Somatostatin (SRIF) Receptor Subtype 2 and 5 Gene Expression in Growth Hormone-secreting Pituitary Adenomas: The Relationship with Endogenous SRIF Activity and Response to Octreotide


Department of Internal Medicine, College of Medicine, Hallym University, Hallym Sacred Heart Hospital, Kyunggi 431-070, Korea
*Department of Internal Medicine, Kyunghee University School of Medicine, Seoul 130-701, Korea
**Department of Pharmacology and Medical Science and Engineering Research Center for Reactive Oxygen Species, Kyunghee University School of Medicine, Seoul 130-701, Korea

Abstract. To investigate the potential pathophysiologic role of human SRIF receptor gene expression in GH-secreting adenomas in acromegalic patients, we studied the relationship between the SRIF receptor gene expression, endogenous SRIF activity and exogenous response to octreotide in 16 acromegalic patients. Hypothalamic somatostatinergic activity (HSA) was assessed by glucose-induced suppression of TRH-stimulated TSH secretion. As an indicator of somatotrope sensitivity to HSA, glucose-induced suppression of TRH-stimulated GH secretion was determined. For the acute octreotide response, a 100 μg bolus of octreotide was injected intravenously and GH was measured hourly for 6 hr. Pituitary tumor SRIF receptor subtype 2 and 5 (sst2 and sst5) mRNA levels were measured by real-time RT-PCR. Gsp oncogene was also detected by direct PCR sequencing. Sst2 and sst5 mRNA levels were detected in all tumors. Sst2 mRNA levels positively correlated with that of sst5. Sst2 and sst5 mRNA levels did not show any correlation with basal GH values (nadir or peak). Expression of sst2, but not sst5, showed a positive correlation with the GH response to HSA, while the octreotide response positively correlated with the sum of sst2 and sst5 mRNA levels. Individuals with gsp-positive tumors were more responsive to octreotide than those with gsp-negative tumors but sst2 and sst5 mRNA levels did not differ between these two groups. These results suggest common transcriptional and/or post-transcriptional regulatory mechanisms for these SRIF receptor subtypes within GH-secreting pituitary adenomas. The functional observations suggest that the degree (or level) of sst2 and sst5 expression is critical for the ultimate GH response of somatotropinomas to endogenous SRIF tone and exogenous SRIF analogue therapy. However, sst2 and sst5 mRNA levels are not the only factors mediating the response to SRIF.

Key words: Somatostatin receptor, Pituitary adenomas, gsp oncogene, Hypothalamic somatostatinergic activity

SOMATOSTATIN (SRIF) inhibits proliferation of somatotropes as well as growth hormone (GH) release through specific G-protein coupled receptors [1, 2]. Five human SRIF receptor (sst1–5) genes have been cloned and characterized [3, 4]. Expression of all subtypes, except sst4, has been observed in GH-secreting adenomas [5, 6], although sst2 and sst5 are the most dominant isoforms [5–7]. It is thought that sst2 and sst5 are the primary mediators of the inhibitory actions of SRIF on GH release since sst2 and sst5 selective agonists suppress GH release from primary pituitary cell cultures at concentrations 1000-fold less than sst1,
sst3 and sst4 agonist [8–10]. Sst2 exhibits a higher affinity for SRIF-14 than SRIF-28, while sst5 has greater affinity for SRIF-28 than for SRIF-14 [7]. The SRIF analogs, octreotide and lanreotide, which are used as an adjunctive therapeutic agent for the treatment of acromegaly, bind with high affinity to sst2 and with less affinity to sst5 [10].

A positive correlation between octreotide inhibition of plasma GH levels with in vitro SRIF binding and SRIF inhibition of adenylyl cyclase has been reported in GH-secreting adenomas [11]. Given the preferential binding of octreotide to sst2 and sst5, these observations predict that the level of sst2 and sst5 synthesis may affect somatotropinoma response to SRIF analogue therapies. Therefore, in this study we sought to determine if sst2 and sst5 mRNA levels in GH-secreting pituitary adenomas are associated with in vivo response to octreotide.

As previously reported by others and us [12, 13], hypothalamic somatostatinergic activity (HSA) is highly variable in patients with acromegaly, as assessed by the ability of glucose to suppress TRH-mediated TSH release. Since the synthesis of many G-protein-coupled receptors have been shown to be regulated by their own ligands [14, 15], one might predict that SRIF receptor expression in GH-secreting adenomas may also be regulated by HSA. Therefore, in the current report we examined the association between HSA and expression of pituitary tumor sst2 and sst5 in acromegaly.

Finally, it has been reported that patients with gsp-positive GH-secreting tumors show a higher response to SRIF and octreotide [16–18], suggesting the mutation of this stimulatory G protein may increase the expression of SRIF receptor. Therefore, in the current study we compared the HSA and octreotide response in patients with gsp-positive and gsp-negative tumors.

Subjects and Methods

Patients and endocrine tests

Sixteen acromegalic patients (6 men and 10 women, aged 24–61 years) were enrolled. None of the patients had received any treatment before the study. The diagnosis of acromegaly was made by the lack of GH suppression less than 2 µg/L during the oral glucose tolerance test. Pituitary adenomas were identified in all patients by magnetic resonance imaging. This study was approved by the Kyunghee University Hospital Ethics Committee and informed consent was obtained from each patient before the study.

Endocrine tests were performed on separate days. Before each test, subjects fasted overnight and were recumbent for 1 hr. On day 1, the TRH stimulation test was performed. TRH (Relefact TRH, Hoechst, Frankfurt, Germany; 200 µg bolus) was administered intravenously. Blood sampling was performed every 30 min for 2 hr. On day 2, the oral glucose tolerance test was performed by oral administration of 75 g glucose with blood sampling as described above. On day 3, blood was obtained every hour from 0900–1600 hr for determination of the basal daytime GH secretion pattern. On day 4, the combined glucose-TRH test was undertaken by administering 75 g glucose, orally, 30 min before the injection of TRH as reported previously [19]. HSA was assessed by glucose-induced suppression of TRH-stimulated TSH secretion as described previously [13]. It was expressed as percent suppression of serum TSH concentration at 30 min after TRH injection during the combined glucose-TRH test compared to that during the TRH test. The GH response to HSA was expressed as percent suppression of GH at 30 min during the combined glucose-TRH test compared to that during the TRH test. On the day 5, for determination of somatotrope response to an exogenous SRIF stimulus, a 100 µg bolus of octreotide (Sandostatin, Sandoz, Switzerland) was injected intravenously, and GH levels were determined in blood samples taken every hour for 6 hr.

Hormone assays

Commercial immunoradiometric assay kits were used for GH (Nichols Institute Diagnostics, San Juan Capistrano, CA) and TSH (Daiichi, Tokyo, Japan) determinations. The sensitivity of the GH assay was 0.02 µg/L. The intra- and interassay coefficients of variation were 3.3% and 5.1%, respectively. The sensitivity of the TSH assay was 0.1 mU/L, and the intra- and interassay coefficients of variation were 2.1% and 2.5%, respectively.

Sequencing of the gsp oncogene

Genomic DNA was extracted from the frozen tumor tissue and peripheral blood leukocytes from each patient as described previously [18]. The region between
codons 184 and 251 of the α subunit of stimulatory G protein (Gαs) was sequenced by direct PCR using a set of primers (upper primer, 5'-GTG ATC AAG CAG GCT GAC TAT GTG-3'; lower primer, 5'-GCT GCT GGC CAC CAC CAC GAA GAT GAT-3'). The cyclic sequencing kit (SequiTherm, Epicentre Technologies, Madison, WI) and a thermal cycler (Genes and PCR System 9600, Perkin-Elmer, Norwalk, CT) were used for the PCR.

**Real-time RT-PCR of pituitary SRIF receptor sst2 and sst5 mRNA**

We used a real-time RT-PCR assay to quantify pituitary SRIF receptor (sst2 and sst5) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH; as an internal standard) mRNA levels. Total RNA (1 μg) was reverse transcribed using the Superscript II reverse transcriptase (Life Technologies, Inc., St. Louis, MO) with random hexamer priming. The resultant complementary DNA (cDNA) was amplified using Roche LightCycler (Roche Diagnostics Ltd., Lewes, UK). PCR primer sequences for sst2, sst5 and GAPDH were as follows: sst2: sense, 5'-CAT CAA GTC GGC CAA GTG GAG-3'; and antisense, 5'-TGA AGA CAG CCA CGA CTG TGG-3' [GenBank Acc No. (ACC) XM_012697]; sst5: sense, 5'-CGC CGT CTT CAT CAT CTA CAC-3'; and antisense, 5'-CAGCCA ACA TCC CGC AAA CAC-3' (ACC No. XM_012665); and GAPDH: sense, 5'-AAT GCC TCC TGC ACC ACC AAC-3'; and antisense, 5'-AAG GCC ATG CCA GTG AGC TTC-3' (ACC No. M33197). The expected sizes of PCR products were 356bp for sst2, 193 bp for sst5, and 254 bp for GAPDH.

PCR reactions were performed in a 20-μl volume capillary with 2-μl RT product, 0.5 μM primers and MgCl₂ concentration optimized between 3–5 mM. Taq polymerase, PCR buffer, dNTPs, and SYBR Green I dye were included in the LightCycler-FastStart DNA Master SYBR Green I mix (Roche Diagnostics Ltd., Lewes, UK). Thermal cycling profile consisted of pre-incubation step at 95°C for 10 min followed by 40 or 50 cycles of 95°C denaturation step for 10 sec, 59°C annealing step for 5 sec, and 72°C extension step for 20 sec. After each extension step, the temperature was raised to 88°C (sst2 and GAPDH) or 90°C (for sst5) to measure SYBR Green I fluorescence at a temperature 2°C below the product Tₘ and above the Tₘ of the primer-dimers to prevent the interference of unspecific primers-dimers. At the end of the PCR a melting curve analysis was performed by gradually increasing temperature from 65°C to 95°C (0.1°C/sec) to confirm the amplification specificity of the PCR products. The level of expression of each mRNA and their estimated crossing points (Cₚ) in each sample were determined relative to the standard preparation using the LightCycler computer software (v. 3.5). The PCR standards for each sst2, sst5 and GAPDH consisted of known number of molecules of purified PCR product purified using a gel extraction kit (Qiagen Inc., Valencia, CA, USA) and quantified spectrophotometrically. Standards were made to a concentration of 10⁸ copies/μl. PCR amplification was performed with a series of standards prepared by successive dilutions and a linear standard curve was automatically generated. A standard curve was constructed for each PCR run. All samples to be compared were run in the same assay. A ratio of sst2 or sst5 mRNA/GAPDH mRNA amplification was then calculated, to correct for any differences in efficiency at RT reaction. GAPDH was considered an appropriate control, in that GAPDH expression levels did not significantly differ between groups of comparison.

**Statistical analysis**

In order to test whether sst2 and sst5 mRNA levels show normal distribution, normality test was performed using the Kolmogrov-Smirnov test. Both variables passed normality test. Statistical differences in % suppression of GH by octreotide between the high and low sum of sst2 and sst5 mRNA and in sst2 and sst5 mRNA levels between gsp-positive and gsp-negative GH-secreting adenomas were determined by two-tailed Student's t-test. To determine the correlation between pairs of variables without specifying dependency, Pearson correlation calculations were performed. The statistical calculations were carried out using statistical software GraphPad Prism (GraphPad Software, Inc., San Diego, CA, USA).

**Results**

To test the sensitivity of the real-time PCR used in this study, standard curves were constructed from known amounts of purified PCR products (each diluted 10-fold from 10⁶ to 10² copies). All standard
curves showed correlation coefficients >0.99. Each graph of fluorescence against cycle number demonstrates that as few as 10 template copies could be distinguished from background levels because any signal from primers-dimers was avoided. Fig. 1 represents an example of a linear standard curve from $10^1$ to $10^6$ copies of GAPDH template (A) and a plot of fluorescence against cycle number demonstrates discrimination down to 10 copies of GAPDH template. (B) Melting curves: The $T_m$ of the PCR product can be visualized as a peak.

Table 1. Clinical and endocrinological findings in the subjects

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Size (mm)</th>
<th>GH (µg/L)</th>
<th>Response to TRH</th>
<th>HSA (%)</th>
<th>Response to HSA (%)</th>
<th>Octreotide response (%)</th>
<th>gsp oncogene</th>
<th>ssl2/ GAPDH</th>
<th>ssl5/ GAPDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>39</td>
<td>18</td>
<td>7.2</td>
<td>36.5</td>
<td>–</td>
<td>64</td>
<td>n.a.</td>
<td>98</td>
<td>201, CGT/TGT</td>
<td>0.171</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>42</td>
<td>5</td>
<td>55.5</td>
<td>116.0</td>
<td>+</td>
<td>0</td>
<td>61</td>
<td>98</td>
<td>201, CGT/TGT</td>
<td>0.129</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>37</td>
<td>18</td>
<td>24.1</td>
<td>80.3</td>
<td>+</td>
<td>31</td>
<td>17</td>
<td>95</td>
<td>201, CGT/TGT</td>
<td>0.440</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>45</td>
<td>5</td>
<td>6.6</td>
<td>13.3</td>
<td>+</td>
<td>0</td>
<td>74</td>
<td>91</td>
<td>227, CAG/CTG</td>
<td>0.286</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>24</td>
<td>30</td>
<td>17.0</td>
<td>29.8</td>
<td>+</td>
<td>0</td>
<td>56</td>
<td>89</td>
<td>201, CGT/TGT</td>
<td>0.465</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>46</td>
<td>30</td>
<td>20.2</td>
<td>39.5</td>
<td>+</td>
<td>0</td>
<td>55</td>
<td>87</td>
<td>None</td>
<td>0.618</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>58</td>
<td>8</td>
<td>9.1</td>
<td>13.8</td>
<td>–</td>
<td>34</td>
<td>n.a.</td>
<td>83</td>
<td>201, CGT/TGT</td>
<td>0.072</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>43</td>
<td>12</td>
<td>15.9</td>
<td>29.2</td>
<td>–</td>
<td>0</td>
<td>n.a.</td>
<td>80</td>
<td>None</td>
<td>0.120</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>37</td>
<td>17</td>
<td>34.9</td>
<td>93.5</td>
<td>+</td>
<td>46</td>
<td>29</td>
<td>78</td>
<td>None</td>
<td>0.079</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>44</td>
<td>45</td>
<td>29.2</td>
<td>66.8</td>
<td>+</td>
<td>25</td>
<td>97</td>
<td>90</td>
<td>None</td>
<td>0.956</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>28</td>
<td>32</td>
<td>6.9</td>
<td>24.2</td>
<td>+</td>
<td>0</td>
<td>87</td>
<td>0</td>
<td>None</td>
<td>0.184</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>36</td>
<td>13</td>
<td>10.0</td>
<td>17.1</td>
<td>+</td>
<td>77</td>
<td>16.3</td>
<td>44</td>
<td>201, CGT/TGT</td>
<td>0.153</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>45</td>
<td>20</td>
<td>39.2</td>
<td>74.7</td>
<td>+</td>
<td>62</td>
<td>81</td>
<td>99</td>
<td>201, CGT/TGT</td>
<td>0.436</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>53</td>
<td>6</td>
<td>4.1</td>
<td>7.0</td>
<td>+</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>201, CGT/TGT</td>
<td>0.133</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>61</td>
<td>8</td>
<td>16.2</td>
<td>22.0</td>
<td>+</td>
<td>n.d.</td>
<td>n.d.</td>
<td>96</td>
<td>201, CGT/TGT</td>
<td>0.344</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>37</td>
<td>30</td>
<td>108.6</td>
<td>288.8</td>
<td>–</td>
<td>8</td>
<td>n.a.</td>
<td>76</td>
<td>None</td>
<td>0.129</td>
</tr>
</tbody>
</table>

n.a.: non-applicable  
n.d.: not determined
tion down to 10 copies of GAPDH template (B). Fig. 1(C) shows a melting peak analysis of the GAPDH, sst2 and sst5 primer pairs amplified a single predominant product with a distinct Tm.

Eleven patients had macroadenomas and 5 patients had microadenomas. The nadir and peak levels of GH were in a wide range and did not correlate with the tumor size. The HSA of the patients ranged from 0% to 77% and the response of GH to the HSA also ranged from 0% to 97%. The HSA did not correlate with the GH response to the HSA. The response of GH to octreotide ranged from 0% to 99.5% and did not correlate with either the HSA or the GH response to the HSA (Fig. 2).

Sst2 and sst5 mRNAs were found in all tumors (Table 1). The amount of sst2 mRNA positively correlated ($r^2 = 0.56$, $P < 0.01$) with that of sst5 mRNA (Fig. 3). In addition, tumor size measured by magnetic resonance imaging positively correlated both sst2 ($r^2 = 0.40$, $P < 0.01$) and sst5 ($r^2 = 0.25$, $P < 0.05$) mRNA levels (Fig. 4).

The level of sst2 and sst5 expression did not correlate with the nadir or peak level of basal GH. However, the amount of sst2 mRNA showed a positive correlation ($r^2 = 0.31$, $P < 0.05$) with the GH response to the HSA (Fig. 5, upper panel). The tumors with a higher expression of sst2, of which the relative mRNA levels were above the median value, showed a higher suppression of GH by the HSA than the tumors with a lower expression (67% vs. 19%, $P = 0.0036$). In contrast, sst5 mRNA levels were not associated with HSA (Fig. 5, lower panel).

Despite the increased sensitivity of GH response to endogenous somastatinergic activity in patients with a high level of sst2 expression, the GH response to exogenous octreotide did not show any significant correlation with the mRNA amount of sst2 or sst5 (data not shown). However, the octreotide response was higher (93% vs. 66%, $P = 0.0352$) in the tumors with a higher sum of sst2 and sst5 mRNA than that in the tumors with a lower sum of sst2 and sst5 mRNAs (Fig. 6).

The gsp oncogene was found in 10 of 16 (62.5%) adenomas (Table 1). All the point mutations were found at codon 201 except one (patient 4) that occurred at codon 227. Arginine (CGT) of codon 201 was replaced with cysteine (TGT) in one allele of genomic DNA from 8 tumors and with serine (AGT) in one tumor. Glutamate (CAG) of codon 227 was replaced with leucine (CTG). The gene expression of sst2 or sst5 in gsp-positive tumors did not differ from that in gsp-negative tumors (Fig. 7). However, as previously reported [16–18], the gsp-positive tumors showed a higher response to octreotide than the gsp-negative tumors (88% vs. 55%, $P = 0.0432$). This increase in sensitivity to an exogenous SRIF stimulus did not translate into an increase in sensitivity to endogenous SRIF tone in that the HSA and the GH

---

Fig. 2. Correlation between HSA and % suppression of GH by HSA (A), % suppression of GH by octreotide and HSA (B) and % suppression of GH by octreotide and % suppression of GH by HSA (C). Correlations were assessed using Pearson’s analysis.
response to the HSA of the patients with gsp-positive tumors did not differ from those of the patients with the gsp-negative tumors.

**Discussion**

This is the first report examining the relationship between the SRIF receptor gene expression and functional endpoint of SRIF activity and sensitivity in GH-secreting adenomas. In the present study, we confirmed the previous findings that sst2 gene and sst5 gene are expressed in most of GH-secreting adenomas but their relative level of expression is variable [5, 20]. We also found that the sst2 and sst5 mRNA levels
are closely correlated suggesting these subtypes are coordinately regulated at the transcriptional or posttranscriptional level in GH-secreting adenomas of acromegalic patients.

We could not find any correlation between SRIF receptor gene expression and basal GH levels suggesting basal GH secretion is not determined solely by expression of SRIF receptors. However, SRIF receptor expression was associated with response to endogenous and exogenous SRIF tone. Since the SRIF levels cannot be measured directly in the patient, we estimated HSA by the percent suppression of TSH during the combined glucose-TRH test as we reported previously [13]. Previous studies demonstrated that the increased secretion of SRIF induced by oral glucose loading suppressed the basal and TRH-stimulated TSH release [19, 21]. Therefore, measurement of TSH secretion after modulation of SRIF neuronal activity by glucose can be a useful method to evaluate HSA activity. HSA did not correlate with the gene expression of SRIF receptors in this study, indicating that the level of stimulated SRIF activity does not mediate SRIF receptor expression. However, the GH response to HSA was positively correlated with sst2 mRNA levels indicating that SRIF receptor synthesis is critical for the ultimate response of GH-secreting adenomas to endogenous SRIF input. A similar association was not observed for sst5, suggesting sst2 is the dominant isoform in transmitting endogenous SRIF effects on GH release. This hypothesis is supported by the fact that sst2 has a higher affinity [7] to the natural hypothalamic SRIF than sst5 [22]. However, it should be noted that some patients (patients 2, 4, 5, 6 and 11) with high levels of SRIF receptors and high GH responses to the HSA, had very low HSA, suggesting that another factor(s) in the signal transduction pathway for SRIF may enhance the effect of SRIF. For example, Goα signaling, that is associated with SRIF receptor and mediates the effect of SRIF, is less expressed in bromocriptine-resistant prolactinomas [23, 24]. Therefore, increased activity or expression of Goα protein remains to be investigated.

And we cannot exclude the possibility of different mechanisms regulating GH and TSH secretion in pitui-
tary adenomas. It should be noted that case 11 is a unique case that showed no response of GH to octreotide and 0% of HSA, but marked response of GH to HSA. The resistance to octreotide treatment might be associated with mutations in SRIF receptor genes [25]. We also might speculate that glucose suppresses GH responses to TRH by a non-SRIF-mediated mechanism.

Although the effect of octreotide is known to be mediated through sst2 [9], the acute GH response to octreotide did not correlate with the expression of sst2 in this study. As the differences in sst2 mRNA do not necessarily mean comparable differences in functional sst2 receptors on the somatotrope membrane, and while it is possible that we could not find a correlation, this possibility is less likely because the GH response to the HSA did correlate with SRIF receptor mRNA levels. Three alternative explanations should be considered. First, as octreotide binds to sst2 with the half affinity of that of the hypothalamic SRIF [9], a significant correlation may be masked. Second, the octreotide response may not be determined by sst2 levels alone. Even though sst5 has the affinity of about 1/10 of sst2’s affinity for octreotide [9], tumors with higher expression of sst5 may show a better response to octreotide, as did some patients (patients 1, 3 and 4) in this study. In fact, the tumors with higher sum of sst2 and sst5 showed a better response to octreotide. These findings suggest that both subtypes participate in the determination of the octreotide response in GH-secreting adenomas. However, when a tumor shows a higher expression of sst5 gene, it seems reasonable to use a sst5-selective SRIF analog with octreotide. This notion is supported by the results of an earlier study that some adenomas respond more favorably to sst2-preferential analogs, while in others sst5-selective analog suppressed GH more potently [10]. Finally, \( \text{G}_{\alpha_\text{q}} \) protein may be less expressed in tumors with a lower response to octreotide as were the protein in bromocriptine-resistant prolactinomas [23, 24]. However, this possibility is less likely because the tumors with a lower octreotide response did not show a lower GH response to the HSA.

Mutation of \( \text{G}_{\alpha_\text{q}} \) protein is a candidate as an intracellular factor that may increase the expression of SRIF receptor genes. Considering that \( \text{G}_{\alpha_\text{q}} \) mutant constitutively increases the intracellular cAMP level [26], and that the SRIF receptor subtype 2 gene expression is enhanced by increase of intracellular cAMP in AtT-20 cells [27] and in rat pituitary cells [28], one might expect that \( \text{gsp} \) oncogene increases the SRIF receptor gene expression. In fact, this expectation was also derived from the previous studies that GH-secreting adenomas with \( \text{gsp} \) oncogene showed a higher response to SRIF and its analogs [16–18]. Although we observed in this study that individuals with \( \text{gsp} \)-positive tumors showed a higher response to octreotide, these same tumors did not exhibit a higher expression level of sst2 or sst5. Corbetta et al. [29] have also reported that sst2 and sst5 mRNA levels in GH-secreting pituitary adenomas did not correlate with the presence of \( \text{gsp} \) oncogene. Taken together, these results suggest that \( \text{gsp} \) oncogene is not a major intracellular determinant for SRIF receptor gene expression. Although the rat sst2 gene expression was increased in GH3 cells stably transfected with \( \text{gsp} \) oncogene (our unpublished data), other intracellular or extracellular factors may be involved in the regulation of SRIF receptor gene expression in the adenomas of acromegalic patients.

In conclusion, the present study suggests that sst2 and sst5 are expressed and regulated similarly in most of GH-secreting adenomas, and that the degree of their expression is related to the GH response of tumors to HSA and octreotide.

Acknowledgment

This work was supported by grants No. R13-2002-020-01004-0 and R01-2001-000-00127-0 (2002) from the Korea Science & Engineering Foundation. We would like to extend our thanks to Dr. R. D. Kineman (Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA) for proofreading this manuscript.

References

2. Lamberts SW (1988) The role of somatostatin in the


