Review

Somatostatin analogs: does pharmacology impact antitumor efficacy?

Mounira Chalabi[1,2], Camille Duluc[1,2], Philippe Caron[1,2,3], Delphine Vezzosi[1,2,3], Julie Guillermet-Guibert[1,2], Stéphane Pyronnet[1,2], and Corinne Bousquet[1,2]

[1] Institut National de la Santé et de la Recherche Médicale (INSERM), Unité Mixte de Recherche (UMR) 1037, Centre de Recherche en Cancérologie de Toulouse (CRCT), Equipe labellisée Ligue Contre le Cancer and Laboratoire d'Excellence Toulouse Cancer (TOUCAN), 31432 Toulouse, France
[2] Université Toulouse III Paul Sabatier, 31062 Toulouse, France
[3] Service d'Endocrinologie et Maladies Métaboliques, Pôle Cardio-Vasculaire et Métabolique, Centre Hospitalier Universitaire (CHU) Larrey, 31059 Toulouse, France

Somatostatin is an endogenous inhibitor of secretion and cell proliferation. These features render somatostatin a logical candidate for the management of neuroendocrine tumors that express somatostatin receptors. Synthetic somatostatin analogs (SSAs) have longer half-lives than somatostatin, but have similar activities, and are used for the treatment of these types of disorders. Interest has focused on novel multireceptor analogs with broader affinity to several of the five somatostatin receptors, thereby presenting putatively higher antitumor activities. Recent evidence indicates that SSAs cannot be considered mimics of native somatostatin in regulating signaling pathways downstream of receptors. Here we review this knowledge, discuss the concept of biased agonism, and highlight what considerations need to be taken into account for the optimal clinical use of SSAs.

Somatostatin, somatostatin receptors, and somatostatin analogs

Discovered in 1973, somatostatin is a native inhibitory peptide hormone distributed throughout the central nervous system and peripheral tissues [1]. Somatostatin inhibits endocrine and exocrine secretions, gastric and intestinal motility, and gallbladder contraction. It also inhibits tumor growth through the inhibition of cell proliferation and angiogenesis, and by the induction of apoptosis [2,3]. Synthesized as a large precursor peptide, somatostatin undergoes tissue-specific degradation to produce two mature forms of 14 and 28 amino acids (somatostatin 14 and somatostatin 28), respectively [2]. Five G protein-coupled receptor (GPCR) subtypes of somatostatin receptors (ssts) subtypes have been identified (sst1–5) that bind to native somatostatin. The hormone activates receptors located primarily in the central and peripheral nervous systems, gastrointestinal (GI) tract, and endocrine organs. Upon activation, each receptor recruits specific G proteins, enzymes, and/or scaffold proteins, resulting in the activation or inhibition of several transduction pathways specific to each receptor subtype and to the cell type in which the receptor is expressed [1,3]. All five ssts are expressed in a variety of normal human tissues, although sst2 and sst5 are the predominant subtypes found in endocrine organs (including the pancreas, pituitary, thyroid, and parathyroid) [4]. In rodents

Glossary

Biased agonism: also known as functionally selective agonism, the term describes the concept that different agonists, acting through a single sst, can selectively activate different signaling pathways. It is theorized that different agonists exhibit different affinities for a receptor and that they stabilize different active receptor conformations; the latter determines the affinity of the sst for a variety of intracellular proteins that mediate signaling, growth regulation, and receptor internalization, recycling, or degradation. Thus, based on pharmacologic properties, the relative potency, therapeutic efficacy, or both, of two different agonists may differ in any given cell type, despite triggering a single sst.
Gastroenteropancreatic (GEP) NET: NET arising from the GI tract. Most GEP NET express multiple sst subtypes, with sst2 being the most prominent.
Neuroendocrine tumors (NET): originate from neuroendocrine cells in neuronal and endocrine tissue throughout the body.
Octreotide and lanreotide: synthetic somatostatin analogs (SSAs) with longer half-lives than native somatostatin. These analogs primarily target sst2, and bind to sst5 with lower affinity. SSAs improve the symptoms of severe diarrhea and flushing associated with carcinoid syndrome. SSAs are being investigated for their antitumor activity. Octreotide and Lanreotide are SSAs with documented Phase III trial data, substantiating their antitumor effect in the treatment of patients with NET (PROMID and CLARINET, respectively).
Pasireotide: a multireceptor analog with high affinity for sst1–3 and sst5.
Somatostatin: a native, mostly inhibitory, peptide hormone that inhibits both endocrine and exocrine secretions, gastric and intestinal motility, and gallbladder contraction. It also inhibits tumor growth through the inhibition of cell proliferation and angiogenesis, as well as via the induction of apoptosis. The short plasma half-life of natural somatostatin has prohibited its therapeutic development.
Somatostatin receptors (ssts): G protein-coupled receptors that bind to somatostatin. Somatostatin receptors are seven transmembrane receptors, and are expressed in a tissue-specific manner. Five subtypes, sst1 to sst5, have been identified to date.

Corresponding author: Bousquet, C. (corinne.bousquet@inserm.fr).
Keywords: somatostatin analogs; antitumor efficacy; pharmacotherapy; biased agonism; neuroendocrine tumors.

1043-2760/$ – see front matter
 http://dx.doi.org/10.1016/j.tem.2013.11.003

there are two splice variants of sst2 (2a and 2b), whereas only subtype 2a is expressed in humans [4].

Most neuroendocrine neoplasms, including pituitary and gastroenteropancreatic (GEP) neuroendocrine tumors (NET) (see Glossary), express different sst isoforms [3]. The inhibitory actions of somatostatin on hormone secretion and tumor growth render it a logical candidate for treating patients with these disorders. However, the short plasma half-life of native somatostatin (i.e., less than 3 min) precludes its development as a therapeutic agent [2]. Synthetic derivatives of somatostatin that have longer half-lives but similar actions have been developed. Three SSAs with both antisecretory and antitumor effects – octreotide, lanreotide, and pasireotide – are currently in clinical use and/or testing. Octreotide (Sandostatin®) has been available in both immediate-release and long-acting formulations (long-acting release – LAR) for injection since the mid-1980s and the mid-1990s, respectively [5]. Octreotide is approved to manage symptoms in patients with metastatic carcinoid tumors (diarrhea and flushing), diarrhea associated with vasoactive intestinal peptide tumors, glucagonomas, gastrinomas (Zollinger–Ellison syndrome), insulinomas, GRFomas (growth hormone-releasing factor-secreting tumor), and acromegaly [6]. Lanreotide (Somatuline®) is approved to manage symptoms associated with NET (in Europe only) and for the long-term management of acromegaly [7]. The sustained-release formulation of lanreotide became available in the mid-1990s, followed by the Autogel® formulation in the early to mid-2000s [5]. Recently, pasireotide (Signifor®) was approved in the EU and the USA (December 2012) as first-line treatment for patients with Cushing's disease [8]. Octreotide and lanreotide primarily target sst2 and bind sst5 with lower affinity; by contrast, pasireotide is a multireceptor analog with high affinity for sst1–3 and sst5 [5]. In addition to their approved use for indications based on their antisecretory effects, these SSAs are also being investigated for their antitumor activity in patients with acromegaly [growth hormone (GH)-secreting pituitary adenomas], NET, and polycystic liver disease, as well as in patients with cancers of the thyroid, prostate, breast, ovary, GI tract and other solid tumors [3,5,9,10].

Recent evidence indicates that SSAs cannot be considered simple mimetics of native somatostatin in regulating signaling pathways downstream of sst because of the functional selectivity of each of these analogs (biased agonism). Differences in mechanism of action among SSAs must be taken into account to optimize their effective use in the clinic. Based on which ssts are expressed in a specific tumor, and the pharmacology of each SSA binding to a specific sst, personalized pharmacotherapies using SSAs will become available in the future. The choice of a personalized SSA therapy will depend on the answers to the following: (i) sst expression in a specific tumor type; (ii) detailed knowledge regarding the intracellular signal transduction pathway for each sst; (iii) the receptor subtype interactions (i.e., dimerization, internalization, constitutive activity) utilized in modulating signaling; (iv) knowledge of sst monomer/homodimer/heterodimers differential effects on SSA signaling and how this may translate to improved patient treatment and outcomes. Although we are, as yet, unable to answer these questions fully, we review herein the current state of knowledge regarding mechanisms of action for the antitumor role of SSAs with the goal of attaining a clearer understanding of their clinical efficacy, focused primarily on neuroendocrine neoplasms.

Expression of ssts on tumor cells

Receptor expression patterns are related directly to the choice of SSA therapy. Different NET types express varying sst subtypes. Heterogeneous receptor subtype expression is not well understood, although it appears to depend more on individual characteristics of the tumor than on universal features of NET [11]. Further studies are required to define sst profiles for specific NET subtypes and the factors that may regulate their expression.

Tumors from somatostatin-target tissues with a high density of ssts include pituitary adenomas, GEP NET, paragangliomas, pheochromocytomas, carcinoids, small-cell lung cancers, medullary thyroid carcinomas, malignant lymphoma, and breast cancers [12,13]. Pituitary tumors are generally benign, slow-growing tumors that display different patterns of sst expression, based on the hormone-secreting cells from which they originate. GH-secreting pituitary adenomas predominantly express sst2 and, to a lesser extent, sst5. Adrenocorticotropic hormone (ACTH)-secreting adenomas predominantly coexpress sst5 and sst2, and prolactinomas predominantly express sst1 and sst5. In clinically nonfunctioning pituitary adenomas, sst3 is highly expressed, followed by sst2 and then sst5. In thyroid-stimulating hormone (TSH)-secreting tumors, sst2 is mainly coexpressed with sst3 and sst5.

More than three-quarters of GEP NET express multiple sst subtypes, although sst2 generally predominates, followed by sst5; in fact, simultaneous expression of these two subtypes is associated with better prognosis, and only weak expression of subtypes sst1, sst3, and sst4 is observed in these tumors. Considerable variation exists, however, in sst subtype expression between different tumor types and among tumors of the same type [1,11,14].

Somatostatin receptors are expressed to varying degrees in solid organ tumors. sst1 dominates in prostate cancer tissue, although all five receptors are present. Other cancers that express all five receptors include breast (primarily sst1–3), thyroid, melanoma, and GI tumor tissue. sst1–3 and sst5 are expressed in ovarian tissue (both benign and malignant). sst5 is the predominant receptor expressed in hepatocellular carcinoma, although sst1–3 are also present [5,10]. Some studies have demonstrated that octreotide and, to a lesser extent, lanreotide are associated with positive outcomes in patients with solid tumors in which sst2 and/or sst3 predominate, such as prostate and gastric cancers [5].

Recently, studies have successfully characterized the expression of sst2, sst3, and sst5 in human normal and neoplastic tissues using rabbit monoclonal antibodies (UMB-1, UMB-4, and UMB-5). Investigators have concluded that use of these monoclonal antibodies may be of value in the assessment of receptor subtype status in NET during routine histopathologic examination [13,15,16], and this could represent a first step for personalized