

Perspectives of new potential therapeutic applications of somatostatin analogs*

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Abstract

At the present time only two long-acting somatostatin (SS) analogs, octreotide and lanreotide, are commonly used in the routine therapy. Both analogs have a high affinity mainly to a somatostatin receptor subtype 2 (SSTR₂). The established indications for SS analogs treatment include acromegaly, neuroendocrine tumors of the pancreas and gastrointestinal tract, and some gastro-enterologic diseases (pancreatitis, gastrointestinal bleedings, refractory diarrheas, pancreatic and intestinal fistulas). The recent investigations allow to predict the enlargement of therapeutic applications of SS analogs. It concerns pituitary tumors other than somatotropinoma, tumors of other endocrine glands like thyroid and adrenal gland, as well as some non-endocrine tumors. The progress depends on the introduction of new SS analogs with high affinity for SS receptor subtypes other than SSTR₂, because some tumors present the high expression of SSTR₁ (e.g. prostatic cancers) or SSTR₅ (e.g. colonic cancers). Great hopes are connected with the coupling of SS analogs with the radioactive isotopes or non-radioactive cytotoxic agents to destruct the neoplastic cells highly expressing the specific subtypes of SS receptors.

The pre- or postoperative *in vivo* imaging of SS receptors by means of the receptor scintigraphy, as well as the post-operative identification of SS receptor subtypes in the excised tumor tissues using immunohistochemistry, should play an important role in the prediction of the effects of SS analog treatment.

Beside oncology, new therapeutic applications of SS analogs could be presumed among others in ophthalmology; it concerns the treatment of progressive Graves-Basedow ophthalmopathy, diabetic retinopathy, glaucoma and corneal diseases connected with corneal vascularization.

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Introduction

When in 1973 Brazeau *et al* [1] accidentally isolated from ovine hypothalamus an agent inhibiting growth hormone secretion, somatostatin, nobody assumed how fascinating carriers would display this neurohormone and its synthetic analogs. In mammals, native somatostatin (SS) exists mainly in two active forms: 14-amino acid cyclic peptide (SS-14) and 28-amino acid cyclic peptide (SS-28), but several other forms also exist [1, 2]. Somatostatin has a very short plasma half-life of about 3 min. Beside hypothalamus the presence of SS has also been found in other structures of central and peripheral nervous system (25% of SS content), in pancreas (5%) and in the gut (65%), which is the main source of SS in the body. The peptide is released in large amounts from storage pools of neuroendocrine cells or in small amounts from activated immune and inflammatory cells. Not only the presence of SS is ubiquitous, it regulates also ubiquitously many physiological functions. Somatostatin inhibits the secretion of pituitary hormones: not only of growth hormone, but also of thyrotropin [4]. It inhibits also the secretion of almost all hormones from gastrointestinal track, such as: insulin, glucagon, gastrin, CCK, VIP, GIP and others. Somatostatin influences exocrine function of the gastrointestinal system, its motility, intestinal transport, blood flow and resorption. The role of SS in the gut was reviewed by Yamada [5]. Another important role of SS is the control of cell proliferation. The direct antiproliferative activity of SS was described for the first time in 1978, by one of us [6]. Somatostatin not only inhibits the growth of normal but also of neoplastic tissues [7], acting directly via specific SS receptors [8], or indirectly via inhibition of angiogenesis [9], immunomodulation [10], and inhibition of the secretion and attenuation of the action of growth factors [4, 5]. Thus, in addition to its endocrine effect on pituitary hormones, SS can act as an autocrine/paracrine regulator and the targets tissues of SS are often the same tissues in which the peptide is localized [3, 5].

Somatostatin analogs

Despite so many physiological effects, native SS was not useful for therapeutic application, because of its short plasma half-life. Thus, simultaneously with the studies concerning the role of SS in the body, the intense research work has been continued to synthesize more stable SS analogs. It was succeed in, and in 1982 Bauer *et al.* [11] from Sandoz laboratory synthesized the first highly potent SS analog, octreotide. It is a cyclic octapeptide with much longer plasma half-life than native SS of about 90 min and with the duration of action after subcutaneous injection of about 6 to 8 hours. Octreotide, which trade name is Sandostatin (Novartis, Switzerland), is 45 times more potent than SS in inhibition of growth hormone secretion and 11 times more potent in inhibition of glucagon secretion. It does not evoke "rebound effect" and its influence on gastrointestinal functions is transient [12]. The sec-

ond long acting and highly potent SS analog, lanreotide (trade name Somatuline L.P.; Beaufour Ipsen, France) was approved for clinical use in Europe in 1994. It should be administered intramuscularly. Its duration of action after one injection lasted from 7 to 14 days. So far, there are 4 pharmacological formulations of SS analogs available for the treatment in humans, e.g.: Sandostatin (Novartis) for subcutaneous (sc) or intravenous (iv) injections, which should be given usually 3 times a day, Sandostatin LAR (Novartis) (the new formulation of octreotide incorporated in polyD,L(lactide-co-glycolide) glucose microspheres) which can be administered intramuscularly every 4 weeks; mentioned earlier Somatuline L.P. (Beaufour Ipsen) and Somatuline Autogel (Beaufour Ipsen) which can be administered sc every 4 weeks.

Somatostatin receptors

It has been established that SS and its analogs exert their effects through specific SS receptors. So far, five distinct receptor subtypes 1–5 (SSTR₁-SSTR₅) have been cloned and characterized [13]. They are encoded by separate genes located on different chromosomes. Somatostatin receptors (SSTRs) belong to the family of membrane receptors, G-protein-coupled receptors with seven transmembrane domains. These receptors are widely distributed in normal and cancerous tissues, with cells often expressing more than one receptor subtype [14] and with over expression of SSTRs on some cancers. While native SSs (SS-14 and SS-28) have roughly similar high affinity to all SSTRs (SS-14 has higher affinity for SSTR₁₋₄ than SS-28 and lower for SSTR₅), synthetic analogs, octreotide and lanreotide, bind preferentially to SSTR₂ and SSTR₅, and display moderate affinity to SSTR₃ and low affinity to SSTR₁ and SSTR₄ [15]. These five receptors share common signaling pathways, such as: the inhibition of adenylyl cyclase, activation of phosphotyrosine phosphatase (PTP), and modulation of mitogen-activated protein kinase (MAPK). Some of the subtypes are also coupled to voltage-dependent Ca²⁺ channels (SSTR_{1,2}), phospholipase C (SSTR_{2,5}), and phospholipase A₂ (SSTR₄). SSTRs block cell secretion by inhibiting intracellular cAMP and Ca²⁺, SSTR_{1,2,4,5} induce cell cycle arrest via PTP-dependent modulation of MAPK with the induction of Rb and p21 protein. SSTR₃ triggers PTP-dependent apoptosis with activation of p53 and Bax [13].

Clinical applications of somatostatin analogs

Wide spectrum of SS effects implicates the wide spectrum of clinical disciplines in which synthetic somatostatin analogs are useful in therapy, e.g.: endocrinology, surgery and gastroenterology, imaging analysis, oncology, ophtalmology and others.

Acromegaly is the oldest and the most examined indication for therapy with SS analogs. These drugs are effective in 50 to 80% of patients with acromegaly. In these patients SS analogs caused a normalization

of hormonal disturbances (return of GH and IGF-I levels to normal range for sex and age) and, what is the most important, caused relieve of reversible acromegalic symptoms, and often caused even the shrinkage of tumors [16]. Somatostatin analogs are also effective in the treatment of the others pituitary tumors, such as: thyrotropinoma. In the case of these very rare tumors, SS analogs caused relieve of hyperthyroidism and normalization of hormonal disturbances [17].

The introduction of SS analogs in the treatment of gastroenteropancreatic tumors was a real, big step in the therapy of patients with these tumors. Somatostatin analogs are the drugs of choice in the treatment of patients with carcinoid syndrome, VIP-oma and glucagonoma. These drugs are effective in symptomatic improvement in over 70% of patients with a.m. tumors, in biochemical improvement in 30 to 70% of patients, but the inhibition of tumor growth after them is described as "rather rare" [18, 19, 20].

Somatostatin analogs are very useful and effective drugs in the treatment of various surgical and gastroenterological diseases, such as: portal hypertension and oesophageal variceal bleeding (arresting bleeding and preventing rebleeding, decreasing mortality), other gastrointestinal haemorrhages (peptic ulcers, colonic varices) [21, 22]; refractory diarrhoeas (chemotherapy-induced, AIDS-related, GVHD, caused by neuromuscular disorders: diabetes mellitus and systemic sclerosis) [23]; dumping syndrome (reducing gastrointestinal and vasomotor symptoms) [24]; short bowel syndrome (reducing need for intravenous fluids) [23]. These drugs play also an important role in pancreatic surgery. It is well known, that approximately 40% of patients undergoing major pancreatic surgery develop complications and around 10% die. Somatostatin analogs are the best drugs in both the prevention and treatment of postoperative complications [25]. They have also beneficial effects in the management of some cases of acute and chronic pancreatitis [26].

The modified octreotide coupled with ¹¹¹In-DTPA-DPhe¹ is used in somatostatin receptor scintigraphy (SRS, OctreoScan) [27] to visualize many pathological processes, mainly to localize autoimmunological processes and tumors expressing SS receptors (tumor cells and activated immune cells over expressed SSTRs). The proven and unproven indications for SRS are presented in Table I according to Jensen [28] with our slight modifications.

New applications of somatostatin analogs

The other applications for SS analogs should be presented as a new and/or potential and was summarized in Table II.

Oncology is one of these new fields. The usefulness of SS analogs in the treatment of various cancers has been very intensively examined from many years. At first, it is worth to outline the biological reasons for the control of cancer growth by SS and its analogs. Somatostatin and its analogs exert an antiproliferative action on a variety of normal and tumoral cells [29] acting

Table I. **Clinical uses of SRS**

1. Proven imaging usefulness	
a/	pancreatic endocrine tumors
b/	carcinoid tumors
c/	paragangliomas
d/	CNS tumors (meningiomas, astrocytomas)
e/	small and non-small cell lung cancer
f/	pituitary adenomas
2. Potential useful for imaging – unproven	
a/	medullary thyroid cancer
b/	lymphomas
c/	pheochromocytomas, metastatic ganglioneuroblastomas
d/	breast cancer
e/	prostate cancer
f/	reumatoid arthritis
g/	Graves' ophthalmopathy
h/	granulomatosis disease

Table II. **New and/or potential therapeutic applications of SS analogs**

Oncology	
	Endocrine tumors
	Clinically non-functioning pituitary adenomas
	Differentiated thyroid cancers?
	Adrenocortical tumors?
	Pheochromocytomas?
	Non-endocrine tumors
	Small cells lung cancer?
	Melanoma?
	Breast cancer?
	Colonic cancer?
	Renal cell cancer?
	Pancreatic cancer?
	Prostatic cancer?
	Hepatocellular cancer?
	Laryngeal cancer?
	Thymoma?
	Lymphomas?
Ophthalmology	
	Graves-Basedow ophtalmopathy?
	Diabetic retinopathy?
	Senile macular degeneration?
	Glaucoma?
Others	
	Rheumatoid arthritis?
	Hypothalamic growth hormone deficiency?
	Growth hormone deficiency in the aging ("somatopause")?

Table III. **The presence of various subtypes of SSTRs in non-endocrine tumors**

Tumors	SSTR ₁	SSTR ₂	SSTR ₃	SSTR ₄	SSTR ₅
Pancreatic Ca	-/+	-/+	+		+
Colon Ca	-	-/+	-/+	-/+	+
Breast Ca	-/+	+	-/+		
Prostatic Ca	+	-/+	-		+
Ovarian Ca	+	+	+		+
Renal cell Ca		+			+
SCLS	+	+			
Thymoma	+	+	+		
Astrocytoma		+			

directly via SS receptors (mainly via SSTR_{1, 2, 5}) over expressed on tumoral cells of both neuroendocrine and non-neuroendocrine origin [8, 30, 31], or indirectly via inhibition of the secretion and action of growth promoting hormones and factors [32, 33]. The presence of various types of SSTRs in non-endocrine tumors was shown in Table III [34, 35, 36]. Moreover, the anticancer effect of SS analogs seems to be a result of an increased incidence of cancer cell apoptosis [37] mediated via SSTR₃ [38], a decrease in tumor angiogenesis [9] and the immunomodulatory effects of these drugs [10].

New candidates for the treatment with SS analogs are clinically non-functioning pituitary adenomas. These tumors, although do not present the clinical and biochemical features of pituitary hyperfunction, in majority express the gonadotropins or their subunits. The treatment with octreotide was effective in some cases of these tumors in terms of tumor shrinkage [17]. Our unpublished studies indicate that in almost all cases of clinically non-functioning pituitary adenomas SS receptors proteins could be visualized by immunohistochemistry. However, the strongest immunostaining was found with antibody against a subtype 5, whereas the subtype 2A immunopositivity is usually weak or absent. It means that the analogs with enhanced affinity to SSTR₅ might be more useful in the treatment of such tumors than octreotide or lanreotide.

The presence of SS receptors on follicular cells of well-differentiated thyroid cancers allows to utilize SS receptor scintigraphy in the follow-up of thyroid cancer patients without the need to withdraw thyroxine suppression [39]. Moreover, the antiproliferative effect of SS and its analogs on thyroid follicular cells [40] seems to suggest the use of SS analogs in the treatment of differentiated thyroid cancers. Somatostatin receptors are also present in normal adrenal medulla and cortex and in adrenal tumors, what allows to visualize these tumors by SRS (especially in the case of pheochromocytomas) [41] and even to treat some of them with octreotide [42].

In the treatment of non-endocrine tumors SS analogs are applied: as a monotherapy in some advanced and resistant to current therapies cancers (hepatocellular cancer [43]); in combination with other hormonal treatment (for prostate [44] and breast cancer [45]); or as a joint treatment with chemotherapy (for melanoma [46]). The results concerning the therapeutic efficacy of SS analogs in oncology are conflicting and rather disappointing, but the number of both experimental and clinical studies in this subject has increased every year. In some of these reports, the application of SS analogs resulted in higher response rate and longer survival time for patients with cancers [43, 45]. In other studies these drugs caused an increase in symptom-free survival time [44] or produced tumor regression and even complete remission, as for example in some cases of metastatic melanoma, when SS analogs were applied together with chemotherapy [46]. The beneficial effects of SS analogs in the diagnosis and therapy of several others cancers have been proposed and observed in some studies for cancers, such as: SCLC and non-SCLC

[27, 47], colon cancers [48], exocrine pancreatic cancers [49, 50], renal cell cancers [51,52], non-Hodgkin lymphomas and T-cell lymphomas [53], meningiomas [54], laryngeal carcinomas [55] and thymomas [56]. These encouraging effects of SS analogs have been presented by some authors and not confirmed by others. Summing up, the antitumor effects of these drugs are rather poor and data on this subject are rather conflicting. However, in oncology, SS analogs are useful also in the treatment of some cancer-associated symptoms, such as: malignant intestinal obstructions (80% effectiveness) [57], chemotherapy-induced diarrheas [58] and in the treatment of malignant pain [59]. Moreover, SS receptor-targeted chemotherapy and radiotherapy seem to be the most important events in the progress of SS analogs therapy. This targeted-mode of application of radio- and chemotherapeutic particles allows to avoid the most adverse events after those therapies applied in traditional ways. Some of these ideas are very close to be introduced in the clinical practice. For example, OctreoTher is an octreotide analog labelled with high-energy beta-emitting isotope ⁹⁰Y, which could potentially deliver a lethal dose of radiation to the tumor expressing SSTRs without damage of surrounding healthy tissues. Kvols *et al.* [60] have conducted the phase I study with OctreoTher, in 22 patients with symptomatic and progressive SS-sensitive neuroendocrine tumors, and found many favorable effects: tumor stabilization (10 patients), antitumor effect (3 persons) and symptomatic improvement (12 patients). Moreover, in oncology, a new hope appears with the introduction to the therapy a new formulation of octreotide, OncoLAR. This pamoate salt of octreotide permits the loading of higher concentrations of octreotide and was recently investigated (phase I study) in 14 patients with advanced gastrointestinal cancers. The conclusions, that all examined doses were well tolerated and even disease stabilization has been observed [61].

Diabetology is another field in medicine, where SS analogs seem to be useful. It has been suggested, that they decrease resistance to insulin in NIDDM and decrease also a daily dose of insulin in IDDM [62,63]. Moreover, these drugs are given as a prevention and therapy in diabetic retinopathy [64] and nephropathy [65]. In the case of proliferative retinopathy the use of SS analogs suppressed new bleedings and stop visual loss in patients for whom conventional photocoagulation therapy failed. In nephropathy these drugs seem to lower glomerular filtration and partially reverse proteinuria.

The beneficial effects of these drugs have been also observed in patients with Graves' ophthalmopathy. In one of the first reports on this subject, therapeutic effects of SS analogs in progressive ophthalmopathy were comparable with effectiveness of steroid therapy [66]. However, in other reports this encouraging effect of SS analogs in Graves' eye disease has not been confirmed [67]. Moreover, Colao *et al.* [67] resumed that although in many studies these drugs have rather poor effectiveness in the treatment of Graves ophthalmopathy, SRS seems to be very informative and positive

OctreoScan predicts a good responsiveness to steroid therapy. Recently, it has been found that a new, non-peptide SSTR₄ agonist occurred useful in the cure of glaucoma [68]. A further new indication for SS analogs treatment seems to be rheumatoid arthritis. It was found that the intra-articular injections of SS caused many beneficial effects with a decrease in synovial thickness in patients suffering from this disease [69]. On the other hand, antagonistic SS analogs could be useful in treatment of some cases of GH deficiency. It is suggested that the impairment of GH secretion in aging humans and animals ("somatopause") depends on higher secretion of hypothalamic SS [70, 71] and can be restored in the animal experiment by administration of anti-SS antibodies. Moreover, high SS levels seem to play some role in the low stature pathogenesis [72]. Thus, the application of SS antagonists seems to be a more rational treatment than the use of recombinant GH.

Concluding remarks

In conclusion, therapy with SS analogs is very effective in various diseases. This effectiveness is long lasting and does not decrease with time (13 years effectiveness in the treatment of acromegaly). Side effects after these drugs, such as: nausea, vomiting, diarrhea, gallstones are rather rare and not dangerous, and interactions with other drugs occur very occasionally (cyclosporin, cimetidine). The route of administration and the cost of therapy are the only drawbacks, which seem to decrease in future. It seems to be obvious that the progress in the treatment with SS analogs is connected with the introduction to the clinical practice new SS analogs binding preferentially to others, than octreotide and lanreotide, subtypes of SSTRs (e.g. SSTR_{1,3,4}). The introduction of these new SS analogs to the image analysis allows to visualize pathological processes expressing other SSTRs (e.g. SSTR_{1,3,4}) than can be shown by OctreoScan and allows to treat these diseases with SS receptor-targeted chemo- and radiotherapy. The last hit in SS analogs therapy is SOM 230, a SS analog, called also an universal analog, because it preferentially binds to almost all SSTRs (without SSTR₄) and seems to be the most effective in anti-tumor action. In endocrinology, new perspectives are connected with hybrids of SS analogs and dopamine agonists and with a new SS analog – BIM23244, which seems to be more potent in the inhibition of GH secretion than presently available analogs. The investigation of all a.m. problems and goals may profoundly improve our understanding and knowledge concerning SS analogs effectiveness in various diseases and may allow utilizing these beneficial effects of these drugs in medical practice.

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