*Acta Medica Okayama*

*Volume* 51, *Issue* 1 1997 *Article* 1

FEBRUARY 1997

# The effect of somatostatin analogue on glucose homeostasis in conscious dogs

Ichiro Nakanishi* Toshihiko Ishida† Hitoshi Hosokawa‡
Koichi Kawanishi** Craig J. Hartley†† Jiro Takahara‡‡

*Kagawa Medical University,
†Kagawa Medical University,
‡Kagawa Medical University,
**Kagawa Medical University,
††Baylor College of Medicine,
‡‡Kagawa Medical University,

# The effect of somatostatin analogue on glucose homeostasis in conscious dogs*

Ichiro Nakanishi, Toshihiko Ishida, Hitoshi Hosokawa, Koichi Kawanishi, Craig J. Hartley, and Jiro Takahara

## Abstract

Our aim was to clarify the effect of a somatostatin analogue (octreotide) on glucose flux in conscious dogs. We monitored the effects with catheters in the portal vein, hepatic vein and femoral artery and Doppler flow probes on the portal vein and hepatic artery before and after oral glucose administration. A significant increase of portal vein plasma flow after oral glucose was completely suppreed by both 4 and 1 $\mu$g/kg octreotide. All doses of octreotide (4, 1 and 0.1 $\mu$g/kg) suppreed the glucose-induced increment of arterial glucose by dose response. Only 4 $\mu$g/kg of octreotide slightly but significantly suppreed hepatic glucose output. Marked suppreion and delayed glucose absorption by the intestine was observed after 4 $\mu$g/kg of octreotide. One and 0.1 $\mu$g/kg octreotide also suppreed glucose absorption without delayed absorption. Total amounts of absorbed glucose during 3h after oral glucose were 24 $\pm$ 11% with 4 $\mu$g/kg of octreotide, 37 $\pm$ 16% with 1 $\mu$g/kg of octreotide, and 48 $\pm$ 8% with 0.1 $\mu$g/ kg of octreotide, all of which were significantly le than that of the control (73 $\pm$ 8%). Using 4 $\mu$g/kg of octreotide treatment, the liver took up only 5 $\pm$ 4% of the absorbed glucose, while the liver took up 35 $\pm$ 6% and 43 $\pm$ 9% of the absorbed glucose with 1 and 0.1 $\mu$g/kg of octreotide. These latter values were similar to that of the control value of 34 $\pm$ 4%. In conclusion, we found that octreotide administered before oral glucose had a remarkable stabilizing effect on postprandial glycemic surges. Both the direct inhibitory effect of octreotide on portal vein plasma flow and impaired glucose absorption would contribute to this decreased postprandial hyperglycemia, while its suppreive effect on other hormones, such as insulin and glucagon, did not seem to influence the reduction of hyperglycemia.

**KEYWORDS:** octreotide, portal venous flow, glucose absorption, hepatic glucose uptake

---

*PMID: 9057928 [PubMed - indexed for MEDLINE]

ACTA MED OKAYAMA 1997; 51(1): 1-7

# The Effect of Somatostatin Analogue on Glucose Homeostasis in Conscious Dogs

Ichiro NAKANISHI, Toshihiko ISHIDA*, Hitoshi HOSOKAWA, Koichi KAWANISHI[a], Craig J HARTLEY[b] and Jiro TAKAHARA

Department of Medicine and [a]Department of Central Laboratory, Kagawa Medical University, Kagawa 761-07, Japan and [b]Section of Cardiovascular Science, Department of Medicine, Baylor College of Medicine, Houston, TX 77030, USA

Our aim was to clarify the effect of a somatostatin analogue (octreotide) on glucose flux in conscious dogs. We monitored the effects with catheters in the portal vein, hepatic vein and femoral artery and Doppler flow probes on the portal vein and hepatic artery before and after oral glucose administration. A significant increase of portal vein plasma flow after oral glucose was completely suppressed by both 4 and 1 $\mu$g/kg octreotide. All doses of octreotide (4, 1 and 0.1 $\mu$g/kg) suppressed the glucose-induced increment of arterial glucose by dose response. Only 4 $\mu$g/kg of octreotide slightly but significantly suppressed hepatic glucose output. Marked suppression and delayed glucose absorption by the intestine was observed after 4 $\mu$g/kg of octreotide. One and 0.1 $\mu$g/kg octreotide also suppressed glucose absorption without delayed absorption. Total amounts of absorbed glucose during 3h after oral glucose were 24 $\pm$ 11% with 4 $\mu$g/kg of octreotide, 37 $\pm$ 16% with 1 $\mu$g/kg of octreotide, and 48 $\pm$ 8% with 0.1 $\mu$g/kg of octreotide, all of which were significantly less than that of the control (73 $\pm$ 8%). Using 4 $\mu$g/kg of octreotide treatment, the liver took up only 5 $\pm$ 4% of the absorbed glucose, while the liver took up 35 $\pm$ 6% and 43 $\pm$ 9% of the absorbed glucose with 1 and 0.1 $\mu$g/kg of octreotide. These latter values were similar to that of the control value of 34 $\pm$ 4%. In conclusion, we found that octreotide administered before oral glucose had a remarkable stabilizing effect on postprandial glycemic surges. Both the direct inhibitory effect of octreotide on portal vein plasma flow and impaired glucose absorption would contribute to this decreased postprandial hyperglycemia, while its suppressive effect on other hormones, such as insulin and glucagon, did not seem to influence the reduction of hyperglycemia.

**Key words:** octreotide, portal venous flow, glucose absorption, hepatic glucose uptake

Continuous infusion of somatostatin has been reported to decrease fasting (1-2) and postprandial hyperglycemia (3) in insulin-dependent patients with diabetes mellitus. Despite these potential benefits of somatostatin as a therapeutic agent in diabetic patients, the need for continuous infusion, due to its short half-life of a few minutes (4), its relative inactivity after subcutaneous injection (5) and its multiple hormone suppressive effects (6) render the native peptide impractical for clinical use. However, a somatostatin analogue (octreotide) has a 10 to 60 times higher inhibitory effect on insulin and growth hormone secretion than somatostatin and has a biological half-life longer than somatostatin (7-9). Octreotide has been used for the treatment of acromegaly (10), VIPoma (11) and gastrinoma (12).

Improvement in postprandial blood glucose profiles after administration of octreotide has been reported in insulin-dependent diabetes (13, 14), but not in patients with non-insulin dependent diabetes mellitus (15). The precise mechanisms of the effects of octreotide on glucose metabolism after oral glucose are not clearly understood. We studied the effects of octreotide on glucose flux in conscious dogs with catheters in the portal vein, hepatic vein and femoral artery and Doppler flow probes on the

* To whom correspondence should be addressed.

portal vein and hepatic artery before and after oral glucose administration.

## Materials and Methods

***Animals and surgery.*** Forty healthy adult male and female mongrel dogs, weighing 8–18 kg, were anesthetized with pentobarbital sodium (25 mg/kg body weiglht) after an overnight fast. Doppler flow probes designed by Hartley *et al.* (16) were placed around the portal vein and hepatic artery as described in detail previously (16). Polyvinyl catheters (Tygon Co., New York, NY, USA) were also inserted into the portal vein, left common hepatic vein and femoral artery for blood sampling as previously reported (16).

***Experimental procedure.*** Experiments were done with conscious unrestrained dogs after an overnight fast and at least 2 weeks after surgery. Only animals whose hematocrits were over 30 %, appeared in healthy condition, and had a good appetite and normal stools were used. Phasic and mean control aortic blood pressure was measured using a Statham p 23 db pressure transducer (Nihon Koden Co., Tokyo, Japan) connected to the arterial catheter. Blood samples for glucose, insulin and glucagon were obtained simultaneously from the portal vein, hepatic vein and femoral artery with continuous measurements of the portal vein and hepatic artery blood flow (16). The blood flow measurements were corrected to plasma flow based on hematocrits obtained every 30 min, since glucose, insulin and glucagon levels in each vessel were determined by multiplying plasma flow by plasma concentrations as previously reported (16).

After a 30 min control period, octreotide (0.1, 1.0 or 4.0 $\mu$g/kg) was administered subcutaneously and again one hour later just before glucose administration. An interval of at least 7 days separated each experiment. Glucose (1.0 g/kg) was administered orally and was consumed within 2 min. Blood samples were collected in chilled tubes containing 500 U aprotinine (Trasyrol; Sigma Chemical Co., St. Louis, MO, USA) and 1.2 mg EDTA/ml of blood at $-30$, $-20$, $-10$, 0, 30, 45, 60, 70, 80, 90, 105, 120, 135, 150, 180, 210 and 240 min.

***Analysis.*** Plasma glucose was measured using a Beckman glucose autoanalyzer (Beckman Co., New York, NY, USA) and a glucose oxidase method. Plasma insulin and glucagon were assayed as previously reported (16, 17). Net hepatic glucose output (HGO), splanchnic glucose output (SGO), hepatic glucose uptake (HGU) after glucose load and glucose absorption rate by the intestine were calculated as described in detail elsewhere (18). The data are presented as means $\pm$ SEM. The basal value was the mean $\pm$ SEM of the four values obtained from $-30$ to 0 min. Significant changes from the basal value were determined by two-way analysis of variance, followed by Duncan's new multiple range test. Comparison of two means was by paired Student's $t$-test (19). After oral glucose administration, differences between the data sets from control and octreotide treated groups were evaluated by calculations of the area under the curve in each dog followed by the Fisher's PLSD test using the Statview software package. $P < 0.05$ was considered to indicate a significant difference.

## Results

***The effect of octreotide on basal and glucose-induced plasma flow.*** Blood pressure did not change significantly throughout each experiment.

Both 4 and 1 $\mu$g/kg octreotide suppressed the basal portal vein plasma flow to $82 \pm 4$ % and $87 \pm 8$ %, respectively, although these were not statistically significant. Hepatic arterial plasma flow did not change significantly after octreotide injection (data not shown). A significant increase of portal vein plasma flow after oral glucose was completely suppressed by both 4 and 1 $\mu$g/kg octreotide (Fig. 1).

***The effect of octreotide on basal and glucose-induced plasma arterial glucose level.*** Basal arterial plasma glucose tended to decrease after octreotide injection, but not significantly. With 4 $\mu$g/kg of octreotide treatment, arterial glucose increased gradually and continuously, but not significantly to $125 \pm 15$ % of the basal level. Even 0.1 $\mu$g/kg of octreotide suppressed the glucose-induced increment of arterial glucose ($136 \pm 13$ % *vs* $162 \pm 25$ % for the controls, $P < 0.05$, respectively) (Fig. 2).

***The effect of octreotide on basal hepatic glucose output.*** Only 4 $\mu$g/kg of octreotide slightly but significantly suppressed HGO from the basal value of $2.6 \pm 0.3$ mg/kg/min to $2.2 \pm 0.2$ mg/kg/min. Both 1 and 0.1 $\mu$g/kg of octreotide did not alter basal HGO.

***The effect of octreotide on glucose absorption rate by intestine after oral glucose administration.*** Glucose absorption by the intestine was markedly suppressed and delayed after 4 $\mu$g/kg

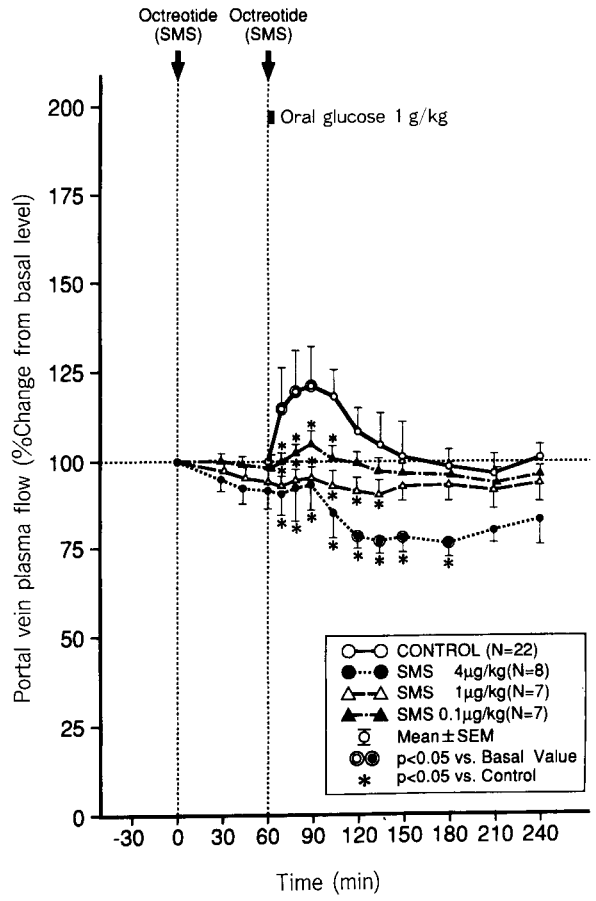


**Fig. 1** Portal vein plasma flow before and after oral glucose (1 g/kg) in control and octreotide treated dogs. Control (○) (N = 22); somatostatin analogue (SMS) 4 $\mu$g/kg (●) (N = 8); SMS 1 $\mu$g/kg (△) (N = 7); and SMS 0.1 $\mu$g/kg (▲) (N = 7). Mean ± SEM, ◎● $P < 0.05$ *vs.* Basal Value and * $P < 0.05$ *vs.* Control.

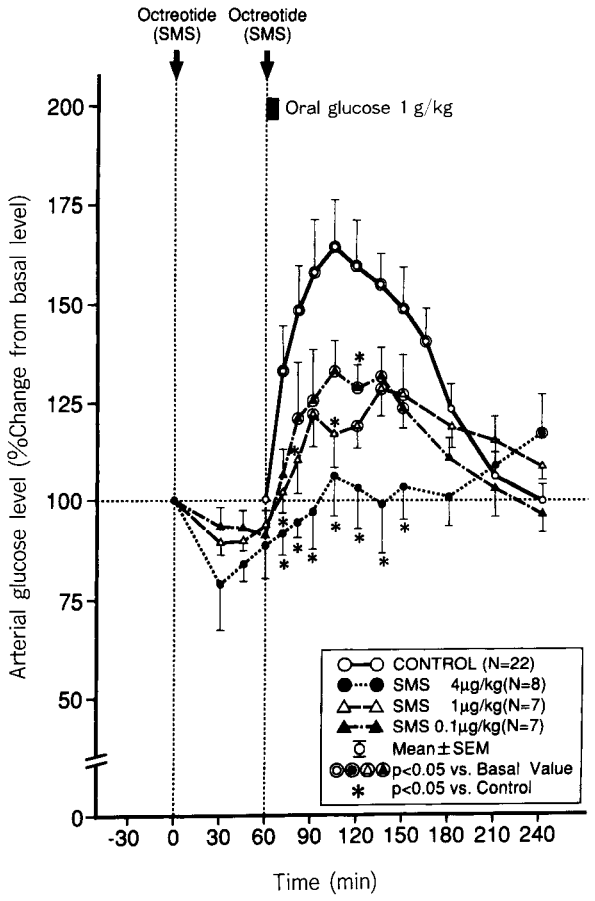


**Fig. 2** Percentage changes of the arterial glucose level before and after oral glucose (1 g/kg) in control and octreotide treated dogs. Control (○) (N = 22); somatostatin analogue (SMS) 4 $\mu$g/kg (●) (N = 8); SMS 1 $\mu$g/kg (△) (N = 7); and SMS 0.1 $\mu$g/kg (▲) (N = 7). Mean ± SEM, ◎●△▲ $P < 0.05$ *vs.* Basal Value and * $P < 0.05$ *vs.* Control.

of octreotide, but not after the other two doses. Total amounts of glucose absorbed during the 3 h after oral glucose were 24 ± 11 % of the administered dose with 4 $\mu$g/kg of octreotide, 37 ± 16 % with 1 $\mu$g/kg of octreotide, and 46 ± 8 % with 0.1 $\mu$g/kg of octreotide. These amounts were all significantly less than that of the control (73 ± 8 %) (Fig. 3).

***The effect of octreotide on hepatic glucose uptake after oral glucose administration.*** The liver of the dogs receiving 4 $\mu$g/kg of octreotide took up only 5 ± 4 % of the absorbed glucose. The values for the dogs receiving 1 and 0.1 $\mu$g/kg of octreotide were 35 ± 6 % and 43 ± 9 % of the absorbed glucose, respectively, which were similar to the control value of 34 ± 4 % (Fig. 4).

***The effect of octreotide on basal and glucose-induced plasma insulin levels.*** After octreotide administration, the portal venous insulin levels in the three groups decreased to 45 ± 12 % of the basal level. A dose-related suppression of insulin was not observed. With octreotide, the increments of portal insulin after glucose were significantly less than those of the control, concomitant to the suppressed glucose absorption (Fig. 5).

***The effect of octreotide on basal and glucose-induced plasma glucagon levels.*** Octreotide did not alter the basal portal venous glucagon levels with the exception of a 4 $\mu$g/kg dosage of

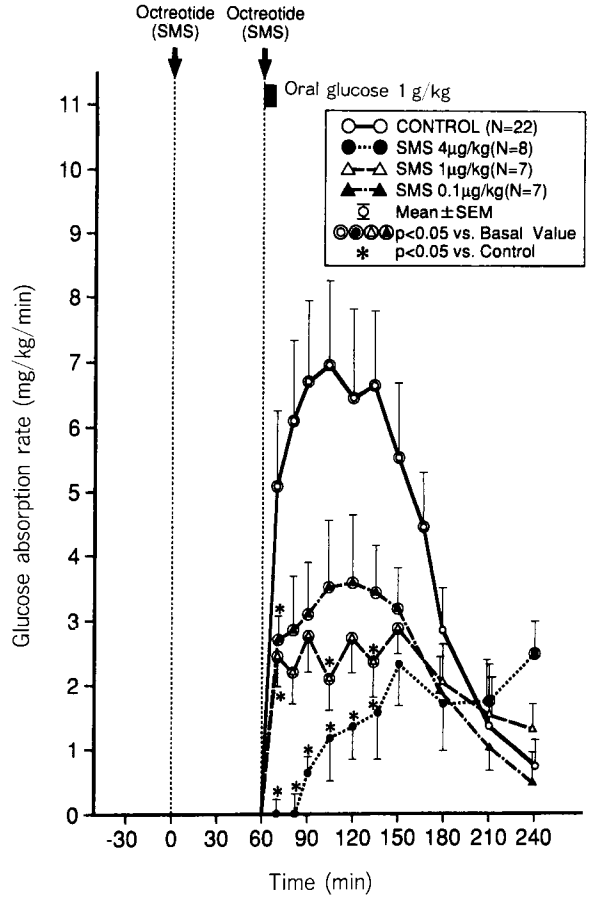


Fig. 3

octreotide. The suppression of portal glucagon after oral glucose was significantly less than that of the control. Using all doses of octreotide, this was associated with suppressed glucose absorption with octreotide (Fig. 6).

## Discussion

Glucose homeostasis is regulated by several factors. In the postabsorptive state, plasma glucose is regulated both by hepatic glucose output and peripheral glucose utilization. After glucose ingestion, many factors regulate arterial plasma glucose concentration. The first of these is gastric emptying time, the second is the rate of glucose absorption by the intestine, the third is the rate of hepatic uptake of glucose which is delivered to that organ by both the portal vein and the hepatic artery, and the fourth is the rate of peripheral utilization of glucose which is released into systemic circulation by the liver. The liver can minimize postprandial hyperglycemia both by increas-

**Fig. 3** Absorption rate by the intestine (portal vein glucose appearance rate) of glucose administered orally in control and octreotide treated dogs. Control (○) (N = 22); somatostatin analogue (SMS) 4 μg/kg (●) (N = 8); SMS 1 μg/kg (△) (N = 7); and SMS 0.1 μg/kg (▲) (N = 7). Mean ± SEM, ◎●△▲ $P < 0.05$ *vs.* Basal Value and * $P < 0.05$ *vs.* Control.

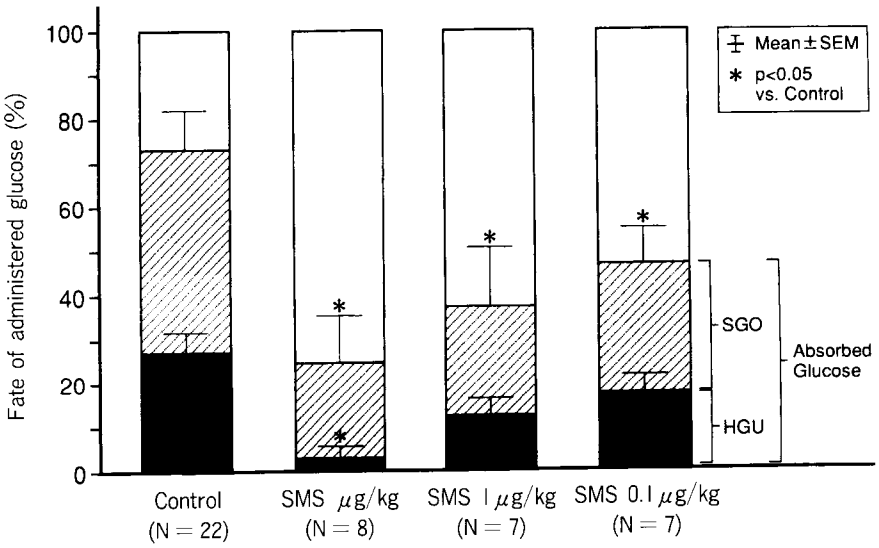


**Fig. 4** Fate of orally administered glucose in control and octreotide (4 μg/kg, 1 μg/kg, and 0.1 μg/kg) treated dogs. Total amount of absorbed glucose, SGO (splanchnic glucose output) and HGU (hepatic glucose uptake) during 3h after oral glucose administration. The data were presented as the rate of total amount of administered glucose. Mean ± SEM, * $P < 0.05$ *vs.* Control.

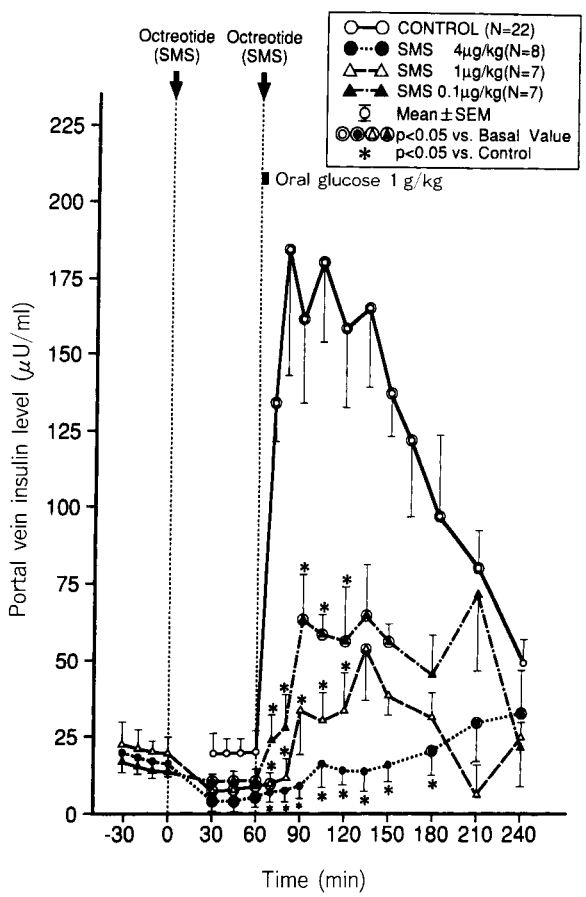


**Fig. 5** Portal vein insulin level before and after oral glucose (1 g/kg) in control and octreotide treated dogs. Control (○) (N = 22); somatostatin analogue (SMS) 4 $\mu$g/kg (●) (N = 8); SMS 1 $\mu$g/kg (△) (N = 7); and SMS 0.1 $\mu$g/kg (▲) (N = 7). Mean ± SEM, ◎●◎▲ $P < 0.05$ *vs.* Basal Value and * $P < 0.05$ *vs.* Control.

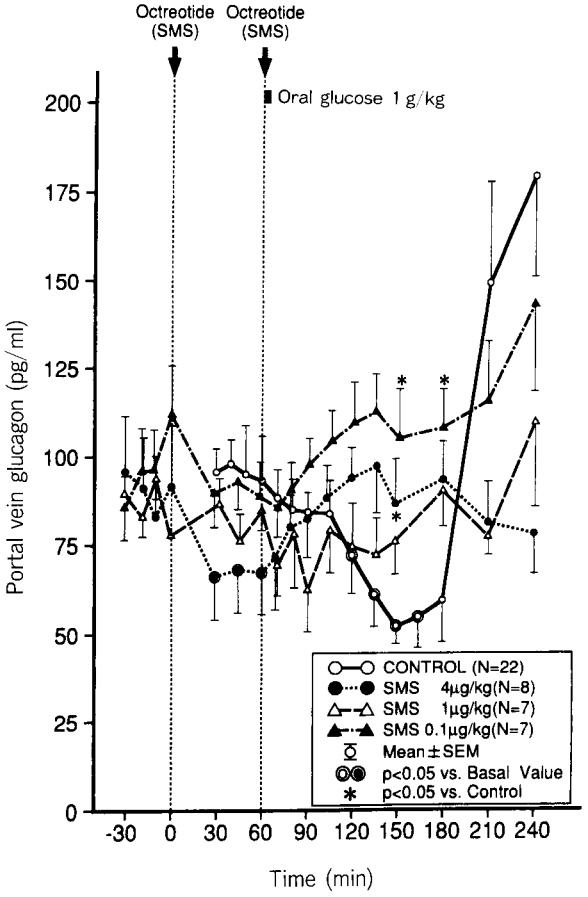


**Fig. 6** Portal vein glucagon level before and after oral glucose (1 g/kg) in control and octreotide treated dogs. Control (○) (N = 22); somatostatin analogue (SMS) 4 $\mu$g/kg (●) (N = 8); SMS 1 $\mu$g/kg (△) (N = 7); and SMS 0.1 $\mu$g/kg (▲) (N = 7). Mean ± SEM, ◎● $P < 0.05$ *vs.* Basal Value and * $P < 0.05$ *vs.* Control.

ing hepatic glucose uptake and by suppressing endogenous hepatic glucose production (19, 20).

The present study demonstrates that a single subcutaneous injection of 0.1, 1 and 4 $\mu$g/kg octreotide diminished postprandial hyperglycemia in comparison to normal control dogs. This effect was associated with both inhibition of gastric emptying time and a reduction of intestinal glucose absorption. Similar effects of octreotide have been reported by several authors (21-24). However, del Pozo *et al.* (25) reported that the pattern of the absorption curve was not modified despite a retardation of glucose absorption. The present study also showed a similar absorption pattern in comparison to the control group with 1 and 0.1 $\mu$g/kg octreotide, although the absolute amounts of glucose absorption was markedly suppressed. Jenkins *et al.* (28) showed a suppression of portal venous and hepatic arterial blood flows at the basal state after infusion of a somatostatin analogue, though we did not obtain a significant suppression of the basal portal venous plasma flow. Although octreotide did not change blood pressure and heart rate, splanchnic plasma blood flow after oral glucose was suppressed. Many factors from intestine during oral glucose ingestion affect the portal blood flow. The suppression of the postprandial increment of splanchnic blood flow by atropine (26), epinephrine (20), phentolamin (20), propranolol (20), and guanabenz (27) treatments was demonstrated in our previous studies.

Since octreotide has many inhibitory effects on gastrointestinal hormone secretion (22-24), such effects could cause a reduction in net glucose absorption as well as the inhibition of postprandial increased blood flow. Other mechanisms for reduced postprandial hyperglycemia have also been suggested (13, 29). Spinas *et al.* (13) showed a rapid and sustained decrease of pancreatic glucagon concentrations by a single injection of a somatostatin analogue, and suggested that the early decrease and the absent postprandial increase in blood glucose resulted in part from glucagon suppression. We also showed a rapid decrease of glucagon by a single injection of octreotide $4\mu g/kg$. However, we could not obtain a sustained decrease of glucagon after oral glucose under octreotide treatment. This suggests that octreotide inhibited hyperglycemia-induced glucagon suppression. The reason for this discrepancy is not known, but we demonstrated that glucagon did not modify hepatic glucose uptake after oral glucose ingestion (30). Since a somatostatin analogue also suppressed growth hormone (7, 10, 31), this would contribute to reduce postprandial hyperglycemia. Bratusch Marrain *et al.* (32) demonstrated that growth hormone decreased hepatic glucose uptake after oral glucose compatible with higher peripheral glucose levels. Although increased hepatic uptake of orally administered glucose might be responsible for reduced postprandial hyperglycemia, we did not find that octreotide increased hepatic uptake of glucose. Although a markedly lower rate of hepatic glucose uptake was observed after $4\mu g/kg$ octreotide, this value may be misleading, since much less glucose was reaching the liver.

All dosage of octreotide inhibited the basal portal venous insulin level and reduced the increment of that hormone after glucose in the present study. Despite the suppression of insulin and no change of glucagon, fasting blood glucose level tended to decline concomitant with the decreased hepatic glucose output using $4\mu g/kg$ octreotide. Such a suppressive effect of octreotide on the hepatic glucose output might be the direct effect of somatostatin (33, 34). The inhibitory effect of octreotide on glucose-induced insulin secretion probably reflects markedly diminished postprandial hyperglycemia as well as a direct effect on insulin secretion. The effect of inhibiting insulin without inhibition of glucagon might be expected to raise glucose concentration.

In conclusion, we found that octreotide administered before oral glucose had a remarkable stabilizing effect on postprandial glycemic surges. Both the direct inhibitory effect of octreotide on the portal vein plasma flow and impaired glucose absorption would contribute to this decreased postprandial hyperglycemia, while its suppressive effect on other hormones, such as insulin or glucagon, did not seem to influence hyperglycemia.

Acknowledgement. The authors thank Dr. James B. Field for constructive comments.

## References


1. Del Guercuio M, diNatale B, Gargantini L, Garlaschi C and Chiumello G: Effect of somatostatin on blood sugar, plasma growth hormone and glucagon levels in diabetic children. Diabetes (1976) **25**, 550-553.
2. Gerich J, Lorenzi M, Schneider V, Karam J, Rivier J, Guillemin R and Forsham P: Effects of somatostatin on plasma glucose and glucagon levels in human diabets mellitus: Pathophysiologic and therapeutic implications. J Med (1975) **291**, 544 547.
3. Gerich J, Lorenzi M, Karam J, Schneider V and Forsham P: Abnormal pancreatic glucagon secretion and postprandial hyperglycemia in diabetes mellitus. JAMA (1975) **234**, 159 165.
4. Sheppard M, Shapiro B, Berelowitz M and Pimstone B: Metabolic clearance and plasma half disappearance time of exogeneous somatostatin in man. J Clin Endocrinol Metab (1979) **48**, 50-53.
5. Barnes AJ, Rivier JE, Hanley J, Ghateri MA, Sarson DL and Bloom SR: Effect of a long-acting octapeptid analogue of somatostatin on growth hormone and pancreatic and gastrointestinal hormones in man. Clin Sci (1981) **61**, 653-656.
6. Gottesman IR, Mandarino IJ and Gerich JE: Somatostatin: Its role in health and disease: in Special Topics in Endocrinology and Metabolism. Vol. 4. Cohen J and Foa P eds, Alan R Liss, Inc., New York, (1982) pp177 243.
7. Bauer W, Briner U, Doepfner W, Haller R, Huguenin R, Marbach P, Petcher TJ and Pless J: SMS 201-995: A very potent and selective octreotide analogue of somatostatin with prolonged action. Life Sci (1982) **31**, 1133 1140.
8. Whitehouse I, Beglinger C, Fried M and Gyr K: The effect of an octapeptid somatostatin analogue (SMS 201-995) and somatostatin-14 (SST-14) on pentagastrin-stimulated gastric acid secretion: A comparative study in man. Hepato-Gastroenterology (1984) **31**, 227-229.
9. Whitehouse I, Beglinger C and Gyr K: SMS 201-995 (a long acting, octapeptid, somatostatin analogue): Efficacy and duration of action after s. c. administration on pentagastrin-stimulated gastric acid secretion in man. Dig Dis Sci 29 (1984) (Suppl. 8) 96s.
10. Lamberts SMJ, Uitterlinden P and del Pozo E: SMS-201-995 induces a continuous decline in circulating growth hormone and somatomedin-C levels during therapy of acromegalic patients for over two years. J Clin Endocrinol Metab (1987) **65**, 703 710.
11. Williams G, Anderson JV and Bloom SR: Treatment of gut-associated neuroendocrine tumors with the long-acting somatostatin analog, SMS 201-995; in Somatostatin: Basic and Clinical Status, Reichlin S ed, Plenum Press, New York (1987) pp343-356.
12. Anderson JV and Bloom SR: Neuroendocrine tumors of the gut: Long-term therapy with the somatostatin analogue SMS 201-995. Scand J Gastroenterol (1986) **21**, (Suppl. 19) 26-36.
13. Spinas GA, Bock A and Keller U: Reduced postprandial hyperglycemia after subcutaneous injection of a somatostatin-analogue (SMS 201-995) in insulin-dependent diabetes mellitus. Diabetes Care (1985) **8**, 429-435.

14. Serrano Rios M, Navascues I, Saban J, Ordonez A, Sevilla F and del Pozo E: Somatostatin analogue SMS 201-995 and insulin needs in insulin-dependent diabetic patients studied by means of an artificial pancreas. J Clin Endocrinol Metab (1986) **63**, 1071-1074.
15. Williams G, Fuessl HS, Burrin JM, Chilvers E and Bloom SR: Postprandial glycemic effects of a long-acting somatostatin analogue (octreotide) in non-insulin dependent diabetes mellitus. Horm Metabol Res (1988) **20**, 168 170.
16. Ishida T, Lewis RM, Hartley CJ, Entman M and Field JB: Comparison of hepatic extraction of insulin and glucagon in conscious and anesthetized dogs. Endocrinology (1983) **112**, 1098-1109.
17. Ishida T and Field JB: Hepatic handling of glucagon; in Glucagon II, Handbook of Experimental Pharmacology, Lefebvre PJ ed, Vol 66/II Springer-Verlag, Berlin (1983) pp205 219.
18. Ishida T, Chap Z, Chou J, Lewis RM, Hartley CJ, Entman M and Field JB: Differential effects of oral, peripheral intravenous and intraportal glucose on hepatic glucose uptake and insulin and glucagon extraction in conscious dogs. J Clin Invest (1983) **72**, 590-601.
19. Wallenstein S, Zucker CL and Fleiss JL: Some statistical methods useful in circulation research. Circ Res (1980) **47**, 1-9.
20. Chap Z, Ishida T, Chou J, Michael L, Hartley C, Entman M and Field JB: Effects of alpha and beta adrenergic blockade on hepatic glucose balance before and after oral glucose; Role of insulin and glucagon. J Clin Invest (1986) **77**, 1357-1369.
21. Johansson C, Wisen O, Efendic S and Uvans-Wallensten K: Effects of somatostatin on gastrointestinal propagation and absorption of oral glucose in man. Digestion (1981) **22**, 126-137.
22. Fuessl HS, Carolan G Williams G and Bloom SR: Effect of long-acting somatostatin analogue (SMS 201-995) on postprandial gastric emptying of 99 mTc-Tin colloid and mouth-to-caecum transient time in man. Digestion (1987) **36**, 101-107.
23. Moller N, Petrany G, Cassidy D, Sheldon WL, Johnston DG and Laker MF: Effects of somatostatin analogue SMS 201-995 (sandostatin) on mouth-to caecum transit time and absorption on fat and carbohydrates in normal man. Clin Sci (1988) **75**, 345-350.
24. Lembcke B, Creutzfeldt W, Schleser S, Ebert R, Shaw C and Koop I: Effect of somatostatin analogue sandostatin (SMS 201-995) on gastrointestinal, pancreatic and biliary function and hormone release in normal men. Digestion (1987) **36**, 108-124.
25. del Pozo E, Schlueter K, Neufeld M, Tortosa F, Wendel L and Kerp L: Hormonal and biological profile of SMS 201 995, a new long-acting somatostatin analogue. Acta Endocrinol (Kbh) (1987) **54**, 124 129.
26. Chap Z, Ishida T, Chou J, Michael L, Hartley C, Entman M and Field JB: Effects of atropine and gastric inhibitory polypeptide on hepatic glucose uptake and insulin extraction in conscious dogs. J Clin Invest (1985) **76**, 1174-1181.
27. Hosokawa H, Ishida T, Daikuhara H, Iwamoto M, Amino Y, Nakanishi I, Watanabe K, Kawanishi K, Hartley CJ and Takahara J: The effect of $\alpha$ 2-agonist on glucose and insulin homeostasis. Ther Res (1992) **13**, 72-77.
28. Jenkins SA, Baxter JN, Corbert WA and Shields R: Effects of a somatostatin analogue SMS 201-995 on hepatic haemodynamics in the pig and on intravariceal pressure in man. Br J Surg (1985) **72**, 1009-1012.
29. Gomez-Pan A, Rodriguez-Arnao MD and del Pozo E: Advances in somatostatin research; in Dopamine and Neuroendocrine Active Substances, del Pozo E and Flueckiger F eds, Academic Press, London (1984) pp223-230.
30. Ishida T, Hosokawa H, Watanabe K, Kawanishi K, Matsusita K, Hartley CJ and Irino S: The role of glucagon on impaired hepatic glucose uptake after oral glucose in conscious dogs. Biomed Res (1988) (Suppl) **3**, 117 123.
31. Press M, Tamborlane WV and Sherwin R: Importance of raised growth hormone levels in mediating the metabolic derangements of diabetes. N Engl J Med (1984) **310**, 810-815.
32. Bratusch Marrain PR, Gasic S, Waldhausl WK and Nowotny P: The effect of growth hormone on splanchnic glucose and substrate metabolism following oral glucose loading in healthy man. Diabetes (1984) **33**, 19-25.
33. Ishida T, Rojdmark S, Bloom G, Chou MC Y and Field JB: The effect of somatostatin on the hepatic extraction of insulin and glucagon in the anesthetized dog. Endocrinology (1980) **106**, 220-230.
34. Wahren J, Efendic S, Luft R, Hargenfeldt L, Bjorkman O and Felig P: Influence of somatostatin on splanchnic glucose metabolism in postabsorptive and 60-hour fasted humans. J Clin Invest (1977) **59**, 299 237.


Received August 7, 1996; accepted November 5, 1996.