Lanreotide and beyond: extending the therapeutic horizons

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Thirty years after the growth hormone inhibiting effects of somatostatin were first described, greater understanding of its activities is opening the door to potential treatments for diabetes, cancer and other disorders. Recent identification of five somatostatin receptor subtypes is allowing treatment to be carefully targeted in order to maximize efficacy, and minimize unwanted effects.

The inhibitory effects of somatostatin on growth hormone (GH) secretion from the pituitary gland were first reported by Krulich et al (1968), and the polypeptide structure of the hypothalamic extract was elucidated 4 years later. Subsequently, 14- and 28-amino acid molecules (somatostatin 14 and somatostatin 28) were identified as the main biologically active forms of the hormone.

The physiological activities of somatostatin are triggered when the peptide binds with specific membrane-bound, high affinity receptors on the surface of responsive cells, such as those in the pituitary gland, pancreatic islets, and the central nervous system. Somatostatin receptors (SSTRs) are of the guanine nucleotide binding (G) protein-coupled type seen in many tissues and are most closely related to the opioid receptor family. Somatostatin and opioid receptors share about 30% sequence homology (Reisine and Bell, 1995).

The cloning and functional characterization of five SSTR subtypes has facilitated investigation of the therapeutic potential of somatostatin analogues. The receptor subtypes selectively bind somatostatin 14 and somatostatin 28 and have distinct patterns of expression in the central nervous system (CNS) and peripheral tissues.

SOMATOSTATIN RECEPTORS

The first receptor subtype, named somatostatin receptor 1 (SSTR1), was identified on insulin-secreting β cells, but SSTR2 is considered the prototypic SSTR since it is the subtype which mediates inhibition of GH secretion (Reisine and Bell, 1995). SSTR sequences are highly conserved across different species, with 81–97% of subtype sequences identical in human and rat proteins.

All subtypes are expressed in the CNS, although levels of SSTR5 expression are lower in rat brain than SSTR1–4. Expression of the latter receptor subtypes is high in areas of the brain involved in locomotor activity, learning and memory and in processing primary sensory information (Reisine and Bell, 1995).

All five receptor subtypes are expressed in the hypothalamus, suggesting that they are involved in regulating autonomic and neuroendocrine function, and in the pituitary and spleen. High levels of SSTR2 mRNA are expressed in the adrenal glands, and SSTR4 mRNA in the heart. In humans, SSTR1 mRNA is additionally expressed in the small intestine, stomach and lung and SSTR2 mRNA in the kidney.

Recent studies have confirmed that all five SSTR subtypes are expressed in normal human pancreatic islet cells, but with varying patterns of activity across the β, α and δ cells (Kumar et al, 1999). Thus, SSTR1 and 5 are the predominant subtypes expressed by the β cells, while SSTR2 is the predominant subtype found on α cells. SSTR5 is the predominant subtype expressed by δ cells.

SSTR mRNA has been identified in a range of tumour types, particularly of the endocrine system, hence the therapeutic benefits of somatostatin analogues in inhibiting tumour proliferation and hormone secretion.

SOMATOSTATIN ANALOGUES IN ACROMEGALY

The GH-inhibiting effect of somatostatin was the first property to be utilized therapeutically.

Surgery is the primary treatment for acromegaly, a condition in adults in which increased GH secretion from a pituitary ade-

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noma leads to excessive skeletal and soft tissue growth. However, in 40–60% of patients, there is persistent excessive GH secretion, usually as a result of incomplete removal of the adenoma (Bouloux, 1998). Radiotherapy may ultimately achieve good GH control but treatment may be required for up to 10 years to achieve maximal benefit.

Extensive experience with the somatostatin analogue lanreotide has demonstrated that it is possible to achieve rapid reduction of GH and insulin-like growth factor (IGF-1), an effector hormone produced by the liver in response to GH secretion, with accompanying improvement in symptoms and morphology (Giusti et al, 1996; Caron et al, 1997).

The introduction of the long-acting formulation of lanreotide (Somatuline LA, Ipsen, France) removed the need for multiple daily doses of somatostatin analogues, with obvious advantages for patient compliance and improved GH control. Lanreotide is released from a microparticle suspension, administered by intramuscular injection, over a period of 10–14 days.

Results of the recently completed long-term, multicentre study of Somatuline LA in the UK (unpublished data, Ipsen, 1999), showed that treatment substantially reduced GH levels, effectively relieved symptoms and significantly improved left ventricular hypertrophy (LVH) — a complication of acromegaly which contributes to the 2–3-fold increase in mortality compared with the general population.

Three-quarters of patients who completed 48 weeks therapy with Somatuline LA every 14, 10 or 7 days had GH levels less than 5 mU/litre and/or normalized IGF-1. In just over one-third of cases this was achieved with the lowest dosing regimen of Somatuline LA.

At 48 weeks, symptoms of perspiration, acral enlargement, malaise and snoring were greatly improved, and the number of patients with LVH had fallen from 21 to 12. There was also a reduction in pituitary tumour size in seven out of eight assessable patients in the study.

SOMATOSTATIN ANALOGUES IN CANCER

Carcinoid tumours

Carcinoid tumours usually occur in the gastrointestinal tract, commonly the appendix and ileum, but also the bronchi and genitourinary tract, and most are malignant. They secrete serotonin and other vasoactive substances which are responsible for causing the carcinoid syndrome characterized by cutaneous flushes, diarrhoea, bronchoconstriction and, sometimes, cardiac fibrosis.

About 90% of patients with carcinoid syndrome present with metastatic disease, especially in the liver, which is not amenable to surgery. Since medical treatment achieves poor results, therapy is generally palliative in nature. Administration of Somatuline LA has been accompanied by marked improvements in symptoms such as flushes and diarrhoea (Scherübl et al, 1994; Ruszniewski et al, 1996).

In a study of 39 patients with carcinoid syndrome treated with Somatuline LA 30 mg intramuscularly every 14 days for 6 months, 54% of patients experienced at least a 50% decrease in flushing episodes and 56% had a comparable reduction in bowel movements (Ruszniewski et al, 1996). No clear signs of tumour regression were seen but, equally, there was no increase in tumour size.

Breast cancer

The possible benefits of somatostatin in the treatment of cancer were the subject of recent controversy focused on claims made by a retired Italian physiologist (Simini, 1998). The massive publicity which surrounded the 'cure' forced the Italian health minister to initiate an observational trial of the cocktail of drugs which appears to include somatostatin, melatonin and vitamins.

At a more scientific level, studies have demonstrated that somatostatin analogues can inhibits the growth of breast carcinoma cells, both directly and indirectly via multiple endocrine effects, including reduction of IGF-1, a potent mitogen for breast tumour cells (Ingle et al, 1999). However, a comparative trial carried out in 135 postmenopausal women failed to show any benefit of adding the somatostatin analogue, octreotide, to the standard treatment of tamoxifen 10 mg twice daily (Ingle et al, 1999).

Nevertheless, tissue studies have demonstrated a high ratio of SSTR2 over other SSTRs on breast tumours cells, suggesting a possible future role for more potent SSTR2-specific analogues (Vikic-Topic et al, 1995).

Other cancers

Somatostatin and its analogues have been tested in a range of other cancers, including prostate, bowel and renal cell carcinomas, with mixed results (Goldberg et al, 1995; Maulard et al, 1995). However, more potent receptor-specific treatment may provide new opportunities for better targeting of therapy, with improved efficacy.

Another option already under investigation could be to use somatostatin analogues in combination with conventional cytotoxic therapy, possibly as 'holding treatment' to prevent tumour progression between courses of chemotherapy while patients recover from toxic effects on bone marrow and other tissues.

SOMATOSTATIN ANALOGUES IN ACUTE GASTROINTESTINAL BLEEDING

Oesophageal variceal bleeds are usually managed by emergency sclerotherapy, but a clear view of the lesion may be hampered by active bleeding during endoscopy. Somatostatin reduces portal and intravariceal pressure and portal collateral blood flow and both it and the analogue octreotide have been used with some success to control variceal bleeds during sclerotherapy (Besson et al, 1995).

In a recent double blind, prospective trial of 205 patients with cirrhosis with upper gastrointestinal bleeding, early infusion of somatostatin continued for 120 hours, combined with additional bolus injections, was more effective than placebo in the overall control of acute variceal haemorrhage during sclerotherapy (Avgerinos et al, 1997).

Treatment failed in 35 somatostatin and 57 placebo-treated patients (P=0.004). Somatostatin-treated patients required approximately one unit less of transfused blood products over 120 hours, active bleeding was less frequent (P=0.012) and the sclerotherapy procedure was rendered easier (P=0.0027).

To investigate the potential for the wider use of somatostatin analogues in gastrointestinal bleeding, two clinical trials are underway in Europe and the USA involving 2500 patients to explore the role of an instant release formulation of lanreotide in acute gastrointestinal bleeding associated with portal hypertension. The aims are to evaluate the efficacy of the drug both in acute treatment during the first 4–5 days of emergency therapy and, in the longer term, for the prevention of recurrent bleeding.

SOMATOSTATIN ANALOGUES IN DIABETES

A second generation of somatostatin analogues with enhanced efficacy and greater specificity for SSTR subtypes than lanreotide or octreotide is under development (Shimon et al, 1997). Following the discovery that SSTR5 is selective for inhibiting insulin secretion from the β cells and SSTR2 for inhibiting glucagon secretion from the α cells (Zambre et al, 1999), a series of second generation somatostatin analogues have been tested for their effects on release of pancreatic hormones and their potential for treating type 2 diabetes.

In phase I studies in healthy human subjects, the SSTR2 agonists, BIM 23190 and 23197, suppressed both basal and amino acid-stimulated secretion of glucagon, as well as basal insulin secretion. Amino acid-stimulated insulin secretion in the presence of the SSTR2 agonists, however, was normal. In contrast, the SSTR5 agonist, BIM 23268, induced a rapid, dose-dependent suppression of both basal and amino-acid insulin secretion (Orskov et al, 1999). It was concluded that, while BIM 23268 had a direct effect on insulin secretion via SSTR5 receptors on β cells, BIM 23190 and 23197 had a direct effect on glucagon secretion from α cells and an additional indirect effect on insulin release from β cells.

Such compounds may be useful in breaking the spiral of insulin resistance, hyperinsulinaemia and excessive glucagon release which frequently leads to type 2 diabetes in people who are obese and/or have a genetic predisposition to the disease.

SOMATOSTATIN ANTAGONISTS

In healthy adults, somatostatin exerts a dominant role over growth hormone-releasing hormone (GHRH) in the control of GH release. However, in certain pathological states it may be advantageous to override the normal control mechanisms, so that GH release is increased. Obvious examples include wasting/cachexia, severe burns, cardiomyopathy and Turner's syndrome. The elderly and those recovering from major surgery or undergoing chronic steroid therapy might also benefit.

It has been suggested that declining GH levels in the elderly may play a role in many of the problems of ageing, including loss of muscle mass and impaired immune function. There is some evidence to suggest that both impaired response to GHRH and an increase in somatostatin activity, possibly in response to impaired cholinergic activity, may be responsible for the fall in GH (Arvat et al, 1996).

GH treatment in elderly subjects has been shown to restore IGF-1 levels and reverse age-related body changes (Arvat et al, 1996). However, adverse effects, such as oedema, were common and sometimes necessitated stopping treatment. Early studies with GHRH and growth hormone-releasing peptide (GHRP) have demonstrated that it is possible to boost GH levels in other ways (Arvat et al,

1996), but the rise in cortisol levels associated with GHRP may limit its application. A third option may be to induce a pharmacological reduction in somatostatin activity in an effort to return GH levels to normal. Preliminary animal studies have confirmed the potential of this approach, but the true value of boosting GH levels both in the elderly and others has yet to be confirmed.

CONCLUSIONS

Since its discovery in 1968, the widespread effects of somatostatin on the hypothalamus–pituitary axis, CNS, gastrointestinal tract, kidneys, adrenal and thyroid glands have gradually been elucidated. However, it was only the differentiation of SSTRs into five distinct subtypes which has made it possible for researchers to begin to target novel somatostatin analogues at conditions beyond those affecting the pituitary gland.

Extensive experience with Somatuline LA has confirmed its value as an easy-to-use, long-acting treatment for acromegaly. It provides effective reduction of GH and IGF-1 levels, and relief of clinical symptoms. There are also indications that it can halt the progression of cardiac complications which frequently contribute to the excess mortality associated with the condition.

Somatuline LA has also proved useful for symptomatic relief in patients with carcinoid tumours and a short-acting formulation of the compound is the subject of clinical trials in gastrointestinal bleeding.

Second generation somatostatin analogues are in development for the management of diabetes and associated metabolic disorders, and preliminary studies suggest they may have a role to play in the management of hyperproliferative diseases such as cancer. Research into somatostatin antagonists suggests they may have potential in restoring GH levels to normal in the elderly and in pathological conditions where enhanced GH release may aid recovery. **HM**

Conflict of interest: Dr M Culler is an employee of Beaufour Ipsen in the USA.

Arvat G, Gianotti L, Ramunni J et al (1996) Human aging and the GH-IGF-1 axis. *J Pediatr Endocrinol Metab* **9:** 271–8

Avgerinos A, Nevens F, Raptis S et al (1997) Early administration of somatostatin and efficacy of sclerotherapy in acute oesophageal variceal bleeds: the European Acute Bleeding Oesophageal Variceal Episodes (ABOVE) randomised trial. *Lancet* **350:** 1495–9

Besson I, Ingrand P, Person B (1995) Sclerotherapy with or without octreotide for acute variceal bleeding. *N Engl J Med* **333:** 555–60

Bouloux P-MG (1998) Somatuline LA: a new treatment for acromegaly. *Hosp Med* **59:** 642–5

Caron P, Morange-Ramos I, Cogne M et al (1997) Three year follow-up of acromegalic patients treated with intramuscular slow-release lanreotide. *J Clin Endocrinol Metab* **82:** 18–22

Giusti M, Gussoni G, Cuttica CM et al (1996) Effectiveness and tolerability of slow release lanreotide treatment in active acromegaly: six-month report on an Italian Multicenter Study. *J Clin Endocrinol Metab* **81:** 2089–97

Goldberg RM, Moertel CG, Wieand HS et al (1995) A phase III evaluation of a somatostatin analogue (octreotide) in the treatment of patients with asymptomatic advanced colon carcinoma. North Central Cancer Treatment Group and the Mayo Clinic. *Cancer* **76:** 961–6

Ingle JN, Suman VJ, Kardinal CG et al (1999) A randomized trial of tamoxifen alone or combined with octreotide in the treatment of women with metastatic breast carcinoma. *Cancer* **85:** 1284–92

Krulich L, Dhariwal APS, McCann SM (1968) Stimulatory and inhibitory effects of purified hypothalamic extracts on growth hormone release from rat pituitary in vitro. *Endocrinology* **83:** 787–90

Kumar U, Sasi R, Suresh S et al (1999) Subtype-selective expression of the five somatostatin receptors (hSSTR1-5) in human pancreatic islet cells: a quantitative double-label immunohistochemical analysis. *Diabetes* **48:** 77–85

Maulard C, Richaud P, Droz JP et al (1995) Phase I-II study of the somatostatin analogue lanreotide in hormone-refractory prostate cancer. *Cancer Chemother Pharmacol* **36:** 259–62

Orskov H, Moller N, Schmitz O et al (1999) Study of two somatostatin receptor (SSTR) subtype specific analogues in healthy male subjects. 81st Annual Meeting of the Endocrine Society, San Diego. Abstract OR44-4: 123

Reisine T, Bell GI (1995) Molecular biology of somatostatin receptors. *Endocrine Rev* **16:** 427–42

Ruszniewski P, Ducreux M, Chayvialle J-A et al (1996) Treatment of the carcinoid syndrome with the long acting somatostatin analogue lanreotide: a prospective study in 39 patients. *Gut* **39:** 279–83

Scherübl H, Wiedenmann B, Riecken EO (1994) Treatment of the carcinoid syndrome with a depot formulation of the somatostatin analogue lanreotide. *Eur J Cancer* **30A:** 1590–1

Shimon I, Taylor JE, Dong JZ et al (1997) Somatostatin receptor subtype specificity in human fetal pituitary cultures — differential role of SSTR2 and SSTR5 for growth hormone, thyroid stimulating hormone and prolactin regulation. *J Clin Invest* **99:** 789–98

Simini B (1998) Somatostatin fever mounts in Italy. *Lancet* **351:** 428

Vikic-Topic S, Raisch KP, Vuk-Pavlovic S (1995) Transcripts of somatostatin receptor subtypes in breast carcinoma, carcinoid tumors and renal cell carcinoma. *Proc Ann Meet Am Assoc Cancer Res* **36:** A3151

Zambre Y, Ling Z, Chen M-C et al (1999) Inhibition of human pancreatic islet insulin release by receptor-selective somatostatin analogs directed to somatostatin receptor subtype 5. *Biochem Pharmacol* **57:** 1159–64

KEY POINTS

- Five subtypes of the somatostatin receptor (SSTR1–5) have been identified.
- The specificity of receptor subtypes for certain tissues is providing opportunities for new types of treatment.
- In a recent multicentre trial, the somatostatin analogue lanreotide substantially reduced growth hormone levels, relieved symptoms and improved left ventricular hypertrophy in acromegalic patients.
- Lanreotide has also been shown to relieve symptoms of carcinoid syndrome and it is being tested in gastrointestinal bleeding associated with portal hypertension.
- Somatostatin analogues are in development for the management of diabetes.