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SOMATOSTATIN: THE HISTORY OF DISCOVERY

Malgorzata Trofimiuk-Müldner and Alicja Hubalewska-Dydejczyk

Department of Endocrinology with Nuclear Medicine Unit, Medical College, Jagiellonian University, Krakow, Poland

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ABBREVIATIONS

FDA	the Food and Drug Administration
GIF	growth hormone-inhibiting factor
PET	positron emission tomography
SPECT	single photon emission computed tomography
SRIF	somatotropin release-inhibiting factor

Now, here, you can see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!
Lewis Carroll, Through the Looking Glass

The beginning of the second half of the twentieth century, the great era of discovery of factors regulating anterior pituitary hormones synthesis and release, resulted also in isolation and characterization of somatostatin. The history started with search for growth hormone-releasing factor. In 1968, Krulich and colleagues noted that extracts from different parts of rat hypothalamus either stimulated or inhibited release of pituitary growth hormone [1]. The inhibiting substance was named growth hormone-inhibiting factor (GIF). The group of Roger Guillemin developed highly sensitive assay for rat growth hormone, which enabled the confirmation of negative linear

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relationship between the production of the growth hormone by anterior pituitary cell culture and amount of hypothalamic extract added [2]. About 500,000 sheep hypothalami later Brazeau and Guillemin isolated the substance responsible for inhibiting effect—somatotropin release-inhibiting factor—SRIF. The structure of 14-aminoacid peptide was then sequenced, the sequence of the residues confirmed, and the molecule was resynthesized. The synthetic molecule inhibiting properties were confirmed in both *in vivo* and *in vitro* experiments. The result of the discovery was paper published in *Science* in 1973 [3]. Roger Guillemin renamed the hormone—since 1973 it has been known as the somatostatin [4]. The new hormone was extracted also from hypothalami of other species.

Those times were also regarded the gut hormones era. In 1969, Hellman and Lernmark announced the inhibiting effect of extract from alfa-1 cells of pigeon pancreas on insulin secretion from pancreatic islets derived from obese, hyperglycemic mice [5]. In 1974, group of C. Gale from Seattle noticed the lowering of fasting insulin and glucagon levels in baboons as well as tampering of arginine-stimulated insulin release by somatostatin—directly and in dose-dependent manner [6]. This finding was confirmed also in other animal models and humans shortly after. As the hypothalamic somatostatin seemed to act locally, the search for local, pancreatic source of the hormone started. The antibodies against somatostatin proved to be useful tool. The presence of somatostatin in delta (D) cells of the pancreas (formerly alfa-1 cells) was proved by immunofluorescence [7, 8]. In 1979, somatostatin was isolated from the pigeon pancreas, and next from other species [9]. The somatostatin-reactive cells were also found in gastrointestinal mucosa, and then in other tissues, including tumors. Concurrently, the multiple groups worked on the somatostatin action and its pan-inhibiting properties were gradually characterized. In 1977, Roger Guillemin and Andrew Schally were awarded the Nobel Prize in medicine and physiology for their work on somatostatin and other regulating hormones. Of interest, somatostatin-like peptides were also discovered in plants [10].

Other somatostatin forms, somatostatin-28 particularly, and somatostatin precursor—preprosomatostatin—were characterized in late 1970s/early 1980s. Human cDNA coding preprosomatostatin was isolated and cloned in 1982 [11, 12].

The possible pathological implications and potential therapeutic use of somatostatin were postulated early in the somatostatin discovery era. The clinical description of somatostatin-producing pancreatic tumor in human came from Larsson and colleagues in 1977 [13]. Somatostatin administration to block the growth hormone secretion in acromegalic patients was reported as early as in 1974 [14]. The potency of the hormone to block carcinoid flush was also observed in late 1970s and early 1980s [15, 16]. Somatostatin was the first human peptide to be produced by bacterial recombination. In 1977 Itakura, Riggs and Boyer group synthesized gene for somatostatin-14, fused it with *Escherichia coli* beta-galactosidase gene on the plasmid and transformed the *E. coli* bacteria with chimeric plasmid DNA. As the result, they obtained the functional human polypeptide [17]. The synthesis of recombinant human somatostatin led to the commercial human recombinant insulin production.

Although it was possible to produce somatostatin in large quantities, the short half-life of the hormone was one of the reasons why the native hormone was not feasible for routine clinical practice. The search for more stable yet functional hormone analogue started

in 1974. The search was focused on the peptide analogues. The somatostatin receptor agonists were first to be used in clinical practice. In 1980–1982, octapeptide SMS 201–995 was synthetized and proved to be more resistant to degradation and more potent than native hormone in inhibiting growth hormone synthesis [18]. The drug, currently known as octreotide, was the first Food and Drug Administration (FDA)-approved somatostatin analogue. It was followed by other analogues, such as lanreotide (BIM 23014), and by the long-acting formulas. High selective affinity of octreotide and lanreotide for somatostatin receptor type 2 (lesser to the receptor types 3 and 5) was one of the triggers for further research. In 2005 vapreotide (RC160), somatostatin analogue with additional affinity to receptor type 4, was initially accepted for treatment of acute oesophageal variceal bleeding and granted the orphan drug status in 2008 in the United States (although final FDA approval has not been granted). Lately, promising results of large phase III studies on "universal" multitargeted somatostatin analogue, cyclohexapeptide SOM-230 pasireotide, in acromegaly and Cushing's disease, have been published [19, 20]. The drug has been granted the European Medicines Agency and the FDA approval for pituitary adrenocorticotropic hormone (ACTH)-producing adenomas treatment. The research on first nonpeptide receptor subtype selective agonists was published in 1998; however, none of tested compounds have been introduced to clinical practice [21]. The studies on somatostatin receptors antagonists have been conducted since 1990s.

The other areas for research were somatostatin receptors. The high affinity-binding sites for somatostatin were found on pancreatic cells and in brain surface by group of J.C. Reubi in 1981–1982. The different pharmacological properties of the receptors were noted early. At the beginning two types of somatostatin receptors, with high and low affinity for octreotide, were characterized [22, 23]. In 1990s, all five subtypes of somatostatin receptors were cloned and their function was discovered. The other important step was the discovery of the somatostatin receptors overexpression in tumor cells, particularly of neuroendocrine origin [24]. This led to the first successful trials on diagnostic use of radioisotope-labeled hormones. The iodinated octreotide was used in localization of the neuroendocrine tumors in 1989–1990 [25, 26]. The Iodine-123 was replaced by the Indium-111, and later on by the Technetium 99 m [27–29]. The first Gallium-68 labeled somatostatin analogues for positron emission tomography (PET) studies were proposed in 1993 [30]. Feasibility of labeled somatostatin receptor antagonist for single photon emission computed tomography (SPECT) or PET tumor imaging has been reported in 2011 [31]. Together with diagnostics, the concept of therapeutic use radioisotope labeled somatostatin analogues has evolved. The first peptides for therapy were those labeled with Indium-111 [32]. In 1997, the Yttrium-90 labeled analogues, followed by Lutetium-177 labeled ones, were introduced in palliative treatment of neuroendocrine disseminated tumors [33, 34].

The co-expression of somatostatin and dopamine receptors, as well as discovery of receptor heterodimerization, led to the search for chimeric somatostatin-dopamine molecules, dopastatins [35]. Other area of recent research is cortistatin, a member of somatostatin peptides family, with somatostatin receptors affinity but also with distinct properties [36].

Summing up the multicenter research on somatostatin led to the discovery of the hormone probably second only to the insulin in its clinical use.

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