Pancreatic Polypeptide and Insulin Contents in Diabetic and Nondiabetic Human Pancreas and Their Relationship to the Stability of the Fasting Serum Glucose

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Tasaka, Y., Inoue, S., Marumo, K. and Hirata, Y. Pancreatic Polypeptide and Insulin Contents in Diabetic and Nondiabetic Human Pancreas and Their Relationship to the Stability of the Fasting Serum Glucose. Tohoku J. exp. Med., 1983, 141 (4), 443–450—The amounts of insulin and pancreatic polypeptide (PP) in twenty-four autopsied diabetic and nineteen nondiabetic human pancreases were determined and their relationship to the stability of the fasting serum glucose level was investigated. The PP content of the tail of the pancreas in diabetic and nondiabetic subjects was 9.55±2.41 and 7.71±1.52 μg/g pancreas, and that of the head of the pancreas was 16.86±5.51 and 15.82±5.38 μg/g, respectively. No significant differences in content were found between diabetic and nondiabetic pancreases. The PP content of the head pancreas of some diabetics and nondiabetics was higher than that of the tail. The insulin content of the tail of the diabetic pancreas was lower than that of the nondiabetic pancreas. In those diabetics where there was less than 0.5 U/g of insulin in the tail pancreas, the stability of the fasting serum glucose was very poor, indicating an unstable type of diabetes. There was a significant inverse correlation between standard deviation of FBS and the amount of insulin, but the PP content of the pancreas had no relation to the stability of the fasting serum glucose.

Pancreatic polypeptide (PP) was discovered for the first time in the chicken pancreas in 1968 by Kimmel et al., then in the bovine, porcine and human pancreas (Chance 1972). Several years later an immunoassay method for PP was established (Langslow et al. 1973). In human subjects, besides pancreatic islets, PP producing cells are distributed in the pancreatic duct and acinus in minute amounts (Gersell et al. 1979). Many investigations regarding the secretion of human PP have been reported (Polak et al. 1976; Floyd et al. 1977; Sive et al. 1978; Skare et al. 1980; Tasaka et al. 1980), but no study has yet been done on the amount of PP in the human diabetic pancreas in comparison with that found in nondiabetic human pancreas.

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in the nondiabetic human pancreas. In this investigation we determined the amount of PP in diabetic and nondiabetic human pancreases from autopsied cases together with that of insulin, and also investigated their relationship to the stability of fasting serum glucose in the diabetics.

Materials and Methods

Autopsied human pancreases from 24 diabetics (16 males, 8 females, mean age 62 years) and 19 nondiabetics (8 males, 11 females, mean age 55 years) were examined. The diabetics had been treated as follows: 14 with insulin injection, 9 with diet therapy alone and 1 with a hypoglycemic agent (sulfonylurea). Clinical data for the diabetic patients are presented in Table 1. In a previous study (Tasaka et al. 1981) we confirmed that about 81.3±13.9% of the pancreatic PP and 68.5±5.1% of the pancreatic IRI were preserved after 6 hr at room temperature using surgically operated pancreases. Considering these results, in this study autopsied human pancreases obtained within 6 hr after death were used. The tail or the head of the pancreas was minced and the tissue was extracted with acid alcohol (Hayashi et al. 1977; Gingerich et al. 1978; Tasaka et al. 1979) for the determination of pancreatic PP and IRI or CPR. Anti-bovine PP serum (Lot 615-1054B-248-19) was kindly donated by R.E. Chance (Eli Lilly & Co., Indianapolis, Ind.) and polyethylene glycol was used for the separation of free and bound PP. Insulin was determined by the two antibody system of Morgan and Lazarow (1963), and CPR by an immunoassay kit supplied by Daiichi Radio Isotope Laboratories Ltd. (Tokyo). The recovery of unlabeled porcine insulin or PP added to lymphoid gland was 90% and 87%, respectively.

In the gel filtration experiment the separation of insulin, PP and C-peptide was made by Sephadex G-50 superfine (1.5×80 cm) equilibrated and eluted with 1 M acetic acid. 0.1 ml of pancreatic extract prepared by the above method was charged on the column and 1.2 ml fractions were collected. The lyophilized fraction was dissolved in the diluent for the immunoassay of IRI.

The values were expressed as mean±s.e., and tests for significance were performed using Student's t test. p-Value of less than 0.05 was considered statistically significant.

Results

Gel filtration of pancreatic extract

The gel filtration pattern of pancreatic extract was investigated by passing the extract through a Sephadex G-50 superfine column (Fig. 1). IRI, PP and C-peptide were measured in each fraction. The peaks of IRI and PP appeared almost at the same place with the C-peptide peak following immediately.

Pancreatic PP and IRI in the diabetic and nondiabetic human pancreas

Tails of 15 diabetic and 19 nondiabetic pancreases and heads of 8 diabetic and 9 nondiabetic pancreases were determined for PP (Fig. 2). 23 diabetic and 19 nondiabetic pancreases tails and 10 diabetic and 8 nondiabetic pancreases heads were analysed for IRI. The PP content of the diabetic pancreas tails was 9.55±2.41 μg/g and that of nondiabetics 7.71±1.52 μg/g. The values were not significantly different. On the other hand, the amount of PP from the head of diabetic pancreas was 16.85±5.51 μg/g, and that of the nondiabetic pancreas was 15.82±5.38 μg/g. In both cases, the head of the pancreas was more abundant in PP.
compared with the tail. Of the total cases of diabetic and nondiabetic pancreases the amount of PP of the head of the pancreas was significantly higher than that of the tail \( (p<0.02) \). The quantity of IRI in the tail of the diabetic pancreas was \( 1.26 \pm 0.19 \text{ U/g} \), significantly lower than that of the nondiabetic one which showed \( 2.55 \pm 0.35 \text{ U/g} \) \( (p<0.01) \). In the head of the pancreas, IRI values in the diabetics and nondiabetics were \( 1.14 \pm 0.27 \text{ U/g} \) and \( 1.60 \pm 0.23 \text{ U/g} \), respectively. These values were not significant.
Stability of fasting serum glucose and the relationship to the amount of pancreatic PP and IRI

The relation between the stability of fasting serum glucose and the amount of pancreatic PP or IRI in the diabetics was investigated (Figs. 3 and 4). As an
index of the stability of fasting serum glucose, the standard deviation (s.d.) of the mean of the 15 successive determinations of fasting serum glucose was adopted. There was no significant correlation between the s.d. of the fasting serum glucose and the PP amount of pancreas \((r = -0.448)\).

On the contrary, in the 3 cases with less than 0.5 U/g IRI in the tail of the pancreas, the s.d. of the fasting serum glucose was extremely high; the values were 98, 161 and 104 mg/100 ml, respectively, suggesting the unstable type of diabetes. The correlation between s.d. of FBS and the amount of insulin was calculated. It was significantly related \((r = -0.46, p < 0.05)\).
DISCUSSION

In untreated diabetics except for cases of chronic pancreatitis (Sive et al. 1978; Glaser et al. 1980), plasma PP levels were reported to be high not only at the fasting or ketoacidotic state (Skare et al. 1980), but also after meat soup loading (Floyd and Fajans 1978; Bergen et al. 1981). These high values decreased to the normal levels after diabetic treatment.

In the juvenile diabetic pancreas, hyperfunctions of PP cells were shown morphologically (Gepts et al. 1977). In this study the amount of IRI in the tail part of the diabetic pancreas was significantly lower than that found in the nondiabetic one as already reported by Wrenshall et al. (1952), Rastogi et al. (1973), and Tasaka et al. (1979), but the amount of PP was similar in both diabetic and nondiabetic pancreases at both the tail and the head. In this study, the values of PP in the pancreas tail of the diabetic and nondiabetic subjects are similar to those reported by Gersell et al. (1979), but the PP values of the head were a little lower than those found in their study. This might have been due to the different sites of PP extraction. In the results of Gersell et al., also the values of the head varied greatly.

In spite of the decrease of pancreatic IRI in the diabetics, pancreatic PP did not show any decrease or increase. This finding suggests that diabetes mellitus may be primarily caused by pancreatic B cell lesions rather than by F cells, and that pancreatic PP might be normalized after suitable treatment of diabetes mellitus just as pancreatic somatostatin did after treatment of streptozotocin diabetic rat (Berelowitz et al. 1979). The already reported high levels of plasma PP in untreated diabetes mellitus may have been mainly due to hypersecretion independent of storage or biosynthesis at least for some length of time.

Gersell et al. (1979) reported that PP cells are especially rich in the uncinate process or head of the pancreas, and glucagon or insulin producing cells are abundant in the tail or body of the pancreas. In our investigation also, the amount of PP in the head of diabetic and nondiabetic pancreases was higher than that of the tail. Plasma PP levels were reported to increase with age (Floyd and Fajans 1978; Mizuno et al. 1979), and Gepts et al. (1978) showed that PP cells of the pancreas increase with age. Since the difference in mean age between our two groups of autopsied cases was only seven years, there may be no significant chronological difference in the amount of PP in the pancreas.

Insulin and C-peptide quantities were reported to be greatly decreased in the pancreas of the unstable type of diabetes (Tasaka et al. 1979, 1980). Standard deviation of the mean of the 10 successive determinations of fasting serum glucose was significantly related to the M value of serum glucose level which is another index of unstablleness of blood sugar level (unpublished results). In this connection, the relationship between the amount of pancreatic PP and IRI and the s.d. of fasting serum glucose was investigated. Although the PP content in the
pancreas showed no special relationship to the unstableness of the fasting serum glucose, the relation between IRI content and s.d. of FBS showed a curve similar to a hyperbola.

At less than 0.5 U/g of IRI in the tail of the pancreas, the s.d. of the FBS was tremendously high. Thus very low amount of pancreatic IRI was considered to be associated with a low response of insulin secretion, contributing to the unstableness of the blood sugar level.

References

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