Neuroendocrinology 1995;61:112–116

Effects of Somatostatin on Human Satiety

Rob J. Lieverse[a]
Jan B.M.J. Jansen[b]
Ad A.M. Masclee[a]
Cornelis B.H.W. Lamers[a]

Departments of Gastroenterology and Hepatology, University Hospitals of
[a] Leiden and
[b] Nijmegen, The Netherlands

Abstract

Somatostatin (ST) inhibits gastrointestinal motility and exocrine and endocrine secretions. In animals, ST has been demonstated to decrease food intake. We investigated, in a randomized double-blind investigation in 10 healthy humans, the effects of an intravenous ST infusion compared to saline on subjective hunger feelings. After 1 h, a low dose of fat was given intraduodenally to induce the release of endogenous upper-intestinal satiety factors. Ninety minutes later sandwiches were served and eaten until satiation. In the first hour, when no intraduodenal fat was given, there was a significant decrease in feelings of hunger with ST ($p < 0.05$). During the intraduodenal fat infusion this pattern reversed with a trend towards less satiety with ST. Food intake during intraduodenal fat infusion tended to be higher during ST (305 ± 42 g) than during saline (205 ± 36 g) although not significantly. In the 5 h after the experiment hunger feelings were significantly less after ST. In conclusion, we found evidence for a satiety effect of ST in humans which reversed towards less satiety when intraduodenal intralipid, which presumably produced endogenous satiety factors, was given. Postmeal satiety is higher after ST.

Key Words
Somatostatin
Clinical neuroendocrinology
Satiety

Introduction

Somatostatin is a cyclic tetradecapeptide with a distribution throughout the nervous system, the gastrointestinal tract, and other parts of the body [1]. Among its actions are the inhibition of the release of several gastrointestinal peptides including gastrin [2], secretin [3], vasoactive intestinal polypeptide [4], cholecystokinin [5], and motilin [6], as well as insulin [7, 8] and glucagon [7]. In addition, somatostatin has been demonstrated to affect end-organ responses to selected stimuli in several animal species. For example, direct inhibition of human parietal cell secretion of acid [9, 10], pancreatic acinar cell secretion of enzymes [11], β-cell secretion of insulin [7], and primate resting lower esophageal sphincter pressure [12] have been reported. Furthermore, it has been demonstrated that exogenous ST inhibits motility functions in the human gastrointestinal tract [13]. In animals ST has been demonstrated to decrease food intake [14–16].

In the present study, we wanted to investigate the satiety effects of ST in humans, basally, during low-dose intraduodenal intralipid infusion which may induce release of gastrointestinal hormones without disturbing gastrointestinal motility, and postprandially.

Subjects and Methods

Ten healthy volunteers (5 M, 5 F, mean age 26) participated in this double-blind, randomized study. Informed consent was obtained from all subjects. The study was approved by the local ethics committee of the University of Leiden.

For every experiment each subject presented, after an overnight fast, at 8 a.m. at our research unit where a PVC Freka tube CH8 was introduced through one of the nostrils into the duodenum using a guide wire. After correct positioning as ascertained by fluoroscopy the guide wire was removed and the tube fixed to the nose. The following hour the volunteers accustomed to the intraduodenal tube and at 9 a.m. an intravenous catheter was placed into each forearm.

From one catheter blood was drawn from 9.15 a.m. (t(time) – 15 min) at 15-min intervals until the end of the study at 1 p.m. for deter-

Received:
February 28, 1994
Accepted after revision:
August 30, 1994

Prof. Dr. C.B.H.W. Lamers
Department of Gastroenterology and Hepatology
University Hospital
Building 1, C4-P, Rijnsburgerweg 10
NL–2333 AA Leiden (The Netherlands)

0028–3835/95/0612–0112
$8.00/0

mination of plasma CCK. The other catheter was used for infusion of saline or ST from 9.30 a.m. (t = 0 min) until 1 p.m. (t = 210 min).

At 9.30 a.m. (t = 0 min), the intravenous infusion of saline or somatostatin [14] (UCB, Brussels, Belgium, 125 μg/h after a loading dose of 125 μg) was started. This dose was given because we and others previously found that higher doses increased abdominal discomfort and nausea [13]. At t = 60 min the intraduodenal infusion of intralipid 20% (KabiVitrum®) 30 ml/h was started. From t = 60 min until the end of the infusion at t = 210 min 15 g intralipid was infused into the duodenum.

At noon (t = 150 min) identical sandwiches with 10 g margarine and 15 g cheese (3.33 kcal/g) were served and the volunteers were invited to eat until they were fully satiated. The amount eaten was carefully determined as was the duration of the meal. They were allowed to drink mineral water (without carbon dioxide) as wanted.

Basally and every 15 min hunger feelings, fullness feelings, prospective feeding intentions and wish to eat were scored as hunger parameters on 100-mm visual analogue scales as described by Blundell and Burley [17] and Silverstone [18].

The subjects were also asked to fill in these hunger scores at home after the experiment at 2, 3, 4, 5 and 6 p.m. to assess satiety.

As described by Hill [19] and modified to Dutch feeding customs, every 30 min from t = 0 min to t = 210 min, a list and photograph of 6 protein-rich, 6 fat-rich, 6 carbohydrate-rich items (the amount of each item on the photograph containing 200 kcal) and 6 low-energy items were presented. From each of these 24 items the subjects were asked if they wanted to eat the amount shown, double the amount, half the amount or nothing independent of the other items. At each time interval the total amount of caloric items was calculated (half the amount = ½ caloric item, double the amount is 2 caloric items). Also, the amount of protein, fat and carbohydrate items that the subjects wanted to eat was calculated independently. Plasma CCK was determined in one run using a sensitive and specific radioimmunoassay as has previously been described. The intra-assay variation was between 4.6 and 11.5% [20].

Results are expressed as means ± SEM. Statistical analysis of hunger feelings was performed by calculating the integrated area under the curve followed by Wilcoxon's test for paired results. These nonparametric tests were also used for the other comparisons.

Results

During the first 60 min, when no intraduodenal fat was given there was a significant decrease in hunger during ST infusion compared to saline ($p < 0.05$). The same trend was seen for the other hunger parameters (fig. 1, 2).

During the intraduodenal fat infusion this pattern reversed with a trend towards less satiety with ST (fig. 1, 2). There were no significant differences for the protein, fatty or carbohydrate-rich items. Food intake during the intraduodenal fat infusion was higher during ST (305 ± 42 g) than during saline (205 ± 36 g) although not significantly.

In the 5 h after the experiment, feelings for hunger, wish to eat and prospective feeding were significantly less after ST ($p < 0.05$) (fig. 3).

Mean basal plasma CCK was comparable in the saline (2.6 ± 0.1 p*M*) and ST experiment (2.9 ± 0.4 p*M*). In the first 60 min of the intravenous infusion ST induced a significant decrease in plasma CCK to 1.9 ± 0.2 p*M* ($p < 0.01$). During the intraduodenal fat infusion plasma CCK did not change anymore (fig. 4). In the saline experiment there was a significant increase in plasma CCK during the intraduodenal fat infusion to 4.8 ± 0.4 p*M* at t = 150 min ($p < 0.001$).

During the experiments no adverse effects were recorded, but 3 of the 10 subjects reported nausea in the afternoon after ST infusion.

Discussion

This study indicates that ST may also induce satiety in humans. We hypothesize that the reversal towards less satiety with ST compared to saline after the intraduodenal intralipid infusion may be explained by inhibition of endogenous satiety factors by ST.

In the first hour, when no intraduodenal fat was given, there was a trend to more satiety with ST for all parameters tested which reached significance for the hunger feelings ($p < 0.05$). During the low-dose intraduodenal fat infusion, which presumably induced the release of endogenous satiety factors, this pattern reversed with a trend (most clearly in the last 15 min) towards less satiety during ST and also food intake thereafter was nearly 50% higher during ST.

Cholecystokinin (CCK) may be an important endogenous satiety factor. In many studies in animals and humans it has been demonstrated that CCK decreases food intake [21–25]. We have shown that ST prevents the release of CCK during low-dose intraduodenal intralipid infusion. ST also prevents the release of other hormones, some of which may have satiety effects [1]. We hypothesize that the inhibition of the release of endogenous satiety factor during low-dose intraduodenal fat infusion is the mechanism whereby ST may decrease satiety and increase food intake in that period.

In animals ST has been demonstrated to decrease food intake [14, 15]. We have now shown that ST may also have satiety effects in humans, because hunger feelings were significantly less with ST in the first hour of our experiments and in the hours after the experiment. The mechanism whereby ST induces satiety may involve effects on gastrointestinal motility, gastrointestinal hormones or a direct effect of ST as a neurotransmitter or a satiety agent. It is also possible that ST acts by direct stim-

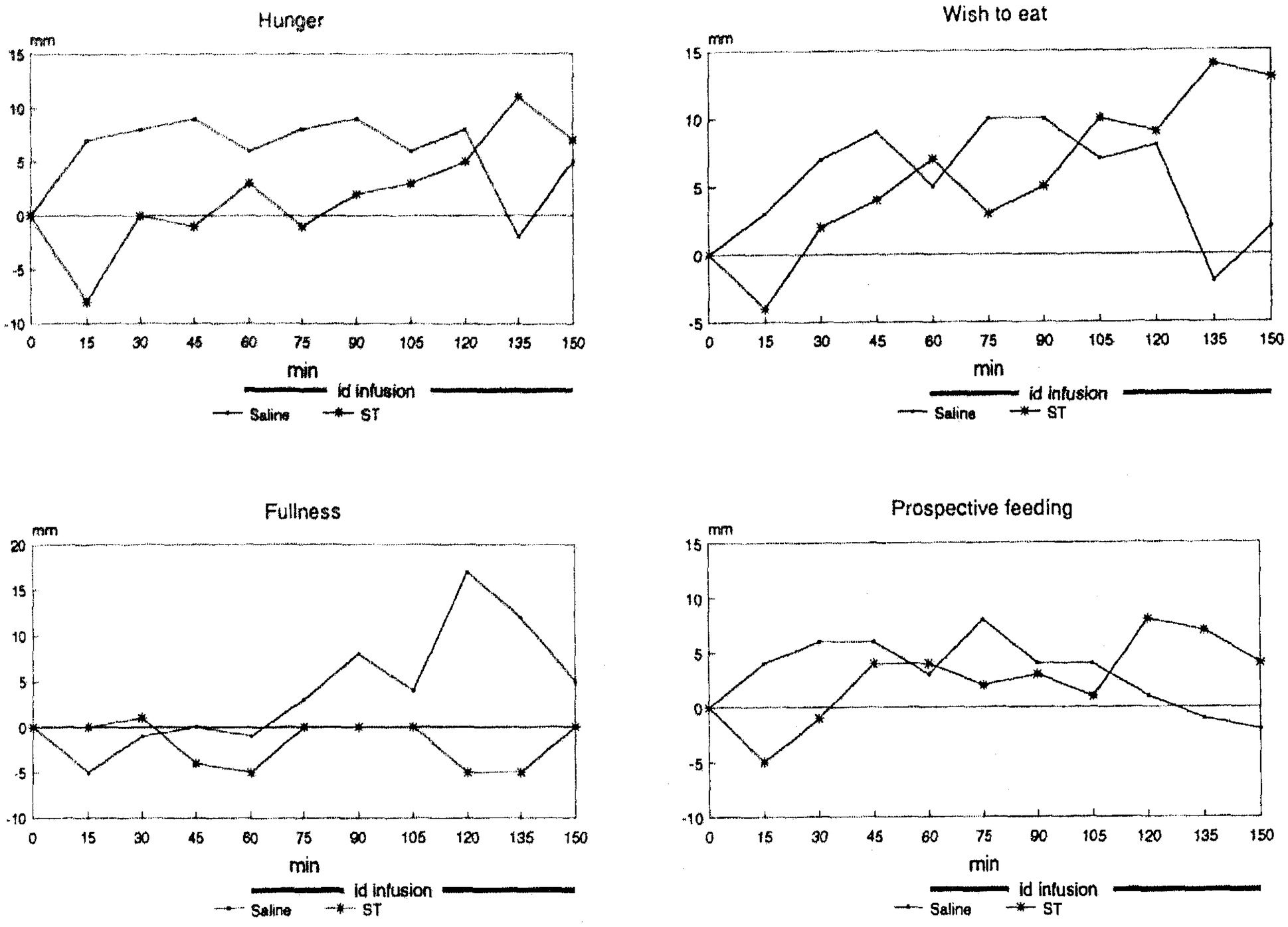

Fig. 1. Hunger, wish to eat, fullness and prospective feeding intentions during saline (dots point) or somatostatin (asterisk) (ST) infusion (a loading dose of 125 μg followed by 125 μg/h). Differences form basal are plotted. From t = 60 till t = 150 an intraduodenal infusion of 6 g intralipid 20%/h was given. Feelings of hunger were significantly less during the first 60 min of ST infusion ($p < 0.05$).

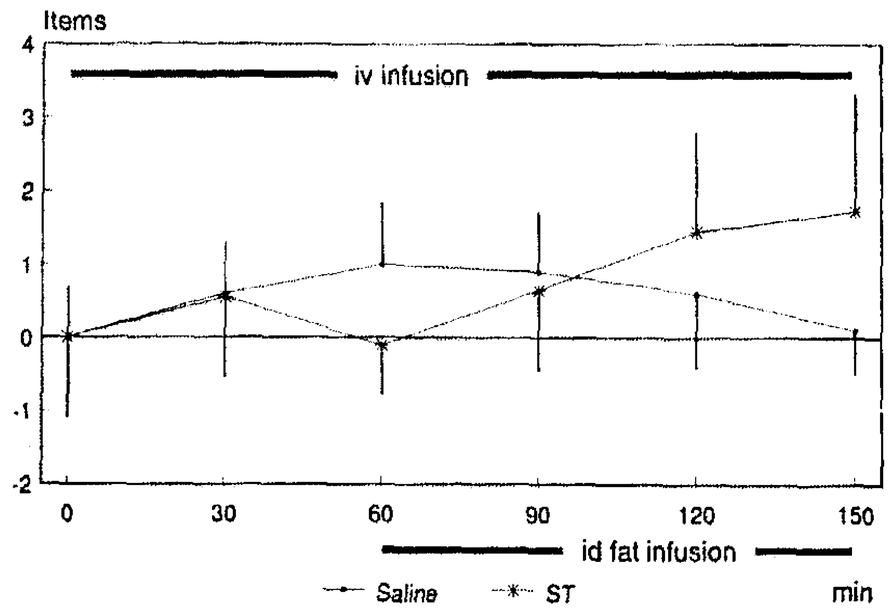

Fig. 2. Food selection. Wish to eat caloric items during saline (dots point) or somatostatin (asterisk) infusion (a loading dose of 125 μg followed by 125 μg/h). Differences from basal are plotted. From t = 60 till t = 150 an intraduodenal infusion of 6 g intralipid 20%/h was given.

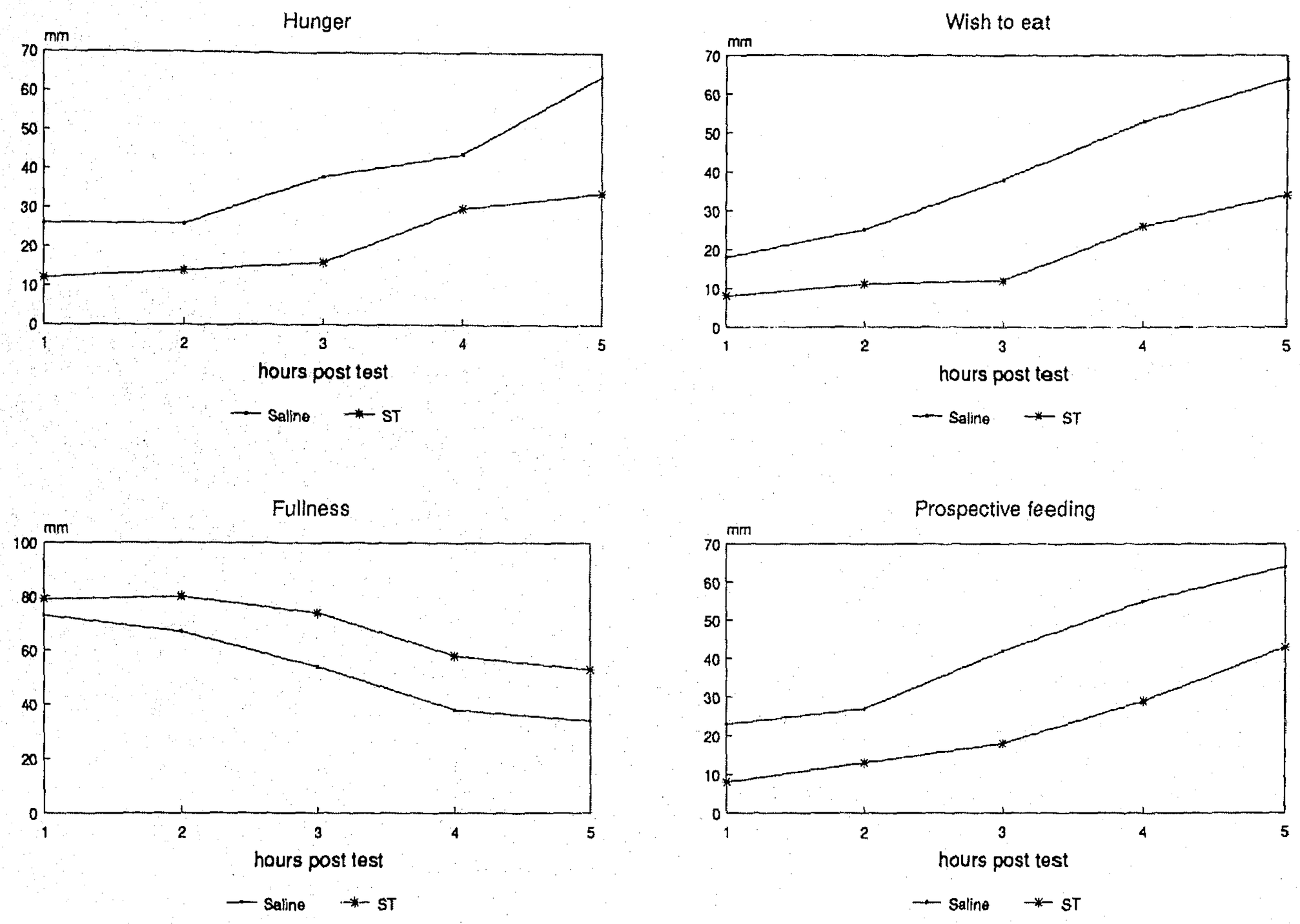

Fig. 3. Hunger, wish to eat, fullness and prospective feeding intentions in the hours after the saline (dots point) or somatostatin (asterisk) (ST) infusion (a loading dose of 125 μg followed by 125 μg/h). Differences from basal are plotted. Hunger, wish to eat and prospective feeding intentions were significantly less after ST ($p < 0.05$).

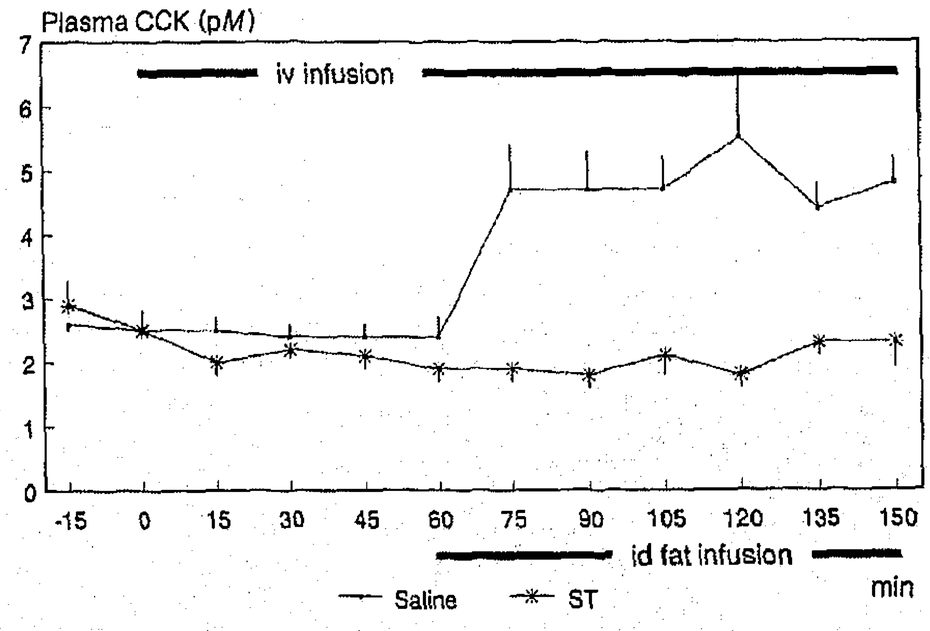

Fig. 4. Plasma cholecystokinin levels during saline (dots point) or somatostatin (asterisk) infusion (a loading dose of 125 μg followed by 125 μg/h).

ulation of digestive sensory endings or indirectly by interference with release or action of mediators of satiety. Interactions between ST and the cholinergic system on the one hand and with CCK on the other may also be involved [26]. Activation of the somatostatin receptor is linked with various guanine nucleotide binding proteins with different physiological actions [26]. ST's universal inhibitory effect is believed to be due to intracellular dephosphorylation of cellular proteins by phosphatases [26]. The final step in somatostatin action appears to be its ability to inhibit gene expression [26].

It has been demonstrated that the long-acting somatostatin analogue sandostatin (SMS) induces a threefold prolongation of mouth to cecum transit time [27, 28] and also ST dose-dependently prolonged intestinal transit time in man [13]. This disturbed motility may contribute to the satiety or even nausea-inducing effects of ST.

Also the interference with absorption of the meal may contribute to the satiety effects of ST after the meal [13, 28, 29] and the higher food intake may also have contributed to the prolonged satiety. In rats there is evidence that ST reduced feeding by a vagally mediated mechanism and that this decrease in food intake is not due to illness or malaise [14–16]. This is rather similar to the satiety effects of CCK which are also mediated through the vagus nerve [15].

In conclusion, we found evidence for a satiety effect of ST which reversed towards less satiety when a low dose of intraduodenal fat, which presumably induced endogenous satiety factors, was given. Postmeal satiety is higher after ST.

References

1 Arnold R, Lankisch PG: Somatostatin and the gastrointestinal tract. Clin Gastroenterol 1980; 9:733–753.
2 Bloom SR, Mortimer CH, Torner MO, et al: Inhibition of gastrin and gastric-acid secretion by growth-hormone release-inhibiting hormone. Lancet 1947;ii:1106–1109.
3 Boden G, Sivitz M, Owen OE: Somatostatin suppresses secretin and pancratic exocrine secretion. Science 1975;109:163–174.
4 Besser GM: Clinical implications of growth hormone release inhibiting hormone (GH-RIH); in Labrie F (ed): Hypothalamus and Endocrine Functions. New York, Plenum, 1979, pp 115–125.
5 Schlegel W, Raptis S, Dollinger HC, Pfeiffer EF: Inhibition of secretin, pancreozymin and gastrin release and their biological activities by somatostatin; in Bonfils S, Fromageot P, Rosselin G (eds): Hormonal Receptors in Digestive Tract Physiology. Amsterdam, Elsevier/North Holland, 1977, pp 361–377.
6 Bloom SR, Ralphs DN, Besser GM, et al: Effect of somatostatin on motilin levels and gastric emptying (abstract). Gut 1975;16:834.
7 Alberti KGMM, Christensen SE, Iversen J, et al: Inhibition of insulin secretion by somatostatin. Lancet 1973;ii:1299–1301.
8 Koerker DJ, Ruch W, Chideckel E, et al: Somatostatin: Hypothalamic inhibitor of the endocrine pancreas. Science 1974;184:482–484.
9 Arnold R, Kobberling J, Track NS, Creutzfeldt W: Lowering of basal and stimulated serum immunoreactive gastrin and gastric secretion in patients with Zollinger-Ellison syndrome by somatostatin. Acta Endocrinol (Copenh) 1975; 193(suppl):75.
10 Rapits S, Dollinger HC, von Berger L, Schlegel W, Schroder KE, Pfeiffer EF: Effects of somatostatin on gastric secretion and gastrin release in man. Digestion 1975;13:15–26.
11 Creutzfeldt W, Lankisch PG, Folsch UR: Hemmung der Sekretin- and Cholezystokinin-Pankreozymin-induzierten Saft- und Enzymsekretion der Pankreas- und der Gallenblasenkontraktion beim Menschen durch Somatostatin. Dtsch Med Wochenschr 1975;100:1135–1138.
12 Bybee DE, Brown FC, Geoges LP, Castell DO, McCuigan JE: Somatostatin effects on lower esophageal sphincter function. Am J Physiol 1979;237:E77–81.
13 Johansson C, Wisén O, Efendić S, Uvnäs-Wallensten K: Effect of somatostatin on gastrointestinal propagation and absorption of oral glucose in man. Digestion 1981;22:126–137.
14 Lotter EC, Krinsky R, McKay JM, Treneer CM, Porte D Jr, Woods SC: Somatostatin decreases food intake of rats and baboons. J Comp Physiol Psychol 1981;5:278–287.
15 Levine AS, Morley JE: Peripherally administered somatostatin reduces feeding by a vagal mediated mechanism. Pharmacol Biochem Behav 1982;16:897–902.
16 Lin MT, Chen JJ, Ho LT: Hypothalamic involvement in the hyperglycemia and satiety actions of somatostatin in rats. Neuroendocrinology 1987;45:62–67.
17 Blundell JE, Burley VJ: Satiation, satiety and the action of fibre on food intake. Int J Obes 1987;11:9–25.
18 Silverstone T: Measurement of hunger and food intake in man; in Silverstone T (ed): Drugs and Appetite. London, Academic Press, 1982, pp 81–92.
19 Hill AJ: Investigation of short-term influence on hunger, satiety and food consumption; thesis, Leeds University, 1987.
20 Jansen JBMJ, Lamers CBHW: Radioimmunoassay of cholecystokinin in human tissue and plasma. Clin Chim Acta 1983;131:305–316.
21 Linden A: Role of cholecystokinin in feeding and lactation. Acta Physiol Scand 1989; 585(suppl):I–VII, 1–49.
22 Smith GP: The therapeutic potential of cholecystokinin. Int J Obes 1984;(suppl 1):35–38.
23 Stacher G, Steinringer H, Schmiere G, et al: Cholecystokinin octapeptide decreases intake of solid food in man. Peptides 1982;1:133–136.
24 Kissileff HR, Pi-Sunyer X, Thornton J, Smith GP: C-terminal octapeptide of cholecystokinin decreases food intake in man. Am J Clin Nutr 1981;34:154–160.
25 Pi-Sunyer X, Kissileff HR, Thornton J, Smith GP: C-Terminal octapeptide of cholecystokinin decreases food intake in obese man. Physiol Behav 1982;29:627–630.
26 Chiba T, Yamada T: Gut somatostatin; in Walsh JH, Dockray GJ (eds): Gut Peptides: Biochemistry and Physiology. New York, Raven Press, 1993, pp 123–145.
27 Fuessl HS, Carolan G, Willims G, Bloom SR: Effect of a long-acting somatostatin analogue (SMS 201-995) on postprandial gastric emptying of ^{99m}Tc-Tin colloid and mouth-to-caecum transit time in man. Digestion 1987;36:101–107.
28 Lembeke B, Creutzfeldt W, Schleser S, Ebert R, Shaw S, Koop I: Effect of the somatostatin analogue sandostatin (SMS 201-995) on gastrointestinal, pancreatic and bililary function and hormone release in normal men. Digstion 1987;36:108–124.
29 Kreis GJ, Bovine R, Raskin P: Effect of intravenous somatostatin on jejunal absorption of glucose, amino acids water and electrolytes. Gastroenterology 1980;78:26–31.