Current Aspects of Clinical Application of Somatostatin

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At the end of the first paper reporting the discovery of growth hormone inhibiting peptide (SRIF, somatostatin) of hypothalamic origin, Brazeau et al.[1] stated that "Should SRIF be active in humans, its possible clinical significance, particularly in the treatment of acromegaly and the management of juvenile diabetes, has not escaped our attention". Soon after the paper appeared, it has been elucidated that the peptide inhibits strongly not only the release of growth hormone but also the pancreatic endocrine[2] such as insulin and glucagon. This fact abetted many clinical investigators to apply the peptide to the treatment of diabetes, aiming at the following points. 1) Somatostatin can control hyperglycemia through inhibiting glucagon or growth hormone secretion which is known to act as a diabetogenic hormone, and also serve seemingly to prevent the development and/or progressive deterioration of diabetic angiopathy, especially in belief[3),4)] that growth hormone plays a role to some extent, in producing either microangiopathy or macroangiopathy. 2) Since somatostatin seems to be in some way related to the nutrient homeostasis[5)-9)] between the inner environment and the digestive tract, one can expect some effect on controlling nutrient absorption and therefore the improvement of metabolic dysarrangement in diabetes.

In 1974[10)] somatostatin was actually used for the treatment of diabetes in combination with insulin particularly in IDDM. And when somatostatin was applied to the patients under treatment with artificial pancreas, it had resulted in a remarkable decrease of the insulin requirement from 38 to 70 per cent.[11)] On the other hand, it was confirmed that when somatostatin was given to patients sustaining normal or even a little reserve to secrete insulin, it gave the reverse effect, resulting in the deterioration of diabetic state.[12)-14)] Such reverse effect of somatostatin on glucose metabolism is due to a marked suppression of endogenous insulin which abolishes the beneficial effect of hypoglucagonemia induced by somatostatin on blood sugar. To enable the peptide useful as a supplemental drug to the insulin therapy, the development of analogs which can inhibit selectively glucagon and growth hormone without losing the effect on nutrient absorption, is in recent desired. Another obstacle in the clinical use of somatostatin is that somatostatin has so short half-life as 1.1 to 3.0 minutes in humans.[15)] Even if this obstacle were resolved, what clinical usefulness we could find in this peptide?

In our previous experiment, the authors had such impression that somatostatin was not so useful practically for clinical purposes except for

ソマトスタチンの臨床応用に関する最近の見解：金沢大学医学部第2内科 竹田亮祐，中林 肇，上野敏男，前川信政，石川県立中央病院 三輪梅夫．

diagnostic ones. In this report we are briefly informing of our experimental and clinical results of somatostatin.

Hyperglycemic Effect of Somatostatin on Cortisone-Induced Diabetes with Hyperinsulinemia in Rabbits

To prepare hyperinsulinemic diabetic state in rabbits, cortisone acetate (10 mg/kg bw) was injected intramuscularly into male rabbits (2.8 kg/ bw) every day for a week. After confirmed the development of diabetic state, 40 μg per kg bw of des Ala[1], Gly[2]-[D-Trp[8], D-Asu[3,14]] somatostatin was infused for an hour and changes in the serum levels of IRI, IRG and triglyceride were measured every 15 minutes during the 60 minutes. In Fig. 1, the dotted line shows the results obtained from rabbits given saline solution instead of cortisone acetate and the solid one shows that of rabbits infused the somatostatin analog. From the values of blood sugar and serum IRI on GTT, it was obvious that the rabbits treated with cortisone acetate has become in a state of hyperinsulinemic diabetes. As shown in the dotted line, somatostatin infusion

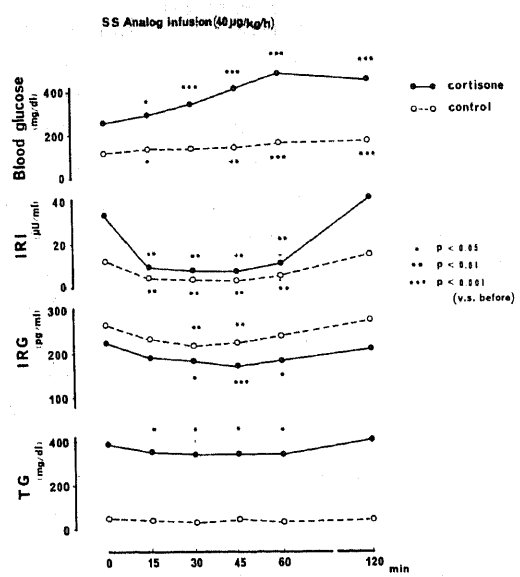

Fig. 1. Effects of des Ala[1], Gly[2]-[D-Trp[8], D-Asu[3,14]-somatostatin on blood glucose, IRI, IRG and serum triglyceride in cortisone-induced diabetic rabbits.

induced significant decreases in the serum levels of IRI and IRG. Serum level of IRI far below than that of IRG, which was reduced down to 29.2% of the initial level at 15 min after infusion and remained at the almost same level until the end of infusion in the cortisone group. At 120 min serum IRI raised to the higher level more than the initial level while serum IRG did not show such a rebound. On the contrary, the blood sugar has raised progressively throughout the infusion and reached up to the level of 478 mg/dl at the end of the infusion from 257 mg/dl of the initial level. In the cortisone group, marked hypertriglyceridemia developed (380.0 mg/dl) but which showed only a slight decrease during the infusion of somatostatin analog, and the agarose gel electrophoretic pattern of lipoprotein of the plasma still remained unchanged. It is esteemed that under the conditions of this experiment the secretion of endogenous insulin was exaggerated to compensate the counter-regulatory action of cortisone to glucose metabolism, but was significantly suppressed by the somatostatin analog. The hyperglycemia resulted from insulin suppression during somatostatin infusion, has overcome the beneficial effect on blood sugar through glucagon suppression.

Effect of 24 Hour Infusion of Cyclic Somatostatin on Diabetic Patients

Case 1. Fig. 2 shows the effect of cyclic somatostatin on blood sugar, serum levels of IRI, IRG and lipid metabolism in a diabetic patient with ketoacidosis. In this case the diabetic state improved to the condition of glycosuria 30 g per day with 200 to 300 mg/dl of blood sugar in diurnal profile with 24 IU of Lente insulin injection, but the 24-hour-continuous infusion of c-somatostatin (150 μg/h) significantly ameliorated the diurnal profile of blood sugar with decrease in the serum level of C-peptide, IRI and IRG. As shown in the dotted line, neither significant elevation of IRG or growth hormone was observed except for a sleep-induced rise in the control day. Therefore, the amelioration of diabetic state by somatostatin infusion is not

ascribed only to the fact of reduction of these two hormones in this case. Prompt and continuous lowering of serum triglyceride level throughout day, suggests that a significant improvement of diabetic control is mostly due to the effect of somatostatin on nutrient homeostasis.

Case 2. This case is another example of an IDDM treated with somatostatin infusion under insulin therapy ·(Fig. 3). The patient showed poor control even with 40 IU of MC Lente insulin and so blood sugar raised up near to the 400 mg/dl after dinner, accompanying massive glycosuria more than 83 g/day on the control day. Though the serum levels of IRG and growth hormone are not so elevated throughout the whole day. 24-hour continuous infusion of c-somatostatin (300 μg/h) as performed with 4 IU reduction of insulin dose. With this infusion the diurnal profile of the blood sugar was bettered, and serum triglyceride and FFA were suppressed with marked decreases in glycosuria to 6 g per day. This case also seems to be an example, indicating the inhibiting effect of somatostatin on nutrient absorption.

Case 3. In contrast to the above two cases, Case 3 shown in Fig. 4 is a female patient with maturity onset diabetes who recently became refractory to sulfonylurea therapy. From the response of serum IRI to breakfast, it was suspected that the patient sustained still some secretory reserve of endogenous insulin 24-hour-continuous infusion of c-somatostatin (300 μg/h) under diet therapy

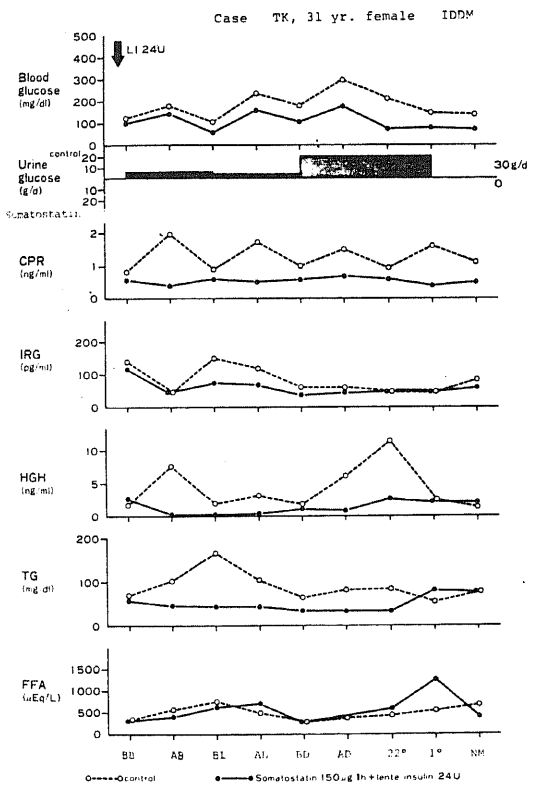

Fig. 2. Effect of 24-hour infusion of cyclic somatostatin on blood glucose, glycosuria, CPR, IRG, HGH serum triglyceride and FFA in a patient with IDDM. Abbreviations: BB; before breakfast, AB; after breakfast, BL; before lunch. AL; after lunch, BD; before dinner, AD; after dinner, NM; next morning.

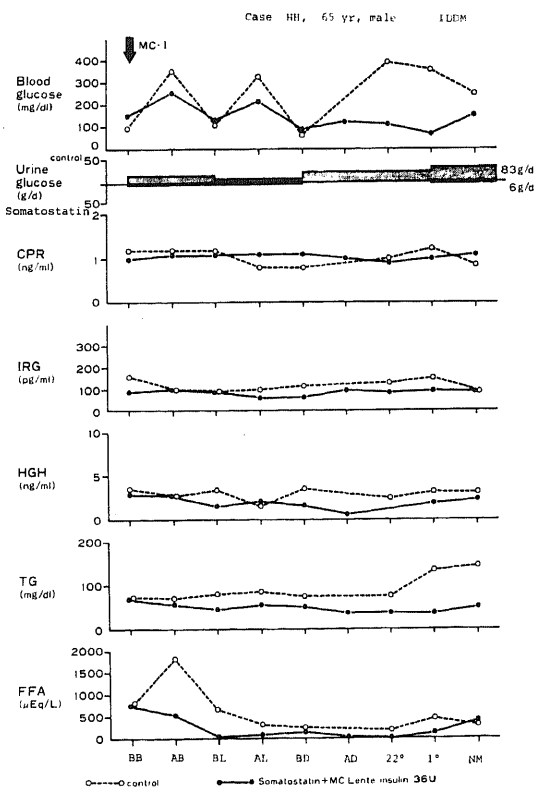

Fig. 3. Effect of 24-hour infusion of cyclic somatostatin on blood glucose, glycosuria, CPR, IRG, HGH, serum triglyceride and FFA in a patient with IDDM.

of 1800 cal, resulted in the almost complete suppression of endogenous insulin, glucagon and growth hormone for 24 hours. In this case, any improvement in blood sugar was not observed as the above two cases, and the blood sugar was rather increased after lunch about 100 mg/dl higher than those on the control day. The deterioration of blood sugar control induced by somatostatin was considered to be due to the suppressive effect of the peptide on insulin secretion, seeming quite similar to the result obtained in the experimental rabbits with contisone-induced diabetes.

From these observations of the either experimental or clinical studies, the following possibility was assumed: 1) The effect of somatostatin on the glucose metabolism depends upon the secretory activity of endogenous insulin. 2) The antidiabetic action induced by somatostatin, observed in the insulin dependent diabetics without significant increase of glucagon and growth hormone, seems to be resulted from the suppressive effect on nutrient homeostasis rather than on the secretion of diabetogenic hormones. 3) The fact that the serum triglyceride was decreased without delay, also supports the above assumption.

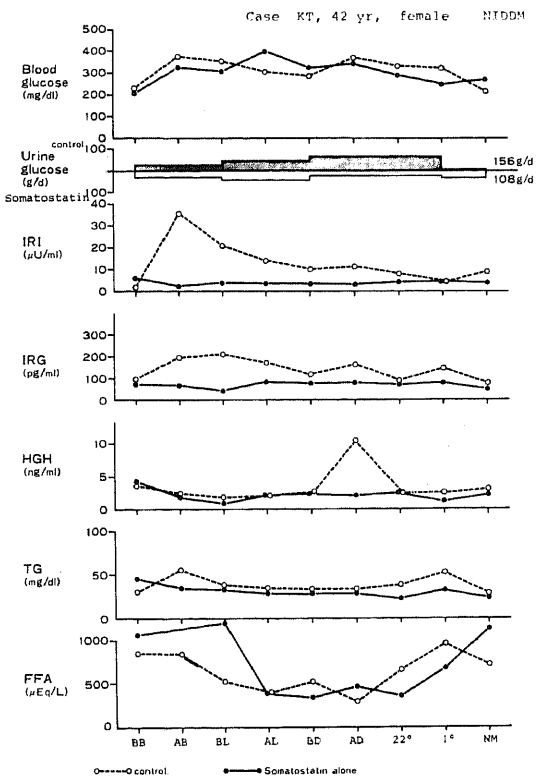

Fig. 4. Effect of 24-hour infusion of cyclic somatostatin on blood glucose, glycosuria, IRI, IRG, HGH, serum triglyceride and FFA in a patient with NIDDM.

Recent Advances in Synthetic Somatostatin Analog

Aside the various biological activities of the native somatostatin, synthetic modifications of the peptide have been studied to prolong its effect with more selectivity for glucagon and growth hormone. To attain this aim the modification of structure, including 1) substitution of a D form for the L-form amino acids, 2) removal or addition of one or more amino acid(s) from the C-terminal end or N-terminal end, 3) replacement of aminoacids, and 4) alteration of cyclic

Table 1. Glucagon-selective somatostatin analogs.

[D-Cys^{14}] Somatostatin;	
Brown. M. et al.	1977
Lien. E. L.	1978
[D-Trp^{8} D-Cys^{14}] Somatostatin	
Brown. M. et al.	1977
Gordin. A. et al.	1977
[Ala^{2} D-Cys^{14}] Somatostatin	
Gordin. A. et al.	1977
des-Ala^{1} Gly^{2} [His^{4,5}-D-Trp^{8}] Somatostatin (WY-41. 747)	
Sarantakis D. et al.	1978
Lien. E. et al.	1979
des-Ala^{1} Gly^{2} [D-Trp^{8} D-Asu^{3,14}] Somatostatin	
Harano Y., Sakakibara T. et al.	1979
[C Gln (Gly)^{2} D-Trp^{8}] Somatostatin	
[Ala^{2} D-Trp^{8} D-Cys^{14}] Somatostatin	
Voyles N. R. et al.	1979

structure[16], have been investigated. Some of the analogs shown in Table 1 have been proved to share the properties capable to suppress the glucagon and the insulin in the ratio of 6 to 10 : 1, but they are still not satisfactory for therapeutic purposes, because of short-acting. Recently, an octapeptide; des AA 1, 2, 4, 5, 12, 13, D-Type somatostatin[17] has been demonstrated to sustain the effect for 24 hours continously as given subcutaneously, but has no selectivity for glucagon and growth hormone. Somatostatin with native structure, itself, is not suitable for therapeutic use. If such an analog should be discovered as to block the glucagon and growth hormone secretion without inhibitin other hormones including insulin and moreover delay or inhibit the nutrient absorption, its analog with long-acting may enable us very much possibily to treat the obese diabetics. Further, when one accepts the etiological significance of glucagon in brittleness of blood sugar or development of diabetic ketoacidosis, and the hypothesis of A cell abnormality[18] as a primary defect of Type I diabetes, somatostatin might be useful, as a supplementary drug to insulin therapy. Much interest has been taken in the debate about the A cell defect is primary or secodary to the diabetic state. According to the recent aspect of pancreatic endocrine, however, hyperglycagonemia seen in the states above-mentioned, is not primary defect and is considered as a phenomena secondary to insulin deficiency. Hyperglucagonemia in NIDDM also seems likely to be secondary to the diabetic state. In fact, it has been demonstrated that insulin could normalize A cell dysfunction[19)-22)] even in severe ketoacidotic state. Consequently, it is difficult at present to accept the opinion that somatostatin is useful in itself for the treatment of diabetes. Moreover, we are still at the stage as yet a thorough study has not been completed on the so many biological activities of somatostatin. Therefore, there still remains one of difficulties to define properly what is the side effect when used much of the peptide in human experimentation. It means in return that more accumulation of the basic knowledge of the peptide will be required to obtain the final conclusion.

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ソマトスタチンの臨床応用に関する最近の見解：金沢大学医学部第２内科　竹田亮祐，中林　肇，上野敏男，前川信政，石川県立中央病院内科　三輪梅夫．金沢市，920，日本．金沢大学十全医学会雑誌，第89巻，679－685，(昭和55年)．

抄　録　糖尿病患者に対するソマトスタチンの臨床応用の限界，ならびにソマトスタチン類縁化合物における最近の進歩について，自験成績を参考に簡単にレビューした．