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Peptic Ulcer and Glucose Homeostasis

I. Insulin, Gastrin and Glucagon Responses to Oral Glucose and Intravenous Arginine in Peptic Ulcer Patients

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Introduction

DRAGSTEDT⁷⁾ has proposed that duodenal ulcer arises from hyper-secretion caused by excessive vagal stimulation and Davenport⁵⁾ suggested that the basic abnormality in gastric ulcer is an increased permeability of gastric mucosal barrier to hydrogen ion. It seems well established that, on average, gastric ulcer patients show hypo-secretion of acid. However, gastric ulcer patients sometimes show hyper-acidity, and there has been very few investigation about glucose metabolism in peptic ulcer patients, especially in gastric ulcer patients with hyper-acidity. Previous study showed that duodenal ulcer patients have glucose intolerance and augmented insulin response to oral glucose load³⁾¹¹⁾.

In an attempt to further elucidate glucose homeostasis in peptic ulcer patients, serum glucose, immunoreactive insulin (IRI), immunoreactive gastrin (IRGA), and immunoreactive pancreatic glucagon (IRGL) responses to oral glucose and intravenous (i. v.) arginine were studied in gastric ulcer patients with hyper-acidity and normo-acidity, duodenal ulcer patients and normal subjects.

Materials and Methods

Four groups were studied : normal subjects, gastric ulcer patients with normo- and hyper-acidity and duodenal ulcer patients. All patients were ambulatory patient volunteers who had been given fully informed written consent for the study.

Nine normal subjects (7 men and 2 women) were studied : their ages ranged from 31 to 69 years, with a mean age of 46 years. All had normal carbohydrate tolerance as determined by oral glucose tolerance testing, and had normal liver function test. None had a family history of diabetes mellitus.

Twenty-four peptic ulcer patients (19 men and 5 women) were studied : their ages ranged from 29 to 67 years. with a mean age of 45 years. These patients were divided into

Key words : Gastric ulcer with hyper-acidity, Gastrin, Glucagon, Arginine.

索引語 : 高酸胃潰瘍, ガストリン, グルカゴン, アルギニン.

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3 groups : gastric ulcer patients with normo- and hyper-acidity (normo-GU and hyper-GU, respectively) and duodenal ulcer (DU). The number of normo-GU, hyper-GU and DU patients studied was 7, 8 and 9, respectively. The diagnosis of gastric and duodenal ulceration without other pathological condition, was made in each case on clinical and radiological grounds. Fiberscopic examination was performed on each patient using gastrointestinal fiberscope (Model GIF Type P, Olympus Co.).

Six of the 7 normo-GU patients were found to have single active ulcer at the angle of the stomach and only 1 patient at the proximal part of the body. All of the 9 normo-GU patients had no previous history of duodenal ulceration and 4 of the hyper-GU patients were revealed to have previous duodenal ulceration. Seven of the 9 DU patients had active ulcer at the duodenal bulb and 2 patients at the pyloric channel. All of the DU patients had no co-existent gastric ulcers.

All of the normal subjects and peptic ulcer patients were within 10% of their ideal body weight and had been taking a normal diet before the test. All had no previous abdominal surgery.

After fasting overnight, each peptic ulcer patient had nasogastric tube placed in the most dependent part of the stomach. The first 15 min. were spent in aspirating "resting juice". Basal secretion was then collected in four consecutive 15 min. periods. Five μg per kg. of tetragastrin (Nissui Seiyaku Co.) was injected intramuscularly to stimulate maximal acid output (MAO) and gastric juice was collected for further four consecutive 15-min. periods. Volumes (ml.) were recorded and acid concentration (mEq) was determined by titration of pH 7.0 with NaOH (Autoburette, Radiometer, Copenhagen). The sum of the four consecutive 15-min. acid outputs before and after tetragastrin injection was taken as basal acid output (BAO) and MAO, respectively.

After a 12 hour overnight fast, an indwelling canula was inserted into the antecubital vein for blood sampling. Each individual ingested 50 gm. glucose in 200 ml. of water, and blood samples were collected over 3 hours at fasting, 15, 30, 45, 60, 90, 120, 150 and 180 min.

On another day, intravenous arginine hydrochloride (Levargine, Taisho Seiyaku Co.) was given in a dose of 1/2 body weight (ml.) over 2 min. Venous blood was sampled at fasting, 1, 2, 5, 10, 15, 30 and 60 min. Blood samples were immediately centrifuged at room temperature and the serum frozen and stored at -20°C for serum glucose, immunoreactive insulin (IRI), immunoreactive gastrin (IRGA) and immunoreactive glucagon (IRGL) determinations.

Assays

Serum glucose levels were measured by the glucose oxydase method. Serum IRI was assayed by the Insulin-Riakit (Dinabott RI Institute). Serum IRGA and IRGL were measured by the Gastrin-Riakit (Dinabott RI Institute) and by a modification of the Unger and Eisentraut immunoassay using 30K, respectively. The t-test was used for testing signi-

ificance of results. P-values of less than 0.05 were considered significant, and results are expressed as mean ± SEM.

Results

Gastric secretion in patients with peptic ulcer

BAO and MAO of hyper-GU and DU patients were almost identical and significantly higher than those of normo-GU patients (Table 1).

Serum glucose response to oral glucose load

Fasting serum glucose concentrations were not statistically different among 4 groups of the patients (83.89±3.55, 89.86±3.79, 89.13±2.61, and 89.89±2.21 mg/dl in normal subjects, normo-GU, hyper-GU, and DU patients, respectively), but after glucose load signi-

Table 1. Mean (±SEM) of basal and maximal acid output after i.m. tetragastrin injection (5µg/kg. BW) in peptic ulcer patients.

	BAO (mEq/h)	MAO (mEq/h)
Gastric ulcer (normo-acidity) (n=7)	0.968±0.354	5.500±1.135
Gastric ulcer (hyper-acidity) (n=6)	2.840±0.333	16.668±2.069
Doudenal ulcer (n=7)	2.842±0.849	14.963±2.482

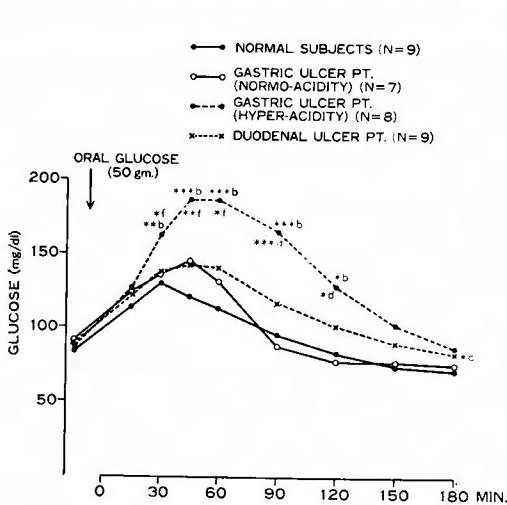


Fig. 1 Serum glucose responses to oral glucose load in normal subjects and peptic ulcer patients. *= $p < 0.05$; **= $p < 0.01$; ***= $p < 0.05$
 b=significant difference between hyper-GU patients and normal subjects
 c=significant difference between DU patients and normal subjects
 d=significant difference between hyper-GU patients and normal-GU patients
 f=significant difference between hyper-GU patients and DU patients

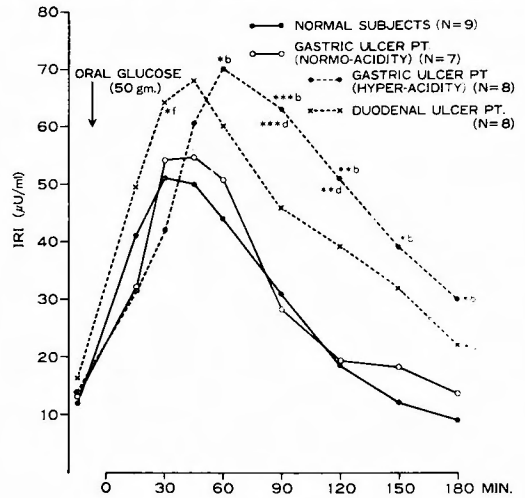


Fig. 2 Serum IRI responses to oral glucose load in normal subjects and peptic ulcer patients *= $p < 0.05$; **= $p < 0.01$; ***= $p < 0.05$
 b=significant difference between hyper-GU patients and normal subjects
 c=significant difference between DU patients and normal subjects
 d=significant difference between hyper-GU patients and normal-GU patients
 f=significant difference between hyper-GU patients and DU patients

Table 2. Integrated response (180 and 60 min.) of glucose, IRI, IR-Gastrin, and IR-Glucagon to oral glucose load and i.v. L-arginine load in controls and patients with gastric ulcer (normo-acidity and hyper-acidity) and duodenal ulcer.

	Oral Glucose Load			
	Glucose (mg/dl. 180 min)	IRI (μ U/ml. 180 min)	IR-Gastrin (pg/ml. 180 min)	IR-Glucagon (pg/ml. 180 min)
Controls	2308.33 \pm 586.61	3077.42 \pm 467.90	- 122.50 \pm 884.05	- 3204.00 \pm 6514.3
Gastric Ulcer (Normo-acidity)	1968.21 \pm 1106.93	3128.25 \pm 435.72	9670.7 \pm 8628.1	1323.0 \pm 1123.45
Gastric Ulcer (Hyper-acidity)	9232.50 \pm 1420.90	6298.50 \pm 540.46	6394.3 \pm 1066.38	- 608.00 \pm 561.03
Duodenal Ulcer	4285.00 \pm 1367.67	5101.59 \pm 938.49	1079.44 \pm 379.98	- 1657.50 \pm 2312.98
	N.S.	N.S.	N.S.	P<0.01
	P<0.001	P<0.001	N.S.	P<0.01
	P<0.01	N.S.	N.S.	N.S.
	P<0.05	N.S.	N.S.	N.S.

ificantly increased serum glucose concentrations of hyper-GU patients were found at 30, 45, 60, 90 and 120 min. compared with those of normal subjects (163.87 ± 8.43 vs. 129.89 ± 6.76 mg/dl, $p < 0.01$; 187.25 ± 10.51 vs. 121.4 ± 7.07 mg/dl, $p < 0.005$; 186.87 ± 10.62 vs. 113.89 ± 5.72 mg/dl, $p < 0.05$; 166.00 ± 13.00 vs. 96.00 ± 5.12 mg/dl, $p < 0.005$ and 129.25 ± 18.19 vs. 83.00 ± 6.29 mg/dl, $p < 0.05$, respectively), and at 30, 45, and 60 min. compared with those of DU patients (163.87 ± 8.43 vs. 139.11 ± 5.60 mg/dl, $p < 0.05$; 187.25 ± 10.51 vs. 143.89 ± 8.20 mg/dl, $p < 0.01$ and 186.87 ± 10.62 vs. 141.00 ± 17.01 mg/dl, $p < 0.05$, respectively) (Fig. 1). Total glucose concentrations were estimated by comparing the area beneath the serum glucose curve from 0 to 3 hours. The results of these measurement are shown in Table 2. Glucose concentrations over the three-hour period were significantly increased in hyper-GU patients compared with those of controls (9232.50 ± 1420.90 vs. 2308.33 ± 586.61 mg/dl/3h, $p < 0.001$), normo-GU patients (9232.50 ± 1420.90 vs. 1968.21 ± 1106.93 mg/dl/3h, $p < 0.01$), and even DU patients (9232.50 ± 1420.90 vs. 4285.00 ± 1367.67 mg/dl/3h, $p < 0.05$).

Serum IRI response to oral glucose load

Fasting serum IRI concentrations were not significantly different among the four groups of patients (11.82 ± 2.48 , 13.40 ± 2.23 , 13.52 ± 2.33 and 16.51 ± 2.42 μ U/ml in controls, normo-GU, hyper-GU, and DU patients, respectively), but after oral glucose load significantly increased serum IRI concentrations in hyper-GU patients were found at 60, 90, 120, 150 and 180 min. (69.97 ± 7.27 vs. 50.67 ± 10.85 μ U/ml, $p < 0.05$; 63.05 ± 6.62 vs. 28.27 ± 5.13 μ U/ml, $p < 0.001$; 50.67 ± 8.67 vs. 19.37 ± 4.24 μ U/ml, $p < 0.01$; 38.97 ± 8.96 vs. 18.30 ± 4.46 μ U/ml, $p < 0.05$ and 29.76 ± 7.23 vs. 13.91 ± 2.68 μ U/ml, $p < 0.05$, respectively) compared with normo-GU patients. Serum IRI concentrations in DU patients were

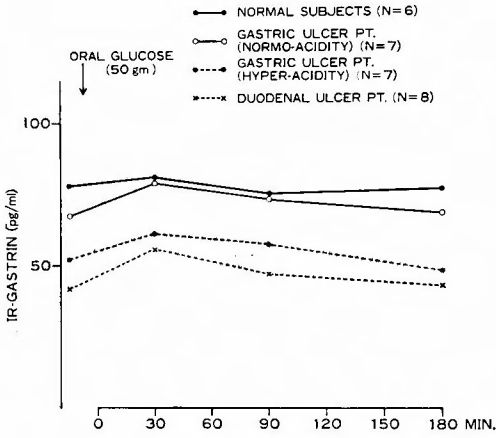


Fig. 3. Serum IR-gastrin responses to oral glucose load in normal subjects and peptic ulcer patients.

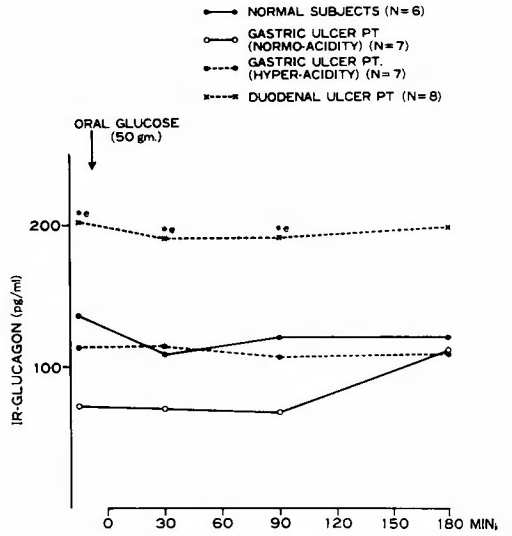


Fig. 4. Serum IR-glucagon responses to oral glucose load in normal subjects and peptic ulcer patients.
 *= $p < 0.05$
 e=significant difference between DU patients and normo-GU patients

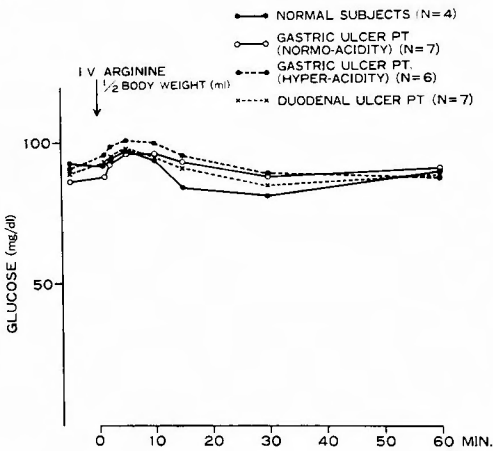


Fig. 5. Serum glucose responses to i.v. arginine load in normal subjects and peptic ulcer patients.

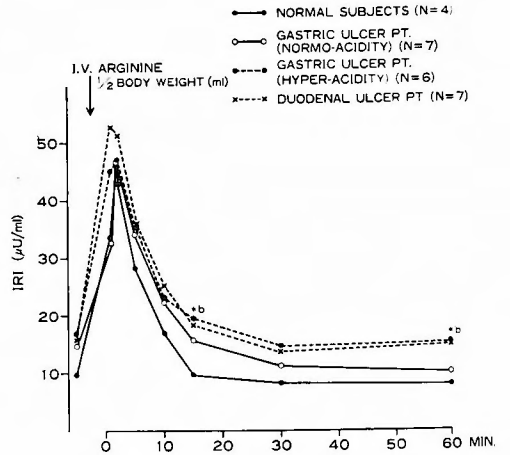


Fig. 6. Serum IRI responses to i.v. arginine load in normal subjects and peptic ulcer patients
 *= $p < 0.05$
 b=significant difference between hyper-GU patients and normal subjects

pg/ml/3h, $p < 0.01$) compared with that of normal subjects (Table 2).

Serum glucose response to i. v. L-arginine load

Serum glucose concentrations at each time interval after i. v. L-arginine load were not significantly different among the four groups of the patients (Fig 5). Integrated glucose concentrations for 60 min. were significantly increased in normo-GU, hyper-GU and DU patients (245.50 ± 146.97 vs. -489.0 ± 60.78 mg/dl/3h, $p < 0.01$; 59.50 ± 130.76 vs. -357.38 ± 60.78 mg/dl/3h, $p < 0.05$ and -18.50 ± 26.78 vs. -357.38 ± 60.78 mg/dl/3h, $p < 0.05$, respectively) compared with those of normal subjects (Table 2).

Serum IRI response to i. v. L-arginine load

Serum IRI concentrations after i. v. L-arginine load in hyper-GU patients were significantly raised at 15 min. (19.68 ± 1.72 vs. 9.87 ± 2.64 μ U/ml, $p < 0.05$) and 60 min. (15.47 ± 1.73 vs. 8.00 ± 1.79 μ U/ml, $p < 0.05$) compared with those of normal subjects (Fig. 6). Integrated insulin concentrations over the 60-min. period were not significantly different among the four groups (Table 2).

Serum IR-gastrin response to i. v. L-arginine load

Fasting serum IRGA concentrations in DU patients were significantly lower than those of normal subjects, normo-GU and hyper-GU patients (28.33 ± 2.81 vs. 50.85 ± 6.60 , 47.10 ± 7.10 , and 55.02 ± 8.96 pg/ml, $p < 0.05$, respectively) (Fig. 7). Integrated IRGA concentrations over the 60-min. period of DU patients were significantly greater than those of

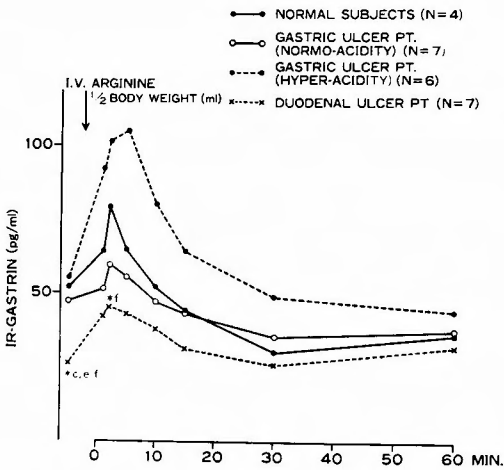


Fig. 7. Serum IR-gastrin responses to i.v. arginine load in normal subjects and peptic ulcer patients.

*= $p < 0.05$

c=significant difference between DU patients and normal subjects

e=significant difference between DU patients and normo-GU patients

f=significant difference between DU patients and hyper-GU patients

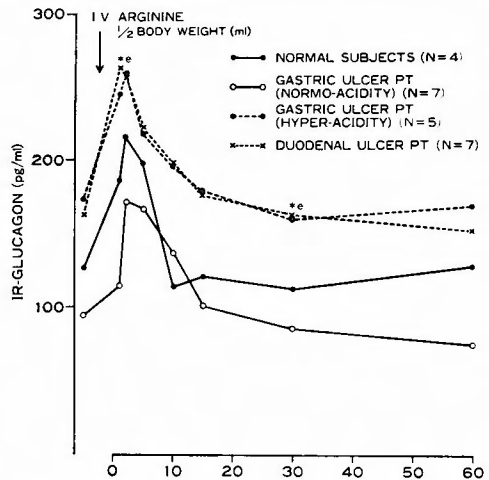


Fig. 8. Serum IR-glucagon responses to i.v. arginine load in normal subjects and peptic ulcer patients.

*= $p < 0.05$

e=significant difference between DU patients and normo-GU patients

normal subjects and normo-GU patients (200.39 ± 173.69 vs. -605.93 ± 183.16 pg/ml/1h and 200.39 ± 173.69 vs. -378.54 ± 143.36 pg/ml/3h respectively, $p < 0.05$) (Table 2). Total gastrin secretion in hyper-GU patients was greater than that of DU patients (245.28 ± 327.99 vs. 200.39 ± 173.69 pg/ml/1h), but there was no significant difference.

Serum IR-glucagon response to i. v. L-arginine load

After i. v. arginine serum IRL concentrations in DU patients were significantly higher at 1 and 30 min. than in normo-GU patients (262.94 ± 43.83 vs. 115.37 ± 18.64 pg/ml at 1 min., $p < 0.05$; 162.26 ± 27.59 vs. 85.03 ± 20.95 pg/ml at 30 min., $p < 0.05$). Integrated IRL concentrations were not statistically different among the four groups (Table 2).

Discussion

JOHNSON et al.¹³⁾ claimed that peptic ulcers be Could classified not anatomically but rather on the basis of hypo- or hyper-secretion and defined three groups of gastric ulcer; type 1 consisted of single ulcers on the lesser curve associated with hypo-secretion of acid, and type 2 and 3 were gastric ulcers associated with duodenal ulcers and prepyloric ulcers, respectively. I divided gastric ulcers into two groups: gastric ulcers with normo-acidity and hyper-acidity (normo-GU and hyper-GU, respectively) irrespective of previous occurrence of duodenal ulcers. In this series, half of the hyper-GU patients had no known former duodenal ulceration, and ulcers in all of the hyper-GU patients located distant from the pylorus. It may be that these kinds of gastric ulcers have different pathogenesis from type 2 and 3 of JOHNSON's classification.

I observed abnormal hyperglycemic and hyperinsulinemic response to oral glucose in DU patients which is in agreement with the previous reports of BUCHANAN et al.³⁾ and HUMPHREY et al.¹¹⁾. Furthermore, hyper-GU patients were found to have a significantly greater rise in blood glucose and insulin output after oral glucose than DU patients. Normo-GU patients showed a pattern of glucose and insulin output after glucose ingestion almost identical to that in normal subjects.

It has been suggested that altered gastrointestinal physiology which accompanies duodenal ulceration, in particular the hyper-secretion of acid, is accompanied by an increased release of one or more of the intestinal hormones (HUMPHREY et al.¹¹⁾). CATALAND et al.⁴⁾ showed an augmented gastric inhibitory polypeptide (GIP) release by a mixed meal in duodenal ulcer patients although they did not measure insulin output. Arnold et al.¹²⁾ showed increased response of GIP and IRI to a high caloric meal in duodenal ulcer patients in particular with pathological oral glucose test, suggesting that feedback control of GIP release by endogenous insulin is disturbed in duodenal ulcer patients by an increased number of GIP-producing cells, an increased vagal tone, or increased duodenal acidity. Secretin enhances the secretion of insulin (DUPRE et al.⁸⁾, and suppresses that of glucagon (SANTEUSANIO et al.¹⁸⁾). UNGER et al.²⁰⁾ indicated that absolute or relative hyperglucagonemia may contribute to diabetic hyperglycemia, and BREUER et al.²¹⁾ showed that the intolerance to oral glucose after gastric surgery may be related to elevated glucagon-like immunoreactivity levels due

to decreased secretin release as a result of a diminished secretion of hydrochloric acid after partial gastrectomy. In this series, serum IRGL concentrations in fasting and following oral glucose were significantly greater in DU patients than in hypo-GU patients. Secretin response has been reported to be blunted in DU patients¹⁷⁾. Therefore, augmented pancreatic glucagon response may be one of the causative factors of abnormal glucose homeostasis at least in DU.

FRIESEN et al.⁹⁾ found that subjects with some degree of glucose intolerance had higher IRGA and IRI levels after oral glucose load than did the normal subjects, and suggested a common event related to islet cell activity as the source of the changes in the plasma level of both hormones during the glucose tolerance test. In our study, serum IRGA concentrations during oral glucose testing were highest in the DU patients compared to other groups studied but the difference was not statistically significant. The role of gastrin in glucose homeostasis in peptic ulcer patients remains to be elucidated.

Intravenous infusion of arginine has been reported to be a powerful stimulus of endogenous gastrin release (KALK et al.¹⁵⁾ ; VINIK et al.²¹⁾ ; KAJIWARA et al.¹⁴⁾, and SEINO et al.¹⁹⁾, while others claimed poor response of gastrin to intravenous arginine⁶⁾ ISENBERG et al.¹²⁾ and KONTUREK et al.¹⁶⁾ showed that intravenous administration of amino acid stimulates gastric acid without mediation of gastrin. KONTUREK et al.¹⁶⁾ also showed that cimetidine (histamine H₂-receptor antagonist) added to intravenous amino acid infusions cause almost complete suppression of acid secretion, suggesting that the stimulation of gastric secretion by amino acid could be mediated by histamine and H₂-receptors on the oxyntic cells. We can not state the relationship between gastric acidity and gastrin output after i. v. arginine as gastric acidity was not measured in this study. I. v. arginine may stimulate the gastrin cells directly¹⁰⁾, but VINIK et al.²¹⁾ suggested that the gastrin responses may be consequent upon electrolyte (potassium) changes rather than a primary effect on the gastrin cells.

In this study, L-arginine was administered in a dose of 1/2 body weight (ml.) over 2 min. (Dr. KAJIWARA, personal communication) and found to be a useful method for the assessment of the gastric and pancreatic hormonal environment. Interestingly was serum IRGA response to arginine injection significantly greater in hyper-GU patients than in DU patients. It is possible to speculate that i. v. arginine stimulate some receptors of the gastrin cell either directly or indirectly and there is some difference in altered physiology of the receptors in hyper-GU and DU patients. I. v. arginine seems to stimulate only the gastrin cell of the antrum as VINIK et al.²¹⁾ showed no rise in serum gastrin in antrectomized patients, and I also confirmed this finding (unpublished observation).

Different patterns of acid secretion existed in DU patients ranging from normal to hyper-secretion. There was no significant differences in serum IRGA responses to arginine injection between normal and hyper-secretion in DU patients (unpublished observation). It would seem that abnormality of gastrin secretion is more important in the etiology of hyper-GU than in that of DU. This study comprises of very small numbers of subjects, and it would seem difficult to draw any conclusion. It would only possible to conclude from this

small study that : 1) hyper-GU patients show abnormal hyperglycemic and hyperinsulinemic responses to oral glucose as do DU patients, 2) hyper-GU may be caused by different etiology from normo-GU and DU, 3) gastrin may be more important factor in the etiology of hyper-GU than in that of DU, 4) glucagon may be one of the causative factors of abnormal glucose homeostasis of DU.

Acknowledgement

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GIP study in the peptic ulcer patients is in progress in collaboration with Dr. I. G. M. Cleator, St. Paul's Hospital, Vancouver, Canada, and also study of glucose metabolism after gastric surgery in the patients is in progress.

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和文抄録

消化性潰瘍と糖代謝. 1. 糖経口負荷及びアルギニン静注によるインスリン, ガストリン及びグルカゴン反応

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中 安 顕

十二指腸潰瘍は高酸, 胃潰瘍は低~正酸を呈する事が多いが, 胃潰瘍でも高酸を呈する症例が存在する. 高酸胃潰瘍と十二指腸潰瘍における糖代謝とガストリン反応等につき検討を加えた.

高酸胃潰瘍 (hyper-GU) 患者 8 名 (内 4 名は十二指腸潰瘍の既往あり), 正酸胃潰瘍 (normo-GU) 患者 7 名, 十二指腸潰瘍 (DU) 患者 9 名及び対照 9 名に対し, 1) 50 g ブドー糖経口負荷後 180 分にわたりグルコース, インスリン (IRI), ガストリン (IRGA) 及び膵グルカゴン (IRGL) を, 2) アルギニン静注後 60 分わたりグルコース, IRI, IRGA, IRGL を測定した.

空腹時血糖は有意差はなかったが, ブドー糖経口負荷後, hyper-GU と DU 患者では normo-GU 患者と対照に比べて有意に耐糖能低下があり, 特に hyper-GU 患者で著明であった. IRI 反応も hyper-GU と

DU 患者で高反応を認め特に hyper-GU 患者で著明であった. IRGL 反応は DU 患者で最も高値を認めた. アルギニン静注後の IRGA 反応は DU において, normo-GU 患者と対照よりも有意に高かったが, hyper-GU 患者は DU 患者よりも更に高反応が見られた. IRGL 反応はアルギニン静注後も DU に於て高反応であった.

結論として, 1) 高酸胃潰瘍ではブドー糖経口負荷後, グルコース, インスリンの高反応が見られ, 消化管ホルモンの異常の存在を思わせた. 2) ガストリン高反応は DU よりも hyper-GU 患者に著明に見られ, hyper-GU の発生にガストリンの役割の重要性を思わせた. そして hyper-GU は DU や normo-GU とは発生機序を異にすると思われた. 3) DU における糖代謝の異常に膵グルカゴンの関与が示唆された.