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# Somatostatin

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## 1. General

Somatostatin (SS), also known as somatotrophin release inhibitory factor, was originally described by Krulich (74) as a factor present in hypothalamic extracts capable of inhibiting growth hormone (GH) release by cultured rat anterior pituitary cells. A few years later, Brazeau (16) characterized this factor as a cyclic peptide consisting of 14 amino acids (SS14). Seven years later, a second bioactive form of SS, an $NH_2$-terminally extended somatostatin molecule, consisting of 28 amino acids (SS28), was isolated and characterized (109). Further research on this newly discovered SS-14 peptide indicated that it was present not only in the hypothalamus, but also throughout the central nervous system, in peripheral nerves and in other tissues including those of the gastrointestinal tract, pancreatic islets and thyroid. Interestingly, it was found that tissue targets of SS action were often the same tissues as those in which it was localized. In light of these findings, the concept arose that SS, besides acting effectively as an endocrine hormone, could be regionally limited as a neuroendocrine factor or in other tissues, as an autocrine or paracrine regulator (115).

Somatostatin cDNAs from the anglerfish, catfish, rat, mouse and human have been isolated and sequenced (41, 42, 59, 90, 136). In mammals, both SS-14 and SS-28 originate from an approximate 10.3 kDa prohormone called pre-prosomatostatin (4, 9). Two more neuropeptides related to this pro-form but of unknown hormonal role have been identified: one of 12 amino acids which is the N-terminal of SS-28 (SS-28 (1-12) (7) and the other peptide of 76 amino acids whose C-terminal end is the 12 amino acids preceding the 8 kDa SS-28 (1-12) (8). To process this somatostatin precursor, Morel described an enzyme named SS-28 convertase, present in the rat cortex and able to convert a 15 kDa precursor peptide into SS-28 (1-12) and SS-14 (19, 91). One year later, these same authors described an aminopeptidase II associated with the SS-28 convertase that can liberate SS-14 (47).

The SS-14 peptide has been characterized in different organs of many species including ovine and porcine hypothalamus (16, 128), pigeon (145), anglerfish (98) and rat (6) pancreas with all having the same primary structure. The hormone has been localized and quantified by RIA in many structures of the central nervous system, in the pituitary and in most organs of the gastrointestinal system (102). Within the GI tract and pancreas, D

cells containing SS have been demonstrated in the fundus and antral areas of the stomach and the islets of Langerhans, whereas a more scattered distribution has been shown in the small and large intestine (133). In the stomach of rat and human, the somatostatin immunoreactive cells have long, non-luminal processes extending from the epithelium along the basement membrane of the glands. These processes come into contact with many different glandular epithelial cells. In the stomach, many of these processes ended on G cells in the antrum as well as on the parietal cells in the oxyntic mucosa. In the pancreas, somatostatin cells are present in the neighbourhood of the other endocrine cells and the D cells processes are therefore thick and short (78). In the pancreas, soon after SS discovery in the hypothalamus, Orci had identified the pancreatic D cells containing somatostatin by immunoflurorescence in the pigeon (100). These somatostatin pancreatic D cells locations have also been confirmed in the six following different species: the calf, pig, horse, dog, rat and human by immunohistochemistry and image analysis by confocal microscopy (95).

Studies on the ontogeny of the four pancreatic islet hormones have been limited to few mammalian species, namely the rat, human, sheep and pig (3, 79, 113, 165). In the rat (87), the pancreatic somatostatin contents increased constantly from fetal to adult age with values in the low thousands (4 to 8) early up to 71,000 in the adult. When expressed in ng/organ (46), similar variations were also observed in the rat pancreas. However, the percentage of somatostatin-positive cells in the rat islet remains quite stable over time, at 13, 10 days after birth down to 6 in the adult islets (86).

## Regulation of Somatostatin Secretion

The proximity of the D-cells in the pancreatic islets and GI tract to their target cells favors a local or paracrine function and has fostered doubts regarding their hormonal status. To establish such a hormonal status, it had to be demonstrated that when SS is infused it produces a rise in plasma SLI levels comparable to physiological levels observed after a meal. In humans, doses of 31 and 61 pmol $kg^{-1}$ $h^{-1}$ SS-14 produced increments in plasma SLI of 4 and 7 pM, comparable to a value of 4 pM after a meal (53). In another study in humans, fasting SLI levels of 8 pg $ml^{-1}$ in volunteers rose to 18 and 20 pg $ml^{-1}$ at 60 and 120 min, respectively, after a meal; this rise approximates that produced by infusing SS-14 at 2 µg $h^{-1}$. Such data supports a hormonal role for somatostatin in man (168). Similar increases in plasma SLI were observed in dog after the intraduodenal instillation of a 20% liver meal (5 ml $min^{-1}$). Such rises in pancreatic vein SLI were not reduced after truncal vagotomy or during atropine infusion (131). The individual dietary components, glucose, fat and casein hydrolysate instilled in the GI tract of anaesthetized dogs stimulated SLI release from the pancreas and stomach (130). Among the organs responsible for SLI released into dog plasma, under basal conditions, the pancreas is responsible for 521 pg/$min^{-1}$ and the GI tract for 8088 pg $min^{-1}$, indicating a rather small contribution from the pancreas. In response to isoproterenol, a beta-adrenergic agonist, SLI output from the pancreas increases by 684 pg $min^{-1}$ and that from the GI tract by 23,911 pg $min^{-1}$, thus indicating that the pancreas was a minor source of circulating SLI (153). These data suggest that circulating plasma SLI levels should not be used as an index of secretory activity of the pancreatic D cells.

Among the positive releasers of somatostatin in addition to the components of a normal diet, is the supradiaphragmatic vagal trunk which when stimulated at different frequencies of 1.5 up to 12 cps, caused increases in portal SLI blood levels with a maximum release of 2524 pg-min $ml^{-1}$ for 6 cps (52). However, this rise happened 10 min after the end of stimulation suggesting it might not be a direct effect of vagal stimulation. Dissection of the results of the vagal nerve stimulation on blood SLI release seems to indicate that vagal

nerve stimulation increased pancreatic and extrapancreatic SLI in the dog. Non-muscarinic mechanisms likely mediate the vagally-induced extrapancreatic SS secretion, whereas pancreatic SLI responses are under both the muscarinic and non-muscarinic mechanisms, possibly peptidergic (1). Direct acetylcholine infusion at a dose of 0.5 μg $kg^{-1}$ $min^{-1}$ for 10 min in the cranial pancreaticoduodenal artery of anesthetized dogs caused a prompt increase of plasma SLI levels in the cranial pancreaticoduodenal vein, an effect abolished by prior local infusion of atropine at a dose of 5 μg $kg^{-1}$ $min^{-1}$ (69). These data support a stimulating role of the parasympathetic nerves in the regulation of pancreatic SLI release.

Besides control of by the adrenergic and muscarinic systems, the secretion of gastrointestinal SLI is also influenced by a number of gastrointestinal hormones. Exogenous cholecystokinin (CCK) has been reported to increase systemic levels of SLI (57,123). In the baboon, CCK-8 infusion for 5 min at 1, 2 and 4 μg $kg^{-1}$ i.v., all resulted in significant elevations in peripheral plasma SLI from a basal level of 200 pg $ml^{-1}$ to 268, 265 and 263 pg $ml^{-1}$, respectively (36). In isolated rat pancreatic islets, glucose at 11.1 mM significantly enhanced somatostatin release in response to 10 nM CCK- 8 (166). In this same system, 11.1 mM glucose significantly increased SS secretion when CCK-8 reached 1 nM in the medium. This relatively weak secretory effect of CCK-8 on somatostatin release is in line with data obtained from the infused dog pancreas (62). Such amounts of SLI released may not rule out a role for CCK on the pancreatic D cells but in vivo the major part of CCK-mediated SS release comes from the fundic mucosal cells (142) and other GI sources. In one study, bombesin perfused into the isolated canine pancreas did not affect somatostatin release (64). Using this same model, it was demonstrated that VIP infused at 50 ng $ml^{-1}$ for 9 min resulted in a 2-3 fold increase in SS release. In situ, VIP could operate through VIP-containing nerve fibers and endocrine cells (63). The Unger group also demonstrated that infusion of prostaglandin $E_2$ in anesthetized dogs elicited a greater than two-fold rise in pancreatico-duodenal vein SLI (132). Starvation was associated with reduced basal SS release from an isolated perfused rat pancreas from 33 pg $ml^{-1}$ in the fed to 15 pg $ml^{-1}$ in the 48-h fasted rat. However, when arginine-induced somatostatin response is expressed as the sum of increment above the basal level, SS secretion in 48-h fasted rats is significantly greater than that in the fed rats (134). Under similar conditions, it was shown that the decrease in basal SS was associated with an increased tissue level, thus suggesting the possibility of reduced secretion (135).

In fasted states in the human (155) and dog (26), the GI tract exhibits motor activity called the interdigestive contractions or phase III of the interdigestive myoelectric complex. These contractions occur after a post-prandial interval and they are of fixed duration and occur at regular intervals. Somatostatin given at pharmacological doses inhibited the regular occurrence of the contraction in the stomach and upper intestine, but not in the lower intestine (101). In the dog, plasma SLI levels were higher during the gastric interdigestive contractions (GIC) and lowest at 60 and 80 min after cessation of the GIC. This observed SLI increase can be obtained by exogenous motilin, a known stimulus of GIC when infused at a physiological dose of 0.1 μg $kg^{-1}$ $h^{-1}$ during the period in which plasma SLI levels were low. These variations in plasma SLI concentrations seem to be involved in this regulation of GIC and suggest an interrelationship between motilin and somatostatin (2).

## Intracellular Mode of Action of Somatostatin

Different types of action have been classically postulated to be involved in the transduction of the somatostatin message within the target cell. Among the first systems described was the decrease in cAMP production through inhibition of adenylate cyclase (21). Such an adenylate cyclase inhibition led to inhibition of cyclic AMP-

dependent protein kinase activity (22). Besides its effect on adenylate cyclase, somatostatin from 0.01 to 1 µM increased the activity of phosphodiesterase (PDE) in a GH4C1 cell homogenate only when $Ca^{2+}$ and calmodulin were added to the medium. Such an effect on PDE activity can thus reinforce SS-14 inhibitory effects on the cyclase (154). It was also reported that somatostatin can enhance the activity of guanylate cyclase and thus the production of cGMP. This effect was seen not only in the anterior pituitary but also in the pancreas, stomach, liver and small intestine at physiological concentrations with an inhibitory effect at high concentrations (157).

Besides its action on the adenylate cyclase system, somatostatin has been shown to be involved in the inhibition of $Ca^{2+}$ cellular influx (116) and activation of a phosphoprotein phosphatase (118). With $Ca^{2+}$ mobilisation known to be mediated by activation of membrane phosphoinositide (InsPs) turnover (85), somatostatin was therefore suspected to inhibit PTdinositol 3-kinase to control stimulated exocrine and endocrine secretions as well as cell growth. In rat pancreatic acini, somatostatin 10 nM inhibited basal $InsP_1$, $InsP_2$ and $InsP_3$ production respectively, as well as bombesin-stimulated $InsP_3$ formation (82). In some instances, the effects of somatostatin on its target cells may depend on the type of somatostatin receptor present on these cells. Indeed, instead of observing the usual inhibition, occupation of the somatostatin SST5 receptor by SS-14 and SS-28 on Chinese hamster ovary K1 cells activated phosphoinositide metabolism (161). Activation of phosphoprotein phosphatase by somatostatin was also observed in the liver, pancreas, gastric fundus, small intestine and colon, suggesting that protein dephosphorylation could account for some of the physiological effects of somatostatin in the digestive tract (117). This effect of somatostatin on activation of a phosphoprotein phosphatase was later challenged at least in the liver since somatostatin dose-dependently (1 to 16 µg $ml^{-1}$) inhibited this enzyme partially purified from rat liver with a maximal inhibition of 60% at the highest dose of 16 µg $ml^{-1}$ (154). It is thus possible that inhibition of the phosphatase activity occurs with occupation of the high affinity sites of the receptor while binding to the low affinity sites would result in its activation (117).

The cellular mechanisms by which hormones and growth factors trigger their mitogenic or antimitogenic signals are much more understood these days than they were years ago. Among the early events stimulated by mitogenic agents are activation of MAP kinases (24), rapid and transient expression of the proto-oncogenes c-fos, c-jun, c-myc and H-ras (18), activation of tyrosine kinase, phosphatidylinositol 3-kinase, phospholipase D (122) and decrease in tyrosine phosphatase (121). In MIN6 cells, growth was significantly inhibited by somatostatin 100 nM and 1 µM with early decreases in MAP kinase activity and c-fos expression (164). In the neuroblastoma cell line (SY5Y), BIM23014, a somatostatin analogue, at 1 nM, completely inhibited the MAP kinase activation induced by both IGF-1 and carbachol (24). In rats, in response to iv infused caerulein, particulate tyrosine kinase and phosphatase (PTase) exhibited sustained increases. SMS alone at 5 µg $kg^{-1}$ $h^{-1}$ caused transient increases in partriculate and crude cytosolic PTase activites during its first hour of infusion with concomitant decreases in particulate and crude cytosolic TRK activities. The transient stimulatory effect of SMS on PTase activity may suggest a role in the early event associated with negative control of proliferation (121). In rats with pancreatic juice diverted, the increases in membrane tyrosine kinase, phospholipase D and PTdinositol 3-kinase activities were all inhibited by SMS infused at 5 µg $kg^{-1}$ $h^{-1}$; a similar inhibition was observed using pancreatic acini. These data identified three important enzymes involved in the growth control of the pancreas, all inhibited by somatostatin (122).

## Actions of Somatostatin

In order to understand how somatostatin-14 and -28 affect their numerous target organs, one has to know that these two hormones operate through six different receptors, all part of a family of G-protein coupled receptors: SSTR1 to 5 with the SSTR2 subtype existing as SSTR2a and SSTR2b (103,104). Even though somatostatin-28 binds to each of the SSTR-14 receptors with less affinity than SS-14, a specific SS-28 receptor was cloned from a rat brian cDNA library (88). With a half-life of about 1.88 min for SS-14 determined in human plasma by RIA, it became important to synthesize analogs of longer stability for use as clinical tools for humans and animals (11). Such analogs were indeed synthesized and are presented in **Table 1** (104).

Because of its topographical distribution in the organism, somatostatin is capable to exert its different effects in various ways. This peptide can act as a neurotransmitter and/or neuromodulator via its presence in or release from peptidergic or adrenergic nerve endings (60,61). The accumulation of somatostatin containing D cells at various levels within the gastrointestinal tract and pancreas provides an ideal basis for regulatory functions in digestive, absorptive and metabolic events. Somatostatin can therefore affect the cells located in close vicinity to the D-cells in some organs or be released into the circulation and thus acts as an endocrine hormone.

When infused iv, somatostatin can be a potent inhibitor of ACTH, STH and TSH release (10,34,138), gastric acid secretion (12), gastric emptying (13), duodenal motility (14), pepsin secretion (49), the release of gastrin (12), motilin (13), secretin (55), GIP (107), CCK (129), GLI (125), gallbladder contraction (27), the absorption of glucose (159), triglycerides (108) and amino acids (48) and interfere with splanchnic blood blow (68). Release of the pancreatic endocrine hormones has also been inhibited by exogenous somatostatin: insulin (44), glucagon (45) and pancreatic polypeptide (38).

## 2. Effects of Somatostatin on the Pancreas

### In vivo studies

The interdigestive pancreatic secretion in dogs (149) and humans (81) was inhibited by somatostatin and its analog octreotide (SMS 201-995).

**Table 1. Structure of somatostatin and its analogues**

| | | |
|---|---|---|
| 1. Somostatin-14 | : | Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp<br>Cys-Ser-Thr-Phe-Thr-Lys |
| 2. Somatostatin-28 | : | Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp<br>Cys-Ser-Thr-Phe-Thr-Lys |
| 3. SMS 201-995 Octreotide | : | D-Phe-Cys-Phe-D-Trp<br>(ol)Thr-Cys-Thr-Lys |
| 4. RC-160 | : | D-Phe-Cys-Tyr-DTrp<br>Trp-Cys-Val-Lys |
| 5. L 362,855 | : | Aha-Phe-D-Trp-Lys-Thr-Phe |
| 6. BIM 23027 | : | Met-Ala-D-Tyr-Trp-Lys-Abu-Phe |
| 7. BIM 23056 | : | D-Phe-Phe-D-Tyr-Tyr-Lys-Val-D-Phe-Nal |
| 8. BIM 23014 | : | DβNal-Cys-Tyr-DTrp<br>Thr-Cys-Val-Lys |

The observation that somatostatin immunoneutralization increased basal volume and amylase output in an isolated rat pancreas model, suggests an intrapancreatic source of somatostatin. This pancreatic somatostatin could therefore cause a tonical inhibition of exocrine pancreatic secretion (97). In conscious rats with bile and pancreatic secretions returned to the intestine, iv somatostatin (5 µg $kg^{-1}$ $h^{-1}$) inhibited basal pancreatic protein and fluid secretion by 84 and 64%, respectively; addition of atropine ip (500 µg $kg^{-1}$ $h^{-1}$) did not cause further inhibition (51). In anesthetized rats, basal secretion of amylase was significantly inhibited by an infusion of somatostatin at a relatively high dose of 100 µg 100 $g^{-1}$ $h^{-1}$. However, when given as a bolus injection of 50 µg 100 $g^{-1}$ BW, amylase release increased fourfold for 20 min (39). In a previous study (25), somatostatin given at doses of 0.4 to 25 µg $kg^{-1}$ $h^{-1}$ to conscious fistula rats resulted in dose-dependent decreases in basal flow, bicarbonate and protein releases. At the highest doses, protein output was reduced by 80%, bicarbonate by 63% and flow by 42%. In urethane anesthetized rats, an initial increase in all pancreatic parameters was observed in the first two minutes, followed by a 30 to 40% decrease in protein output. In such conditions, somatostatin had to reach the dose of 100 µg $kg^{-1}$ $h^{-1}$ to affect basal bicarbonate release. These data on basal pancreatic secretion of fluid and proteins indicate that the inhibitory effect of somatostatin seems species specific and sensitive to anesthesia, as previously shown (17). When rats were infused intraduodenally with SS-14 at doses from 12 to 96 µg $kg^{-1}$ $h^{-1}$, basal total volume and protein outputs were not affected; these results could indicate that luminal duodenal somatostatin does not influence basal pancreatic secretion directly or through basal release of CCK and secretin (126). Contrary to the rat, the iv infusion of SS-28 at 400 ng $kg^{-1}$ $h^{-1}$ totally inhibited basal fluid and protein secretion in the conscious dog (147). Also in dogs prepared with gastric and pancreatic fistulae, somatostatin-14 at 2.5 µg $kg^{-1}$ $h^{-1}$ inhibited basal volume and protein outputs by more than 90% (146).

In humans, pancreatic stimulation by intraduodenal administration of tryptophan or a mixture of amino acids was attenuated by exogenous SS-28 (58). In other studies in man, octreotide inhibited postprandial pancreatic enzyme secretion (81). In the dog, SS-14 given as

iv bolus at 3.5 µg kg-$^{1}$ followed by infusion at 3.5 µg kg$^{-1}$ h$^{-1}$ caused significant reductions of the duodenal activities of trypsin and amylase during a test meal stimulation (70). In the rat, octreotide significantly inhibited pancreatic volume, bicarbonate, amylase and serum levels of secretin and CCK in response to intraduodenal oleic acid, a CCK releaser (137).

In healthy volunteers (30), pure pancreatic juice was obtained by endoscopic cannulation of the main pancreatic duct. In response to synthetic secretin (0.06 CU kg$^{-1}$ h$^{-1}$), bicarbonate concentration in pancreatic juice reached levels of 117 µEq ml$^{-1}$ after 10 min and a juice flow of 7.3 ml/5 min after 15 min of secretin infusion. SS-14 led to a decrease of 47% in pancreatic flow rate after 10 min and of 67% after 15 min. Bicarbonate and protein concentrations in pancreatic juice showed only a tendency to decrease at the somatostatin dose of 5 µg kg$^{-1}$ h$^{-1}$. Also in humans, pancreatic enzyme secretion, but not bicarbonate secretion, stimulated by secretin (250 ng kg$^{-1}$/20 min) and caerulein (25 ng kg$^{-1}$/20 min) was inhibited by SMS 201-995 in a dose-independent manner (73). In conscious dogs (147), secretion of fluid and bicarbonate stimulated by secretin (1 CU kg$^{-1}$ h$^{-1}$) were slightly affected by larger doses of SS-28 (400 ng kg$^{-1}$ h$^{-1}$). At the same dose, protein output stimulated by caerulein was significantly inhibited. In anesthetized rats, linear somatostatin-14 given at 100 µg/100 g$^{-1}$ h$^{-1}$ caused a strong inhibition of pancreatic amylase and trypsin releases stimulated by 3 IVY dog units/100 g$^{-1}$ h$^{-1}$ of CCK with a rapid rebound of these secretions once the somatostatin infusion was terminated (39). In conscious rats with pancreatic juice diversion (51) which caused strong increases in protein and fluid secretions, all five doses of infused octreotide (5,20,80,320 and 1280 ng kg$^{-1}$ h$^{-1}$) significantly inhibited both protein and fluid secretion with $IC_{50}$ of 40 and 60 ng kg$^{-1}$ h$^{-1}$, respectively. Maximal protein and fluid inhibition reached 90% and 75% respectively, at the dose of 1.28 µg kg$^{-1}$ h$^{-1}$. SS-14 when compared to its analog octreotide had an $IC_{50}$ of 0.7 µg kg$^{-1}$ h$^{-1}$ for protein secretion and 1.2 µg kg$^{-1}$ h$^{-1}$ for fluid secretion, with a maximal inhibitory effect obtained at 25 µg kg$^{-1}$ h$^{-1}$ for both protein and fluid secretion. These data indicate that octreotide is 20 times more potent than SS-14 in inhibiting pancreatic protein and volume secretion stimulated by pancreatic juice diversion.

## In vitro studies

Pancreatic enzyme and fluid secretion in vivo is the sum of numerous complex physiological processes that include interplay of endocrine and paracrine hormones as well as neurotransmitter stimulation and release. Because of these multiple interactions, it is often difficult to assess whether a compound that inhibits pancreatic secretion in vivo affects acinar and ductal cell functions directly or alters the release of secretagogues. Therefore, the isolated perfused pancreas, the isolated acinar and ductal cell preparations and cell cultures of both cell types can give answers to some of these questions.

Rat pancreatic acinar cells possess receptors specific for somatostatin-14 and 28 (124,166) which remain present after the cell preparations (40). It has also been reported that in the isolated perfused dog pancreas, the gland can take up to 50-80% of somatostatin perfused over a concentration range of 20 to 4000 pg ml$^{-1}$ compared to less than 21% of insulin or glucagon (71). This observation was later confirmed with extraction of SS-14 by the *in situ* dog pancreas averaging greater than 50% compared to less than 17% for glucagon (152). All these observations let us believe that somatostatin should be able to inhibit directly neural or hormonal stimulated pancreatic enzyme secretion in vitro using the above cited cell preparations.

In spite of many studies, the inhibitory effect of SS-14 and SS-28 on stimulated enzyme release from isolated pancreatic acini is still controversial. To understand some of these opposite results, it may help to make a distinction between effect of SS on stimulation where the agonist such as VIP

works through cAMP, where the SS inhibits and agonists such as CCK where some investigators observed an inhibitory effect and others not. In perfused guinea pig acini, the kinetic profile of amylase release in response to VIP was significantly decreased by SS (100 nM) (140). On the other hand, octreotide (100 nM) significantly inhibited synergistic amylase release stimulated by secretin + CCK-8 or by VIP + CCK-8 (65). Somatostatin also inhibited the effect of cAMP on calcium-induced amylase secretion from rat pancreatic acini by shifting the dose-response curve to the right (99), another example of SS acting through the cAMP pathway.

Many other studies however clearly show that somatostatin has no inhibitory effects on the exocrine pancreas in vitro, whether it be on the isolated perfused pancreas, the isolated acini or the isolated lobule preparations in which CCK was the stimulus (65,96,99,139,158). In isolated rat pancreas (43), exogenous insulin (10 mU $ml^{-1}$) significantly potentiated CCK and carbachol-stimulated amylase secretion, a potentiation significantly inhibited by SS. The lack of a direct inhibitory effect of SS was also observed in isolated canine parietal cells (106). Indeed, SS at 1 µM failed to inhibit the gastric secretory response to histamine, methacholine and pentagastrin, supporting some of the above-mentioned data. Interestingly, SS-28 at the high concentration of 10 µM was able to stimulate amylase release from guinea pig pancreatic acini to about 68% of that stimulated by 100 pM caerulein. A maximal secretory response identical to that initiated by caerulein was also obtained by two SS-28 analogs, Nat $S_{1-28}$ and [$Nle^{8}$]SS28. Under these conditions, SS-14 had no stimulatory effect (33). As an explanation for this secretory effect of SS-28 on acini, it was proposed that SS-28 can interact with the CCK receptor at high concentrations (34), an effect inhibited by DBcGMP, a CCK receptor antagonist (105). On the other hand, the failure of SS-14 to inhibit stimulated enzyme secretion from isolated acini may result in the release into the incubation medium of an active protease, first observed in the secreted pancreatic juice, and able to degrade SS-14 (127). This serine protease was purified to homogeneity from rat pure pancreatic juice. With a MW of approximately 29 kDa, it corresponds to the rat pancreatic elastase II. Therefore, if secreted into the incubation medium, it would degrade SS-14 and prevent any of its inhibitory effects and thus partly explain why SS-14 was unable to show its inhibitory effects on enzyme release *in vitro* (151). It may also affect the secretory response to SS-28 at lower concentrations in the incubation medium. Another possibility could be that cell calcium-mobilizing agents decrease the affinity of acinar cell somatostatin receptors for somatostatin (33).

## Effects on Growth

Normal growth of an organism results in a complex balance of the hormones involved, such as growth hormone, insulin and thyroid hormones. Since somatostatin can inhibit release of many hormones, its neutralisation should stimulate their secretion and thus increase growth. This approach of auto-immunisation against somatostatin to stimulate growth has been tested in lambs. When significant antibody titers were obtained, the rate of weight gain was greater in SS immunized animals and accompanied by increased height. In these immunized lambs, there was a greater growth hormone response to arginine stimulation as well as basal higher blood levels of somatomedin (143). These data were later confirmed also in this species (75). When given to rats implanted subcutaneously with an Alzet mini-pump, somatostatin delivered at 1.5 µg $h^{-1}$ for 14 days had no effect on their weight gain. However, the infusion of a somatostatin antagonist [cycloAhep-Phe-D-Trp-Lys-Thr(Bzl)] led to a significant increase in weight gain over control (144).

In the rat, the daily injection of somatostatin-14 at 390 µg $kg^{-1}$ $day^{-1}$ in gelatin for three weeks had no effect on body weight but lowered parietal and peptic cell densities per cubic millimeter

compared to controls. However, it antagonized the growth promoting effect of exogenous (130 µg $kg^{-1}$ $day^{-1}$) and endogenous gastrin release following transposition of the antrum onto the colon, causing hypergastrinemia. In these antrum-translocated animals, the increased pancreatic weight was significantly reduced by somatostatin (400 µg $kg^{-1}$ $day^{-1}$) for 3 weeks (80). Over a 5-day period, somatostatin-14 s.c. in gelatin at doses of 11, 33 or 100 µg $kg^{-1}$ every 8 h caused significant decreases of pancreatic amylase, chymotrypsin and protein concentrations and total DNA content only at the two highest doses without any effect on total pancreatic weight. However, rates of protein, RNA and DNA synthesis were significantly reduced immediately after each somatostatin injection over 24 h (92). Somatostatin-14, also given s.c. in gelatin at a dose of 600 µg $kg^{-1}$, three times a day for 2 and 4 days, significantly reduced the trophic effects of caerulein (1 µg $kg^{-1}$, thrice a day) with a strong effect on total DNA content. Interestingly, immunoneutralization against SS-14 significantly increased all growth parameters studied above those observed in response to caerulein (93). Similar inhibitory effects were observed with prolonged administration of long-acting somatostatin, SMS 201-995 (54). Pancreatic juice diversion in the rat causes significant releases of endogenous CCK resulting in increased pancreatic growth (89). Using this procedure of bile-pancreatic juice diversion, such a technique applied 8 h $day^{-1}$ for 4 days led to significant increases in pancreatic weight and serum CCK; both effects were significantly reduced by SMS 201-995 infused at a dose of 5 µg $kg^{-1}$ $h^{-1}$ and by L-364,718, a CCK-1 receptor antagonist, given at 0.5 mg $kg^{-1}$ $h^{-1}$. Under these conditions, both SMS and L-364,718 were equipotent in reducing pancreas growth while SMS was the only antagonist able to reduce to a basal level endogenous CCK liberated by pancreatic-bile diversion (119). These data indicate that somatostatin and analogues can reduce pancreatic growth stimulated by exogenous and endogenously released CCK. Finally, it was observed that somatostatin (SMS) infused at a rate of 5 µg $kg^{-1}$ $h^{-1}$ for 2 days was able to totally prevent 70% casein-induced increases in pancreatic weight and total RNA and DNA contents (94). This is another evidence that somatostatin can control induced pancreatic growth stimulated by endogenous CCK released by a diet rich in proteins (50). Given alone as an iv infusion for 7 days at a dose of 5 µg $kg^{-1}$ $h^{-1}$, SMS 201-995 caused significant reductions in pancreatic and intestinal weights accompanied by decreases in total DNA and RNA in both organs. Plasma CCK and IGF-1 were reduced whereas total pancreatic IGF-1 content was increased (120). Besides endogenous CCK, some observations suggest the possible involvement of IGF-1 in the process of positive growth control in the intestine and pancreas. Indeed, this growth factor is present in the intestine (28) and pancreas (56) and specific receptors were documented on cells of these organs (76,162); paracrine or autocrine mechanisms of action have been postulated (29). Somatostatin may act on the control of these two organs through an inhibition of IGF-1 release accompanied by a similar effect on intestinal CCK.

## Effects of Somatostatin on Pancreatic Tumors

Somatostatin has been characterized as the "universal off switch" because it inhibits most of the organ and cellular functions it has been associated with. A role for somatostatin and its analogues in pancreatic cancer treatments has been suggested because these molecules initially provided positive non-toxic adjuvant therapy.

In the Golden Syrian hamster implanted subcutaneously with WD ductal pancreatic adenocarcinoma cells, a 21-day chronic treatment with the somatostatin analogue (L-5-Br-$Trp^{8}$)SS at a dose of 20 µg b.i.d., diminished tumor weight by 44% and tumor volume by 22% (114). Somatostatin and its analogue RC-160 have also been shown to inhibit preneoplastic changes and decrease the incidence of tumors in hamsters

exposed to the pancreatic carcinogen BOP; these treatments caused increases in the number of apoptotic tumor cells (150). In another study, the number of somatostatin receptors increased on the tumor cells after RC-160 treatment (35). Growth of MIAPaCa-2 cells implanted s.c. in nude mice was dose-dependently inhibited by twice daily injections of octreotide at 250 and 2500 µg $kg^{-1}$ (160). Using another mode of drug delivery, microcapsules, RC-160 delivered at 1250 µg $kg^{-1}$ $d^{-1}$ significantly inhibited growth of the MIAPaCa-2 tumors in nude mice (110). Failure of somatostatin or its analogues to inhibit tumor growth could have resulted from the absence of SS receptor as shown in the human pancreatic cancer cells PGER which are irresponsive to SMS 201-995 (141). In MIAPaCa-2 and PANC-1 cells grown in DMEM containing 10% fetal calf serum, 1 µM SS-14 and SMS 201-995 inhibited growth of the PANC-1 cells with activation of the tyrosine phosphatase SHP-1. On the contrary, SS and its analogue caused growth of the MIAPaCa-2 cell and this growth effect may have resulted from the absence of SHP-1 in these cells (31). In cells responding to somatostatin, it was shown previously that SHP-1 co-purified with the somatostatin receptor (167). A similar growth-stimulating effect of SMS was observed in BON cells (human pancreatic carcinoid cells) at the dose of 1 nM and 100 nM; this growth effect was accompanied by significant reductions in the cells cAMP contents without affecting PI hydrolysis (66).

Most clinical trials of somatostatin analogues in the adjuvant treatment of pancreatic cancer have failed to demonstrate a response. No antitumor effect was observed in 14 patients with metastatic pancreatic cancer with three daily s.c. injections of 100-200 µg of SMS for 7 weeks (72). In another study, nineteen patients with advanced exocrine pancreatic carcinoma were given the somatostatin analog BIM23014 from 250 µg to 1 mg $day^{-1}$ for 2 months. Within this group, one patient had a partial response, 6 had stable diseases, and eleven had progressive disease (20). From studies performed on different pancreatic cancer cells and the various responses obtained on their growth, it seems that one key to success in the critical battle against pancreatic cancer is the expression of specific somatostatin receptors and use of the specific analog (37). The properties of the five cloned subtypes of human somatostatin receptors and the established, probable and unestablished indications for the use of somatostatin analogues have been summarized in reference 77.

### Clinical Usage of Somatostatin

Clinically, octreotide has been used in treatment of acute pancreatitis but there was no unanimous benefit confirmed. In one trial (111), somatostatin was given in an initial bolus dose of 250 µg followed by 250 µg $h^{-1}$ as a continuous infusion; the treatment in 9 out of 12 patients with acute pancreatitis reversed amylasemia and brought clinical improvement but failed to show any reduction in mortality rates. Somatostatin remains however an effective treatment for established local complication of acute pancreatitis, such as pancreatic fistulae and pseudocysts (112). In one study, patients with metastatic pancreatic endocrine tumours were treated initially with 50 µg s.c. octreotide every 12 h and later (6-16 months) the dose was increased to 500 µg every 8 h. Some patients did not respond to treatment while in others it was effective; symptoms improved but eventually they recurred and all patients died once the resistance phase of their illness had been reached (163). These data indicate that somatostatin is not the ideal treatment for pancreatitis but may be useful to treat local complications of the disease. SMS, however, has been shown to be very efficient in eliminating pancreatic diarrhea and allowing correction of dehydration and acidosis. Its effect resulted in the marked reduction in plasma concentrations of VIP (84).

## 3. Tools for the study of somatostatin

a) Peptide

Somatostatin-14 and -28 are commercially available. The major agonist used in vivo is octreotide (SMS 201-995) and the others are: RC-160, BIM-23014, BIM-23056, BIM-23027 and L-362,855. Among the BIM series, BIM-23056 acts as an agonist on the SST-3 receptor as well as an antagonist on the SST-5 receptor (161). The chemical structures of these molecules are presented in **Table 1**.

b) Antibodies and assays

Antibodies to somatostatin -14, -28, SMS 201-995 and RC-160 have been developed in many laboratories. As examples, Guillemin has set up an RIA using a sheep antiserum BARBAR-78; this antiserum was raised against synthetic SS-14 and it cross-reacts with synthetic ovine SS-28 in equimolar ratio (15). A specific antiserum against SS-28 was also developed (67) and RIAs for SMS 201-995 (5) and RC-160 (83) have also been established.

c) Experimental models

Most of the physiological studies performed in humans were done in male and female healthy volunteers (30). Among the experimental animals, studies were mostly performed in conscious dogs with gastric and pancreatic fistulae (146,147), in conscious rats with bile-pancreatic juice diverted (25,127) and in anesthetized rats (39). For chronic effect of somatostatin on the pancreas, rats were treated daily with s.c. injections of somatostatin (92). In vitro studies were performed usually with freshly prepared pancreatic acini, isolated lobules or isolated perfused pancreas from rat, mouse or guinea pig (65, 96,139,158). In **Table 2**, some data on animal species used, doses or concentrations of somatostatin and analogues given and effects are presented.

**Table 2. Effects of somatostatin and analogues on pancreatic functions**

| | Species | Hormones or analogues | Doses or concentrations | Responses | Reference |
|---|---|---|---|---|---|
| 1. | Human | Somatostatin-14 | 5 μg $kg^{-1}$ $h^{-1}$ | ↓pancreatic flow stimulated by secretin | 30 |
| 2. | Dog | Somatostatin-14 | Bolus 3.5 μg $kg^{-1}$ and infusion 3.5 μg $kg^{-1}$ $h^{-1}$ | ↓protein, amylase output and $HCO_3$ conc stimulated by PZ-secretin ↓trypsin,amylase and volume in response to a test meal | 70 |
| 3. | Dog | Somatostatin-28 | 400 ng $kg^{-1}$ $h^{-1}$ | ↓protein output stimulated by caerulein + secretin ↓slightly volume in response to secretin | 147 |
| 4. | Rat | Somatostatin-14 | 100 μg, 100 $g^{-1}$ $h^{-1}$ | ↓basal amylase ↓volume and enzyme stimulated by CCK | 39 |
| 5. | Rat | Somatostatin-14 | 0-1-25 μg $kg^{-1}$ $h^{-1}$ | ↓basal protein and fluid | 51 |
| | | Somatostatin-14 | 1.28 μg $kg^{-1}$ $h^{-1}$ | ↓protein and volume in response to PJD | 51 |
| 6. | Rat | Somatostatin-14 | 11,33,100 μg $kg^{-1}$ 5 days | ↓DNA synthesis, total DNA ↓enzyme concentrations | 92 |
| 7. | Mouse acini | SMS 201-995 | 100 nM | No effect on secretin-stimulated amylase secretion ↓amylase in response to secretin + caerulein | 65 |
| 8. | Rat acini | Somatostatin-28 | $10^{-11}$ – $10^{-5}$ M | ↑amylase release to level of $10^{-10}$ M caerulein | 148 |
| | | Somatostatin-14 | $10^{-11}$ – $10^{-5}$ M | No effect | 148 |

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