MEDICINE REPORTS

Published: 08 May 2009
© 2009 Medicine Reports Ltd

Antiproliferative effects of somatostatin analogs in endocrine tumours

Maria Chiara Zatelli

Address: Section of Endocrinology, University of Ferrara, Via Savonarola 9, 44100 Ferrara, Italy

Email: ztlmch@unife.it

F1000 Medicine Reports 2009, **1**:40 (doi:10.3410/M1-40)

This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (http://creativecommons.org/licenses/by-nc/3.0/legalcode), which permits unrestricted use, distribution, and reproduction in any medium, for non-commercial purposes provided the original work is properly cited. You may not use this work for commercial purposes.

The electronic version of this article is the complete one and can be found at: http://F1000.com/Reports/Medicine/content/1/40

Abstract

Somatostatin has been discovered as a somatotroph release inhibitory factor (SRIF), and it has been demonstrated that SRIF and its analogs can inhibit hormone secretion and control the neoplastic bulk of several endocrine tumours. *In vitro* studies have contributed to the current knowledge of the mechanisms by which SRIF and its analogs may influence endocrine tumour proliferation, opening the way to new possible therapeutic strategies. Here, we focus on the studies concerning the antiproliferative effects of SRIF and its analogs that provide the basis for future investigations, both at basic and clinical levels, into the application of SRIF analogs in the endocrine field.

Introduction and context

On the basis of the antisecretory and antiproliferative effects of somatostatin [somatotroph release inhibitory factor (SRIF)] and its analogs on normal and neoplastic endocrine cells, these compounds have been widely used in the medical field. Many studies have demonstrated that they activate several intracellular pathways, depending on receptor subtype and target cells [1], with highly variable effects depending on the tissue [2]. Currently available SRIF analogs (such as octreotide and lanreotide) are indeed capable of normalizing growth hormone and insulin-like growth factor 1 (IGF-1) levels and of controlling tumour growth in a substantial portion of acromegalic patients. They can also be effective in patients with gastroenteropancreatic endocrine tumours, where they can effectively suppress the production of bioactive peptides and hormones by the tumour cells, and in some cases may display antiproliferative effects. It has been indicated that the inhibitory effects of SRIF and its analogs depend on tissue SRIF receptor (SSTR) expression pattern, agonist-binding profile, and SSTR effector coupling [3]. The clinically available SRIF analogs do indeed display slight differences in SSTR affinity profile; octreotide shows higher affinity for SSTR5 as compared with lanreotide and exhibits some SSTR3 affinity. Moreover, the two compounds have different pharmacokinetic profiles depending on the formulation, which might influence the antitumoural effects [4]. There is also evidence indicating that inhibition of cell proliferation may occur independently of the effects on hormone secretion [5-7], possibly providing an explanation for resistance to somatostatin analogs [8]. In the field of pituitary adenomas, predictive indices for response to SRIF analogs are a decrease in hormone levels after short-term SRIF analog treatment, a positive octreoscan [9], and previous radiotherapy [10]. However, these parameters do not reliably predict antiproliferative effects of somatostatin analogs and do not seem applicable for neuroendocrine tumours [11].

Recent advances

Several studies to elucidate SSTR expression pattern in endocrine tumours have been performed recently. Besides pituitary adenomas [3,12], other endocrine tumours display a variable SSTR expression pattern: thyroid tumours deriving from follicular [13] and parafollicular [14,15] cells, adrenocortical tumours [16], and bronchial [17] and gastroenteropancreatic [18,19] neuroendocrine tumours. Most of these studies correlate SSTR expression pattern with functional data

demonstrating the inhibitory effects of SRIF analogs in specific endocrine tumour subsets, linking the efficacy of these drugs to their affinity for SSTR2. Indeed, it has been indicated that SSTR2 expression level might be a critical factor affecting both tumour progression and SRIF analog treatment outcome [20] since SSTR2 re-expression by gene transfer is able to improve sensitivity toward SSTR2-interacting drugs [21]. The mechanism by which SRIF inhibits endocrine cell proliferation has been widely investigated in immortalized cell lines as well as in endocrine tumour primary cultures, demonstrating the involvement of tyrosine phosphatases [22] that might trigger apoptotic changes [23,24]. Moreover, SRIF and its analogs can cause decreases in cell proliferation [25,26], cell cycle inhibition [27], and growth arrest [23], also acting through the PI3K/Akt signaling pathway [28]. These results confirm that SSTR2 is an important receptor subtype in transducing the antiproliferative signals of SRIF, but they also indicate that more than one SSTR is able to induce antiproliferative effects. Multiple subtypes may indeed cooperate to induce growth arrest since these receptors can homo- and hetero-dimerize with other G protein-coupled receptors [29]. Besides the direct actions on endocrine neoplastic cells, SRIF and its analogs can indirectly influence cell proliferation by inhibiting production and secretion of many angiogenic factors [30]. Moreover, it was recently demonstrated that SRIF analog treatment might result in biochemical/neuroradiological disease remission in a subset of acromegalic patients [31], suggesting that medical therapy might actually cure acromegaly in selected patients.

Implications for clinical practice

The studies performed so far indicate that the antiproliferative effect of SRIF analogs on endocrine tumours depends on tissue SSTR expression pattern (mainly SSTR2), as well as on the different binding profiles of the various agonists, and SSTR-effector coupling. Therefore, the employment of SRIF analogs for 'oncologic' purposes should be based on both clinical and molecular tumour characterization of each patient in order to perform a really tailored targeted therapy. This implies a strict collaboration among endocrinologists, oncologists, nuclear medicine experts, surgeons, pathologists, and molecular biologists in order to provide correct indications for the therapeutical use of SRIF analogs. *In vivo* and *in vitro* data do indeed indicate that currently available SRIF analogs and new upcoming compounds can achieve significant results in terms of tumour volume control in endocrine tumours, especially pituitary adenomas [32,33], but further clinical and basic studies are needed to confirm this effect.

Abbreviations

IGF-1, insulin-like growth factor 1; SRIF, somatotroph release inhibitory factor; SSTR, somatostatin receptor.

Competing interests

The author declares that she has no competing interests.

References

1. Ferjoux G, Bousquet C, Cordelier P, Benali N, Lopez F, Rochaix P, Buscail L, Susini C: **Signal transduction of somatostatin receptors negatively controlling cell proliferation.** *J Physiol* 2000, **94:**205-10.
2. Hofland LJ, van der Hoek J, Feelders R, van der Lely AJ, de Herder W, Lamberts SW: **Pre-clinical and clinical experiences with novel somatostatin ligands: advantages, disadvantages and new prospects.** *J Endocrinol Invest* 2005, **28:**36-42.
3. Zatelli MC, Ambrosio MR, Bondanelli M, degli Uberti EC: ***In vitro* testing of new somatostatin analogs on pituitary tumour cells.** *Mol Cell Endocrinol* 2008, **286:**187-91.
4. Ben-Shlomo A, Melmed S: **Acromegaly.** *Endocrinol Metab Clin North Am* 2008, **37:**101-22.
5. Danila DC, Haidar JN, Zhang X, Katznelson L, Culler MD, Klibanski A: **Somatostatin receptor-specific analogs: effects on cell proliferation and growth hormone secretion in human somatotroph tumours.** *J Clin Endocrinol Metab* 2001, **86:**2976-81.
6. Casarini AP, Pinto EM, Jallad RS, Giorni RR, Giannella-Neto D, Bronstein MD: **Dissociation between tumour shrinkage and hormonal response during somatostatin analog treatment in an acromegalic patient: preferential expression of somatostatin receptor subtype 3.** *J Endocrinol Invest* 2006, **29:**826-30.
7. Resmini E, Dadati P, Ravetti JL, Zona G, Spaziante R, Saveanu A, Jaquet P, Culler MD, Bianchi F, Rebora A, Minuto F, Ferone D: **Rapid pituitary tumour shrinkage with dissociation between antiproliferative and antisecretory effects of a long-acting octreotide in an acromegalic patient.** *J Clin Endocrinol Metab* 2007, **92:**1592-9.
8. Gola M, Bonadonna S, Mazziotti G, Amato G, Giustina A: **Resistance to somatostatin analogs in acromegaly: an evolving concept?** *J Endocrinol Invest* 2006, **29:**86-93.
9. Colao A, Ferone D, Lastoria S, Marzullo P, Cerbone G, Di Sarno A, Longobardi S, Merola B, Salvatore M, Lombardi G: **Prediction of efficacy of octreotide therapy in patients with acromegaly.** *J Clin Endocrinol Metab* 1996, **81:**2356-62.
10. Sherlock M, Fernandez-Rodriguez E, Alonso AA, Reulen RC, Ayuk J, Clayton RN, Holder G, Sheppard MC, Bates A, Stewart PM: **Medical therapy in patients with acromegaly; predictors of response and comparison of efficacy of dopamine agonists and somatostatin analogues.** *J Clin Endocrinol Metab* 2009, **94:**1255-63.
11. Duet M, Guichard JP, Rizzo N, Boudiaf M, Herman P, Tran Ba Huy P: **Are somatostatin analogs therapeutic alternatives in the management of head and neck paragangliomas?** *Laryngoscope* 2005, **115:**1381-4.
12. de Bruin C, Pereira AM, Feelders RA, Romijn JA, Roelfsema F, Sprij-Mooij DM, van Aken MO, van der Lelij AJ, de Herder WW, Lamberts SW, Hofland LJ: **Co-expression of dopamine and somatostatin receptor subtypes in corticotroph adenomas.** *J Clin Endocrinol Metab* 2009, **94:**1118-24.
13. Pisarek H, Stepien T, Kubiak R, Borkowska E, Pawlikowski M: **Expression of somatostatin receptor subtypes in human thyroid tumours: the immunohistochemical and molecular biology (RT-PCR) investigation.** *Thyroid Res* 2009, **2:**1.
14. Zatelli MC, Piccin D, Tagliati F, Bottoni A, Luchin A, Vignali C, Margutti A, Bondanelli M, Pansini GC, Pelizzo MR, Culler MD, degli Uberti EC: **Selective activation of somatostatin receptor subtypes differentially modulates secretion and viability in human medullary thyroid carcinoma primary cultures:**

potential clinical perspectives. *J Clin Endocrinol Metab* 2006, **91:**2218-24.

15. Faggiano A, Grimaldi F, Pezzullo L, Chiofalo MG, Caracò C, Mozzillo N, Angeletti G, Santeusanio F, Lombardi G, Colao A, Avenia N, Ferolla P: **Secretive and proliferative tumour profile helps to select the best imaging technique to identify postoperative persistent or relapsing medullary thyroid cancer.** *Endocr Relat Cancer* 2009, **16:**225-31.
16. Pisarek H, Stepień T, Kubiak R, Pawlikowski M: **Somatostatin receptors in human adrenal gland tumours–immunohistochemical study.** *Folia Histochem Cytobiol* 2008, **46:**345-51.
17. van Hoek M, Hofland LJ, de Rijke YB, van Nederveen FH, de Krijger RR, van Koetsveld PM, Lamberts SW, van der Lely AJ, de Herder WW, Feelders RA: **Effects of somatostatin analogs on a growth hormone-releasing hormone secreting bronchial carcinoid, *in vivo* and *in vitro* studies.** *J Clin Endocrinol Metab* 2009, **94:**428-33.
18. Couvelard A, Deschamps L, Ravaud P, Baron G, Sauvanet A, Hentic O, Colnot N, Paradis V, Belghiti J, Bedossa P, Ruszniewski P: **Heterogeneity of tumour prognostic markers: a reproducibility study applied to liver metastases of pancreatic endocrine tumours.** *Mod Pathol* 2009, **22:**273-81.
19. Corleto VD, Falconi M, Panzuto F, Milione M, De Luca O, Perri P, Cannizzaro R, Bordi C, Pederzoli P, Scarpa A, Delle Fave G: **Somatostatin receptor subtypes 2 and 5 are associated with better survival in well-differentiated endocrine carcinomas.** *Neuroendocrinology* 2009, **89:**223-30.
20. Zou Y, Xiao X, Li Y, Zhou T: **Somatostatin analogues inhibit cancer cell proliferation in an SSTR2-dependent manner via both cytostatic and cytotoxic pathways.** *Oncol Rep* 2009, **21:**379-86.
21. Acunzo J, Thirion S, Roche C, Saveanu A, Gunz G, Germanetti AL, Couderc B, Cohen R, Figarella-Branger D, Dufour H, Brue T, Enjalbert A, Barlier A: **Somatostatin receptor sst2 decreases cell viability and hormonal hypersecretion and reverses octreotide resistance of human pituitary adenomas.** *Cancer Res* 2008, **68:**10163-70.

F1000 Factor 3.0 *Recommended*
Evaluated by Giovanni Tulipano 16 Apr 2009

22. Dasgupta P, Singh AT, Mukherjee R: **Antiproliferative and GH-inhibitory activity of chimeric peptides consisting of GHRP-6 and somatostatin.** *Biochem Biophys Res Commun* 1999, **259:**379-84.
23. Ferrante E, Pellegrini C, Bondioni S, Peverelli E, Locatelli M, Gelmini P, Luciani P, Peri A, Mantovani G, Bosari S, Beck-Peccoz P, Spada A, Lania A: **Octreotide promotes apoptosis in human somatotroph tumor cells by activating somatostatin receptor type 2.** *Endoc Relat Cancer* 2006, **13:**955-62.
24. Luciani P, Gelmini S, Ferrante E, Lania A, Benvenuti S, Baglioni S, Mantovani G, Cellai I, Ammannati F, Spada A, Serio M, Peri A: **Expression of the antiapoptotic gene seladin-1 and octreotide-induced apoptosis in growth hormone-secreting and nonfunctioning pituitary adenomas.** *J Clin Endocrinol Metab* 2005, **90:**6156-61.
25. Weckbecker G, Lewis I, Albert R, Schmid HA, Hoyer D, Bruns C: **Opportunities in somatostatin research: biological, chemical and therapeutic aspects.** *Nat Rev Drug Discov* 2003, **2:**999-1017.
26. Zatelli MC, Tagliati F, Taylor JE, Rossi R, Culler MD, degli Uberti EC: **Somatostatin receptor subtypes 2 and 5 differentially affect proliferation *in vitro* of the human medullary thyroid carcinoma cell line TT.** *J Clin Endocrinol Metab* 2001, **86:**2161-9.
27. Hubina E, Nanzer AM, Hanson MR, Ciccarelli E, Losa M, Gaia D, Papotti M, Terreni MR, Khalaf S, Jordan S, Czirjak S, Hanzely Z, Nagy GM, Goth MI, Grossman AB, Korbonits M: **Somatostatin analogues stimulate p27 expression and inhibit the MAP kinase pathway in pituitary tumours.** *Eur J Endocrinol* 2006, **155:**371-9.
28. Theodoropoulou M, Zhang J, Laupheimer S, Paez-Pereda M, Erneux C, Florio T, Pagotto U, Stalla GK: **Octreotide, a somatostatin analogue, mediates its antiproliferative action in pituitary tumor cells by altering phosphatidylinositol 3-kinase signaling and inducing Zac1 expression.** *Cancer Res* 2006, **66:**1576-82.
29. Rocheville M, Lange DC, Kumar U, Patel SC, Patel RC, Patel YC: **Receptors for dopamine and somatostatin: formation of hetero-oligomers with enhanced functional activity.** *Science* 2000, **288:**154-7.
30. Zatelli MC, Piccin D, Vignali C, Tagliati F, Ambrosio MR, Bondanelli M, Cimino V, Bianchi A, Schmid HA, Scanarini M, Pontecorvi A, De Marinis L, Maira G, degli Uberti EC: **Pasireotide, a multiple somatostatin receptor subtypes ligand, reduces cell viability in non-functioning pituitary adenomas by inhibiting vascular endothelial growth factor secretion.** *Endocr Relat Cancer* 2007, **14:**91-102.
31. Ronchi CL, Rizzo E, Lania AG, Pivonello R, Grottoli S, Colao A, Ghigo E, Spada A, Arosio M, Beck-Peccoz P: **Preliminary data on biochemical remission of acromegaly after somatostatin analogs withdrawal.** *Eur J Endocrinol* 2008, **158:**19-25.

F1000 Factor 6.0 *Must Read*
Evaluated by Robert Murray 18 Dec 2008

32. Zatelli MC, Piccin D, Ambrosio MR, Bondanelli M, degli Uberti EC: **Antiproliferative effects of somatostatin analogs in pituitary adenomas.** *Pituitary* 2006, **9:**27-34.
33. Batista DL, Zhang X, Gejman R, Ansell PJ, Zhou Y, Johnson SA, Swearingen B, Hedley-Whyte ET, Stratakis CA, Klibanski A: **The effects of SOM230 on cell proliferation and adrenocorticotropin secretion in human corticotroph pituitary adenomas.** *J Clin Endocrinol Metab* 2006, **91:**4482-8.

F1000 Factor 3.0 *Recommended*
Evaluated by Gunter Stalla 05 Jul 2007