

A Pancreatic Protein Anabolic Extract

Proposal of a Protein Anabolic Extract from Pancreas.

I. Preliminary Report.

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The pancreatic extract which was isolated by our procedure was a protein. The extract exhibited some protein anabolic action, and it was effective in several patients with myasthenia gravis and aplastic anemia.

Twenty years ago, one of us (Y. T.) observed, for the first time, frequent parotid enlargement among Japanese diabetics. Subsequently many studies have been done attempting to support a theory of endogenous secretion of the salivary glands, especially the parotid gland. Based on 6 years of clinical and experimental observations a theory of a compensatory or feed back mechanism between the parotid gland and pancreas in diabetes mellitus was proposed.

Additionally, parotid gland enlargement as observed among undernourished people seemed to affect protein metabolism. A parotid gland extract, Parotin, was isolated by Emeritus Prof. T. OGATA, Dr. A. OGATA¹⁾ and Dr. Y. ITO²⁾. It was demonstrated³⁾ that Parotin accelerated protein anabolism, and the phosphorylation of thiamine, and that

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it was beneficial in myasthenic patients and in patients with leukopenia.

If one assumes that the hypothesis is correct, i. e. that the parotid gland compensates for relative hypofunction of the pancreas and that Parotin accelerates protein anabolism, then the pancreas should exhibit a stronger protein anabolic action than the parotid gland. In our laboratory during the past 14 years isolation of such a protein anabolic hormone from animal pancreas has been attempted. Recently, a pancreatic extract which was isolated by our procedure produced expected experimental and clinical results. The purpose of this paper is to describe our research on the pancreatic extract up to the present time.

MATERIALS AND METHODS

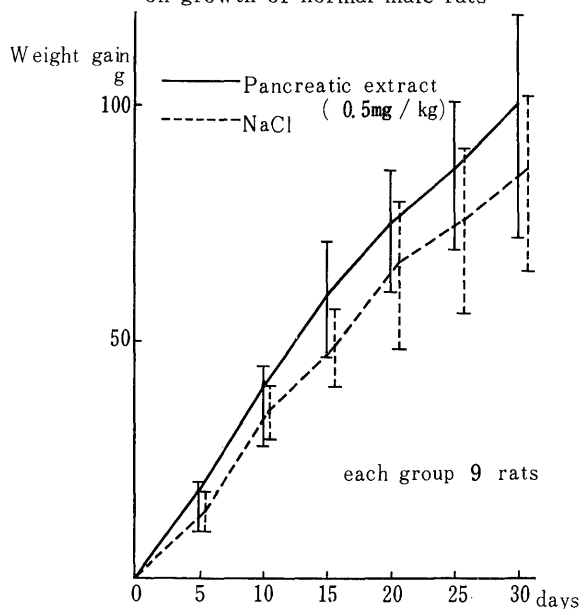
Pancreas of many kinds of animals and fishes were used for the isolation of the pancreatic extract. It is a protein. Only male animals were used for the evaluation of the physiological properties of the extract.

Serum electrolytes were estimated by flame photometry. Serum calcium was measured according to the method of Kramer-Tisdall.⁴⁾ Total protein in serum was determined by the Cu-Folin method.⁵⁾ Amino nitrogen and urea nitrogen in the blood were estimated by the methods of SASAKI⁶⁾ and ORMSBY⁷⁾. Total nitrogen in urine was measured by the macro-Kjeldahl method. Cholinesterase in the serum was determined by the method of SHIBATA.⁸⁾ Succinic dehydrogenase was assayed by the procedure of WANG TISING-YING⁹⁾.

RESULTS

As showing in Fig. 1 the pancreatic extract, administered intraperitoneally in a dose of 0.5mg. per kg. of body weight for 30 days, increased the growth rate of normal young rats compared with control group receiving saline injections (Fig. 1). The extract, in a dose of 3 mg. per kg. of body weight, decreased urinary nitrogen excretion in normal rats (Fig. 2), and increased the rate of incorporation of ¹⁴C-glycine into liver protein of rats (Fig. 3). The extract, in a dose of 3 mg. per kg.

Fig. 1 Influence of pancreatic extract on growth of normal male rats



of body weight in normal rabbits, decreased total protein, amino nitrogen and urea nitrogen in the serum (Fig. 4,5,6). It decreased serum potassium and calcium while showing no effect on serum sodium (Fig.4,7). It decreased the activity of pseudocholinesterase in the serum of normal rabbits (Fig. 8), and it increased the activity of succinic dehydro-

Fig. 2 Influence of pancreatic extract on the urinary nitrogen balance in normal rats

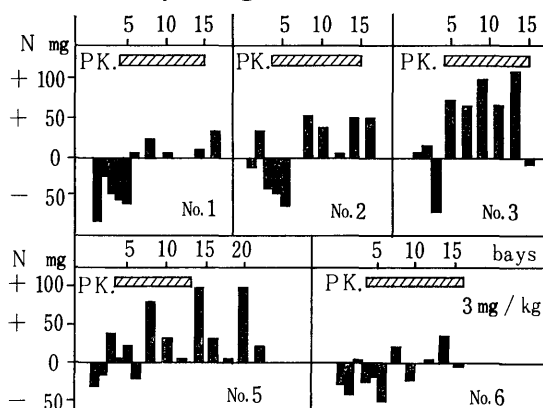


Fig. 3 Influence of the pancreatic extract on the incorporation rate of ¹⁴C-glycine into rat liver protein.

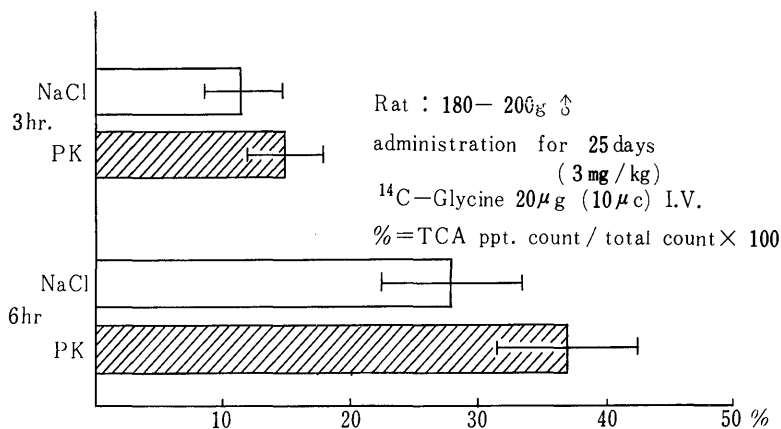


Fig. 4 Influence of the pancreatic extract on the serum calcium and total serum protein of normal rabbits.

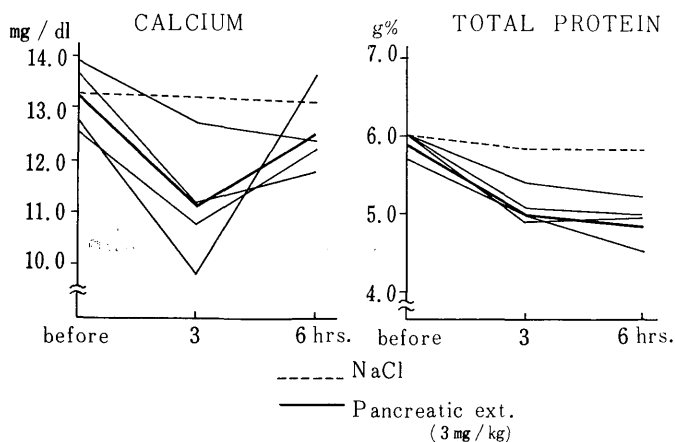


Fig. 5 Influence of pancreatic extract (3mg/kg) on the blood amino-N of normal rabbits.

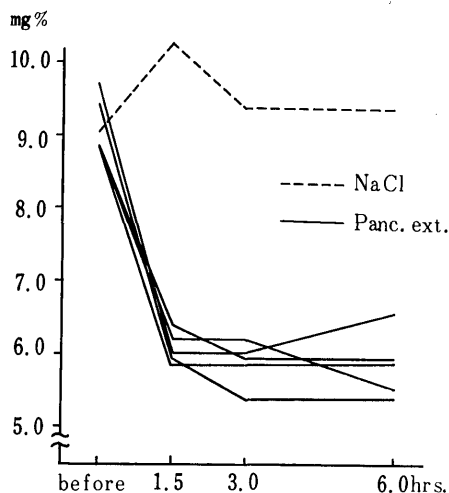


Fig. 6 Influence of pancreatic extract (3mg/kg) on the blood urea-N of normal rabbits.

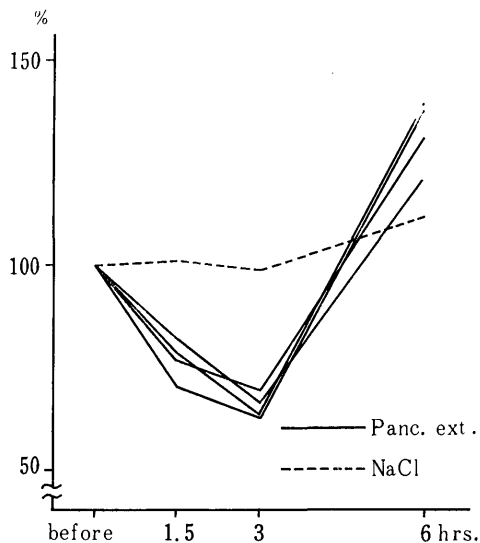
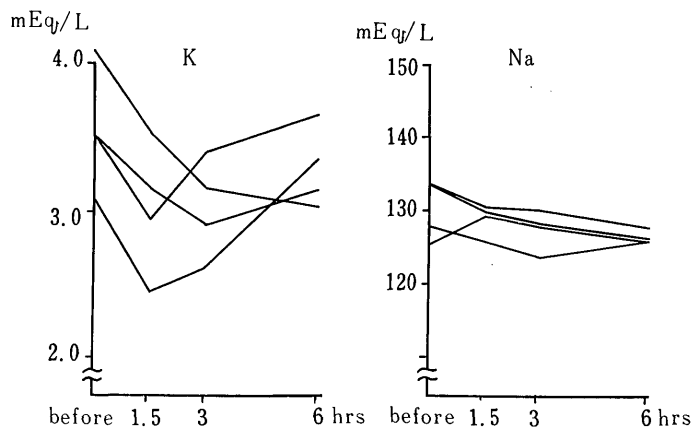


Fig. 7 Influence of pancreatic extract (3mg/kg) on the serum electrolytes of normal rabbits.



genase of rat liver homogenate when given in a dose of 3 mg. per kg. of body weight for 35 days (Fig. 9). The extract caused marked leukocytosis after a transient leukopenia in rabbits (Fig. 10). Furthermore, it prolonged the time of forced swimming in mice (Fig. 11).

Fig. 8 Influence of the pancreatic extract on the serum cholinesterase of normal rabbits

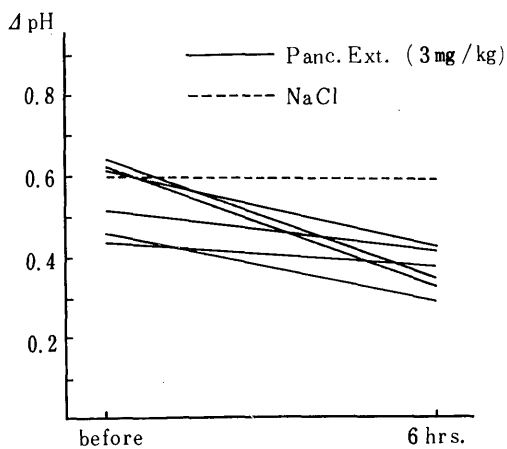


Fig. 9 Changes in the activity of succinic dehydrogenase of rat liver homogenate after the injection of pancreatic extract (3mg/kg) for 35 days.

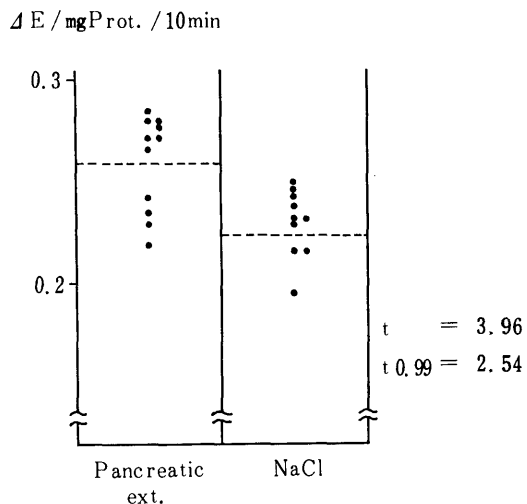


Fig. 10 Influence of pancreatic extract on the number of circulating leukocytes of normal rabbits.

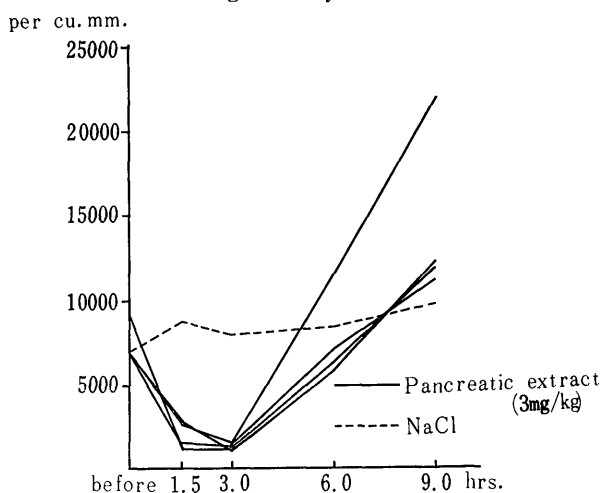
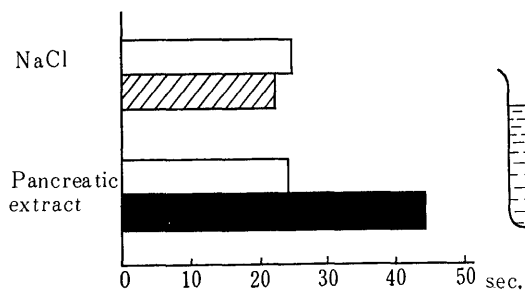
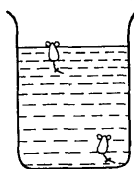


Fig. 11 Influence of pancreatic extract on the forced swimming time of mice.



Administration : intraperitoneal inj. (3mg/kg) 90min. before test
 Mouse : dd, male 20~30g (average of 9mice)
 Water temp : 23°C
 Added load : 5% of body wt.



The pancreatic extract is now being tasted on patients with myasthenia gravis and aplastic anemia. A 27-year old myasthenic woman, tested with the extract for the first time, improved markedly and is in better condition than at any time in last six years. During those years she received several kinds of drugs, including anticholinesterase drugs,

Fig. 12 Influence of pancreatic extract on the course of a myasthenic patient (27 year old female).

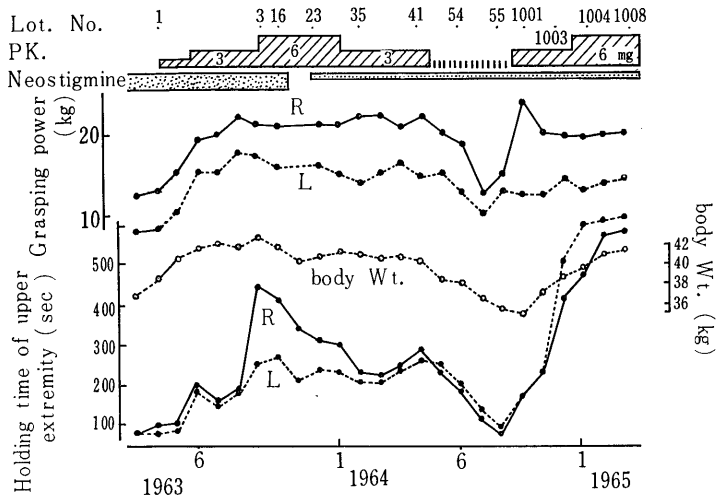
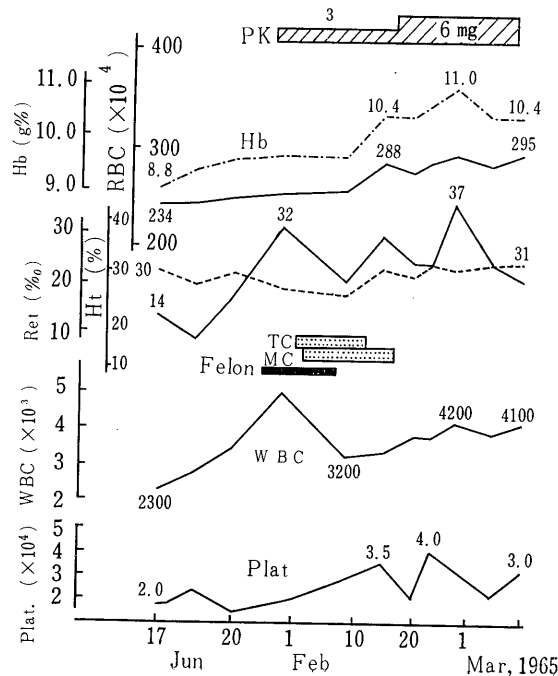


Fig. 13 Influence of pancreatic extract on the the blood of a patient with hypoplastic anemia.



spironolactone and parotin with little effect (Fig. 12). Two other female myasthenic patients also improved markedly when given the extract.

On the other hand, the pancreatic extract was given to two patients with aplastic anemia. One of them improved significantly, as shown in the (Fig. 13). A reticulocytosis up to 32% was observed immediately after the injection of the pancreatic extract, and was followed by a gradual increase of the hemoglobin content and red blood cell counts. The white blood cell count was increased gradually up to over 4000 per cmm. by the extract. His body weight increased from 53.0 to 60.0 kg. There was no effect on platelet count. Two other aplastic anemia patients are now improving gradually.

DISCUSSION

At the end of the World War II, Dr. TAKIZAWA¹⁰⁾ found histologically hypertrophy of the parotid gland and pancreas in Japanese civilian prisoners, despite atrophy of hypophysis, thyroid and adrenal glands. He ascribed the hypertrophy of the parotid gland and pancreas to hyperfunction of these glands in order to survive the malnutrition.

If one assumes that the parotid gland compensates for hypofunction of the pancreas, and that the parotid gland could accelerate protein anabolism, the pancreas should exhibit stronger protein anabolism than parotid gland. The pancreatic extract isolated by our method exhibited some protein anabolic action as expected. However, its purification, physicochemical character and biological activities certainly need further investigations.

SUMMARY

The pancreatic extract which was isolated by us demonstrated some protein anabolic action, and the extract and effective in several patients with myasthenia gravis and aplastic anemia.

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