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EFFECT OF NORMAL $C_{10:0}$-$C_{20:0}$ FATTY ACIDS AND THEIR RELATED COMPOUNDS ON GASTRIC SECRETION AND EXPERIMENTAL ULCERATION IN RATS*

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Fatty acids of $C_{10:0}$, $C_{12:0}$, $C_{13:0}$, $C_{14:0}$, and $C_{16:0}$ significantly inhibited the amount of gastric juice, total acid output, and total peptic activity, but fatty acids of $C_{17:0}$-$C_{20:0}$ entirely failed to show significant inhibitory activity. Only the methyl ester of $C_{14:0}$ showed significant inhibition of these parameters at the dose of 100 mg/kg, while at the dose of 200 mg/kg, methyl esters of fatty acids of fatty acids of $C_{10:0}$, $C_{12:0}$, $C_{14:0}$, and $C_{16:0}$ significantly inhibited these three parameters. α-Monoglyceride of $C_{14:0}$ significantly inhibited the amount of gastric juice at the dose of 100 mg/kg, while α-monoglycerides of $C_{10:0}$, $C_{12:0}$, $C_{13:0}$,$C_{14:0}$, and $C_{16:0}$ significantly inhibited the amount of gastric juice, total acid output, and total peptic activity at the dose of 200 mg/kg. In the case of intraduodenal administration, myristic acid also showed significant inhibition of these parameters at 100 and 200 mg/kg doses. The dose-activity correlation in gastric secretion inhibitory activity was examined with myristic acid and this activity was found to increase with increasing dose of the acid administered. Myristic acid significantly decreased the ulcer index in aspirin-induced ulcer, it was entirely ineffective in preventing histamine-induced ulcer. Finally, inhibitory effect of myristic acid on pepsin and histidine decarboxylase was examined *in vitro* and it was found that myristic acid inhibited peptic activity, but it had almost no effect of inhibiting the histidine decarboxylase activity.

Keywords—$C_{10:0}$-$C_{20:0}$ fatty acids; α-monoglycerides; methyl esters; gastric secretion; aspirin-induced ulcer; histamine-induced ulcer; pepsin; histidine decarboxylase; intraduodenal administration

We reported earlier the isolation of a principle inhibiting gastric secretion in rats from dried brewer's yeast, and also the biological activity of several fatty acids isolated and identified as the active principle.[1] As a part of studies on the structure-activity correlation of saturated fatty acids, we examined the inhibitory activity on gastric secretion in rats of normal fatty acids of $C_{10:0}$ to $C_{20:0}$ and their derivatives. Examinations were also made on the effect of myristic acid, the $C_{14:0}$ fatty acid found to have the most marked activity, on various experimental ulcer models *in vivo* and pepsin or histidine decarboxylase activity *in vitro*.

MATERIALS AND METHODS

Materials —— Decanoic, dodecanoic, and tetradecanoic acids (purity, 98% each) were obtained from Katayama Chemical Co., Japan. Undecanoic (purity, 98%), tridecanoic (purity, 98%), pentadecanoic (purity, 98%), heptadecanoic (purity, 98%), nonadecanoic (purity, 98%), eicosanoic acids (purity, 99%), and methyl tridecanoate (purity, 99%) were obtained from Tokyo Kasei Co., Japan. Hexadecanoic acid and methyl hexadecanoate (purity, 99% each) were

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obtained from Nakarai Chemicals, Ltd., Kyoto, and octadecanoic acid (purity, 100%) from E. Merck AG, Darmstadt, Germany. Methyl decanoate, methyl dodecanoate, and methyl tetradecanoate (purity, 98% each) were obtained from Wako Chemical Industries, Ltd., Osaka. Atropine sulfate J. P. was used as a positive control reagent. α-Monoglycerides and metiamide were kindly supplied by the Nikko Chemicals Co., and Smith Kleine & Fujisawa, respectively.

Animals — Male Wistar rats weighing 150–200 g were used as experimental animals.

Assay of Gastric Secretion Inhibitory Activity in Rats — The rats were deprived of food but allowed free access to water for 48 hr before the experiments. Under ether anesthesia, the pylorus was ligated according to the method described by Shay *et al.*[2] Each sample was ground to fine powder with acacia (final concentration, 5%) and suspended in saline, and this suspension was administered intraperitoneally immediately after pylorus ligation. As a control, only 5% acacia in saline was administered. In the case of intraduodenal administration, each sample was suspended in saline without acacia, and this suspension was administered intraduodenally immediately after pylorus ligation. As a control, only saline was administered. Atropine sulfate was dissolved in saline. After 4 hr, the animals were sacrificed and the stomachs were removed. The gastric contents were centrifuged and gastric volume was measured. Total acid output and total peptic activity were determined according to the privious paper,[3] and they were expressed respectively, as μEq/100g body weight and mg as tyrosine/100 g body weight.

Experimental Gastric Ulcer in Rats — i) Aspirin-induced Gastric Lesions: The rats were fasted for 24 hr before the experiment. According to the method of Okabe *et al.*[4] the rats orally received 100 mg/kg of aspirin suspended in 1% carboxymethylcellulose solution immediately after pylorus ligation. After 6 hr, the rats were sacrificed and the stomachs were removed, treated with 1% formalin, and examined for lesion in the glandular portion. The ulcer index was calculated as the sum of the length of each lesion. Myristic acid or metiamide was administered intraperitoneally immediately after pylorus ligation.

ii) Histamine-induced Gastric Lesions: The rats were deprived of food but allowed free access to water 48 hr before the experiment. According to the method of Buchner *et al.*,[5] the rats were given intraperitoneally at the dose of 300 mg/kg of histamine hydrochloride. After 4 hr, the rats were sacrificed and the stomachs were removed, and examined for lesions in the glandular portion. The ulcer index was estimated by the method of Adami *et al.*[6] Myristic acid or metiamide was administered intraperitoneally 10 min before the administration of histamine hydrochloride.

Effect on Squirming and Capillary Permeability — According to the method of Whittle,[7] male mice (ddy strain), weighing 21 ± 1 g, were used. Myristic acid was administered intraperitoneally to each animal 10 min after intravenous injection of 0.1 ml of a solution of Pontamine Sky Blue 6 BX. Each dose group consisted of eight mice.

Reaction System for Hydrolysis of Casein by Pepsin — The reaction system was carried out according to the procedure described by Anson.[8] For this test, 0.8 ml of 0.02N KCl-HCl buffer (pH 2.0) and 0.1 ml of dimethylsulfoxide solution of myristic acid were mixed and then 0.1 ml of porcine pepsin (7×10^{-2} mg/ml) was added and preincubated for 30 min at 37°. After preincubation, the reaction was initiated by adding 0.1 ml of 0.6% casein solution. After incubation at 37° for 30 min, 2.0 ml of 1.7M perchloric acid was added and the mixture kept for 1 hr at room temperature. It was then centrifuged and the extinction of the acid soluble fraction was read at 280 nm.

Assay of Histidine Decarboxylase Activity — A crude histidine decarboxylase was preapred from the gastric mucosa of the rat according to the method of Håkanson.[9] The extract was incubated with L-histidine in the presence of 2.0×10^{-5}M pyridoxal-5-phosphate in 0.1M phosphate

buffer for 1 hr at 37°. The incubation was interrupted by the addition of trichloroacetic acid and the following interrupted by the accition of trichloroacetic acid and the following procedure involving organic extraction with a 3:2 mixture of *n*-butanol and chloroform was carried out. The organic phase is then shaken for about 1 min with salt-saturated 0.1N NaOH. This washing removes any residual amount of histidine which may be present. The final hydrochloric acid fraction was diluted 3 times with water, and histamine produced was determined fluorometrically as described by Shore *et at*.[10] Myristic acid was dissolved in dimethylsulfoxide.

RESULTS

Inhibitory Effect of Straight-chain Fatty Acids of $C_{10:0}$ to $C_{20:0}$ on Gastric Secretion in Rats

Table I shows the inhibitory effect of straight-chain fatty acids of $C_{10:0}$ to $C_{20:0}$ on gastric secretion in pylorus-ligated rats. It is clear from this result that the acid of $C_{14:0}$ has the strongest inhibitory effect on the amount of gastric juice, total acid output, and total peptic activity, followed by those of $C_{10:0}$, $C_{12:0}$, $C_{13:0}$, and $C_{16:0}$ showing significantly inhibition. The acids of $C_{11:0}$ and $C_{15:0}$ showed significant inhibition only on the amount of gastric juice. Fatty acids of $C_{17:0}$, $C_{18;0}$, $C_{19:0}$, and $C_{20:0}$ did show a tendency to inhibit the amount of gastric juice, total acid output, and total peptic activity but the difference was not significant. On the other hand, atropine sulfate showed a significant inhibition of these parameters at the dose of 1 or 5 mg/kg.

TABLE I. *Effect of Various Fatty Acids administered intraperitoneally on Gastric Scretion in Pylorus-ligated Rats (4 hr)*

Treatment	Dose (mg/kg)	No. of rats	Gastric volume (ml/100g b.w.)	Total acid output (μEq/100g b.w.)	Total peptic activity (mg as tyrosine/100 b.w.)
Control[a]	—	10	2.88±0.45	323.2±66.3	233.6±23.5
$C_{10:0}$	100	10	1.06±0.12***	100.4±14.7**	127.9±39.1*
$C_{12:0}$	100	10	1.53±0.30*	146.9±32.1*	118.3±23.8**
$C_{14:0}$	100	10	0.90±0.07***	88.9± 5.8**	110.0±21.5**
$C_{15:0}$	100	10	1.60±0.23*	192.3±28.6	157.9±27.7
$C_{16:0}$	100	10	1.52±0.27*	158.0±25.2*	113.7±18.6***
Control[a]	—	10	2.28±0.23	244.3±28.6	233.9±20.1
$C_{11:0}$	100	10	1.36±0.27*	166.7±35.7	153.5±48.7
$C_{13:0}$	100	10	1.03±0.15***	96.0±11.7***	123.1±14.4***
$C_{17:0}$	100	10	1.62±0.45	178.2±61.9	152.8±40.8
$C_{18:0}$	100	10	1.68±0.20	168.6±30.2	160.2±30.7
$C_{19:0}$	100	10	1.65±0.32	168.5±33.2	159.4±38.6
$C_{20:0}$	100	10	1.78±0.32	177.4±31.8	169.3±33.9
Control[b]	—	8	3.62±0.53	369.1±73.7	259.9±37.1
Atropine	1	8	1.04±0.20***	86.2±11.4**	87.9±12.2***
sulfate	5	8	0.36±0.07***	33.0± 5.6***	39.2± 5.6***

All values represent mean± SE.
a) 5% acacia in saline.
b) Saline.
Each fatty acid or atropine sulfate was administered immediately after the pylorus ligation.
*Significantly different from control group: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

TABLE II. *Effect of Various Fatty Acids Methyl Esters administered intraperitoneally on Gastric Secretion in Pylorus-ligated Rats (4 hr)*

Treatment with methyl ester of fatty acid	Dose (mg/kg)	No. of rats	Gastric volume (ml/100g b.w.)	Total acid output (μEq/100g b.w.)	Total peptic activity (mg as tyrosine/100 b.w.)
Control[a)]	—	8	2.21±0.33	233.8±41.7	162.3±16.7
$C_{10:0}$	100	8	1.84±0.21	195.8±25.5	135.6±15.8
$C_{12:0}$	100	8	1.93±0.19	223.6±19.4	135.4±17.4
$C_{13:0}$	100	8	1.53±0.33	163.0±32.9	122.4±11.8
$C_{14:0}$	100	8	0.97±0.27*	101.3±19.7*	89.3±16.1**
$C_{16:0}$	100	8	1.50±0.39	175.6±48.5	126.8±22.3
Control[a)]	—	8	2.63±0.28	273.8±36.8	156.3±26.1
$C_{10:0}$	200	8	1.44±0.29**	144.2±31.4*	82.8±12.0*
$C_{12:0}$	200	8	1.12±0.14***	103.9±21.7**	74.9±11.2*
$C_{13:0}$	200	8	1.58±0.31*	152.4±32.9*	117.8±11.8
$C_{14:0}$	200	8	0.90±0.18***	89.9±19.2***	61.2± 7.3**
$C_{16:0}$	200	8	1.22±0.28**	108.1±30.8**	84.4±11.7*

All values represent mean± SE.
a) 5% acacia in saline.
Each methyl ester was administered immediately after the pylorus ligation.
*Significantly different from control group: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

TABLE III. *Effect of Various α-Monoglycerides administered intraperitoneally on Gastric Secretion in Pylorus-ligated Rats (4 hr)*

Treatment with α-monoglyceride of fatty acid	Dose (mg/kg)	No. of rats	Gastric volume (ml/100g b.w.)	Total acid output (μEq/100g b.w.)	Total peptic activity (mg as tyrosine/100 b.w.)
Control[a)]	—	8	2.27±0.21	351.7±36.9	155.1± 8.1
$C_{10:0}$	100	8	1.71±0.32	268.8±56.5	146.9±19.5
$C_{12:0}$	100	8	1.97±0.22	333.3±43.3	160.6±14.7
$C_{13:0}$	100	8	1.71±0.27	262.0±32.6	130.0±11.1
$C_{14:0}$	100	8	1.56±0.20*	247.6±29.7*	139.7±16.2
$C_{16:0}$	100	8	1.41±0.43	251.0±67.3	124.4±26.7
Control[a)]	—	8	2.47±0.10	304.8±18.3	185.1± 6.6
$C_{10:0}$	200	8	0.87±0.05***	88.5± 5.9***	89.0± 9.3***
$C_{12:0}$	200	8	1.23±0.38**	145.2±41.0**	122.3±25.9*
$C_{13:0}$	200	8	1.02±0.22***	120.1±26.2***	139.5± 8.7***
$C_{14:0}$	200	8	0.74±0.09***	81.1±10.3***	75.9± 7.6***
$C_{16:0}$	200	8	0.75±0.12***	82.0±10.7***	65.0± 4.1***

All values represent mean± SE.
a) 5% acacia in saline.
Each α-monoglyceride was administered immediately after the pylorus ligation.
*Significantly different from control group: *$p < 0.05$, **$p < 0.01$, *** $p < 0.001$.*

Effect of methyl Esters of $C_{10:0}$, $C_{12:0}$, $C_{13:0}$, $C_{14:0}$, and $C_{16:0}$ Fatty Acids on Gastric Secretion in Rats

In order to examine whether the presence of a free carboxyl group was a requisite for gastric secretion inhibitory activity, methyl esters of five fatty acids found to have a strong activity in inhibiting gastric secretion in rats were examined. As shown in Table II, at the dose of 100 mg/kg, *i.p.*, methyl myristate alone showed a significant inhibition on the amount of gastric juice, total acid output, and total peptic activity, whereas methyl esters of other acids did not show any

TABLE IV. *Effect of Myristic Acid on Aspirin- or Histamine-induced Ulceration in Rats*

Ulceration	Treatment	Dose (mg/kg)	No. of rats	Ulcer index
Aspirin-induced ulceration	Control[a]	—	8	29.16±4.60
	$C_{14:0}$	100[c]	8	7.83±1.48***
	$C_{14:0}$	200[c]	8	2.80±1.08***
	Control[b]	—	8	30.64±7.79
	Metiamide	50[c]	8	11.07±2.50*
	Metiamide	100[c]	8	1.25±0.84***
Histamine-induced ulceration	Control[a]	—	8	3.00±0.40
	$C_{14:0}$	100[d]	8	3.08±0.32
	$C_{14:0}$	200[d]	8	3.00±0.44
	Control[b]	—	8	3.40±0.40
	Metiamide	50[d]	8	1.91±0.37*
	Metiamide	100[d]	8	1.03±0.30***

All values represent mean± SE.
a) 5% acacia in saline.
b) Saline.
c) Myristic acid or metiamide was administered intraperitoneally immediately after the pylorus ligation.
d) Myristic acid or metiamide was administered intraperitoneally 10 min before the injection of histamine.
*Significantly different from control group: * $p < 0.05$, *** $p < 0.001$.*

TABLE V. *Effect of Myristic Acid administered intraperitoneally on Gastric Secretion in Pylorus-ligated Rats (4 hr)*

Treatment	Dose (mg/kg)	No.of rats	Gastric volume (ml/100g b.w.)	Total acid output (μEq/100g b.w.)	Total peptic activity (mg as tyrosine/100g b.w.)
Control[a]	—	8	4.52±0.43	433.3±38.7	409.3±36.5
$C_{14:0}$	25	8	2.62±0.62*	265.8±80.8	244.6±46.3*
$C_{14:0}$	50	8	2.17±0.37***	177.7±39.4***	220.4±31.7**
$C_{14:0}$	100	8	1.19±0.28***	87.1±28.4***	129.3±22.3***
$C_{14:0}$	200	8	1.00±0.24***	80.7±20.4***	120.5±19.1***

All values represent mean± SE.
a) 5% acacia in saline.
Myristic acid was administered immediately after the pylorus ligation.
*Significantly different from control group. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.*

sighificant inhibitory effect. When the dose was increased to 200 mg/kg, *i.p.*, methyl esters of $C_{10:0}$, $C_{12:0}$, and $C_{16:0}$ acids, as well as that of $C_{14:0}$ acid also inhibited these three parameters significantly, and the methyl ester of $C_{13:0}$ acid significantly inhibited the amount of gastric juice and total acid output.

Effect of α-Monoglycerides of $C_{10:0}$, $C_{12:0}$, $C_{13:0}$, $C_{14:0}$, and $C_{16:0}$ Fatty Acids on Gastric Secretion in Rats

Inhibitory effect on gastric secretion in rats was examined with α-monoglycerides of fatty acids, centered around the most active $C_{14:0}$ acid. As shown in Table III, only the α-monoglyceride of $C_{14:0}$ acid showed significant inhibition on the amount of gastric juice and total acid output at the dose of 100 mg/kg. At the dose of 200 mg/kg, α-monoglycerides of $C_{10:0}$, $C_{12:0}$, $C_{13:0}$, $C_{14:0}$, and $C_{16:0}$ acids all showed a significant inhibition on the amount of gastric juice, total acid output, and total peptic acrivity, especially strong activity was found in the α-monoglycerides of $C_{14:0}$ and $C_{16:0}$ acids.

Anti-ulcerogenic Activity in Rats

The $C_{14:0}$ acid, which significantly decreased the ulcer index in pylorus-ligated rats,[1] was examined for its effect in preventing aspirin- and histamine-induced ulcer. As shown in Table IV, this acid significantly decreased the ulcer index, in a dose-dependent manner, on aspirin-induced ulcer at the dosage of 100 and 200 mg/kg, but showed entirely no effect in preventing histamine-induced ulcer. Metiamide significantly decreased the ulcer index on aspirin- and histamine-induced ulcer at the dosage of 50 and 100 mg/kg.

Dose-Activity Correlation in the Activity of Myristic Acid for Inhibition of Gastric Secretion in Rats

Table V shows the correlation between dose and activity of myristic acid ($C_{14:0}$) in inhibiting gastric secretion in rats.

At the dose of 50 mg/kg, myristic acid significantly inhibited the amount of gastric juice, total acid output, and total peptic activity, and this inhibitory activity tended to appear strongly with increasing dose of 100 and 200 mg/kg. At the dose of 25 mg/kg, myristic acid significantly inhibited only the amount of gastric juice and total peptic activity.

Effect of Intraduodenal Administration of Myristic Acid on Gastric Secretion in Rats

In order to examine whether the inhibitory

TABLE VI. *Effect of Myristic Acid administered intraduodenally on Gastric Secretion in Pylorus-ligated Rats (4 hr)*

Treatment	Dose (mg/kg)	No.of rats	Gastric volume (ml/100g b.w.)	Total acid output (μEq/100g b.w.)	Total peptic activity (mg as tyrosine/100g b.w.)
Control[a]	—	8	2.83±0.20	356.2±31.8	214.0±12.5
$C_{14:0}$	25	8	2.77±0.38	313.3±42.5	173.3±23.5
$C_{14:0}$	50	8	2.26±0.35	249.0±48.5	165.4±21.5
$C_{14:0}$	100	8	1.83±0.25**	213.1±40.5*	153.0±16.8*
$C_{14:0}$	200	8	1.67±0.26**	194.1±37.4**	138.6±17.1**
Control[b]	—	8	2.57±0.40	234.1±49.2	182.8±30.2
Atropine	5	8	0.56±0.10***	50.9± 5.0**	58.8± 6.8**
sulfate	10	8	0.30±0.06***	27.5± 3.5***	35.7± 4.2***

All values represent mean± SE.
a) 5% acacia in saline.
b) Saline.
Myristic acid or atropine sulfate was given intraduodenally immediately after the pylorus ligation.
*Significantly different from control group: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

TABLE VII. *Effect of Myristic Acid on Caseinolysis of Pepsin and Histidine Decarboxylase Activity in Vitro*

Concentration of myristic acid (M)	Inhibition (%)	
	Pepsin	Histidine decarboxylase
0	0	0
10^{-4}	2.3	0
10^{-3}	13.5	3.0
10^{-2}	22.5	4.4

effect of intraperitoneal administration of fatty acids on gastric secretion was due to stimulation, such as surface activity, or not, inhibition of gastric secretion by myristic acid was measured by its intraduodenal administration. As shown in Table VI, intraduodenal administration of 100 or 200 mg/kg of myristic acid significantly inhibited the amount of gastric juice, total acid output, and total peptic activity, but at the dose of 25 or 50 mg/kg, myristic acid did not show a significant inhibition of these three parameters. Atropine sulfate showed a significant inhibition at the dose of 5 or 10 mg/kg.

Effect of Myristic Acid on Squirming and Capillary permeability

Intraperitoneal injection of myristic acid at 50 or 100 mg/kg did not induce squirming and had no effect on peritoneal capillary permeability in mice.

Inhibitory Effect of Myristic Acid on Pepsin and Histidine Decarboxylase Activity

Table VII shows the inhibitory effect of myristic acid, which has a strong inhibitory activity on gastric secretion on pepsin and histidine decarboxylase activity *in vitro*. Inhibition of peptic activity was seen beginning at the level of 10^{-4}M of myristic acid, and about 22.5% inhibition was seen at 10^{-2}M, but the acid showed almost no activity of inhibiting histidine decarboxylase.

DISCUSSION

Measurement of the inhibitory activity of straight-chain fatty acid of $C_{10:0}$ to $C_{20:0}$ on gastric secretion in rats revealed that myristic acid with 14 carbon atoms had the strongest inhibitory activity, and that the inhibitory activity decreased in acids with over and below this number of carbon atoms. Consequently, length of the alkane chain of fatty acids seemed to be an important factor related to inhibitory activity on gastric secretion.

In order to examine whether or not the free carboxyl group was a requisite in imparting this activity, methyl esters of five fatty acids having a marked inhibitory activity on gastric secretion (Table I) were examined for their activity. It was thereby found that only methyl myristate showed a significant inhibition on the amount of gastric juice, total acid output, and total peptic activity at the dose of 100 mg/kg, although methyl esters of other fatty acids also showed a inhibitory activity at the dose of 200 mg/kg.

Comparison of this inhibitory activity between myristic acid and its methyl ester at the doses of 100 and 200 mg/kg showed that the inhibitory activity was lower in the methyl ester. This fact seems to suggest that, when the methyl ester is administered non-orally, the ester linkage is not hydrolyzed and, consequently, is not absorbed well, resulting in decreased inhibitory activity. However, since the dosages of 100 and 200 mg of methyl myristate showed significant inhibitory activity, free carboxyl group is not a requisite to elicite this activity, and there seem to be other factors, such as the physicochemical properties accompanying the length of the carbon chain, that are important for this activity.

In genenal, fatty acids are present as a glyceride or as a phospholipid component in biological tissues. Therefore, in order to examine the activity of these fatty acids in glyceride structure, α-monoglycerides of $C_{10:0}$, $C_{12:0}$, $C_{13:0}$, $C_{14:0}$, and $C_{16:0}$ fatty acids were examine for their activity of inhibiting gastric scretion. As in the case of the methyl ester, only the monoglyceride of myristic acid showed significant inhibitory activity on the amount of gastric juice at the dose of 100 mg/kg, although glycerides of all other fatty acids also showed significant inhibition of the amount of gastric juice,

total acid output, and total peptic activity at the dose of 200 mg/kg. Consequently, it was considered that the monoglyceride is hydrolyzed *in vivo* by the monoglyceride hydrolase to the free acid to exert the inhibitory activity. This is an interesting phenomenon, together with the activity of the methyl ester of these fatty acids, and it will require further examinations in future.

Substances that inhibit gastric secretion are generally considered to be effective in preventing peptic ulcer. Examinations were therefore made on the effect of myristic acid, which significantly decreased the ulcer index in pylorus-ligated rats, on aspirin- and histamine-induced ulcer. At the doses of 100 and 200 mg/kg, myristic acid significantly decreased the ulcer index in aspirin-induced ulcer but was totally ineffective on histamine-induced ulcer. Ulcers induced by aspirin is considered to be due to back diffusion by the destruction of gastric mucosal barrier so that myristic acid seems to show this activity by decreasing total acid output and total peptic activity, which are the direct cause of ulcer. Histamine-induced ulcer is strongly inhibited by ant-acids, anti-cholinergics,[11] but myristic acid was totally ineffective.

Kakinuma[12] reported that fatty acids act as a surfactant, and cause some structural change in the leucocyte membrane and metabolic activation. This fact suggested a possibility that the action of fatty acids to inhibit gastric secretion by intraperitoneal administration might be the result of stimulation of the membrane by the acid, and this activity was measured after different route of administration, such as intraduodenal administration. It was thereby found that the intraduodenal administration of 100 or 200 mg/kg of myristic acid resulted in significant inhibition of the amount of gastric juice, total acid output, and total peptic activity, but at the dose of 25 or 50 mg/kg, myristic acid did not show a significant inhibition of these three parameters, and it would be difficult to consider that the inhibitory activity of fatty acids on gastric secretion were due only to their stimulation on the membrane, and it was also clarified that myristic acid had no irritating effect. Comparison of the inhibitory activity of myristic acid by intraperitoneal and intraduodenal administration showed that intraperitoneal administration resulted in stronger inhibition. This is probably due to the difference in the rate of metabolism and absorption. This point will be further clarified by the examination of *in vivo* distribution of using myristic [1-^{14}C]acid.

Finally, effect of fatty acids on pepsin and histidine decarboxylase, which are considered to play an important role in the induction mechanism of peptic ulcers, was examined *in vitro*, centered around myristic acid which showed a marked effect in gastric secretion inhibitory and anti-ulcerogenic activity. Myristic acid did not show any activity of inhibiting histidine decarboxylase but did show inhibition of peptic activity at 10^{-4}M and showed 22.5% inhibition at the concentration of 10^{-2}M. This is probably due to the difference in the affinity of fatty acids to the proteins of these enzymes.

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