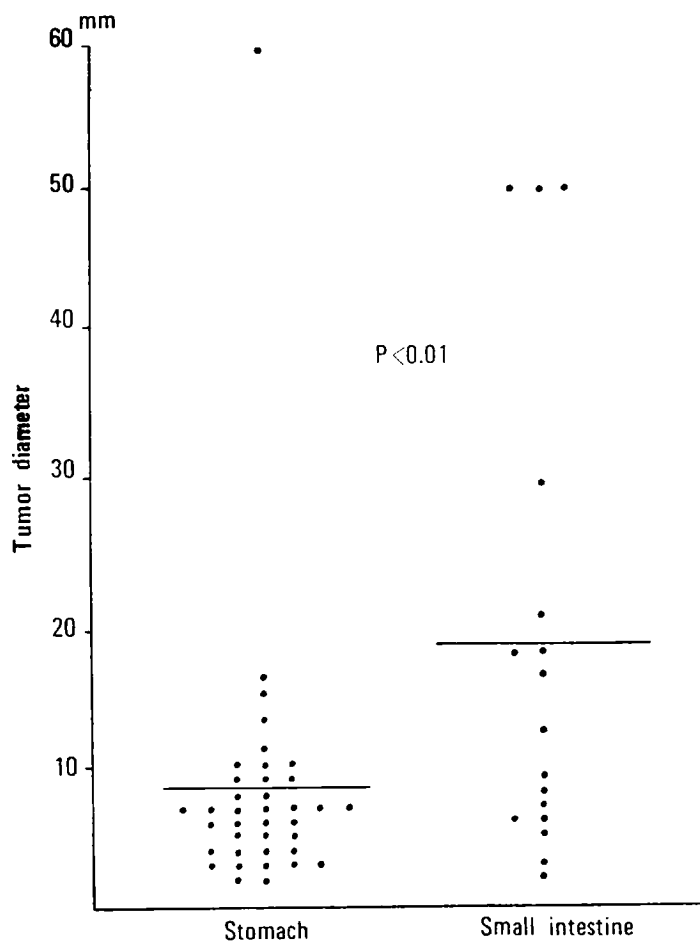

Fig. 2. Tumor size and location. Horizontal bars indicate mean.

Table 4. Pathologic findings of stomach and small intestine

Findings \ Group	S-1	S-2	S-3	S-4	S-5	S-6	S-7	Total
Glandular stomach								
Regenerative hyperplasia		5	2	6	10	2		25
Adenomatous hyperplasia		3	2	4	6	3		18
Adenocarcinoma		5	6	5	13	4		33
Malignant mesenchymal tumor				1	3			4
Small intestine								
Adenoma			1	1				2
Adenocarcinoma		1	4	8	7			20
Malignant mesenchymal tumor				1				1

Table 5. Carcinogenesis in the stomach by high NaCl diet

Group		Total No.	Tumor*** No.	Tumor*** %	Adenocarcinoma No.	Adenocarcinoma %
Control						
S-1	Normal diet	14	0	0.0	0	0.0
S-2	Normal diet+MNNG(100 μg/ml)	20	10	50.0	5	25.0
S-3	Normal diet+MNNG(150 μg/ml)	22	12	45.5*	6	27.3*
Experiment						
S-4	5% Normal diet+MNNG(100 μg/ml)	18	13	72.2	5	27.8
S-5	10% Normal diet+MNNG(100 μg/ml)	21	20	95.2*	13	61.9*
S-6	10% Normal diet after MNNG	15	8	52.3	4	26.7
S-7	10% NaCl diet	20	0	0.0	0	0.0

* S-3 *versus* S-5:Statistically significant difference (P<0.005)
** S-3 *versus* S-5:Statistically significant difference (P<0.025)
*** tumor includes hyperplasia, adenoma, adenocarcinoma and malignant mesenchymal tumor
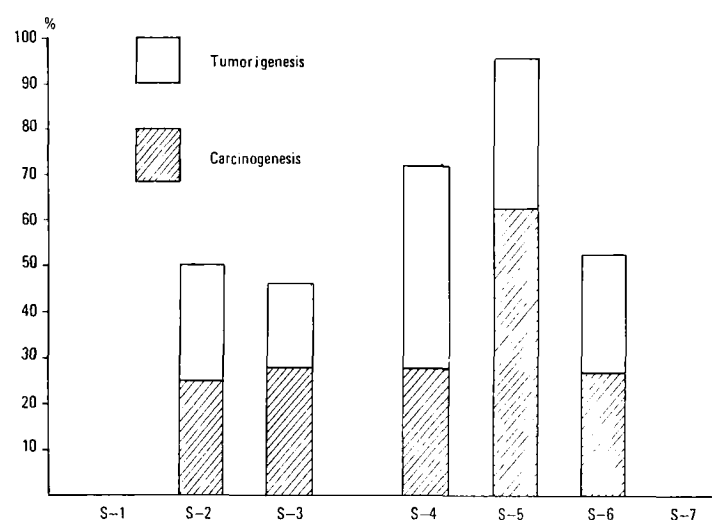

Fig. 3. Relative frequency of neoplasms of the stomach by groups.
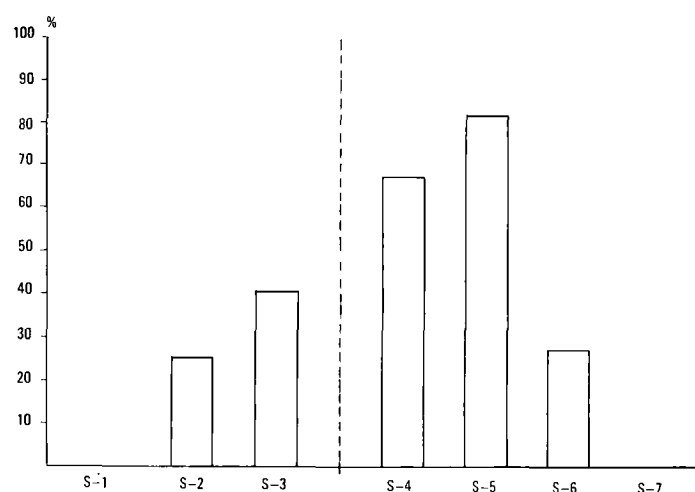

Fig. 4. Relative frequency of carcinogenesis in the stomach and small intestine by groups.

Table 6. Carcinogenesis in the stomach and small intestine

Group		Total No.	Tumor	
			No.	%
Control				
S-1	Normal diet	14	0	0.0
S-2	Normal diet+MNNG(100 μg/ml)	20	5	25.0
S-3	Normal diet+MNNG(150 μg/ml)	22	9	40.9
Experiment				
S-4	5% NaCl diet+MNNG(100 μg/ml)	18	12	66.7
S-5	10% NaCl diet+MNNG(100 μg/ml)	21	17	81.0
S-6	10% NaCl diet after MNNG	15	4	26.7
.S-7	10% NaCl diet	20	0	0.0

*S-3 versus S-5:Statistically significant difference($p < 0.001$)

cinomas and malignant mesenchymal tumors were summarized in Table 5 and Fig. 3. Tumorigenesis in the stomachs of group S-4 and S-5 were 72.2% (13/18) and 95.2% (20/21) respectively. Though the rates were considerably higher compared to that of control group (45.5%, 12/22), significant statistical difference was evident only in group 5 (S-3 versus S-5: $p < 0.005$). The incidence of carcinogenesis in the stomach and small intestine of control groups was 40.9% (9/22). But those of the experimental groups were 66.7% (12/18) and 81.0% -17/22) in group S-4 and S-5, respectively (S-3 versus S-5: $p < 0.001$, Table 6 and Fig. 4). But the rate of tumorigenesis in group S-6 was similar to that in control group (Table 5 and 6).

DISCUSSION

Salt intake varies markedly as individual preference and custom. The average American has a total daily intake of NaCl ranging 10-14.5 gm but the average Asian do that ranging 20-40 gm (Oak 1983). Koreans intake high NaCl diets such as soybean sauce (25.5%), soybean paste (15.8%), hot red pepper paste (10.1%), salted sardiness (29.5%) and kimchi (2.5%). Many Koreans frequently add excessive salt to food (Cha and Suh 1970). The Korean home made soybean sauce contained NaCl ranging 18.3-28.1%; home made soybean paste ranging 6.4-19.6%, hot red pepper paste ranging 5.9-17.4%, kimchi ranging 1.0-5.8% (Park and Park 1974). So it is very important to the Korean to evaluate the role of NaCl in the pathogenesis of stomach cancer.

Since Sugimura and Fujimura (1967) first reported the induction of adenocarcinoma of glandu-

lar stomach of rats by addition of MNNG to their drinking water, there has been many reports (Saito et al. 1980; Sano et al. 1984; Bignami 1984; Tatsuta et al. 1983) on gastric carcinogenesis induced by MNNG in animals. This MNNG model for gastric carcinogenesis has provided suitable system for evaluation of modifying effects of NaCl on gastric carcinogenesis. N-ethyl-N′-nitro-nitrosoguanidine followed by MNNG were stronger carcinogens than those with large alkyl chains among the N-alkyl-N′-nitro-nitrosoguanidine compounds (Sano et al. 1978). The process for cancerization of glandular epithelial cells was completed during the first seven months for MNNG administration (Fujimura et al. 1970; Hattori et al. 1984). Treatment with 50 μg/ml of MNNG in drinking water for 12 weeks is considered to be minimal treatment necessary for induction of tumors in the stomach (Shirai 1978).

When gastric and intestinal tumors were induced by administration of MNNG in drinking water, randomly bred Wistar rats have been most frequently used. Ohgaki et al. (1983) described that resistance to induction of gastric adenocarcinoma in rats is a dominant characteristic and that the incidence of gastric adenocarcinoma in ACI rats was 80% in male and 47% in females, whereas in Buffalo rats the incidence was 18% in males and 0% in females. The susceptibility to a chemical carcinogen assumed to be genetically controlled in gastric carcinogenesis in rats. Authors' study demonstrates that Sprague-Dawley rats developed gastric tumors at a high frequency in response to MNNG.

Since the progression of MNNG induced lesions from regenerative hyperplasia, adenomatous hyperplasia to adenocarcinomas has been well characte-

rized (Saito *et al.* 1970), authors' result provides a strong evidence for enhancing action of sodium chloride in gastric carcinogenesis, especially in initiation stage.

A histopathologic sequence in the intestinal type of gastric cancer has been proposed by Correa *et al.* (1975); in the first stage gastric carcinogenesis may be caused by excessive NaCl intake, protein malnutrition, chronic virus infection or by ingested carcinogens (Such as N-nitroso compounds) or to biliary compounds refluxed into achlorhydric stomach (Hill 1984).

It is also important to clarify whether NaCl is effective in the promotion stage of gastric carcinogenesis. Several attempts to demonstrate the promotive effect of NaCl on carcinogenesis in the glandular stomach have not been successful. Shirai *et al.* (1984) found that 5% sodium chloride diet enhanced the incidence of forestomach papillomas in rats when given as a promotor after a single intragastric application of MNNG. Ohgaki *et al.* (1984) and Takahashi *et al.* (1984) suggested that NaCl also played a role but they did not demonstrate it. The rate of tumorigenesis in group S-6 of which rats were given MNNG for the first 28 weeks and 10% NaCl diet for the ensuing 12 weeks was similar to that in control group. The result may suggest that NaCl do not have a promotive effect. But we cannot establish it because of absence of the experimental group of which rats were given MNNG and NaCl diet simultaneously for the first, then NaCl diet for the ensuing period.

A possible explanation for the enhancing effect is excess intake of carcinogen due to increased thirst while on high NaCl diet (Tatematsu 1975). Obviously the water intake by rats in experimental groups was 1.2-1.5 times more than that by rats in control groups. However animals in the control group S-3, which took drinking water at a concentration of MNNG 150 μg/ml did not show increased incidence of gastric tumors. Thus the enhancing effect could not be explained only by the excess intake of MNNG. The mechanism of the NaCl effect on the gastric carcinogenesis is still unknown. One of the hypotheses (Tatematsu 1975) is that repeated injuries of the gastric mucosa may be one factor causing cancer. The gastric mucosa contains several kinds of acid mucopolysaccharides, including hyaluronic acid, the viscosity of which is known to be markedly decreased in the presence of sodium chloride. Sodium chloride and surfactant might each reduce the protective effect of mucous barrier of the glandular stomach and allow direct contact of the carcinogen with gastric mucosa. Erosion or ulceration per se in the stomach may not evolve into gastric cancer but such lesions may become cancerous in the presence of carcinogen, even at a low concentration. Such experiments were done in the case of aspirin (Chang *et al.* 1983), plastic bead (Fukushima 1976), iodoacetamide (Shirai 1978), and gastrin (Tahara 1982).

Gastric atrophy in person is a natural sequence of aging and very rare in young persons but common in persons more than 60 years old. In the regions of Columbia with a high risk of gastric cancer, gastric atrophy is very common even in young adults and similar results have been in Chile, the Caspian littoral, South India and China (Correa *et al.* 1975). It has been hypothesized that this premature aging may be due to the intake of large amounts of salts which exerts on an osmotic stress on gastric mucosa (Hill 1984). Gastric lesions, such as atrophic gastritis are associated with achlorhydria, providing favorable conditions for colonization or infection by gastric microflora. On the basis of experiment (Sumi and Miyakawa 1981), possible factors that may involve were as follows. The first is that metabolism of MNNG might be affected by gastric microflora. The second is that microflora themselves elaborate a promotor for the development of gastric tumors. The next stage after gastric atrophy in the hypothesized histopathological sequence is intestinal metaplasia. The mucosa may then undergo dysplasia which may vary in degree from mild to severe, and finally progresses to carcinoma. Although intestinal metaplasia is assumed to be precancerous in human stomach cancer, there was no marked relationship between intestinal metaplasia and MNNG induced metaplasia (Fujii *et al.* 1980).

The above results suggest that the concentration of NaCl in diet should be high enough to reduce the protective effect of mucous barrier of the stomach and to exert an osmotic stress on the gastric mucosa being gastric atrophy. These facts explain authors result that the cocarcinogenic effect is more pronounced in the group fed a diet supplemented with concentration of 10% NaCl than 5% NaCl.

Because high NaCl content in the Korean diets probably results in increased incidence of stomach

cancer, further studies are needed to evaluate enhancing effect of high NaCl diet on gastric carcinogenesis on the basis of biochemistry.

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= 국문초록 =

고 NaCl 식이와 N-methyl-N´-nitro-nitrosoguanidine 경구 투여가 Sprague-Dawley 쥐 위·십이지장암 발생에 미치는 영향

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위암 발생율이 높은 지역의 공통된 특징의 하나가 고농도 염분을 포함한 식품 섭취 양상이다. 식염 섭취량이 많은 한국인에게는 위암발생 과정에서의 NaCl 역할을 밝히는 것이 중요하다. 이에 대한 동물실험으로서 고농도 NaCl 식이가 Sprague-Dawley 쥐 위암발생에 미치는 발암성 및 N-methyl-N´-nitro-nitrosoguanidine (MNNG라 약함)에 의하여 유발되는 위암에 미치는 영향을 관찰하기 위하여 164마리 쥐를 7군으로 나누어 실험한 결과 다음과 같은 결과를 얻었다.

1. MNNG를 투여하지 않은 일반 사료군과 10%NaCl 사료군에서는 상부 위장관 암이 전혀 발생하지 않았다.

2. 위에서의 종양발생율은 대조군인 MNNG 투여군에서 45.2%(12/22)이었고, 실험군인 MNNG 및 5%NaCl 사료군에서 72.2%(13/18), 그리고 MNNG 및 10%NaCl 사료군에서 95.2%(20/21)의 종양발생율을 보였다(p<0.005). 따라서 사료의 NaCl 농도에 따른 종양발생율의 차이를 나타내었다.

이상의 결과로 미루어 고농도 NaCl 식이는 MNNG에 의한 위암발생율을 높이며 이러한 공동 발암원 효과는 5% NaCl사료보다 10%NaCl사료에서 뚜렷하였다.