0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(6):3027–3032
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doi: 10.1210/jc.2003-031319

The Novel Somatostatin Ligand (SOM230) Regulates Human and Rat Anterior Pituitary Hormone Secretion

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Currently available somatostatin analogs predominantly bind to the somatostatin receptor subtype (SSTR)2 subtype, and control GH and IGF-I secretion in approximately 65% of patients with acromegaly, their efficacy relating to receptor density and subtype expression. SOM230 is a somatostatin ligand with high affinity to four SSTR subtypes. In primary cultures of rat pituicytes, SOM230 dose-dependently inhibited GH release ($P = 0.002$) with an IC_{50} of 1.2 nM. Ten nanomoles SOM230 inhibited GH and TSH release by 40 ± 7% ($P < 0.001$) and 47 ± 21% ($P = 0.09$), respectively. No effect of SOM230 was observed on prolactin (PRL) or LH release. In cultures of human fetal pituitary cells, SOM230 inhibited GH secretion by 42 ± 9% ($P = 0.002$) but had no effect on TSH release. SOM230 inhibited GH release from GH-secreting adenoma cultures by 34 ± 8% ($P = 0.002$), PRL by 35 ± 4% from PRL-secreting adenomas ($P = 0.01$), and α-subunit secretion from nonfunctioning pituitary adenomas by 46 ± 18% ($P = 0.34$). In contrast, octreotide inhibited GH, PRL, and α-subunit from the respective adenoma by 18 ± 12 ($P = 0.39$), 22 ± 4 ($P = 0.04$), and 20 ± 10% ($P = 0.34$). In all culture systems, no significant difference in the inhibitory action of SOM230, octreotide, and somatostatin 14 on hormone release was observed. SOM230, similar to somatostatin, has high-affinity binding to SSTR1, 2, 3, and 5 and, in keeping with this, has an equivalent inhibitory effect on pituitary hormone secretion. As a consequence of its broader binding profile, SOM230 is likely to find clinical utility in treating tumors resistant to SSTR-2-preferential analogs. (*J Clin Endocrinol Metab* 89: 3027–3032, 2004)

THE CYCLIC PEPTIDE somatostatin (SRIF) is an essential regulator of hypothalamo-pituitary secretion acting via five G protein-coupled receptors [somatostatin receptor (SSTRs) subtypes 1–5] (1). The two major circulating forms of somatostatin, SRIF14 and the amino extended SRIF28, bind with high affinity to all five SSTR subtypes. Therapeutic use of SRIF is constrained by its short half-life and need for parenteral administration necessitating development of analogs with a longer biological half-life. Two analogs of somatostatin, octreotide and lanreotide, that, although requiring injection, have greater biological stability are currently available. Both analogs bind preferentially with high affinity to SSTR2, with lesser affinity for SSTR3 and SSTR5 (2, 3), and are useful in treatment of elevated GH and TSH secretion. In acromegaly octreotide normalizes GH and IGF-I levels in approximately 65% of patients, with its efficacy relating to tumor SSTR density and subtype(s) (4–6). In *in vitro* studies of GH-secreting adenomas, ligands specific for both SSTR2 and SSTR5 are more efficacious in inhibiting GH release than either ligand alone or combinations of two analogs specific for the same SSTR (7). SOM230 is a novel SRIF analog displaying high-affinity binding to human SSTR1, 2, 3, and 5 and could therefore be hypothesized to cause greater inhibition of GH release from GH-secreting adenoma than currently available SRIF analogs. SOM230 is a potent inhibitor of GH and IGF-I in several *in vivo* animal models (8, 9). We therefore compared the relative efficacy of SOM230, octreotide, and SRIF on hormone secretion from primary cultures of rat pituitaries, human fetal pituitary tissue, and pituitary adenomas.

Abbreviations: PRL, Prolactin; RT, reverse transcriptase; SRIF, somatostatin; SSTR, somatostatin receptor.

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Materials and Methods

Materials

SOM230 and octreotide were kindly supplied by Novartis Pharma AG (Basel, Switzerland). SRIF14 and SRIF28 were purchased from Phoenix Pharmaceuticals Inc. (Belmont, CA).

Cell culture and treatments

Primary cell cultures were derived from pituitaries of male Sprague Dawley rats, 18- to 24-wk terminated human fetuses, and pituitary adenomas by mechanical and enzymatic dispersement. Cells were resuspended in low-glucose DMEM containing 10% fetal bovine serum and antibiotics in 48-well plates and incubated in 5% CO_2 at 37 C for 48 h. Cells were washed in serum-free media for 4 h and then incubated in media containing SOM230, octreotide, SRIF14, SRIF28, or vehicle. Media were collected for measurement of hormone levels. Use of human tissue was approved by the Institutional Review Board, and patients gave written consent for anonymous collection. Animal procedures were performed in accordance with institutional guidelines for animal care.

RNA isolation and RT-PCR

Tissue was homogenized in TRIZOL (Invitrogen, Carlsbad, CA), and phase separated with chloroform. RNA was precipitated from the aqueous phase, washed in 75% ethanol, and redissolved in diethylpyrocarbonate-treated water. Three micrograms RNA were incubated with RNase-free deoxyribonuclease-I (Roche Diagnostics, Mannheim, Germany) to eliminate contaminating genomic DNA. For synthesis of first-strand cDNA, RNA was reverse transcribed by incubation with Oligo(dT) primers and Omniscript reverse transcriptase (RT+) (Qiagen, Valencia, CA). A negative control was performed by running the reaction in the absence of RT enzyme (RT−). Fidelity of the RT reaction was

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assessed by PCR using primers for glyceraldehyde-3-phosphate dehydrogenase. Thirty-five cycles of PCR for each of the five SSTR subtypes were performed using Platinum *Taq* DNA polymerase (Invitrogen Life Technologies) and primers specific for the rat SSTR subtypes. Identical negative control reactions were performed on the RT sample. Positive control reactions were performed using plasmids containing the appropriate full-length SSTR as a template.

Assays

Human GH was measured in duplicate using a RIA kit [Diagnostic Products Corp. (DPC), Los Angeles, CA]. Human prolactin (PRL) and TSH were measured by immunoradiometric assay (Coat-a-Count, DPC). Rat GH, PRL, TSH, LH, and human α-subunit were measured in duplicate by double-antibody RIA using materials supplied by Dr. A. F. Parlow (National Institute of Diabetes and Digestive and Kidney Diseases Hormone Distribution Program, Harbor-UCLA Medical Center, Torrance, CA).

Data analysis

Data are presented as mean ± SEM. Differences between control and treatment groups were analyzed using the *t* test and rank sum test for parametric and nonparametric data, respectively. ANOVA was performed to assess differences across treatment groups.

Results

Primary rat pituitary culture

Cultures were incubated with 0.01–100 nM SOM230 or octreotide for 6 h. SOM230 and octreotide inhibited GH secretion in a dose-dependent manner (ANOVA on ranks; $P = 0.002$ and $P < 0.001$, respectively, Fig. 1, A and B). Maximal GH inhibition was observed between 10 and 100 nM for both ligands. Calculated IC_{50} values for SOM230 and octreotide were 1.2 and 0.8 nM, respectively. Further cultures were incubated with 10 nM SOM230 for 3–72 h. Significant GH inhibition was observed at 6 h (37 ± 9%, $P = 0.03$), with maximum inhibition occurring after 20 h incubation (56 ± 6%, $P < 0.001$) (Fig. 1C).

Rat pituicytes incubated with 10 nM SRIF14, SRIF28, octreotide, or SOM230 for 20 h resulted in GH suppression of 40 ± 9 ($P = 0.01$), 38 ± 7 ($P < 0.001$), 42 ± 9 ($P = 0.001$), and 40 ± 7% ($P < 0.001$), respectively, with no difference in magnitude of inhibition between the treatment groups (ANOVA on ranks, $P = 0.90$; Fig. 2A). Similar incubations were performed for assay of PRL, TSH, and LH. PRL inhibition from rat pituicytes was less than observed for GH (7.5–20%), with no difference between treatment groups ($P = 0.88$, Fig. 2B). TSH release was inhibited by 50 ± 10 ($P = 0.007$), 49 ± 17 ($P = 0.05$), 37 ± 29, and 47 ± 21% ($P = 0.09$), respectively, with no difference between treatments (ANOVA on ranks, $P = 0.97$; Fig. 2C). No effect of the four treatments was observed on LH (range +1 to +33%).

Human fetal pituitary tissue

GH secretion from fetal pituitary cultures was suppressed by 26 ± 12 ($P = 0.08$), 48 ± 7 ($P < 0.001$), 45 ± 25 ($P = 0.001$), and 42 ± 9% ($P = 0.002$) by 20 h incubation with 10 nM SRIF14, SRIF28, octreotide, and SOM230, respectively. No difference between treatment types was observed for GH inhibition (ANOVA, $P = 0.41$). TSH secretion was not suppressed significantly.

Pituitary adenomas

Seventeen pituitary adenomas (six GH-secreting, two PRL-secreting, and nine clinically nonfunctioning adenoma) were obtained immediately after transsphenoidal surgery. The tumor type was confirmed by immunohistochemistry for GH, PRL, and α-subunit. Primary cultures were incubated with 10 nM SRIF14, SRIF 28, octreotide, and SOM230 for 20 h and media collected and assayed for the respective hormone secretion.

In five of the six GH-secreting adenomas (tumors 1–6), SRIF14 and SOM230 inhibited GH by more than 20%, whereas octreotide and SRIF28 inhibited GH by more than 20% from only three and two tumors, respectively. Mean GH inhibition observed with SRIF14, SRIF28 octreotide, and SOM230 was 29 ($P = 0.002$), 17 ($P = 0.13$), 18 ($P = 0.39$), and 34% ($P = 0.002$), respectively (Fig. 3). No difference in GH suppression was observed between treatments. SSTR subtype expression assessed by PCR revealed all tumors to ex-

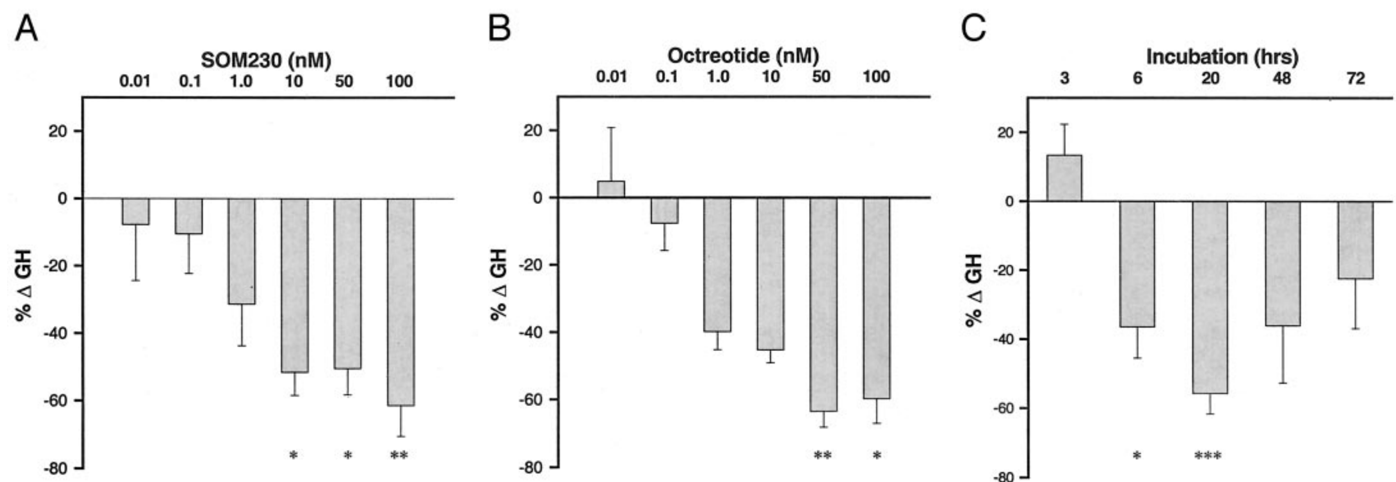

FIG. 1. Effect of dose and incubation time on the inhibition of GH secretion from primary cultures of rat pituicytes. A, Incubation with SOM230 0.01–100 nM for 6 h. B, Incubation with octreotide 0.01–100 nM for 6 h. C, Incubation with 10 nM SOM230 for 3–72 h. *, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$ for comparisons with control wells.

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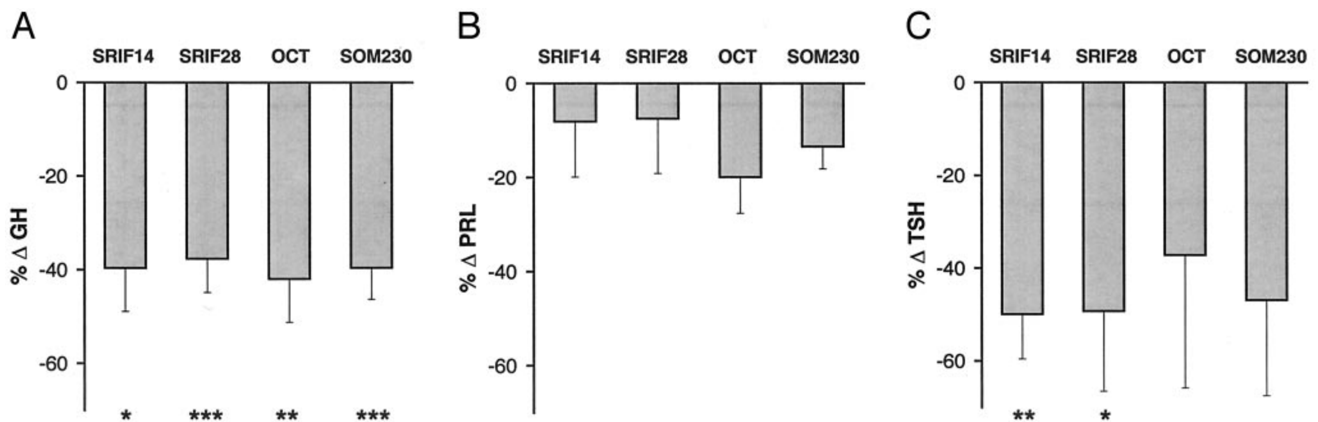

FIG. 2. Effect of SRIF14, SRIF28, octreotide (OCT), or SOM230 on GH (A), PRL (B), and TSH (C) secretion from primary rat pituicyte cultures incubated with 10 nM of the respective drug for 20 h, media collected, and analyzed for hormonal content. *, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$ for comparisons with control wells.

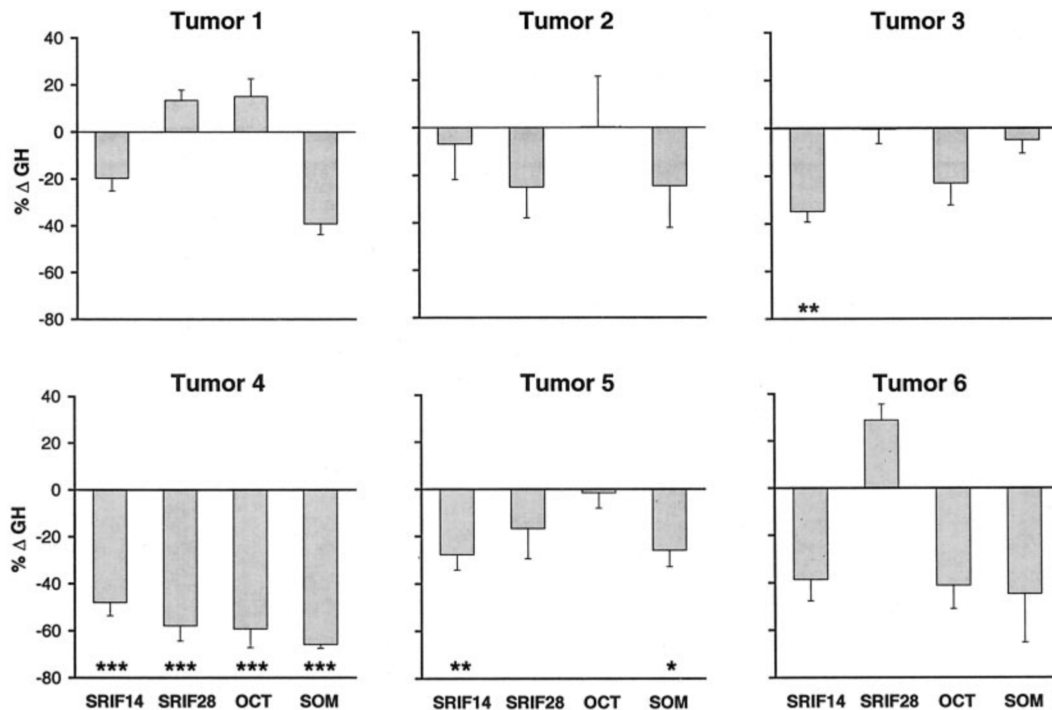

FIG. 3. GH suppression in primary cultures of six GH-secreting adenomas (tumors 1–6) incubated with 10 nM SRIF14, SRIF28, octreotide (OCT), or SOM230 for 20 h. *, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$ for comparisons with control wells.

press SSTR2, and with the exception of tumors 5 and 6, all tumors expressed SSTR5. Four of the tumors expressed SSTR1 (tumors 1, 2, 4, and 6), whereas only tumor 2 also expressed SSTR3.

In the two prolactinomas studied (tumors 7–8, Fig. 4) no difference in PRL inhibition from either tumor was observed between treatments with SRIF14, octreotide, and SOM230. The mean reduction in PRL secretion with SRIF14, octreotide, and SOM230 was 35 ($P = 0.06$), 22 ($P = 0.04$), and 35% ($P = 0.01$), respectively. Both prolactinomas expressed SSTR1 and SSTR2 mRNA by RT-PCR, and tumor 8 also expressed SSTR5 mRNA.

Of the nine cultured nonfunctioning adenomas, α-subunit levels were below the limit of detection in the medium of one adenoma. Additionally, four adenomas were unresponsive to treatments; however, in these four tumors, media levels of α-subunit were at the limit of detection of the assay. In the remaining four tumors (tumors 9–12, Fig. 5), SRIF14, octreotide, and SOM230 inhibited α-subunit by a mean of 32 ($P = 0.02$), 20 ($P = 0.34$), and 46% ($P = 0.34$), respectively, and no difference between treatments was observed. RT-PCR analysis of SSTR subtypes revealed all four nonfunctioning adenomas to express SSTR2, whereas tumors 8 and 10 also expressed SSTR3 mRNA.

Discussion

Currently available SRIF analogs control GH levels in acromegaly in approximately 65% of patients receiving pri-

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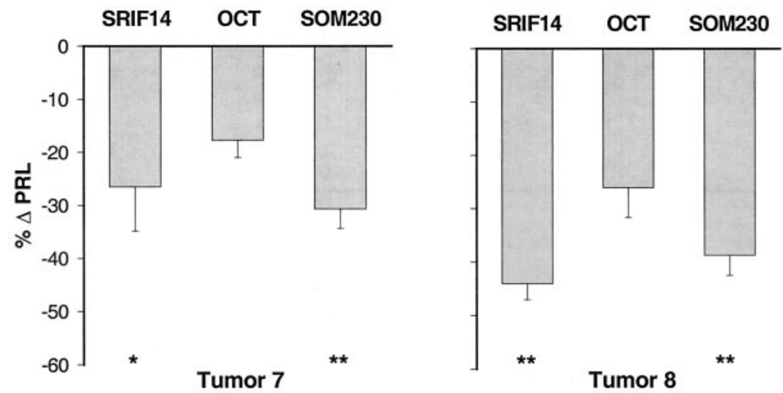

FIG. 4. PRL suppression in primary cultures of two PRL-secreting adenoma (tumors 7–8) incubated with 10 nM SRIF14, octreotide (OCT), or SOM230 for 20 h. *, $P < 0.05$; and **, $P < 0.01$ for comparisons with control wells.

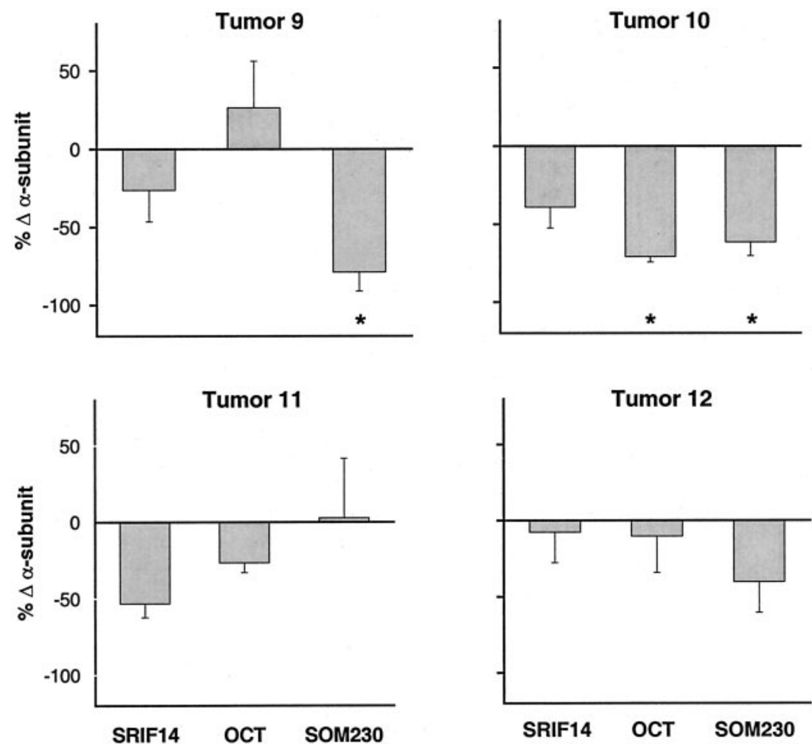

FIG. 5. α-Subunit suppression in primary cultures of four α-subunit secreting nonfunctioning pituitary adenoma (tumors 9–12) incubated with 10 nM SRIF14, octreotide (OCT), or SOM230 for 20 h. *, $P < 0.05$ for comparisons with control wells.

mary therapy or radiotherapy or after failed adenomectomy. A significant proportion of patients therefore have persistently elevated GH and IGF-I levels despite currently available therapies. The need for more effective medical therapy has led to development of new SRIF analogs, including SOM230. To develop a SRIF analog encompassing high-affinity binding to all five SSTR subtypes (10), alanine substitution was performed, and the product of this development, SOM230, is a novel SRIF analog that shows high-affinity binding to four of the five SSTRs: SSTR1, SSTR2, SSTR3, and SSTR5 (9). The premise for development of this analog was based on studies demonstrating that a combination of ligands specific for SSTR2 and SSTR5 were synergistic for GH inhibition from GH-secreting adenoma. Greater inhibition of GH was observed with combination of SSTR2- and SSTR5-specific ligands than either ligand alone or a combination of two ligands specific for the same receptor subtype (4, 7). Given this finding, it would be expected that a ligand, such as SOM230, with high affinity for both SSTR2 and SSTR5 would more effectively lower GH secretion from GH-secreting adenomas, compared with currently available SSTR ligands that preferentially bind SSTR2.

SRIF14 provides the benchmark to which new SRIF analogs are compared with respect to binding affinity and biological efficacy. In contrast, octreotide provides a paradigm that new SRIF analogs need to surpass to be considered clinically advantageous and thus worthy of further development. In the current study, the relative efficacy of SRIF14, SRIF28, octreotide, and SOM230 on hormone secretion were studied in three *in vitro* culture systems: primary rat pituicytes, human fetal pituitary cell, and pituitary adenomas. Because SOM230 binds to SSTR1, 2, 3, and 5 with IC_{50} values in the nanomolar range and SSTR4 is not expressed or expressed at very low levels in the pituitary and pituitary adenoma, SOM230 would be predicted to show similar efficacy to SRIF. Also, as a consequence of synergy between ligand bound

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SSTR subtypes, SOM230 would also be expected to show improved efficacy, compared with octreotide.

SOM230 effectively suppressed GH release from rat and human fetal pituitary cells in culture as well as from cultured GH-secreting adenomas. In the rat pituicyte cultures, SOM230 showed peak inhibition of GH at 20 h, with fall-off in inhibition thereafter, likely representing continued GH release in the setting of reduced bioactivity of SOM230. SOM230 demonstrated a similar mean GH inhibition to SRIF14 and octreotide in all cultures studied. However, a trend toward greater efficacy of SOM230 in GH-secreting adenoma, compared with octreotide, is reflected by significant inhibition of GH release, compared with control, by SOM230 but not octreotide. The relatively greater efficacy of octreotide in the rat pituitary cultures may be explained by the finding that octreotide has 160-fold greater affinity for the rat SSTR5 receptor, compared with the human SSTR5 (IC_{50} 0.2 *vs.* 32 nM) (1, 11). Although no significant difference between SRIF14 and SRIF 28 was observed in the culture systems, the mean GH inhibition in the GH-secreting adenomas suggests the possibility of differences between the two circulating forms. Mean GH inhibition by SRIF28 was, however, artificially reduced by tumor 6, which showed a paradoxical increase in GH secretion. In GH-secreting adenomas, inhibition of hormone release is primarily regulated via SSTR2 and -5, and the majority of GH adenomas express both these receptor subtypes (4, 12–14). Recent evidence suggests an additional regulatory role for SSTR1 (15). Currently available SRIF analogs, including octreotide, preferentially bind SSTR2 (2, 3) and therefore effectively suppress GH secretion in most patients with acromegaly. GH inhibition from GH-secreting adenomas correlates with quantitative expression of SSTR2 but not SSTR5 (4, 6). GH-secreting adenomas resistant to clinically available analogs express low densities of SSTR2 but frequently express high levels of SSTR5 (6). The high affinity of SOM230 for both SSTR5 and SSTR1 may in theory lead to an important clinical role for this analog in managing patients with GH-secreting adenomas resistant to current therapy. Even in GH adenomas considered responsive, SOM230 may improve efficacy as a result of high-affinity binding to, and functional synergy between, SSTR2 and SSTR5 (16). It is unlikely that tumors studied here were octreotide resistant because all expressed SSTR2.

Due to high-affinity binding to four of the five SSTRs, SOM230 may prove beneficial in treatment of other classes of pituitary adenoma. In contrast to observations in rat pituicytes, SOM230 suppressed PRL secretion from PRL-secreting adenomas to a similar extent as SRIF14. Octreotide was less effective in inhibiting PRL. Prolactinomas express a variable combination of SSTR1, -2, and -5; regulation of PRL release occurring via SSTR5 (7, 17) and possibly SSTR1 (15). SOM230 through its ability to bind both SSTR1 and -5 with high affinity may prove a useful adjunct for treating prolactinomas (approximately 25%) nonresponsive to dopamine agonists.

Rat LH secretion was not inhibited by any of the treatments, consistent with the fact that SRIF does not appear to normally control gonadotropin secretion, although it may modulate α-subunit when cosecreted by GH-, TSH-, or glycoprotein-secreting adenoma. In the glycoprotein-secreting adenoma studied, SOM230 demonstrated a trend toward greater suppression of α-subunit, compared with octreotide. Clinically nonfunctioning adenomas most frequently express SSTR2 and -3 (12, 13, 18), and although effects of SRIF analogs on inhibition of glycoprotein hormone secretion do not correlate with tumor growth, the high-affinity binding of SOM230 for SSTR3 may optimize antiproliferative effects via induction of apoptosis that occurs primarily through this receptor subtype.

In summary, SOM230 is a novel SRIF analog designed with the intent of achieving high-affinity binding to all SSTR subtypes as observed for SRIF14. This approach aims to optimize the synergistic effect of SSTR subtype interactions, thereby enhancing GH inhibition and the number of GH-secreting adenomas responsive to treatment. As demonstrated in this study, SOM230 induces similar inhibition of GH, PRL, TSH, and α-subunit as SRIF14 and octreotide. Although SOM230 does not enhance *in vitro* GH suppression over octreotide in most tumors, patients with acromegaly, select cohorts of octreotide-resistant GH-secreting adenomas, and non-GH adenomas that do not express SSTR2 are candidates for SOM230 treatment evaluation.

Acknowledgments

Received July 30, 2003. Accepted March 10, 2004.

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This work was supported by grants from Novartis Pharma and the Doris Factor Molecular Endocrinology Laboratory.

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