Korean J Physiol Pharmacol
Vol 6: 311–317, December, 2002

Altered Secretory Pattern of Pancreatic Enzymes and Gastrointestinal Hormones in Streptozotocin-induced Diabetic Rats

Myung-Jun Kim, Gyeong Ryul Ryu, Sae-Young Yi, Do Sik Min, Duck-Joo Rhie, Shin Hee Yoon, Sang June Hahn, Myung-Suk Kim, and Yang-Hyeok Jo

Department of Physiology, College of Medicine, The Catholic University of Korea, Seoul 137–701, Korea

This study was performed to investigate the pancreatic exocrine dysfunction in streptozotocin-induced diabetic rats. Changes in pancreatic enzymes secretion and in pancreatic enzymes content were observed. The output and the tissue content of amylase were significantly reduced in diabetic rats, while the output and the content of lipase were increased. Plasma secretin and cholecystokinin (CCK) concentrations of diabetic rats were significantly increased compared to those of normal rats. The altered pancreatic exocrine function was abolished by the exogenous insulin administration. The exogenous insulin also restored the increased plasma secretin and CCK concentrations. From the above results, it is suggested that, in streptozotocin-induced diabetic rats, anticoordinated changes in pancreatic enzymes secretion as well as pancreatic enzymes content are attributable to insulin deficiency and that the insulin deficiency is responsible for the increased plasma concentrations of both secretin and CCK. However, it is not clear whether the elevated plasma secretin and CCK concentrations played a direct role in changes of pancreatic exocrine function.

Key Words: Amylase, Lipase, Secretin, Cholecystokinin, Streptozotocin, Diabetes

INTRODUCTION

Pancreas is a unique organ comprising both endocrine and exocrine tissues. The exocrine tissue secretes various digestive enzymes and bicarbonate, which modulate digestion and absorption of nutrients whereas the endocrine tissue releases hormones that regulate the metabolism and disposal of breakdown products of food. The major hormone-producing cells are organized into the islet of Langerhans within the exocrine tissue and regulate pancreatic secretion via the insulo-acinar portal system (Williams & Goldfine, 1985; Lee et al, 1990; Bonner-Weir, 1993).

The pancreatic exocrine secretion is generally controlled by the neural system and hormones such as cholecystokinin (CCK) and secretin (Adler et al, 1991; Jo et al, 1992; Li & Owyang, 1993). Especially, the composition of pancreatic enzymes is altered during the process of enzyme secretion by several factors such as hormones, neurotransmitters, and diet (Bazin & Lavau, 1979; Schick et al, 1984a; Schick et al, 1984b; Okabayashi et al, 1988). It has well been understood that insulin stimulates directly pancreatic secretion and potentiates CCK-stimulated pancreatic secretion (Kanno & Saito, 1976; Korc et al, 1981a; Park et al, 1993; Lee et al, 1994).

However, in the streptozotocin-induced diabetic rats, the anticoordination phenomenon of pancreatic enzymes secretion, decreased amylase activity and increased lipase activity, was observed (Otsuki & Williams, 1982; Bendayan & Levy, 1988; Duan et al, 1989). Meanwhile, exogenous insulin not only alleviates the anticoordinated secretion from diabetic rat, but also changes the synthesis of these enzymes in the normal pancreas (Korc et al, 1981b; Duan et al, 1991; Tsai et al, 1994). Moreover, the increase of secretin concentration seems to be involved in the change of pancreatic secretion in diabetic patients (Chisholm et al, 1970).

Therefore, the present study was undertaken to investigate 1) the effects of the exogenous insulin on the enzymes secretion and the plasma secretin and CCK concentrations and 2) the involvement of plasma secretin and CCK in changes of amylase and lipase activities in pancreatic juice and tissue of streptozotocin-induced diabetic rats.

METHODS

Experimental animals

Male Sprague-Dawley rats, weighing 200~250 g (body wt), were used. Rats were injected intravenously with streptozotocin (70 mg/kg) in 0.1 M citrate buffer (pH 4.5) after a 12-hr overnight fast. After being confirmed as hyperglycemia with glucometer (Glucotrend, Roche Diagnostics, Boeringer Mannheim, Germany), rats were divided

Corresponding to: Yang-Hyeok Jo, Department of Physiology, College of Medicine, The Catholic University of Korea, 505 Banpo-dong, Socho-gu, Seoul 137-701, Korea. (Tel) 82-2-590-1170, (Fax) 82-2-532-9575, (E-mail) yhjo@catholic.ac.kr

ABBREVIATION: CCK, cholecystokinin.

randomly into two groups: one group with daily NPH insulin (20 U/kg) administration for 6 days and the other group with normal physiologic saline, respectively. In the case of normal control, rats were injected with normal saline instead of streptozotocin. All experimental procedures performed on the animals were conducted with the approval of the ethics committee of The Catholic University of Korea and conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications no. 80−23, revised 1996).

Surgical procedure and measurement of pancreatic secretion

For the collection of pancreatic juice in anesthetized state, rats were anesthetized with urethane (25%, 5.2 mg/kg) following 18-h overnight fast on day 6 after streptozotocin injection. The abdominal wall was incised along the abdominal midline and the common bile duct was bypassed towards the duodenum. That is, at the junction to the duodenum, the pancreatic duct was cannulated by polyethylene tube (PE-10, Clay Adams, NJ, USA), which was connected with the microglass capillary for the collection of pancreatic juice. Bile flow was diverted into the proximal jejunum using the same polyethylene tubing (Jo et al, 1994). Meanwhile, for the collection of pancreatic juice in conscious state, rats were anesthetized with pentobarbital sodium (45 mg/kg). The procedure for chronic pancreatic cannulation device was performed following others' (Lee et al, 1990). Briefly, chronic pancreatic cannula was constructed by molding two polyethylene tubings of two different sizes (PE-10 and PE-90) into the internal cavity of a gastric cannula made of stainless steel. One end of PE-10 tubing was placed in the common bile-pancreatic duct proximal to the duodenum and the other end was inserted into the duodenum through PE-90, which reached the lumen of the midduodenum. For the pure pancreatic juice collection, PE-10 tubing of which tip reached the midduodenum was gently pulled out of PE-90 and was connected to the collecting tube. In all experiments, pancreatic juice was collected for two consecutive 20 mins after the lapse of initial 10 min. Subsequently, whole pancreatic tissue was taken out and stored at −70°C for the measurement of amylase and lipase activities.

Chemical Analyses

Plasma glucose concentration: In experimental rats, plasma glucose concentrations were monitored on venous blood from the tail vein with glucometer and test-strips.

Assay of pancreatic enzymes in pancreas and pancreatic juice: Each pancreas was weighed, and homogenized with nine times its weight of cold phosphate-buffered saline (PBS). The homogenate was centrifuged at 14,000 g for 30 min at 4°C and the supernatant was collected for subsequent analyses of enzymes activities. Amylase activity was determined using the procion yellow starch as substrate (Jung, 1980). Absorbance of the procion yellow released was measured using microelisa reader (UV MR 700, Dynatech, Chantilly, VA, USA) at 410 nm. Lipase activity was analyzed by trimetric procedure (Sabb et al, 1986). Briefly, the substrate was an olive oil emulsion consisting of 5 ml olive oil, 41 ml gum Arabic solution (10%, wt/vol) and 4 g ice. The assay solution contained 10 ml substrate, 3ml 1.25 M NaCl, 3 ml 0.25 M $CaCl_2$, 3 ml 0.22 M sodium tauroglycocholate, and 11 ml deionized H_2O. To 2 ml of assay solution, 0.02 ml of sample and 0.02 ml of crude colipase were added. Free fatty acids liberated by lipase were titrated automatically with 0.01 N NaOH. Lipase activity was expressed as units (micromoles of fatty acid liberated per minute). For the correction of error in all samples, protein concentration was estimated with the Lowry's method by using bovine serum albumin as standard (Lowry et al, 1951). Amylase and lipase activities in pancreatic juice were analyzed in the same procedure performed in the pancreas.

Plasma secretin & CCK concentration: Plasma concentration of secretin was measured by radioimmunoassay kit (Amersham, Buckinghamshire, England) according to Chang & Chey's method (1980). Meanwhile, plasma CCK concentration was measured by bioassay using Sep-Pak cartridges (Waters Associates, Milford, MA, USA) (Liddle et al, 1984). Briefly, CCK was extracted from plasma by adsorption onto Sep-Pak cartridges previously washed with 6 ml of methanol and 20 ml of water. The cartridges were then washed again with 20 ml of water and the CCK was eluted with 1 ml of 100% ethanol/1% trifluoroacetic acid (4 : 1, vol/vol). The eluents were used to stimulate amylase release by incubation with acini suspended in Krebs-Henseleit bicarbonate buffer. Subsequently, amylase activity was analyzed in the same procedure above mentioned. Amylase release was compared to a dose-response curve for CCK in order to calculate the CCK content of plasma expressed as CCK (pM) equivalents.

Statistical analysis: All data were expressed as mean± S.E. Statistical evaluations were determined by Student's *t*-test. A probability value of <0.05 was considered significant.

RESULTS

Plasma glucose concentration

Plasma glucose concentrations of normal and streptozotocin-induced diabetic rats were 140±40 mg/dl and 340 ±50 mg/dl, respectively. The high plasma glucose concentration of diabetic rats was restored to normal range on day 7 following daily injection of NPH insulin (20 U/kg) (Fig. 1).

Pancreatic secretion of amylase and lipase in streptozotocin-induced diabetic rats

Rats were subjected to collection of pancreatic juice on day 7 following streptozotocin injection. As shown in Fig. 2, in conscious state, there was no significant difference in the volume of pancreatic juice among the groups. The amylase output in streptozotocin-induced diabetic rats was significantly decreased to 23.66±7.33 U/20 min, a tenth of normal conscious rat, 226.07±74.48 U/20 min ($P<0.05$), whereas that of insulin-treated diabetic rats was restored to normal range. In contrast, the lipase output in diabetic rats was significantly increased to 25.51±4.53 U/20 min ($P<0.05$), 1.5 fold of normal conscious rats, whereas that of insulin-treated diabetic rats was restored to normal range.

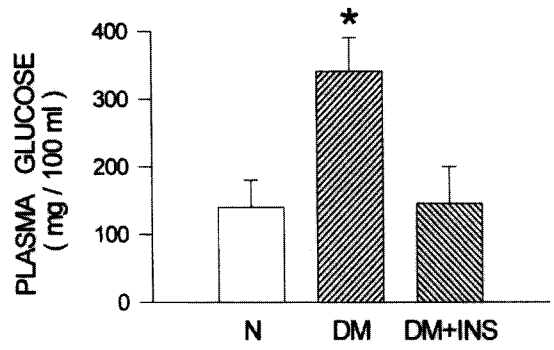

Fig. 1. Plasma glucose concentrations in normal (N), streptozotocin-induced diabetic (DM), and insulin-treated diabetic rats (DM+INS). Diabetic rats were prepared by intravenous injection of streptozotocin (70 mg/kg). One group of streptozotocin-induced rats was treated subcutaneously with NPH insulin (20 U/kg) once a day for 6 days. The number of animals in each group was 8. Results are expressed as mean±S.E. *: vs. N and DM+INS, $P<0.05$.

In anesthetized state, pancreatic juice and enzymes output were reduced compared to those of conscious state. However, the anticoordination in enzymes secretion from diabetic rats was unaffected by anesthesia. The stimulatory effects of insulin administration on the pancreatic exocrine secretion were observed in the anesthetized rats as well.

Pancreatic contents of amylase and lipase in streptozotocin-induced diabetic rats

The weight and total protein content of diabetic rat pancreas were 0.75±0.04 g and 56.82±4.31 mg, respectively, which were significantly reduced compared to those of normal rats (0.99±0.07 g and 80.61±0.11 mg). Also, the weight and total protein content of insulin-treated diabetic rats were restored to normal range (data not shown).

As shown in Fig. 3, the amylase concentration of diabetic, normal, and insulin-treated diabetic pancreas was 45.66± 3.95, 162.82±8.30 and 134.89±7.31 U/mg protein, respectively. On the contrary, the lipase concentration per mg protein of diabetic pancreas was significantly increased

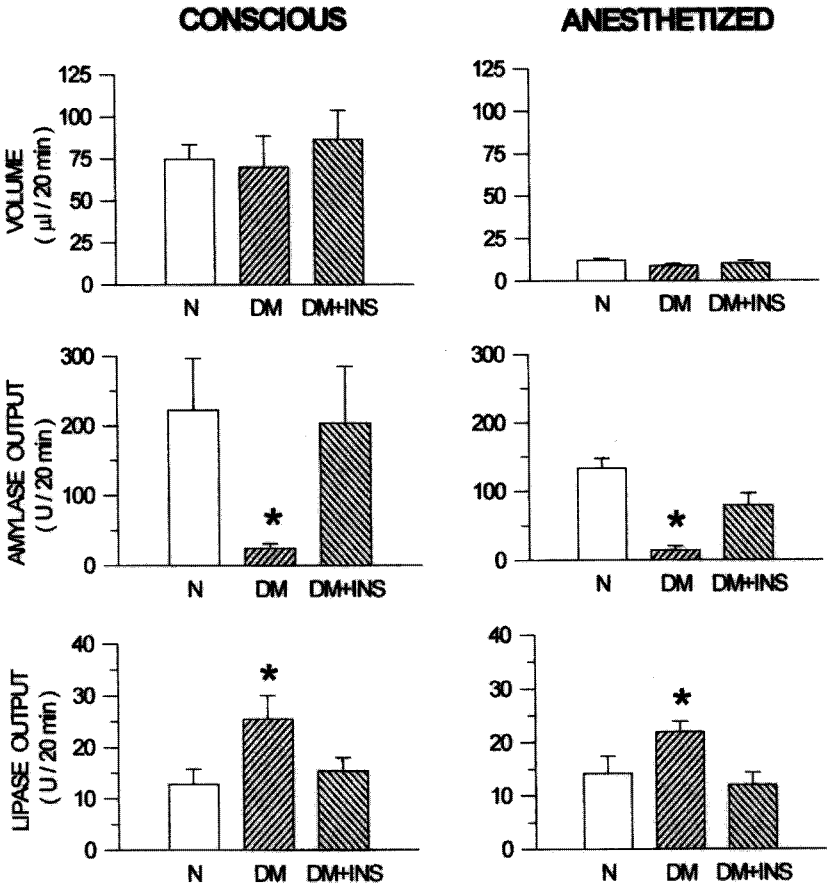

Fig. 2. Pancreatic secretion of amylase and lipase in normal (N), streptozotocin-induced diabetic (DM), and insulin-treated diabetic (DM+INS) rats. Rats were prepared as in Methods. Rats were subjected to collection of pancreatic juice on day 7 following streptozotocin injection. Conscious rats were installed with pancreatic cannula on day 6 and were subjected to experiment in a modified restraint cage. Anesthetized rats were treated with urethane on experimental day. The numbers of animals in N, DM, and DM+INS of conscious rats and anesthetized rats were 6, 5, and 5 and 10, 13, and 11, respectively. Results are expressed as mean±S.E. *: vs. N and DM+INS, $P<0.05$.

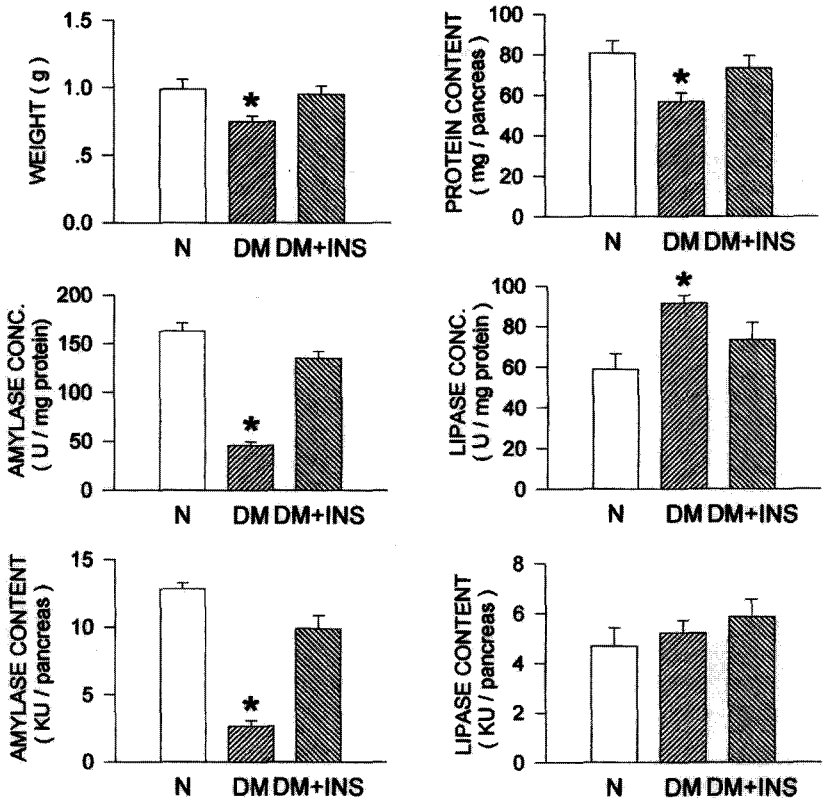

Fig. 3. Pancreatic concentrations and contents of amylase and lipase in normal (N), streptozotocin-induced diabetic (DM), and insulin-treated diabetic (DM+INS) rats. Rats were prepared as in Methods. Rats were subjected to isolation of pancreatic tissue on day 7. The number of animals in each group was 8. Results are expressed as mean±S.E. *: vs. N and DM+INS, $P<0.05$.

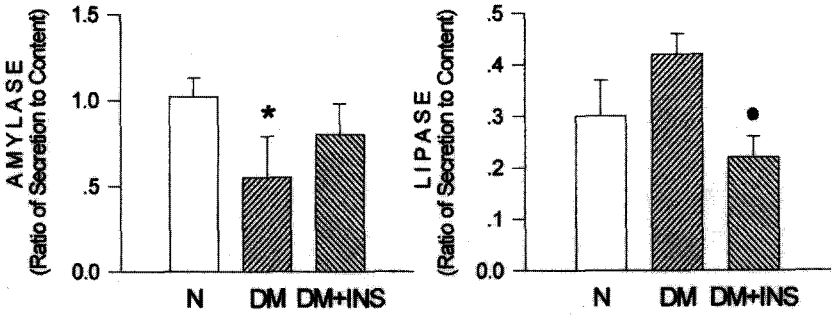

Fig. 4. The ratio of activity of amylase and lipase secreted in pancreatic juice for 20 min to tissue content of each enzyme of pancreas in normal (N), streptozotocin-induced diabetic (DM), and insulin-treated diabetic (DM+INS) rats. Rats were prepared as in Methods. The numbers of animals in N, DM, and DM+INS were 10, 13, and 11, respectively. Results are expressed as mean±S.E. *: vs. N, $P<0.05$, •: vs. DM, $P<0.05$.

compared to that of normal pancreas.

The total amylase content of diabetic pancreas was 2.67± 0.41 KU/pancreas, which was a fifth of normal pancreas, 12.81±0.46 KU/pancreas. However, the total amylase content of insulin-treated diabetic pancreas was restored to normal range. Meanwhile, the total lipase content of diabetic pancreas was not significantly different from that of normal pancreas. Despite high lipase concentration, low pancreas weight of diabetic rats may contribute to this result.

The ratio of activity of amylase and lipase in pancreatic juice to tissue content of each enzyme in diabetic rats

The ratio of amylase secreted in pancreatic juice to tissue

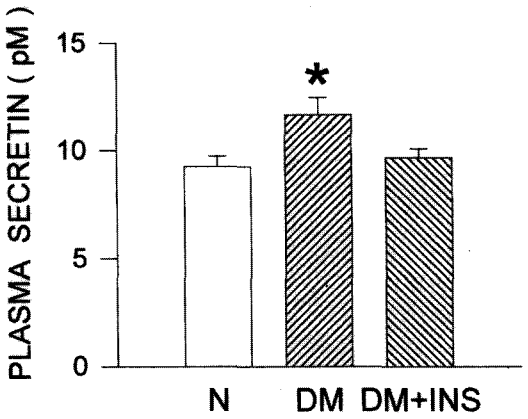

Fig. 5. Plasma secretin concentrations of normal (N), streptozotocin-induced diabetic (DM), and insulin-treated diabetic (DM+INS) rats. Rats were prepared as in Methods. On day 7, rats were anesthetized with ether and blood was obtained from the abdominal aorta without any surgical procedure. The number of animals in each groups was 8. Results are expressed as mean±S.E. *: vs. N and DM+INS, $P<0.05$.

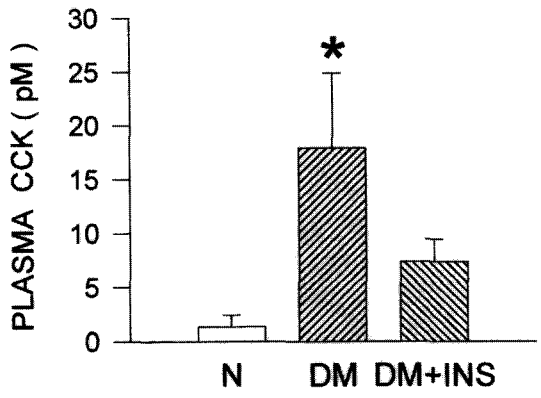

Fig. 6. Plasma CCK concentrations of normal (N), streptozotocin-induced diabetic (DM), and insulin-treated diabetic (DM+INS) rats. Rats were prepared as in Methods. On day 7, rats were anesthetized with ether and blood was obtained from abdominal aorta without any surgical procedure. The numbers of animals in N, DM, and DM+INS were 6, 7, and 16, respectively. Results are expressed as mean±S.E. *: vs. N, $P<0.05$.

content in pancreas of diabetic rats was significantly reduced to 0.55±0.24%, compared to that of normal rats (1.02±0.11%), indicating the inappropriate amylase secretory mechanism besides decreased amylase synthesis. In the case of lipase, there was no significant difference between the diabetic and normal rats, and yet insulin treatment significantly reduced the ratio of lipase secreted per tissue content, compared to that of diabetic rats (Fig. 4).

Plasma secretin and CCK concentration of diabetic rats

As shown in Fig. 5, fasting plasma secretin concentration of diabetic rats was 11.65±0.80 pM, which was significantly increased compared to that of normal rats, 9.25± 0.49 pM ($P<0.05$). After insulin administration, secretin concentration of diabetic rats was decreased to 9.66±0.41 pM. Meanwhile, fasting plasma CCK concentration of diabetic rats was 17.91±6.97 pM, which was 13-fold that of normal rats. After insulin administration, CCK concentration of diabetic rats was decreased to 7.36±2.09 pM (Fig. 6).

DISCUSSION

The decrease of amylase secretion was first reported in diabetic patients (Chey et al, 1963). Since then, insufficient amylase secretion has well been clarified in streptozotocin-induced diabetic rats (Sofrankova & Dockray, 1983; Okabayashi et al, 1988), and yet the pattern of lipase secretion in diabetic rats was not fully understood.

We observed the contents of amylase and lipase in diabetic pancreas to elucidate the pattern of the abnormal pancreatic secretion. The amylase concentration per tissue protein was significantly reduced (Soling & Unger, 1972; Bazin & Lavau, 1979; Duan & Erlanson-Albetsson, 1989; Duan & Erlanson-Albetsson, 1990), whereas the lipase concentration was increased in diabetic rats (Bendayan & Gregoire, 1987; Wicker & Puigserver, 1987; Bendayan & Levy, 1988). Unlike the decreased total amylase content in diabetic pancreas, the total lipase content was not significantly different from that of normal pancreas. This might be due to the low pancreatic weight and total protein content though lipase concentration is increased in diabetic pancreas. Also, the exogenous insulin administration restored the concentrations of amylase and of lipase in diabetic pancreas to normal range. These findings imply that insulin deficiency is involved in the abnormal pancreatic amylase and lipase concentrations. Meanwhile, it was reported that high fat diet induced decreased amylase activity and increased lipase activity while low fat diet caused both decreased amylase and lipase activity (Tsai et al, 1994) suggesting that factors other than insulin deficiency may be involved in the anticoordination of pancreatic enzymes secretion in diabetic rats.

To evaluate the involvement of secretin and CCK in the anticoordinated pancreatic enzymes secretion, plasma secretin and CCK concentrations were measured in diabetic rats. In the diabetic rats, plasma secretin concentration was increased compared to normal rats. This finding is in good agreement with the fact that plasma secretin concentration was increased in diabetic patients (Chisholm et al, 1970; Domschke et al, 1988). There are reports that the administration of exogenous secretin stimulated and increased the lipase synthesis (Rausch et al, 1985; Rausch et al, 1986; Duan & Erlanson-Albertsson, 1989). Therefore, increased lipase activity in diabetic rats may be associated with increased plasma secretin concentration as well as insulin deficiency. Since the exogenous insulin administration restored the increased plasma secretin concentration to normal range, insulin deficiency may be responsible for increased plasma secretin concentration. At present, it is not clear whether the increased lipase activity of diabetic rats resulted from increased secretin concentration.

In the present study, plasma CCK concentration in diabetic rats was also significantly increased compared to that of normal rats. This increase was abolished by the exogenous insulin administration. There are several reports that insulin modified the pancreatic effect of CCK. Insulin potentiates pancreatic exocrine response to CCK in isolated

perfused rat pancreas (Saito et al, 1980), restores the pancreatic secretory response to CCK in diabetic rat (Otsuki & Williams, 1982), and has direct effect on the regulation of CCK receptor and CCK-induced pancreatic secretion (Otsuki & Williams, 1983; Mossner et al, 1985). Taken together, plasma CCK concentration might be increased to meet the need for increased lipase activity because body utilizes fat instead of glucose as primary energy source in diabetes.

The above results may suggest that the anticoordination phenomenon of pancreatic secretion is attributable to metabolic failure by insulin deficiency in streptozotocin-induced diabetic rats. Also, it is presumed that the elevation of plasma secretin and CCK concentrations is secondary effect due to the anticoordination phenomenon in pancreatic enzymes secretion.

ACKNOWLEDGMENT

This work was supported by a grant (200106101) from the Good Health R&D Project and the Ministry of Health and Welfare, Korea.

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